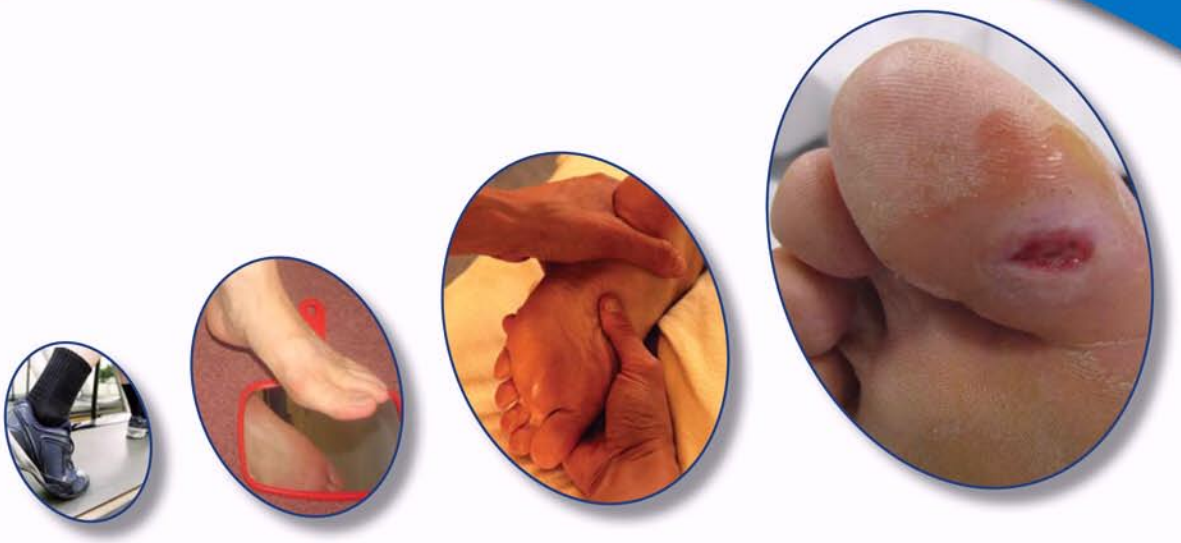
Prevention, Identification and Management of Foot Complications in Diabetes

Technical Report



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Contents

Executive summary

This document outlines the results of a series of systematic reviews, performed to provide evidence-based guidance for the prevention, identification and management of foot complications in type 1 and type 2 diabetes mellitus. The evidence collected was then used to form the basis for a series of evidence statements, which were translated into recommendations by the Expert Working Group. The full guideline document is published elsewhere.

A summary of the evidence-based recommendations (EBR) that were produced based on the evidence in these systematic reviews are provided below, along with an evidence statement map which links to the evidence statements produced from the technical report with the evidence-based recommendations:

For assessing risk:

EBR 1 Assess **all people** with diabetes and stratify their risk of developing foot complications. (Grade C)

EBR 2 Assess risk stratification by **inquiring about previous foot ulceration and amputation, visually inspecting the** feet for structural abnormalities and ulceration, **assessing for neuropathy** using **either the** Neuropathy Disability Score **or** a **10 g monofilament** and **palpating foot pulses**. (Grade C)

EBR 3 Stratify foot risk in the following manner:

- "low risk"- people with no risk factors and no previous history of foot ulcer/amputation
- "intermediate risk"- people with one risk factor (neuropathy, peripheral vascular disease or foot deformity) and no previous history of foot ulcer/amputation
- "high risk" - people with two or more risk factors (neuropathy, peripheral vascular disease or foot deformity) and/or a previous history of foot ulcer/amputation (Grade C)

For the prevention of foot complications in diabetes:

EBR 4 People assessed as having **"intermediate risk"** or **"high risk" feet** should be offered a **foot protection program**. A **foot protection program** includes foot education, podiatry review and appropriate footwear. (Grade C)

Management of foot ulceration in primary care settings

EBR 5 **Foot ulcer severity can be graded** on the basis of wound depth, presence of infection (local, systemic or bone) and presence of peripheral arterial disease. Ulcer grading helps determine the degree of risk to the person and limb (Oyibo et al 2001b; Parisi et al 2008). The **University of Texas (UT) wound classification system** is the most useful tool for grading foot ulcers. (Grade C)

EBR 6 **Topical hydrogel dressings** may be considered for autolytic debridement to assist the management of non-ischaemic, non-healing ulcers with dry, non-viable tissue. (Grade B)

EBR 7 **Pressure reduction**, otherwise referred to as redistribution of pressure or offloading, is required to optimise the healing of plantar foot ulcers. (Grade B)

EBR 8 Offloading of the wound can be achieved with the use of a **total contact cast or other device rendered irremovable**. (Grade B)

EBR 9 People with diabetes-related foot ulceration are best managed by a **multi-disciplinary foot care team** (Grade C)

EBR 10 Remote expert consultation with digital imaging should be made available to people with diabetic foot ulceration living in remote areas who are unable to attend a multi-disciplinary foot care team/service for management (Grade C)

Management in specialist settings

The following may be considered for foot ulcers in specialist centres, as part of a comprehensive wound management program:

EBR 11 Topical negative pressure therapy (Grade B)

EBR 12 Hyperbaric oxygen therapy (Grade B)

EBR 13 Larval therapy (Grade C)

EBR 14 Skin replacement therapies

1. Cultured skin equivalents (Grade B)
2. Skin grafting (Grade D)

Evidence statement map to link evidence statements with recommendations

Evidence statement	Grade	Recommendation	Evidence report section
Research question 1: Which assessments lead to improved foot-related clinical outcomes in people with diabetes?			
The evidence provided indicates that twice daily home-based infrared foot temperature monitoring in addition to standard care when used by diabetic patients at high risk of lower extremity ulceration is effective in preventing foot ulcer	B	–	Research question 1, page 3
The evidence suggests that a two-stage foot screening program, followed by a protection program for those patients identified with a high risk foot for patients visiting a general diabetes clinic may reduce the incidence of major amputation.	C	C (EBR 1–4)	Research question 1, page 7
Research question 2: Which clinical assessments best predict foot ulcer and/or amputation in people with diabetes?			
In a diabetes general population			
The results suggest that the neuropathy disability score is a good screening tool for identifying those at high risk of foot ulceration in a general diabetes population, although it is likely to be associated with a considerable proportion of false positives. Further research is required.	C	–	Research question 2, page 12
Neuropathy disability is a good predictor of foot ulcer in the general diabetes population.	B		Research question 2, page 14
Neuropathy disability score combined with either vibration perception threshold; Semmes-Weinstein monofilament or foot pressure assessments may be poor screening tools to determine those patients at high risk of foot ulcer in the general diabetes population. The NDS combined with Semmes-Weinstein monofilament assessment or	C	–	Research question 2, page 14

Evidence statement	Grade	Recommendation	Evidence report section
vibration perception threshold may be useful to rule out the high risk of foot ulcer.			
The risk assessment tool is a good tool for determining those at risk of foot ulcer in the general diabetes population. Further research would be required.	C	–	Research question 2, page 17
Risk assessment using a combination of patient history, foot pulses, neuropathy and foot deformity is a strong predictor of foot ulcer in the general diabetes population. Further research would be required	C	–	Research question 2, page 17
HDC risk assessment may be an accurate test for ruling out risk of foot ulcer and amputation in the general diabetes population. Further research would be required.	C	–	Research question 2, page 20
The Seattle risk assessment may have moderate performance at accurately identifying those at risk of foot ulcer. It has better performance at accurately ruling out those who are at low risk of subsequent amputation. Further research would be required.	C	–	Research question 2, page 23
The results suggest that foot pressure assessment has variable accuracy at identifying diabetic individuals at high risk of foot ulcer. Further research is required.	C	–	Research question 2, page 25
Diabetic patients with elevated foot pressure, as assessed using peak or mean plantar pressure measurement, have a moderate to substantial increased risk of developing foot ulcer compared to diabetic patients with normal foot pressure.	B	–	Research question 2, page 29
The assessment of vibration sensation perception in the diabetes population, with or without a history of foot ulcer, has moderate accuracy at detecting those patients at risk of a subsequent foot ulcer.	C	–	Research question 2, page 29

Evidence statement	Grade	Recommendation	Evidence report section
Vibration sensation perception is a substantial predictor of foot ulceration in the general diabetes population. Absence of vibration perception at a threshold of >25 Volts significantly increases the risk of subsequent foot ulcer development. There was insufficient evidence to determine whether vibration sensation assessment as is a predictor for lower extremity amputation in the diabetes general population.	B	–	Research question 2, page 35
The use of Semmes-Weinstein monofilament testing to determine patients at risk of foot ulcers or lower extremity amputation in the general diabetes population is not advised, as it's diagnostic accuracy is poor.	C	–	Research question 2, page 37
Peripheral sensory neuropathy and insensitivity to Semmes-Weinstein monofilament testing is a good predictor of risk of foot ulcer, foot injury and amputation in a general diabetes population.	B	–	Research question 2, page 38
In the general diabetes population, the assessment of ankle reflexes is a poor screening technique for identifying those at high risk of foot ulceration and lower extremity amputation.	C	–	Research question 2, page 42
There is inconsistent and inconclusive evidence regarding the role of ankle reflex assessment in predicting foot ulcers in the general diabetes population. Ankle reflex assessment may have a role in predicting risk of amputation in a general diabetes population.	C	–	Research question 2, page 43
The evidence indicates that the presence of foot deformity is a moderate predictor of foot ulcer in the general diabetes population.	B	–	Research question 2, page 47
Based on a single study, the assessment of gait in the general diabetes population is a poor screening technique for identifying those patients at high risk of foot ulcer and amputation	D	–	Research question 2,

Evidence statement	Grade	Recommendation	Evidence report section
			page 49
Evidence suggests that peripheral arterial pulse assessment alone is a poor screening technique to identify those patients in the general diabetes population at high risk of amputation.	C	–	Research question 2, page 51
Peripheral arterial pulse is a moderate predictor of subsequent foot ulcer or amputation in the general diabetes population.	B	–	Research question 2, page 53
On the bases of limited evidence, Ankle Arm Index assessment would appear to be a poor screening technique to predict lower extremity amputation in the general diabetes population.	C	–	Research question 2, page 54
The Ankle Arm Index may be a moderate predictor of foot ulceration and substantial predictor of major amputation in the male diabetes population.	C	–	Research question 2, page 56
Ankle blood pressure may be a moderate predictor of foot ulceration in male diabetes patients. However, further research is required to confirm this association.	C	–	Research question 2, page 56
There is limited evidence suggesting that orthostatic blood pressure is a poor predictor for the development of subsequent foot ulcer in male diabetes patients.	D	–	Research question 2, page 57
Transcutaneous oxygen tension assessment is of limited value as a screening tool for identifying those at high risk of lower extremity amputation in a general diabetic population. However, it has moderate value as a diagnostic tool. Further research is required to confirm this association.	C	–	Research question 2, page 60

Evidence statement	Grade	Recommendation	Evidence report section
Transcutaneous oxygen tension may be a moderate predictor for the development of foot ulcer and the occurrence of amputation in male diabetic patients.	C	–	Research question 2, page 60
Limited evidence suggests that the assessment of glycaemic control has poor accuracy at identifying those at risk of foot ulcer or lower extremity amputation.	C	–	Research question 2, page 63
Limited evidence suggests that glycaemic control may be a moderate predictor of lower extremity amputation as a consequence of arteriosclerotic vascular disease in a general diabetes population.	C	–	Research question 2, page 63
On the basis of limited evidence, creatinine testing would appear to be a poor test for predicting amputation in a general diabetes population.	C	–	Research question 2, page 67
There is insufficient evidence regarding HDL cholesterol as a predictor of lower extremity amputation and major foot injury.	C	–	Research question 2, page 67
In a neuropathic diabetes population			
Despite some inconsistencies, the evidence suggests that foot pressure assessment in a neuropathic diabetes population is not accurate at predicting foot ulcer. However, optical pedobarography may only be of value at ruling out those at risk of foot ulcer.	C	–	Research question 2, page 70
The evidence suggests that foot pressure assessment in a diabetes population with neuropathy is a moderate predictor for the development of foot ulcer.	C	–	Research question 2, page 71

Evidence statement	Grade	Recommendation	Evidence report section
In an Indigenous diabetes population			
Limited evidence suggests that indigenous diabetes patients with a risk categorisation indicating insensitivity to Semmes-Weinstein monofilaments (SWF) or SWF combined with foot deformity or a history of a lower extremity event may be more likely to develop foot ulcers than those with normal sensation.	C	–	Research question 2, page 73
Limited evidence suggests that indigenous diabetes patients who are insensate to the Semmes-Weinstein monofilament assessment are more likely to develop foot ulcers and undergo amputation compared to those patients with normal sensation	C	–	Research question 2, page 73
Research question 3: Which assessments lead to improved foot-related clinical outcomes in people with diabetes?			
There is weak evidence to support the use of bone scans to identify higher risk of amputation in patients with severe diabetic foot ulcers.	D	–	Research question 3, page 78
There is some evidence to suggest that osteomyelitis is a strong predictor of amputation in patients with severe diabetic foot ulcers.	C	–	Research question 3, page 80
APSV measurements may be useful in identifying diabetic patients with foot lesions or gangrene, who are at risk of not healing.	D	–	Research question 3, page 80
It is possible that APSV is an independent predictor of non-healing in diabetic patients with foot lesions or gangrene.	D	–	Research question 3, page 83
It is possible that skin perfusion pressure is able to predict healing in diabetic patients with foot lesions or	C	–	Research

Evidence statement	Grade	Recommendation	Evidence report section
gangrene. In particular, it is possible that skin perfusion pressure may rule out the likelihood of healing in patients with low skin perfusion pressure.			question 3, page 83
There is likely to be an association between poor capillary circulation and non-healing, as well as between increased perfusion and healing of foot ulcers.	C	–	Research question 3, page 86
It is possible that $TcPO_2$ measurement can better identify those ulcers which will improve compared with TBP.	C	–	Research question 3, page 88
There is evidence to indicate that the toe and ankle systolic pressure indices are likely to be higher in patients who achieve primary healing than those who are amputated.	C	–	Research question 3, page 90
There is some evidence to suggest that hyperspectral imaging of tissue oxygenation can identify healing of diabetic foot ulcers.	C	–	Research question 3, page 90
There is some evidence to suggest that plasma fibrinogen levels may identify those at risk of amputation in people with Wagner grade 1 or 2 diabetic foot ulcers.	C	–	Research question 3, page 94
There is some evidence to suggest that there is a strong linear relationship between DEPA score and foot ulcer outcome.	C	–	Research question 3, page 95
There is evidence that there may be a strong association between stage and grade of ulcer, and midfoot or higher amputation in the short term (6 months).	C	–	Research question 3,

Evidence statement	Grade	Recommendation	Evidence report section
			page 96
With regard to non-primary healing, there is evidence that there is an increase in relative risk with increasing Wagner grade.	C	–	Research question 3, page 97
There is evidence that ulcer area, arteriopathy, ulcer site and duration of diabetes are strong independent predictors of time to healing.	C	–	Research question 3, page 98
The evidence provided suggests that the UT classification would better predict the outcome of ulcers and healing compared to Wagner grading. There is reasonable evidence to suggest that the UT classification of diabetic foot ulcer is better able to predict the likelihood of healing or amputation than the Wagner and S(AD)SAD classification systems.	C	C (EBR 5)	Research question 3, page 101
There is evidence that the VA/P classification is moderately correlated with the Wagner grading of foot ulcers.	C	–	Research question 3, page 105
The evidence provided suggests that an increase in DUSS or M.A.I.D score is associated with a decreased probability of foot ulcer healing.	C	–	Research question 3, page 105
The evidence for the association between foot risk score and outcomes is poor.	D	–	Research question 3, page 108
There is some evidence to suggest that the predictive model developed by the Curative Health Services is able to discriminate and accurately predict the risk of non-healing in people with diabetic foot ulcers attending specialist	C	–	Research question 3,

Evidence statement	Grade	Recommendation	Evidence report section
wound care centres.			page 108
There is evidence to suggest that audible posterior tibial pulse on Doppler examination and the presence of pain at the site of the ulcer are strong predictors of non-healing in people with diabetic foot ulcer.	C	–	Research question 3, page 113
This study provides evidence that neuropathy, end stage renal disease, ischaemia and infection are strong predictors of amputation.	C	–	Research question 3, page 114
Research question 4: How often, and by whom, should foot assessments be carried out in people with or without foot ulceration?			
The evidence indicates that home based foot temperature monitoring in addition to standard care should be applied twice daily by the patient to prevent diabetic foot ulceration and lower extremity amputation.	B	–	Research question 4, page 117
The evidence suggests that foot screening, performed by a registrar, should take place in two direct sequential stages to identify those patients at high risk of lower extremity amputation, followed by a protection program to prevent amputation.	C	–	Research question 4, page 118
Research question 5 What are the risk factors for a poor foot-related outcome for people in a primary care setting?			
There is good evidence to show that sensory neuropathy, as measured by VPT, SWF and the Michigan Neuropathy Screening Instrument, is an independent risk factor for amputation, foot ulceration and general functioning (mobility/falls) in people with diabetes managed in a primary care setting.	B	–	Research question 5, page 123
There is some evidence to show that an abnormal NDS score may be a risk factor for the development of foot ulcer in people with diabetes.	C	–	Research question 5,

Evidence statement	Grade	Recommendation	Evidence report section
			page 129
There is some evidence to show that an abnormal high foot pressure (≥ 6 kg/cm^2) may be a moderate risk factor for the development of foot ulcer in people with diabetes.	C	–	Research question 5, page 129
There is insufficient evidence to conclude that absent Achilles and patellar tendon reflexes are risk factors for amputation in people with diabetes.	C	–	Research question 5, page 130
There is some evidence to indicate that increasing systolic and diastolic blood pressure are risk factors lower extremity amputation particularly in American Indians. Less evidence is available for blood pressure as a risk factor for foot ulcer.	C	–	Research question 5, page 133
There is insufficient evidence regarding the relationship between hypertension and poor foot outcomes	C	–	Research question 5, page 136
There is reasonable evidence to indicate that increasing levels of glycosylated haemoglobin (> 6.5%) is a risk factor for lower extremity amputation in people with diabetes. Further evidence is required with regard to foot ulcer development.	C	–	Research question 5, page 138
There is limited evidence to indicate that increasing levels of plasma glucose is a risk factor for lower extremity amputation in people with diabetes.	C	–	Research question 5, page 140
There is reasonable evidence to indicate that increasing severity of retinopathy (including self-reported retinopathy) is a risk factor for lower extremity amputation in people with diabetes. There is also some evidence to suggest that retinopathy is a risk factor for foot ulcer and ulcer recurrence.	B	–	Research question 5, page 142

Evidence statement	Grade	Recommendation	Evidence report section
There is evidence to indicate that the presence of nephropathy or proteinuria is a risk factor for lower extremity amputation in people with diabetes. There is also some evidence to suggest that nephropathy or proteinuria is a risk factor for foot ulcer, ulcer recurrence and mobility impairment.	C	–	Research question 5, page 146
There is reasonable evidence to indicate that the diabetes duration is a weak risk factor for lower extremity amputation in people with diabetes. There is also some evidence to suggest that diabetes duration is a weak risk factor for foot ulcer.	B C	–	Research question 5, page 149
There is insufficient evidence to indicate that age is a (weak) risk factor for lower extremity amputation and foot ulcer in people with diabetes.	C	–	Research question 5, page 151
There is evidence to indicate that male sex is a moderate risk factor for lower extremity amputation in people with diabetes. There is insufficient evidence to indicate that male sex is a risk factor for new foot ulcer.	B B	–	Research question 5, page 153
There is evidence to indicate that an ABI less than 0.9 is a moderate risk factor for lower extremity amputation in people with diabetes. There is also evidence that an ABI greater than 1.3 is a moderate risk factor for lower extremity amputation.	B B	–	Research question 5, page 156
There is limited evidence to suggest that self-reported claudication may be a risk factor for impaired mobility in a population with type II diabetes.	C	–	Research question 5, page 158
There is insufficient evidence to indicate that the absence of two or more peripheral arterial pulses may be a risk factor for amputation due to atherosclerotic disease in a population with type II diabetes.	C	–	Research question 5,

Evidence statement	Grade	Recommendation	Evidence report section
			page 158
There is some evidence to indicate that the presence of medial arterial calcification is a strong risk factor for first lower extremity amputation in a diabetic indigenous population.	C	–	Research question 5, page 159
There is evidence to indicate that a history of cerebrovascular disease is a strong risk factor for lower extremity amputation in people with diabetes.	C	–	Research question 5, page 160
There is some evidence to indicate that increasing total cholesterol concentration, higher than 6.2mmol/l, may be a moderate risk factor for lower extremity amputation, in particular as a result of atherosclerotic vascular disease, in people with diabetes. There is some evidence to indicate that an increasing HDL concentration is a moderate risk factor for foot lesions with a Seattle Classification ≥ 1.3, in people with diabetes.	B C	–	Research question 5, page 162
There is insufficient evidence to indicate that increasing BMI is a risk factor for poor foot outcomes in people with diabetes.	C	–	Research question 5, page 164
Based on the evidence identified, there is insufficient evidence to indicate that smoking is a risk factor for amputation in people with diabetes. For mobility impairment and poor activities of daily living, there is some evidence to suggest that smoking is a moderate risk factor.	C C	–	Research question 5, page 166
There is evidence to indicate that the presence of a foot ulcer is a moderate risk factor for lower extremity	B	–	Research question 5,

Evidence statement	Grade	Recommendation	Evidence report section
amputation or arterial disease.			page 168
There is evidence to indicate that hallux limitus and hammer/claw toe is a moderate risk factor for new foot ulcer and ulcer recurrence.	B	–	Research question 5, page 170
There is some evidence that history of sores or ulcers is a moderate risk factor for amputation in people with diabetes managed in a primary care setting.	C	–	Research question 5, page 173
There is some evidence to indicate that insulin use is a moderate risk factor for falls and mobility impairment in people with diabetes. There is insufficient evidence for insulin use as a risk factor for foot ulcer recurrence in people with diabetes.	C C	–	Research question 5, page 175
There is some evidence that depressive symptoms are a moderate risk factor for difficulties in Activities of Daily Living in people with diabetes.	B	–	Research question 5, page 177
There is insufficient evidence to suggest that the type of diabetes is a risk factor for foot ulcer recurrence.	C	–	Research question 5, page 179
There is evidence to suggest that the weight bearing activity is protective against foot ulcer recurrence and mobility impairment.	B	–	Research question 5, page 181
There is evidence to indicate that high school education level or higher is not a risk factor for first lower extremity	C	–	Research

Evidence statement	Grade	Recommendation	Evidence report section
amputation in indigenous populations with diabetes.			question 5, page 183
There is insufficient evidence to indicate that risk score is a risk factor for amputation or ulceration in an American indigenous population.	C	–	Research question 5, page 183
There is some evidence to indicate that lower extremity pain, indigenous status, poor physical performance, fluency in English and arthritis are risk factors for mobility impairment or physical disability.	C	–	Research question 5, page 184
Research question 6: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer?			
Systemic therapeutic drug interventions			
There is evidence to suggest that systemic administration of ANGIPARS may decrease ulcer size for people with chronic diabetic foot ulcers.	C	–	Research question 6, page 188
Systemic low-molecular-weight heparins in addition to standard wound care provided a significant benefit in Wagner grade 2 ulcers only over a 3 month period in patients with diabetes when compared with placebo and standard wound care. The risk of amputation is similarly reduced in diabetic patients with comorbid peripheral arterial occlusive disease.	B	–	Research question 6, page 192
It is unclear whether iloprost therapy is likely to provide any clinical benefit in addition to standard wound care when treating patients for diabetic foot ulcers. Further large trials are required to determine the impact on wound healing and major amputation rates.	D	–	Research question 6, page 196
It is unclear whether ketanserin therapy is likely to provide any clinical benefit in addition to standard wound care	D	–	Research

Evidence statement	Grade	Recommendation	Evidence report section
when treating patients for diabetic foot ulcers, relative to standard wound care alone.			question 6, page 198
Pentoxifylline therapy is unlikely to provide further benefit in addition to standard wound care when treating diabetic patients with ischaemic foot ulcers of Wagner grade 2 or more.	D	–	Research question 6, page 200
Pycnogenol therapy may reduce ulcer size when used in addition to standard wound care compared to standard wound care alone, in diabetic patients with ischaemic foot ulcers.	C	–	Research question 6, page 202
Drugs that improve immune function			
Tinospora cordifolia therapy is unlikely to provide additional clinical benefit to standard wound care when treating patients for diabetic foot ulcer.	D	–	Research question 6, page 204
Other drugs			
There is evidence to suggest that treatment with fenofibrate may reduce the risk of amputation, and in particular minor amputation, in people with type II diabetes.	B	–	Research question 6, page 206
Surgical interventions			
The results suggest that in addition to immobilisation with a total contact cast and standard wound care, surgical Achilles tendon lengthening is effective at preventing foot ulcer recurrence in diabetic patients, although it does not appear to improve ulcer healing.	C	–	Research question 6, page 209
The results suggest that in addition to standard off loading and wound care, surgical arthroplasty is effective at	C	–	Research

Evidence statement	Grade	Recommendation	Evidence report section
preventing foot ulcer recurrence in diabetes subjects and reduces the healing time of foot ulcer.			question 6, page 212
The results suggest that in addition to standard medical care involving antibiotics, off loading and wound care, conventional orthopaedic surgery accelerates time to foot ulcer healing in diabetes patients with foot osteomyelitis.	C	–	Research question 6, page 215
Human growth factors			
There is evidence to suggest that topical application of recombinant human epidermal growth factor may have some effect at increasing the number of foot ulcers healed or partially healed, relative to standard wound care plus or minus placebo, in patients with Wagner grade I or II diabetic foot ulcers with adequate perfusion.	B	–	Research question 6, page 217
There is insufficient evidence to suggest that higher dose intralesion application of recombinant human epidermal growth factor has any beneficial effect at increasing the number of foot ulcers healed or partially healed, relative to low dose intralesion application of recombinant human epidermal growth factor and standard wound care, in patients with Wagner grade III or IV diabetic foot ulcers at high risk of amputation.	C	–	Research question 6, page 217
In patients with full thickness chronic foot ulcers and adequate perfusion, recombinant human platelet-derived growth factor 100µg/g gel is effective in substantially increasing the number of completely healed ulcers, reducing healing time and reducing the surface area of ulcers not completely healed compared to placebo.	B	–	Research question 6, page 224
In patients with full thickness chronic ulcers with adequate perfusion, recombinant human platelet-derived growth factor 100µg/g gel is effective in substantially increasing the number of completely healed ulcers, reducing healing time and reducing the surface area of ulcers not completely healed compared to standard wound care with saline dressings.	C	–	Research question 6, page 233
Autologous/homologous platelet-rich plasma gel or releasate is moderately effective in increasing the number of ulcers healed, reducing healing time, ulcer volume and surface area of chronic diabetic foot ulcers when	B	–	Research question 6,

Evidence statement	Grade	Recommendation	Evidence report section
compared to standard wound care/placebo.			page 239
Recombinant human granulocyte-colony stimulating factor (rhG-CSF) may reduce the number of amputations and improve ulcer healing in people with severe limb-threatening diabetic foot ulcers and infection when compared to standard wound care/placebo.	C	–	Research question 6, page 247
The evidence is inconclusive regarding whether transforming growth factor β2 is superior to standard wound care. In addition to standard wound care, increasing doses of TGF-β2 provided increased the clinical benefit compared to placebo with regard to number of ulcers healed and reducing ulcer area. However, these findings were not statistically significantly better than standard wound care alone.	C	–	Research question 6, page 258
Vascular endothelial growth factor versus standard wound care/placebo is superior in reducing time to amputation and facilitating clinical improvements in ulcers. However, positive trends for other clinical outcomes did not reach statistical significance in these small studies.	B	–	Research question 6, page 261
There is evidence to suggest that topical basic fibroblast growth factor used as a spray and used daily for six weeks and twice weekly for 12 weeks does not provide any clinical benefits in the treatment of diabetic foot ulcers over standard wound care/placebo.	C	–	Research question 6, page 265
Hyperbaric oxygen therapy			
Hyperbaric oxygen therapy is superior to standard wound care/placebo in reducing the number of amputations, reducing the surface area of ulcers, reducing healing time and increasing the number of ulcers healed in patients with severe diabetic foot ulcers.	B	B (EBR 12)	Research question 6, page 267
Negative pressure wound therapy			
Negative pressure therapy after surgical debridement may improve wound healing and reduce the need for minor amputations when compared to standard wound care for the treatment of non-healing diabetic foot ulcers.	B	B (EBR 11)	Research question 6, page 281

Evidence statement	Grade	Recommendation	Evidence report section
There is some evidence to suggest that treatment with NPWT may increase the number of patients who achieve complete healing of amputation wounds in people with diabetes and evidence of adequate perfusion. There is also evidence that the time taken to achieve complete healing is reduced in patients receiving NPWT compared to standard wound care.	C	–	Research question 6, page 291
Nutritional supplements			
The evidence suggests that nutritional supplements show a positive trend towards improving outcomes for people with diabetic foot ulcers however the differences did not reach statistical significance. Further research is required to confirm any such effect, as well as determine which type of nutritional supplement is associated with the potential benefit.	B	–	Research question 6, page 295
Wound debridement			
Treatment of diabetic foot ulcers with hydrogels produces a substantial increase in the number of ulcers healed and reduced harms over treatment with standard care alone.	B	B (EBR 6)	Research question 6, page 299
There is little evidence to suggest that the use of advanced moist wound therapy dressings offer better clinical outcomes for treating diabetic foot ulcers compared to wet, dry or greasy gauze as a primary dressing for standard wound care.	B	–	Research question 6, page 304
There is little evidence to suggest that one advanced moist wound debridement therapy can consistently outperform another when used in conjunction with standard wound care.	C	–	Research question 6, page 312
The use of Promogran wound dressing with or without the use of autologous platelet derived growth factors offers better clinical outcomes in terms of reduction in ulcer size and time to healing when treating diabetic foot ulcers compared to standard wound care.	B	–	Research question 6, page 316

Evidence statement	Grade	Recommendation	Evidence report section
Surgical debridement using conic ulcerectomy reduces the time for ulcer healing when compared to standard wound care using conventional sharp debridement for patients with diabetic foot ulcers. However, it is uncertain if it has any benefit for overall ulcer healing.	C	–	Research question 6, page 321
Larval debridement therapy may improve foot ulcer healing time and prevent amputation when used in addition to standard wound care over standard wound care with surgical debridement alone in patients with severe diabetic foot ulcers. More research outside this setting is required.	C	C (EBR 13)	Research question 6, page 323
In Indigenous populations			
Treatment of diabetic foot ulcers according to the protocols of professional management programs, instead of standard care at the discretion of the primary care provider, reduces the likelihood that the Native Alaskan and Chippewa Indians with diabetes will require an amputation.	C	–	Research question 6, page 328
There is evidence to suggest that surgical correction of foot deformity may increase healing of foot ulcer and prevent recurrence however, it is not known whether this intervention is more effective than others in this population for these outcomes.	C	–	Research question 6, page 332
Skin replacement therapies			
Split-skin grafting is likely to reduce the time for ulcer healing and length of hospital stay when compared to standard wound care for patients with diabetic foot ulcers.	D	D (EBR 14)	Research question 6, page 334
There is no evidence to suggest that there is any difference in clinical outcomes after meshed skin grafting compared to split-skin grafting for people with chronic diabetic foot ulcers.	D	D (EBR 14)	Research question 6, page 336
There is evidence to suggest that epidermal grafts improve the time to healing for people with chronic diabetic foot ulcers without exposed bone, and that bone scraping plus epidermal grafts reduces the risk of amputation for	D	-	Research question 6,

Evidence statement	Grade	Recommendation	Evidence report section
people with chronic diabetic foot ulcers that are exposed to the bone.			page 338
Treatment with cultured keratinocytes or fibroblasts, when compared with placebo or control, was found to reduce the ulcer size, decrease the time required to heal, and increase the number of ulcers that healed completely for people with chronic diabetic foot ulcers.	D	–	Research question 6, page 340
There is substantial evidence to suggest that clinical outcomes are significantly improved for people with chronic diabetic foot ulcers treated with cultured skin equivalents and standard wound care compared to standard wound care alone.	B	B (EBR14)	Research question 6, page 345
The evidence presented in this study suggests that there is no statistical or clinical advantage when using either Dermagraft or OASIS wound matrix in addition to standard wound care for people with chronic diabetic foot ulcers.	C	–	Research question 6, page 361
The use of GraftJacket wound matrix with Silverlon may increase the likelihood of ulcers healing when used in addition to moist wound therapy in diabetic patients with chronic foot ulcers.	C	–	Research question 6, page 361
The use of GraftJacket wound matrix may aid in reducing the size of ulcers when used in addition to moist wound therapy in diabetic patients with surgically debrided chronic foot ulcers.	C	–	Research question 6, page 361
OASIS acellular wound matrix, used in conjunction with a dressing to protect the healing environment and standard wound care may improve healing in patients with type 2 diabetes and/or plantar ulcers when compared to Regranex Gel, a sodium carboxymethyl cellulose gel with 0.01% recombinant human platelet derived growth factor (rhPDGF), in addition to standard wound care.	D	–	Research question 6, page 364
Radiowave or electric therapy			
There is no evidence to suggest that electric stimulation provides any additional benefit with regard to healing	D	–	Research

Evidence statement	Grade	Recommendation	Evidence report section
compared to standard wound care alone for diabetic foot ulceration.			question 6, page 367
The evidence suggests that non contact normothermic wound therapy in addition to standard wound care is more effective at healing foot ulcers than standard wound care by itself.	D	–	Research question 6, page 371
The evidence suggests that global heat in addition to electric stimulation and standard wound care is more effective than additional local heat or standard wound care alone. Application of heat, either global or local, in addition to electric stimulation and standard wound care is more effective at reducing wound area than standard wound care alone.	D	–	Research question 6, page 376
There is no evidence to support high voltage pulsed current in addition to standard wound care for ulcer healing in patients with chronic leg ulcers.	C	–	Research question 6, page 376
There is insufficient evidence that shock wave therapy in addition to standard wound care is more effective than standard care alone for the healing of neuropathic foot ulcers in diabetic patients. However, the therapy may accelerate the healing process and increase the re-epithelisation of the neuropathic foot ulcer compared to standard wound care alone in diabetic patients.	C	–	Research question 6, page 379
There is no evidence to support the use of shock wave therapy over hyperbaric oxygen therapy in addition to standard wound care for ulcer improvement or healing.	C	–	Research question 6, page 379
The evidence suggests that ultrasound in addition to standard care is more effective at healing diabetic foot ulcer than standard care by itself. However, it should be taken in account that there is an increased risk for mild adverse events with the additional ultrasound treatment.	D	–	Research question 6, page 381

Evidence statement	Grade	Recommendation	Evidence report section
The evidence suggests that foot compression in addition to standard wound care is more effective for healing of infected diabetic foot ulcers than standard care alone.	C	–	Research question 6, page 382
There is insufficient evidence to suggest that radiotherapy in addition to standard care is better than standard care by itself for the treatment of diabetic foot osteoarthropathy.	C	–	Research question 6, page 382
Interventions to improve the clinical management of diabetic foot ulcers			
There is some evidence to suggest that multidisciplinary, staged management care reduces the risk of amputation rate for patients with diabetic foot ulcers compared to standard care.	C	C (EBR 9)	Research question 6, page 383
There is insufficient evidence that a GP training program has had any impact on the mortality and amputation rates in patients with diabetic foot ulcers.	D	–	Research question 6, page 389
Digital imaging of the wound, electronically transferring those images to a remote expert consultant and receiving treatment advice increase the ulcer healing rate and decrease the rate of amputation surgery when compared to treatment at the discretion of the local clinician for patients with lower extremity ulcers, including diabetic foot ulcers.	C	C (EBR 10)	Research question 6, page 391
There is some evidence to suggest that supplying week 4 prognostic algorithms to treatment centres increases the rate of neuropathic foot ulcers that heal compared to supplying no prognostic algorithms.	D	–	Research question 6, page 393
Orthotics			

Evidence statement	Grade	Recommendation	Evidence report section
There is evidence to suggest that off-loading interventions in addition to standard wound care will significantly reduce the time to healing relative to standard wound care alone in people with diabetic plantar foot ulcers.	B	B (EBR7)	Research question 6, page 395
Evidence suggests that use of a total contact cast versus removable cast walker shows a positive trend towards improving clinical outcomes for patients with chronic diabetic foot ulcers in relation to number of ulcers healed and time to heal. Findings however did not always reach clinical significance.	B	–	Research question 6, page 400
There was no evidence to suggest that there were any differences in the proportion of ulcers which healed, or the healing time of ulcers between total contact casts and instant total contact casts in patients with diabetic foot ulcers.	C	–	Research question 6, page 403
The use of a non-removable cast is effective in increasing the likelihood that an ulcer heals, reducing the time it takes for an ulcer to heal and decreasing the risk of developing osteomyelitis compared to the use of a half shoe in patients with foot ulcers.	C	–	Research question 6, page 406
Non-removable casts are moderately effective in reducing the surface area of ulcers at a faster rate compared to therapeutic shoes.	C	–	Research question 6, page 409
Non-removable off-loading devices are more effective for ulcer healing in patients with diabetic plantar foot ulcers with regard to complete ulcer healing compared with removable off-loading devices.	C	B (EBR 8)	Research question 6, page 411
Topical treatments			
The use of zinc hyaluronic acid may provide some benefit in reducing ulcer healing time when used in conjunction with standard wound care to treat diabetic foot ulcers.	C	–	Research question 6,

Evidence statement	Grade	Recommendation	Evidence report section
			page 412
The use of phenytoin powder in addition to standard wound care for patients hospitalised with diabetic foot ulcers is not effective for ulcer healing, ulcer improvement or wound size reduction.	C	–	Research question 6, page 415
Evidence suggests that immersion in pH neural superoxidised solution followed by the same spray is more effective at improving infection parameters e.g. increase granulating tissue, reduce cellulitis and improving the surrounding skin than immersion in saline followed by povidone iodine spray of severely infected diabetic foot ulcers.	C	–	Research question 6, page 419
The results suggest that the use of povidone iodine dressing is as effective as a non-adherent viscose gauze dressing or the Aquacel moist wound dressing for the healing and time to healing in chronic diabetic foot ulcers.	C	–	Research question 6, page 421
The evidence suggests that the use of cadexomer iodine ointment is as effective as gentamicin solution for the healing or reduction of wound area of diabetic foot ulcer.	C	–	Research question 6, page 424
The use of adhesive zinc oxide tape in the treatment of necrotic diabetes foot ulcer might be beneficial for the reduction of initial necrosis, though this treatment still involves risks. Further research would be necessary.	C	–	Research question 6, page 426
The evidence suggests that the use of 0.05% tretinoin solution therapy for 10 minutes in addition to standard care is beneficial for reduction in wound area and depth. Though some mild to moderate adverse effects are involved.	C	–	Research question 6, page 428
The evidence suggests that the use of Argidene gel in addition to standard wound care results in a greater reduction in wound area, and greater healing (> 50% healing or completely healing) of diabetic foot ulcers	C	–	Research question 6,

Evidence statement	Grade	Recommendation	Evidence report section
compared to standard care alone.			page 430
The evidence suggests that the use of 1% doxycycline hydrogel on chronic foot ulcer would improve the healing of foot ulcers in diabetes patients compared to a vehicle hydrogel. Though, further research should be conducted.	C	–	Research question 6, page 432
The evidence suggests that the use of ketanserin in addition to standard wound care was more effective at reducing the area of the foot ulcer than the use of normal saline in diabetic patients hospitalised for foot problems.	C	–	Research question 6, page 434
The evidence suggests that soaking the affected foot in 25% or 50% dimethylsulphoxide solution in addition to standard care was more effective in healing and improving foot ulcer than standard care on itself in diabetic patients with chronic foot ulcers.	C	–	Research question 6, page 436
The evidence suggests that immediate application of 2% Iamin gel after sharp debridement in addition to standard wound care is more effective than standard wound care alone, particularly in large ulcers. Delayed application of either 2% or 4% Iamin gel after sharp debridement provides no additional benefit to standard wound care for the treatment of diabetic foot ulcer.	C	–	Research question 6, page 438
The evidence suggests that, in addition to standard wound care, local insulin therapy is effective in reducing hospital stays in complicated diabetic foot ulcer.	C	–	Research question 6, page 442
The evidence indicates that the use of talactoferrin in addition to standard wound care is no more beneficial than standard wound care alone for healing of severe diabetic foot ulcer.	C	–	Research question 6, page 444
There is some evidence to suggest that 1 µg and 10 µg Chrysalin® in addition to standard wound care is effective in healing and accelerating the healing process of diabetic foot and heel ulcers compared to standard wound care	C	–	Research question 6,

Evidence statement	Grade	Recommendation	Evidence report section
alone. Further research may be required.			page 447
The evidence suggest that the use of ozone in addition to standard care was not more effective in ulcer healing than conventional therapy, but did accelerate the time to healing and reduces the days of hospitalisation.	C	–	Research question 6, page 451
There is insufficient evidence to suggest that Bensal HP in addition to standard care is more effective than silver sulphadiazine cream for the treatment of diabetic foot ulcer.	D	–	Research question 6, page 453
There is insufficient evidence to suggest that either lyophilised collagen or hyaluronic acid in addition to standard care are more effective than standard wound care alone for the treatment of diabetic foot ulcers.	D	–	Research question 6, page 455
There is insufficient evidence to suggest that honey is more effective than povidone solution in preparing diabetic foot ulcers for surgical closure.	D	–	Research question 6, page 457
Miscellaneous interventions			
There is limited evidence to indicate that there is a slight effect on ulcer healing for biofeedback-assisted relaxation in addition to standard wound care, in patients cared for by foot-care physicians.	C	–	Research question 6, page 459
Interventions for people without diabetic foot ulcers			
Drug therapy for improving nerve function to prevent ulceration			
The evidence is inconclusive evidence regarding the use of sorbinil for the prevention of foot ulcers in people with	C	–	Research question 6,

Evidence statement	Grade	Recommendation	Evidence report section
diabetic neuropathy			page 461
On the basis of the evidence available, hydroxyethylrutosides therapy is unlikely to provide any clinical benefit in addition to standard care when treating patients with critical limb ischaemia.	D	–	Research question 6, page 463
Therapeutic footwear			
There is insufficient evidence to support the use of therapeutic footwear over usual footwear to prevent recurrence of diabetic foot ulcers.	C	–	Research question 6, page 466
There is some evidence to suggest that rigid orthotic devices may help improve plantar calluses in people with diabetes and no history of foot ulcer.	C	–	Research question 6, page 468
Miscellaneous therapies			
There is some evidence to indicate that there is no additional effect of using antifungal nail lacquer in addition to a preventive foot program to prevent the development of foot ulcer.	C	–	Research question 6, page 472
Education for the prevention of foot complications			
There is some evidence to suggest that a brief education program in addition to usual care reduces the occurrence of diabetic foot infection, ulcer and amputation in the general diabetic population.	C	–	Research question 6, page 472
There is insufficient evidence to suggest that an education program consisting of multiple teaching sessions provided to a group of patients in addition to usual care, is any more effective than usual care alone to reduce	C	–	Research question 6,

Evidence statement	Grade	Recommendation	Evidence report section
diabetic foot complications in the general diabetic population.			page 476
An education program that focuses on the patient as well as the clinician may be effective in reducing diabetic foot complications, specifically serious foot lesions, dry or cracked skin and ingrown nails, compared to usual care in patients with diabetes.	C	–	Research question 6, page 480
There is insufficient evidence to suggest that a home based education program is more effective than non home education for the prevention of diabetic foot complications or the reduction in hospitalisation and emergency room visits in the general diabetic population.	C	–	Research question 6, page 482
There is insufficient evidence to suggest that an intensive education program is any more effective in the prevention of diabetic foot complications than a brief education program.	B	–	Research question 6, page 484
Management programs for the prevention of foot complications			
Diabetic care management programs have been shown to be substantially effective at reducing the rate of amputations and rate of hospitalisation for diabetic patients with foot-related problems when compared to standard diabetic care.	B	–	Research question 6, page 490
Evidence suggests that diabetic care management plus weight bearing activity has no clinical benefit or disadvantage compared to diabetic care management alone.	C	–	Research question 6, page 493
Research question 7: Under what circumstances are antibiotics effective in the treatment of foot ulceration?			
There was insufficient and inconsistent evidence supporting the supplementation of standard wound care with antibiotic therapy in order to treat diabetic foot ulcers.	D	–	Research question 6, page 495

Introduction

Aim of this systematic review

The primary aim of this systematic review is to provide the evidence base for the 2010 NHMRC clinical practice guidelines *Prevention, identification and management of foot complications in diabetes.*

Objectives

- To identify which assessments lead to improved foot-related outcomes, by best predicting foot ulcer and amputation, in adults with diabetes mellitus.
- To identify which clinical assessments best identify Charcot's neuro-arthropathy.
- To identify which clinical assessments best predict foot ulcer severity and outcomes in people with diabetics with foot ulcer.
- To identify how frequently and by whom, foot assessments should be conducted in people with diabetics without foot ulcer.
- To identify when people with diabetics at high risk of ulcer should be referred to a specialist foot clinic.
- To evaluate management strategies to improve foot outcomes in people with diabetes mellitus (with or without foot ulcer or with Charcot's neuro-arthropathy).

The abovementioned objectives are central to informing the Guidelines Advisory Committee in their task of developing current clinical practice guidelines which make recommendations for the identification and management of foot problems in adults with diabetes mellitus. The aim being to prevent the incidence of foot problems in people with diabetes mellitus and improve their health outcomes.

Reserach questions developed to answer the objectives listed above are described below:

1. Which assessments lead to improved foot-related clinical outcomes in people with diabetes?
2. Which clinical assessments best predict foot ulcer and/or amputation in people with diabetes?
3. Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer?
4. How often, and by whom, should foot assessments be carried out in people with or without foot ulcer?
5. When should a patient be referred to a high risk foot clinic? (What are the risk factors for a poor foot-related outcome for people in a primary care setting?)
6. Which interventions improve foot related clinical outcomes
    a) For people without foot ulceration?
    b) For people with foot ulcer?
7. Under what circumstances are antibiotics effective in the treatment of foot ulceration?

Specific inclusion criteria used to identify the relevant literature to answer these questions are described at the beginning of each review chapter.

Research question 2, page 38

How do we develop clinical practice guidelines?

"*Clinical practice guidelines are systematically developed statements that assist clinicians, consumers and policy makers to make appropriate health care decisions*." Such guidelines present statements of "best practice" based on a thorough evaluation of the evidence from published research studies – in the form of systematic literature reviews – on the outcomes of treatment or other health care procedures (NHMRC 2000a).

Systematic literature reviews use explicit, systematic methods to limit bias and reduce the effect of chance in the review, and therefore provide reliable and consistent results upon which to draw conclusions. This enables the development of evidence-based clinical practice guidelines. The National Health and Medical Research Council (NHMRC) have published a series of "Guidelines for Guidelines" handbooks to assist developers with the process of producing and disseminating clinical practice guidelines (NHMRC 1999; NHMRC 2000a; NHMRC 2000b; NHMRC 2000c; NHMRC 2001). A checklist outlining the minimum requirements for formulating NHMRC evidence-based guidelines has also been developed and is based on these handbooks (NHMRC 2007).

The process recommended by NHMRC to develop evidence-based guidelines is based on the following nine key principles (NHMRC 2007):

1. the guideline development and evaluation process should focus on outcomes;
2. the guidelines should be based on the best available evidence and include a statement concerning the strength of recommendations;
3. the method to synthesise the evidence should be strongest applicable;
4. the guideline development group should be multidisciplinary and include consumers early in the development process;
5. guidelines should be flexible and adaptable to varying local conditions;
6. guidelines should consider resources and should incorporate an economic appraisal;
7. guidelines are developed for dissemination and implementation among their target audiences;
8. the implementation and impact of the guidelines should be evaluated; and
9. guidelines should be updated regularly.

Research question 1: Which assessments lead to improved foot-related clinical outcomes in people with diabetes?

Box 1 Inclusion criteria for the evaluation of clinical assessments for foot problems

Parameter	Inclusion criteria
Population	Adults with type 1 or type 2 diabetes mellitus Subgroups- a) who have a potentially elevated risk of ulceration (eg long duration of disease, injury, smoking, uncontrolled glucose levels for extended periods, age); or b) with the presence of a risk factor (eg PVD, peripheral neuropathy or foot deformity); or c) people with a history of foot ulcer; or d) people with a foot ulcer; or e) people with Charcot's neuroarthropathy; or f) in Indigenous populations[a]
Intervention	Examinations or assessments to detect or evaluate risk factors such as neuropathy, PVD, callus or foot deformity eg clinical history, Semmes-Weinstein monofilaments; plantar foot pressure measurements, vibration perception threshold, joint mobility, toe pressures, ankle/brachial index, dermal thermometry/skin temperature. In people with foot ulcer, clinical assessments may include ulcer grading classification systems such as the Wagner and Texas scores. In people with Charcot's neuroarthropathy this may include diagnostic imaging.
Comparator	No assessment or other assessments.
Outcomes	*Primary outcomes:* Clinical outcomes such as mortality/survival; pre-ulcer lesions; time to foot ulcer; foot ulceration; amputation (major, transmetatarsal, transtibial, ray or toe); time to amputation; mobility restriction; long-term mobility; general functioning; quality of life; independence; healing; deformity. *Cost-effectiveness outcomes:* cost per event avoided; cost per life year gained; cost per quality adjusted life year or disability adjusted life year; incremental cost-effectiveness ratio
Study design	Randomised, pseudo-randomised or non-randomised controlled trials, cohort studies, or systematic reviews of these study designs.
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified.
Publication date	1966 – 11/2009
Limitations	Human

For this question only four articles meeting the inclusion criteria were identified by a systematic search of the literature. These articles assessed home-based foot temperature monitoring as part of a foot screening program. The results are presented below.

Home-based foot temperature monitoring

Three articles reported on the same study at different follow-up times and with different patient numbers. Table 1 provides the results of the pilot phase (Lavery et al 2004) of the good quality randomised controlled trial, as well as at the longest follow-up (Armstrong et al 2007; Lavery et al 2004), with patients receiving home-based foot skin temperature monitoring as an assessment to improve outcome in the incidence of diabetic foot ulceration. The incidence of foot ulceration was reported in the trial, with the pilot phase also reporting on Charcot fractures. To measure skin temperature, the TempTouch© (Xila Medical, San Antonio, Tex) device was used. It is an infrared dermal thermometer equipped with a touch sensor tip to detect contact with the skin. The touch sensor automatically triggers the temperature measurement which is displayed on a liquid crystal display screen. The devices' design enables skin temperature

measurement of the plantar and lateral regions of the feet. The study protocol instructed patients to measure the skin temperature of both feet twice daily and immediately notify a nurse when the difference between the left and right foot was more than 4ºF (~2.2ºC). Furthermore, the patients were advised to reduce their steps until the temperature difference became less than 4ºF (~2.2ºC).

The pilot study recruited patients attending high risk diabetic foot clinics at the University of Texas, and randomly assigned them to either the comparator or intervention group. There were no significant differences between the groups at baseline, except for the vibration perception threshold, which was higher in the comparator group (likely to bias against the intervention). In the intervention group, when foot skin temperature monitoring was combined with the standard care (therapeutic foot wear, diabetic foot education and foot evaluation by podiatrist every 10-12 weeks), significantly more patients in the standard care group developed ulcers than those who monitored their foot temperature twice a day during the six month pilot period (^{2}=6.63, p= 0.01). The authors reported that patients in the standard care group were 10 times more likely to develop ulcerations than those in the skin temperature monitoring group (OR=10.3, 95%CI 1.2, 85.3) (Lavery et al 2004).

Lavery et al (2007) found similar results, in a later and larger study population which followed patients over 15 months. The home-based skin temperature monitoring combined with standard care was more effective in preventing ulcers than standard care alone (OR=4.48, 95%CI 1.53, 13.14). At 18 months' follow-up, skin temperature monitoring with standard care was also compared to home-based foot inspections in addition to standard care and despite the increased intensity of surveillance in the comparator arm, skin temperature monitoring was still found to be more effective (OR = 4.71, [95% CI 1.60, 13.85]) (Lavery et al 2007).

Armstrong et al (2007), in a study of 221 patients, confirmed these results and indicated that home-based skin temperature monitoring had a benefit over standard care alone, patients receiving standard care were 3 times more likely to develop foot ulcers than those who monitored their foot temperature twice daily (OR = 3.0, [95% CI 1.0, 8.5]) (Armstrong et al 2007).

The results of both the pilot study and extension phase of the randomised controlled trial demonstrate that home-based skin temperature monitoring with the TempTouch© appears to reduce the incidence of foot ulcer in high risk diabetic patients. Box 2 summarises the body of evidence according to the NHMRC grading criteria.

Table 1 Home skin temperature monitoring vs standard care

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Lavery et al 2004) USA [pilot]	II (RCT) Good quality	N = 85 Inclusion criteria: Diagnosis of diabetes by WHO, ability to provide informed consent, age 18-80 years and risk group 2 or 3 of the diabetic foot risk classification. Exclusion criteria: Open ulcers or open amputation sites, active Charcot arthropathy, peripheral vascular disease, active foot infection, dementia, impaired cognitive function, history of drug or alcohol abuse <1 year, or other conditions.	N = 44 Standard care and twice daily infrared plantar foot temperature monitoring. When difference between left and right foot was >4ºF (2.2ºC) patient contacted nurse and reduced amount of steps till temperature difference became <4ºF (2.2ºC)	N = 41 Standard care (therapeutic foot wear, diabetic foot education and foot evaluation by podiatrist every 10-12 weeks)	Foot ulcer = 1/44 (2.3%) Charcot fracture = 0 (2%)	Foot ulcer = 7/41 (17%) Charcot fracture = 2 (20%)	^{2}=6.63, p= 0.01 OR = 10.3 [95% CI 1.2, 85.3]
(Lavery et al 2007) USA [15 month follow-up]	II (RCT) Good quality	N = 173 Inclusion criteria: Diagnosis of diabetes, history of foot ulceration, ankle brachial indexes of ≥0.70 and ability to provide informed consent, age 18-80 years. Exclusion criteria: Patients with active or open ulcers, amputation sites, active Charcot arthropathy, severe peripheral vascular disease, non palpable foot pulse or ankle-brachial index <0.8 on either extremity, dementia, impaired cognitive function, history of drug or alcohol abuse <1 year, sight impaired or unable to walk without assistance of wheelchair or	N = 59 Standard care and twice daily infrared skin temperature monitoring on 6 foot sites. When difference between left and right foot was >4ºF (2.2ºC) patient contacted nurse and reduced amount of steps till temperature difference became <4ºF (2.2ºC)	N = 58 Standard care (8 week evaluation of physician, education program focussing on foot complications, self care practice, insoles and footwear)	Foot ulcer = 5/59 (8%)	Foot ulcer = 17/58 (29%)	OR = 4.48, [95% CI 1.53, 13.14]
				N =56 Standard care and twice daily structured foot examination with mirror. When abnormalities observed, patient contacted nurse	Foot ulcer = 5/59 (8%)	Foot ulcer = 17/56 (30%)	OR = 4.71, [95% CI 1.60, 13.85]

		crutches.					
(Armstrong et al 2007) USA	II (RCT) Good quality	N = 221	N = 106	N = 115 Standard care (therapeutic foot wear, diabetic foot education, daily structure foot exam and regular foot care)	Foot ulcer = 5/106 (5%)	Foot ulcer = 14/115 (12%)	OR = 3.0, [95%CI 1.0, 8.5]

Box 2 Evidence statement matrix for home skin temperature monitoring

Component	Rating	Description
Evidence base	B	Two level II studies with a low risk of bias.
Consistency	A	The studies provided consistent results.
Clinical impact	B	The results reflect a rather large clinical impact for patient-relevant primary outcomes (foot ulcer and charcot fractures). The odds ratios ranged between 3.0 and 10.3. This major difference could be ascribed to a smaller sample size used in the pilot study by Lavery et al (2004), which resulted in higher odds. The other results were less varied. The absolute reduction in risk of foot ulcer varied from 7-22%.
Generalisability	B	The study included diabetic patients at high risk of foot complications. In the study the majority of patients were Caucasians, but there were also a large proportion of Mexican Americans included.
Applicability	B	This study concerns patients already receiving care in a high risk diabetic foot clinic, therefore it is likely to be applicable to the Australian healthcare context.

Evidence statement

The evidence provided indicates that twice daily home-based infrared foot temperature monitoring in addition to standard care when used by diabetic patients at high risk of lower extremity ulceration is effective in preventing foot ulcer (Grade B).

Diabetic foot screening program

The average quality study by McCabe et al compared a foot screening program with standard care for the outcomes of foot ulceration and amputation in diabetic patients (McCabe et al 1998b) (Table 2).

The screening program consisted of two stages. In the first stage, 1001 patients, recruited from a weekly general diabetes clinic, were measured with Semmes-Weinstein monofilament, biothesiometer and palpation of pedal pulse. Patients that were found to have a major deficit in one of the measurements above (n=259) were immediately screened for a second time (second stage), which included ankle brachial index calculation, subcutaneous oxygen levels, foot pressure measurements and x-rays in addition to the original screening tests. Those patients classified as high risk (with foot deformities, or a history of foot ulceration, or an ankle-brachial index ≤ 0.75) at the second screening (n=127) were entered into a protection program, which included foot care (chiropody and hygiene maintenance), support hosiery and protective shoes. Those who were perceived as low risk received no further special treatment.

The authors did not provide any information concerning the characteristics of the population and differences between the screening and standard care group at baseline, nor about blinded outcome assessment. The authors do mention that during the randomisation process the allocation protocol was breached. Four patients were placed in the intervention group due to foot ulceration at baseline which may have influenced the lack of statistically significant difference between the two groups for foot ulceration over the 2 year follow-up ($p>0.14$). With regard to amputation the authors reported a statistically significant difference ($p<0.04$). This can mainly be ascribed to the difference in major amputations ($p<0.01$), as opposed to minor amputations ($p>0.15$).

These results show that this screening program effectively decreased the risk of major and total amputations. It is uncertain as to the impact of the program at preventing foot ulcer given the introduction of bias into the study through non-random allocation of four patients. This breaching of the randomisation process, however, would have acted against the intervention (foot screening) for both the foot ulcer and amputation outcomes and so the results are most likely conservative.

Table 2 Included study which compared screening versus standard treatment

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Effect measure [95% CI]
(McCabe, 1998) UK	II (RCT) Average quality	N = 2001 Inclusion criteria: Diabetes I and II patients who visit a weekly general diabetic clinic Exclusion criteria: Not reported	N = 1001 Screening with Semmes-Weinstein monofilament, biothesiometer, palpation pedal pulse, ankle-brachial index, subcutaneous oxygen levels, foot pressure and x-ray + foot protection program	N = 1000 Standard care (Chiropody service and protection for damaged tissue)	Foot ulcer = 24/1001 (2%)	Foot ulcer = 35/1000 (3%)	RR = 0.67 [95% CI 0.41, 1.14] p>0.14 NNTB = 91 [95% CI NNTH 250 to ∞ to NNTB 38]
					Minor amputation= 6/1001 (0.6%)	Minor amputation= 13/1000 (1.3%)	RR = 0.46 [95% CI 0.18, 1.21] p>0.10 NNTB = 143 [95% CI NNTH 542 to ∞ to NNTB 60]
					Major amputation= 1/1001 (0.1%)	Major amputation= 12/1000 (1.2%)	RR = 0.08 [95% CI 0.01, 0.64] p<0.005 NNTB = 91 [95% CI 244, 50]
					Total amputations= 7/1001 (0.7%)	Total amputations= 23/1000 (2.3%)	RR = 0.31 [95% CI 0.13, 0.71] p<0.005 NNTB = 62 [95% CI 185, 36]

CI = confidence interval; NNTB = number needed to treat to benefit one additional patient; NNTH = number need to treat to harm one addional patient

Box 3 Evidence statement matrix for foot screening program versus standard treatment

Component	Rating	Description
Evidence base	C	One level II study with a low risk of bias due to the likely to result in a conservative estimate of the treatment effect as a result of the breach of randomisation.
Consistency	N/A	Only one study.
Clinical impact	B	Although the study did not show a statistically significant reduction in the risk of foot ulcer compared to the control group, a substantial reduction in the relative risk of major amputation and consequently total amputation was apparent, both of which were statistically significant.
Generalisability	B	The study included patients from a general diabetes clinic in the UK. There are no patient characteristics presented.
Applicability	B	The study was performed in the UK which has a similar healthcare context to the Australian health care system.

Evidence statement

The evidence suggests that a two-stage foot screening program, followed by a protection program for those patients identified with a high risk foot for patients visiting a general diabetes clinic may reduce the incidence of major amputation. (Grade C)

Research question 2: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes?

Box 4 Inclusion criteria for the evaluation of clinical assessments for the prediction of foot ulcer and/or amputation

Research Question 2	
Which clinical assessments best predict foot ulcer and amputation in people with diabetes? *(This question will only be answered in the absence of evidence for question 1)*	
Parameter	Inclusion criteria
Population	Adults with type 1 or type 2 diabetes mellitus without foot ulcer including people a) who have a potentially elevated risk of ulceration (eg long duration of disease, injury, smoking, uncontrolled glucose levels for extended periods, age); or b) with the presence of a risk factor (eg PVD, peripheral neuropathy or foot deformity); or c) people with a history of foot ulcer; or d) with Charcot's neuroarthropathy; or e) in indigenous populations
Intervention	Clinical examinations or assessments to detect or evaluate risk factors such as neuropathy, PVD, callus or foot deformity eg clinical history, Semmes-Weinstein monofilaments; plantar foot pressure measurements, vibration perception threshold, joint mobility, toe pressures, ankle/brachial index, dermal thermometry/skin temperature.
Comparator (if available)	Observed risk of foot ulcer and/or amputation
Outcomes	Prognostic outcomes: Observed risk of foot ulcer and amputation Diagnostic outcomes: Sensitivity and specificity (and therefore rates of false positives and negatives), positive and negative likelihood ratios, positive and negative predictive values, diagnostic odds ratios, receiver operator characteristic curves, area under the curve, accuracy.
Study design	Prognostic studies: Prospective cohort studies [a]; all or none study; analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial; retrospective cohort study; case series or cohort study of persons at different stages of disease; or systematic reviews of these study designs. Diagnostic studies: Cross-classification studies where subjects are cross-classified on the test and comparator; or systematic reviews of cross-classification studies. Case-control diagnostic studies, or uncontrolled studies are only acceptable if cross-sectional studies are not available.
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified.
Publication date	1966 – 11/2009
Limitations	Human

For this question twelve articles were identified in the systematic literature search that met the inclusion criteria; one systematic review and 11 cohort studies. Results of these studies are discussed according to the population and subgroups, described in Box 4 and stratified according to diagnostic accuracy (n=1) and the predictive value of the tool for the development of ulcers or amputations (n= 6). Five studies have reported on both outcomes and thus are discussed in both sections. Per assessment, the results are discussed followed by a graded evidence statement according to the NHMRC grading criteria. Furthermore, the diagnostic accuracy studies have been critically appraised with the QUADAS tool, while the predictive studies have been assessed with the SIGN quality assessment tool for cohort studies.

Given the large number of prospective cohort studies included in this systematic review, it should be noted that the diagnostic accuracy results are likely to have been influenced by the time difference between baseline clinical assessment and the actual occurrence of foot ulcer or

amputation. This has been taken in account in the NHMRC quality grading and will therefore not be further mentioned in the evidence statement matrix. Results of the studies are presented below.

Diabetes general population

Neuropathy disability score assessment

Diagnostic accuracy of neuropathy disability score assessment

The average quality study by Pham et al evaluated the accuracy of the neuropathy disability score (NDS) in predicting foot ulcer over a mean of 30 months (range 6–40 months) (Table 3).

The NDS included a physical examination for the presence of the Achilles / patella tendon reflex and evaluation of sensory modalities, using for example a pinprick with a pointed metal or wooden pin, vibration perception with tuning fork, light touch with cotton ball and temperature perception with a cold water test tube. The patient was scored as follows: failed to perceive stimulus at 1 = toe; 2 = mid foot; 3 = the heel; 4 = lower leg, 5 = the knee. Scoring with regard to the Achilles / patella tendon reflex occurred as follows: normal reflex, score = 0; reflex elicited with reinforcement, score = 1; reflex absent, score = 2. The average score of both feet was summed with a reflex and NDS score of 5 or higher defined as moderate to severe neuropathy. The assessment yielded a high test sensitivity of 92%, minimising the 'at risk' patients who would be missed. In contrast, the specificity of 43% indicates that testing would result in a substantial proportion of false positive cases. The NDS score had a PPV of 28% such that less than half of those with a positive result would actually developed a foot ulcer. The interpretation of these results is complicated by the absence of reported confidence intervals.

From the evidence it can be concluded that the NDS assessment is a good tool for identifying those who are at high risk of foot ulcer in the general diabetes population with the caveat, that there would also be a substantial proportion of false positives cases identified and so further testing would likely be required before intensive risk management would be instituted. Box 5 summarizes the body of evidence according to the NHMRC grading criteria.

Box 5 Evidence statement matrix for the diagnostic accuracy of neuropathy disability score assessment

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study available
Clinical impact	B	The results indicate good test sensitivity with the use of NDS score, but relatively poor specificity. This tool would be associated with substantial false positives but is likely to capture all those at high risk. The results were not reported with confidence intervals and so there is uncertainty regarding the precision of these test characteristics.
Generalisability	B	The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population.
Applicability	C	One study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.

Evidence statement

The results suggest that the neuropathy disability score is a good screening tool for identifying those at high risk of foot ulceration in a general diabetes population, although it is likely to be associated with a considerable proportion of false positives. Further research is required (Grade C).

Table 3 Studies included neuropathy disability score assessment

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Abbott et al 2002) UK	II (prospective cohort) SIGN cohort: Good quality	N = 9710 Patients from general practice setting in six health districts Characteristics: ≤2 pedal pulses 21.2%, monofilament insensitivity 20.9%, socio economic class 86%	NDS	Vibration sensation measured with 128Hz tuning fork dorsal; temperature sensation using warm/ cold rods; and Achilles tendon reflex. NDS score between 6 and 10 is defined as abnormal.	Foot ulceration (>14 days to heal)	RR	2.3 [95%CI 1.6, 3.4]
(Pham et al 2000) USA	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Good quality	N = 248 Patients from three large primary care diabetic foot centres Characteristics: History of foot ulcer (87%)	NDS	Physical examination: Achilles / patella tendon reflex (yes = 0; no = 2) and sensory modalities:- pinprick with metal pointed or wooden pin, vibration with tuning fork, light touch with cotton ball and temperature perception with cold water test tube. (Score: failed to perceive stimulus at toe = 1; mid foot = 2; the heel = 3; lower leg = 4; the knee = 5) An NDS score of 5 or higher was defined as abnormal.	First incidence of foot ulceration after baseline	Sensitivity Specificity PPV OR	92% 43% 28% 3.1 [95%CI 1.3, 7.6]

RR= Relative Risk, OR= Odds Ratio, PPV= Positive Predictive Value, NDS= neuropathy disability score; VPT= vibration perception threshold; SWF= Semmes Weinstein monofilament

Predictive value of neuropathy disability score

As outlined in Table 3, the same two good quality studies provided evidence of the predictive value of neuropathy disability for foot ulceration in the general diabetes population.

Abbott et al (2002) reported that patients with an NDS of 6 or more had 2.3 times the risk of developing foot ulcer over a 2 year period compared to those with lower NDS, when controlled for absence of vibration perception, ankle reflex, foot deformity SWF insensitivity and foot pulse (RR=2.3 [95%CI 1.6, 3.4]). Pham et al (2000) found similar results with increased odds of 3.1 for foot ulcer over a mean follow-up period of 30 months in patients with an NDS of 5 or more (OR=3.1 [95%CI 1.3, 7.6]). The results of Pham et al however, may be influenced by the inclusion of a large proportion of patients with a history of foot ulcer, which is an independent risk factor for foot ulcer and for which the result was not adjusted.

From the results above it seems that neuropathy disability is a reasonable predictor of foot ulcer in the general diabetes population. Even though the studies used slightly different cut-off points, HDS of 5 and 6 respectively, they were still able to discriminate between those at high and low risk of foot ulcer. Box 6 provides an overview of the body of evidence for neuropathy disability according to the NHMRC criteria.

Box 6 Evidence statement matrix for the predictive value of neuropathy disability score

Component	Rating	Description
Evidence base	B	Two level II studies with low risk of bias.
Consistency	A	Both studies reported consistent results even though the studies used slightly different cut-off points.
Clinical impact	B	The studies reported an odds ratio of 3.1 and relative risk of 2.3. Although the results should be interpreted with some caution as Pham et al included patients with a history of foot ulcers, which may have influenced the numbers of foot ulcers observed.
Generalisability	B	Abbott et al had a large proportion of patients of low socio economic status, which might have influenced the incidence of foot ulcer. The sample in Pham et al included patients with a history of ulcer. Both these samples make the results reasonably generalisable to the target population, with some caveats.
Applicability	B	One study took place in the USA and one in the UK, both of which have similar health care for diabetes patients compared to the Australian health care context.

Evidence statement

Neuropathy disability is a good predictor of foot ulcer in the general diabetes population (Grade B).

NDS combined with other assessments

Diagnostic accuracy of NDS combined with other assessment

Pham et al's (2000) average quality study investigated the accuracy of NDS in combination with either vibration perception threshold (VPT), Semmes-Weinstein monofilament (SWM) or foot pressure (Table 4).

The combination of an NDS >4 and/or a VPT >24 Volts to indicate patients at high risk of foot ulcer, yielded a sensitivity, specificity and PPV of 94%, 38% and 26% respectively. Similarly, the combination of a NDS >4 and/or SWF insensitivity yielded test sensitivity, specificity and PPV of 99%, 22% and 23% respectively. For both combinations, the sensitivity indicated that nearly all patients at high risk of foot ulcer would be correctly identified, resulting in a low rate of missed cases. The specificity was low for both combinations indicating that the combination of assessments incorrectly classified patients at low risk as being at high risk. For both combinations, less than half of the patients who tested positive went on to develop foot ulcer.

In contrast, the combination of NDS >4 and/or foot pressure ≥6kg/cm² yielded a low sensitivity (58%), indicating that almost half of the patients who went on to develop a foot ulcer were not identified by the test. In contrast, the specificity (78%) suggests that this combined assessment has a moderate false positive rate and the PPV (38%) provides additional evidence of this. As mentioned earlier, the study by Pham et al did not provide confidence intervals, so the uncertainty associated with these estimates is unknown.

The evidence provided suggests that all three combinations which include NDS assessment performed poorly at accurately identifying those at high risk of foot ulcer in the general diabetes population. With its high sensitivity, the NDS combined with SWF or VPT might, however be used to rule out those at low risk of foot ulcer. Box 7 summarises the body of evidence according to the NHMRC grading criteria.

Box 7 Evidence statement matrix for the diagnostic accuracy of NDS combined with other assessments

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study
Clinical impact	C	The results of Pham et al indicate that while the combinations of NDS with VPT and SWF would identify those truly at high risk, and therefore rule out high risk in those with a negative result, there would also be a substantial proportion of false positives. The NDS and foot pressure assessment provided moderate specificity, but low sensitivity indicating that it would not be useful in identifying those at high or low risk of foot ulcer. Furthermore, the confidence intervals associated with these estimates are unknown and therefore significant error cannot be ruled out.
Generalisability	B	The study included a sample of patients attending foot or diabetes clinics, making them reasonably generalisable to the target population.
Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australian health care context.

Evidence statement

Neuropathy disability score combined with either vibration perception threshold; Semmes-Weinstein monofilament or foot pressure assessments may be poor screening tools to determine those patients at high risk of foot ulcer in the general diabetes population. The NDS combined with Semmes-Weinstein monofilament assessment or vibration perception threshold may be useful to rule out the high risk of foot ulcer (Grade C).

Table 4 Studies reporting on NDS combined with other assessments

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Pham et al 2000) USA	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Good quality	N = 248 Patients from three large primary care diabetic foot centres Characteristics: History of foot ulcer (87%)	NDS and VPT	Physical examination: Achilles / patella tendon reflex (yes = 0; no = 2) and sensory modalities;- pinprick with metal pointed or wooden pin, vibration with tuning fork, light touch with cotton ball and temperature perception with cold water test tube. (Score: failed to perceive stimulus at toe = 1; mid foot = 2; the heel = 3; lower leg = 4; the knee = 5a) An NDS score of 5 or higher was defined as abnormal.	First incidence of foot ulceration after baseline	Sensitivity Specificity PPV	94% 38% 26%
			NDS and SWF			Sensitivity Specificity PPV	99% 22% 23%
			NDS and foot pressure			Sensitivity Specificity PPV	58% 78% 38%

PPV= Positive Predictive Value, NDS= neuropathy disability score; VPT= vibration perception threshold; SWF= Semmes Weinstein monofilament

Risk assessment tool

Diagnostic accuracy of risk assessment tool

The average quality study by Leese et al (2006) investigated the accuracy of their risk assessment tool, which was based on previous studies and a pilot. The risk assessment tool included: a patient history concerning foot ulcer and the ability to see or reach the feet, followed by measurements for absence of both dorsalis pedis and posterior tibial pulse in either foot, presence of neuropathy or foot deformities (Table 5). Foot deformities were defined as changes in the foot shape that resulted in difficulty to fit standard shoes. Neuropathy was determined using a 10g monofilament to determine sensation on the plantar aspect of both feet (1, 2, 3 and 5th metatarsal head and great toe). Insensitivity to the 10g monofilament was defined as neuropathy. After assessment, the patients were classified as high, moderate or low risk. High risk was defined by two or more of the above risk factors, while moderate risk was defined by the presence of one risk factor. Over a follow-up of 1.7 years, with re-screening every 6 months, grouping the patients at baseline into high risk, and moderate or low risk, the tool had a sensitivity and specificity of 84% and 90% respectively. This indicates that the tool had a high proportion of true positives and true negatives. The PPV and NPV were reported as 29% and 99% respectively, which can be explained by the low prevalence of foot ulceration in the population (4.7%). This suggests that the risk assessment tool is fairly accurate at identifying those patients at risk of foot ulcer in the general diabetes population.

When the patients at moderate and high risk were grouped together, the sensitivity increased to 95%, but the specificity and PPV decreased (67% and 12% respectively). These results suggest that while the risk assessment tool is capable of identifying the majority of patients at high risk of foot ulcer, additional confirmatory assessments would be required to exclude the small proportion of false positives. Box 8 provides an overview of the body of evidence for the risk assessment tool according to the NHMRC criteria.

Box 8 Evidence statement matrix for the diagnostic accuracy of risk assessment tool

Component	Rating	Description
Evidence base	B	One level II study with low risk of bias.
Consistency	N/A	Only one study
Clinical impact	A	The results indicated that the risk assessment tool is fairly accurate at identifying all those at high risk of foot ulcer, and the number of false positive is small.
Generalisability	B	The study included a large sample from foot or diabetes clinics in hospital and general practice, which makes them generalisable to the target population.
Applicability	B	The study took place in the UK, which has similar health care for diabetes patients compared to the Australia health care context.

Evidence statement

The risk assessment tool is a good tool for determining those at risk of foot ulcer in the general diabetes population. Further research would be required (Grade C).

Predictive value of risk assessment

Leese et al (2006) also examined the value of risk assessment for the prediction of foot ulcer in the general diabetes population (Table 5). Similar to the method described above, the study sample was divided, based on the results of a risk assessment, into three categories low, moderate and high risk. The authors found that patients classified as high risk were 48 times more likely to develop foot ulcers compared to those with moderate and low risk over a mean 1.7 years (OR= 48 [95% CI 31, 75]). When the high and moderate risk patients were compared

to the low risk patients, the odds ratio decreased to 40 (OR=40 [95%CI 20, 81]).Given the width of the confidence intervals there is uncertainty regarding these estimates, but even despite this the risk appears to be substantially elevated. This is perhaps explained by the combination of different assessments for peripheral vascular disease, neuropathy and foot deformity.

These results suggest that risk assessment is a very strong predictor of foot ulcer. Box 9 summarizes the body of evidence according to the NHMRC grading criteria.

Box 9 Evidence statement matrix for the predictive value of the risk assessment tool

Component	Rating	Description
Evidence base	B	One level II study with low risk of bias.
Consistency	N/A	Only one study
Clinical impact	A	The results indicated that there is a very large odds for those patients with a risk assessment result of high and moderate to develop foot ulcer.
Generalisability	B	The study included a sample from foot or diabetes clinics in hospital and general practice, which makes them fairly generalisable to the target population.
Applicability	B	The study took place in the UK, which has similar health care for diabetes patients compared to the Australian health care context.

Evidence statement

Risk assessment using a combination of patient history, foot pulses, neuropathy and foot deformity is a strong predictor of foot ulcer in the general diabetes population. Further research would be required (Grade C).

Table 5 Studies included risk assessment tool

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Leese et al 2006) UK	II (prospective cohort) Quadas: Good quality SIGN cohort Average quality	N = 3526 Patients receiving diabetes care in hospital and general practice	Risk assessment tool	Patient history: see or reach feet, history of ulcers Foot pulses: absence of both dorsalis pedis and posterior tibial pulse in either foot. Neuropathy: 10g monofilament sensation on more than one site of 10 sites on the plantar aspect of both feet. (1,2,3 and 5th metatarsal head and great toe) Foot deformities: change in foot shape that results in difficulty in fitting standard shoes, subjectively assessed by practitioner	Foot ulceration defined by full thickness skin break below the level of the malleoli	High risk vs moderate and low	
						Sensitivity	84% [95%CI 78, 89%]
						Specificity	90% [95%CI 89, 91%]
						PPV	29% [95%CI 25, 34%]
						NPV	99% [95%CI 98, 99%]
						OR	48 [95%CI 31, 75]
						High and moderate risk vs low risk	
						Sensitivity	95% [95%CI 90, 98%]
						Specificity	67% [95%CI 65, 68%]
						PPV	12% [95%CI 11, 14%]
						NPV	99% [95%CI 98, 99%]
						OR	40 [95%CI 20, 81]

PPV= Positive Predictive Value, NPV= negative predictive value; OR= odds ratio

Hansen's Disease Centre risk assessment

Diagnostic accuracy of Hansen's disease centre risk assessment

Only the average quality study by Ahroni et al (1997) investigated the accuracy of the Hansen's Disease Centre (HDC) risk assessment for the development of foot ulcer and occurrence of amputation in a male diabetic population (Table 6).

The HDC risk assessment is a four level risk categorisation scheme that involves evaluation for the loss of protective sensation (using SWF monofilaments); structural deformity (prominent metatarsal heads, hammer or claw toes, Charcot deformity, bony prominence, hallux valgus or hallux limitus), skin and nail abnormalities; callus; gait analysis over 50 feet; history of ulceration; history of amputation; and vascular disease (ankle-arm index (AAI) and ankle pulse palpation). Patients were scored as: 0 = patient without loss of protective sensation; 1 = loss of protective sensation but without weakness, deformities, callus, pre ulcer or history of ulceration; 2 = loss of protective sensation and any weakness, deformities, callus, pre ulcer or history of ulceration; or 3 = patient with history of ulceration or ischaemic index (according to AAI) less than 0.45. After the assessment, patients were categorised as low risk (score 0 and 1) or high risk (score 2 and 3). The patient follow up was a mean of 2.6 ± 1.4 years.

The HDC assessment was shown to have a sensitivity and specificity of 94% and 43% respectively. Given the low specificity, it is apparent that this risk assessment has a notable false positive rate although there is likely to be minimal 'at risk' patients overlooked given the high sensitivity. Furthermore, the authors reported a 1.65 positive likelihood ratio (PLR) and 0.14 negative likelihood ratio (NLR) resulted in a calculated diagnostic odds ratio of 12, indicating a strong ability to discriminate between presence or absence of risk for foot ulcer. Similar results were found by the authors when testing a revised version of the HDC risk assessment, from which the AAI and callus examination were excluded and the assessment of foot deformities revised. The sensitivity, specificity, PPV and NPV were found to be 91%, 49%, 25% and 96%, respectively. The results suggest that the HDC risk assessment is a reasonable tool to identify those patients at high risk for foot ulcer, although consideration must be given to the high false positive rate.

Ahroni et al (1997) also investigated the predictive accuracy of both HDC risk assessments for the occurrence of amputation in the general diabetes population. Again, the revised HDC risk assessment performed marginally better than the HDC risk assessment, with higher specificity and PPV but similar sensitivity and NPV. The 100% sensitivity indicates that the assessment is capable of ruling out patients identified as low risk. This is further supported by the NPV of 100%. In contrast, the specificity of both versions of the HDC risk assessment, 38% and 43% (revised HDC) respectively, indicates that there were a substantial number of patients who did not undergo amputation after being classified as high risk. For amputation as an outcome, the HDC risk assessment and revised version are good tools to rule out patients identified as low risk of amputation. The study sample mainly included male, which makes it difficult to transfer the results to the general diabetes population.

The results above suggest that the HDC risk assessment is a good rule out test for patients identified as at low risk of developing of foot ulcer, however all patients identified as high risk may need further testing before preventive management is commenced, given the high rate of false positives. Box 10 provides an overview of the body of evidence for HDC risk assessment according to the NHMRC criteria.

Box 10 Evidence statement matrix for the diagnostic accuracy of HDC risk assessment

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study
Clinical impact	B	The (revised) HDC assessment is good for predicting amputation, the high sensitivity can rule out risk of amputation in those testing negatively, which considering the severity of the outcome is important
Generalisability	B	The study included patients attending foot or diabetes clinics, which makes the results fairly generalisable to the target population. However, the sample mainly included male which may make it difficult to generalise to the results to females.
Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.

Evidence statement

HDC risk assessment may be an accurate test for ruling out risk of foot ulcer and amputation in the general diabetes population. Further research would be required (Grade C).

Table 6 Studies included Hansen's Disease Centre risk assessment

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Ahroni 1997) USA	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Good quality	N = 778 Patients from Seattle Diabetic Foot Study, patients at Internal Medicine Veterans Affairs Puget Health Care Characteristics: IDDM (6%); NIDDM (92%); male (98%)	HDC	Examining loss of protective sensation; structural deformity; callus; history of ulceration; history of amputation; vascular disease (AAI and pulse palpation); gait analysis and skin and nail abnormalities. Four level risk categorisation: low risk = 0 and 1; high risk = 2 and 3.	Full thickness cutaneous foot ulcer below the ankle and >14 days to heal	Sensitivity Specificity PPV NPV LR^+ LR^-	94% 43% 24% 97% 1.65 0.14
					Amputation	Sensitivity Specificity PPV NPV LR^+ LR^-	100% 38% 4.6% 100% 1.62 0
			HDC revised	Examining loss of protective sensation; structural deformity (revised); history of ulceration; history of amputation, vascular disease (with pulse palpation only); gait analysis; and skin and nail abnormalities. Four level risk categorisation: low risk = 0 and 1; high risk = 2 and 3.	Full thickness cutaneous foot ulcer below the ankle and >14 days to heal	Sensitivity Specificity PPV NPV LR^+ LR^-	91% 49% 25% 96% 1.76 0.19
					Amputation	Sensitivity Specificity PPV NPV LR^+ LR^-	100% 43% 5.0% 100% 1.77 0

DM= diabetes Mellitus; NIDDM= non insulin dependent diabetes mellitus; PPV= Positive Predictive Value, NPV= Negative Predictive Value, PR= Positive Ratio, NR= Negative Ratio; HDC = Hansen's Disease Centre

Seattle risk assessment tool

Diagnostic accuracy of Seattle risk assessment

Ahroni et al (1997) developed a multivariate risk assessment tool for the prediction of both foot ulcer and amputation in a diabetic population. This study investigated the predictive accuracy of both assessments (Table 7)

The Seattle risk assessment tool for foot ulcer included evaluation of neuropathy, history of amputation, toe vibration perception, use of insulin treatment and history of ulceration. Low risk was defined by having 0, 1 or 2 of the above criteria present, while high risk was defined by having more than 2 of the above criteria. The assessment had a sensitivity and specificity of 65% and 75% respectively, and a PPV and NPV of 36% and 91% respectively. The low PPV can be partly explained by the low prevalence of foot ulcer (15%) in the study population. Overall, these measures suggest that the predicted risk from the model has a moderate fit with the observed data.

For amputation, the assessment yielded a 100% sensitivity and NPV indicating that this assessment is able to rule out from further testing those classified as low risk by the model. In contrast, this assessment had a relatively poor specificity (54%) and thus nearly half of all patients testing positive would not progress to amputation.

From the results, the Seattle risk assessment appeared useful in ruling out those classified as at low risk, from subsequent amputation. For foot ulcers prediction, the Seattle risk assessment tool was less accurate with only moderate sensitivity and specificity. Box 11 summarises the body of evidence according to the NHMRC grading criteria.

Box 11 Evidence statement matrix for the diagnostic accuracy of Seattle risk assessment

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study
Clinical impact	C (foot) B (amputation)	The assessment had moderate sensitivity and specificity for foot ulcer. For amputation, the results indicated a good sensitivity and NPV of 100%, which indicates a substantial impact at ruling out those not at risk. Though, the results were not supported by confidence intervals which makes it hard to interpret the uncertainty in the estimate.
Generalisability	B	The study included patients attending foot or diabetes clinics, which makes them generalisable to the target population. Though the sample included mainly males if may be difficult to generalis,e to the target population as sex might be an effect modifier
Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.

Evidence statement

The Seattle risk assessment may have moderate performance at accurately identifying those at risk of foot ulcer. It has better performance at accurately ruling out those who are at low risk of subsequent amputation. Further research would be required (Grade C).

Table 7 Studies reporting on Seattle risk assessment

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Ahroni 1997) USA	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Good quality	N = 778 Patients from Seattle Diabetic Foot Study attending Internal Medicine clinic at Veterans Affairs Puget Health Care Characteristics: IDDM (6%); NIDDM (92%); male (98%)	Seattle risk assessment	Assessment of neuropathy; history of amputation; toe vibration perception; insulin treatment; and history of ulceration.	Full thickness cutaneous foot ulcer below the ankle and >14 days to heal	Sensitivity Specificity PPV NPV LR^+ LR^-	65% 75% 36% 91% 2.6 0.46
				Assessment of history of ulceration or amputation; Charcot foot; diabetes duration >10 years; hammer or claw toes; and self-reported nephropathy.	Amputation	Sensitivity Specificity PPV NPV LR^+ LR^-	100% 54% 5.9% 100% 2.2 0.00

IDDM = insulin dependent diabetes mellitus; NIDDM = non insulin dependent diabetes mellitus; PPV = Positive Predictive Value, NPV = Negative Predictive Value, PR = Positive Ratio, NR = Negative Ratio

Foot pressure assessment

Diagnostic accuracy of foot pressure assessment

Two average quality cohort studies reported on the diagnostic accuracy of foot pressure assessment at determining foot ulceration in the general diabetes population (Table 8).

The study by Pham et al (2000) measured the maximum plantar pressure of the entire foot with the F-scan mat system© (Tekscan, Boston, MA) using an average of three readings. The cut-off point for risk of ulceration was set at a foot pressure higher then 6kg/cm^2. The results indicated that the F-scan mat system© is poorer at detecting risk of foot ulceration (sensitivity=59%), than at identifying true negatives (specificity=69%). The likely consequence of this is that patients who are at risk would not be detected. The positive predictive value (PPV) for the F-scan mat system© indicates, that only 31% of patients identified as being at high risk actually develop foot ulcer. It should be noted that this population did include people with a history of foot ulcers, neuropathy and neuropathic symptoms, which are other risk factors for the development of ulceration. Despite the higher prevalence of risk in this population, the F-scan mat system did not perform well. The negative predictive value (NVP) of the system was not reported, nor could it be calculated. From these results, it can be concluded that foot pressure assessment using the F-scan mat system on its own is not an accurate method of detecting those patients who are at high risk of developing foot ulcer.

The average quality study by Veves et al (1992) reported results that are contradictory to those discussed above. The peak plantar pressure (PPP) was measured with optical pedobarography under the metatarsal heads, heel, great toe and any other area with expected high pressure. Of the three footsteps that the patient made, the authors used the measurement of the footstep closest to the normal gait. A cut-off point of 12.3 kg/cm^2 yielded a sensitivity of 100% [95% CI 74, 100] and specificity of 39% [95% CI 28, 52%] implying that the PPP assessment detected all patients that developed ulcers, but has a very poor ability to correctly identify those who will not develop ulcers. At peak pressures higher than 12.3 kg/cm^2, the PPV was 26% [95%CI 16, 39%] and the NPV 100% [95% CI 85, 100%]. The PPP assessment was found to be a good 'rule out' test in this population, in that a negative PPP assessment would effectively rule out the development of foot ulcers in diabetic patients with and without neuropathy over a follow up of 30 months. Still, caution is advised as the results are based on a small sample (n=86) that had high attrition.

The results above seem to indicate that the accuracy of plantar foot pressure assessment in the general diabetic population is likely to depend on the assessment method that is used, as well as the cut-off that is employed. The calculated sensitivity of 100% by Veves et al (1992), while the PPV was low, might be explained by the cut-off point of 12.3kg/cm^2 which was twice as high as the 6kg/cm^2 of Pham et al (2000). There were no substantial differences in patient characteristics or follow up between studies. Both studies reported low PPV's that suggest that less than half of those that tested positive would actually get an ulcer, indicating that a large proportion could receive a change in management unnecessarily. In contrast, foot pressure assessment was unlikely to yield a large number of false negatives with the NPV being 100%, according to Veves et al (1992). Box 12 summarises the body of evidence according to the NHMRC grading criteria.

Box 12 Evidence statement matrix for the diagnostic accuracy of foot pressure assessment

Component	Rating	Description
Evidence base	C	Two level II studies with moderate risk of bias.
Consistency	D	The studies were inconsistent. Pham et al indicated that more patients would be treated unnecessarily and that patients at risk would be missed. In contrast, Veves et al indicated that patients who were not at risk would be identified but that many patients would receive unnecessary treatment.
Clinical impact	C	Veves et al presented results that suggest a 100% sensitivity and negative predictive value, indicating that patients not at risk of ulcer could be accurately identified and thus not need follow up treatment. However, Pham et al's results were less clear cut and in the opposite direction so it is unclear whether the different intervention types have different clinical impact.
Generalisability	A	Both studies included diabetic patients (type I and II), with neuropathy and or history of ulceration, visiting foot or diabetes clinics, which makes them generalisable to the target population.
Applicability	B	One study took place in the USA and one in the UK, which both have similar health care for diabetes patients compared to the Australia health care context.

Evidence statement

The results suggest that foot pressure assessment has variable accuracy at identifying diabetic individuals at high risk of foot ulcer. Further research is required (Grade C).

Table 8 Studies reporting on foot pressure assessment (general diabetes population)

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Crawford et al 2007) UK	I (systematic review) SIGN SR: Good quality	N= 1729 K = 2 Characteristics: See Pham et al and Lavery et al	Peak plantar pressure (N/cm^2)		Foot ulceration	SMD (pooled estimate)	0.47 [95%CI 0.24, 0.70]
(Pham et al 2000) USA	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Good quality	N= 248 Patients from three large primary care diabetic foot centres Characteristics: History of foot ulcer n=87, NSS mean± SD (range)= 3.9±4.1 (0-16), NDS mean± SD (range)= 10±8 (0-28), VPT (Volt) mean± SD (range)= 29±17 (1-51), SWF mean± SD (range)= 5.4±1.4 (1.85-7.00)	Plantar Foot Pressure (kg/cm^2)	F-scan mat system © (Tekscan, Boston, MA) mean reading of three assessments, foot pressure ≥6kg/cm² at risk for foot ulcer	First incidence of foot ulceration	Sensitivity Specificity PPV OR	59% 69% 31% 2.0 [95%CI 1.2, 3.3]
(Kastenbauer et al 2001) Austria	II (prospective cohort) SIGN cohort: Good quality	N= 187 Outpatients at Diabetes centre at hospital Characteristics: Type II DM, history of ulcers 0% limited ankle joint mobility 52%, Hammer/claw toe 21%, SWM absence12%	Mean Plantar Pressure (kg/cm^2)	Novell SF platform device© one typical left and one typical right foot gait was selected. Abnormal when >2SD above the corresponding area of the foot in a healthy subject (control group)	Foot ulceration defined by full thickness neuropathic plantar or lateral forefoot ulcerations penetrating the curtis and subcurtis.	RR	6.3 [95%CI 1.2, 33]
(Veves et al 1992) UK	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Good quality	N= 86 Patients attending clinics at Manchester Diabetes Centre Characteristics: Neuropathy 67%, history of ulceration 0%, active foot ulcers 0%, unable to walk without aid 0%	Peak Plantar pressure: (kg/cm^2)	Measured with optical pedobarography under the metatarsal heads, heel, the great toe and any other high area of pressure. >12.3kg/cm² is seen as abnormal Most normal gait footstep of three footsteps measured	First incidence of foot ulceration	Sensitivity Specificity PPV NPV	100% [95%CI 74, 100%] 39% [95%CI 28, 52%] 26% [95%CI 16, 39%] 100% [95%CI 85, 100%]

- = no data available/ given; NNS= Neuropathy Symptom Score; NDS= Neuropathy Disability Score; VPT= Vibration Perception Threshold; SWF= Semmes-Weinstein Monofilament; SMD= standardised mean difference; OR= odds ratio, PPV= Positive Predictive Value; NPV= Negative Predictive Value; SD= standard deviation; DM= diabetes mellitus

Predictive value of foot pressure asessment

One good quality systematic review and an additional good quality cohort study reported on the predictive value of foot pressure assessment for foot ulceration in the general diabetes population (Table 8).

Crawford et al's systematic review included cohort studies that evaluated the assessment of risk factors used to predict diabetic foot ulcers. The authors included results from Lavery et al and Pham et al in their meta-analysis. The results indicated that a high peak plantar pressure increases the risk for ulceration. The pooled standardised mean difference was 0.47 [95% CI 0.24, 0.70], which indicates that there was a moderate mean pressure difference between the group that developed ulcers and those who did not. The results had significant heterogeneity, which could be explained by the use of different foot pressure measurements (Crawford et al 2007).

Kastenbauer et al (2001) used the Novell SF platform device© (Novel, Munich, Germany) to measure the mean plantar pressure of the hallux, lesser toe, 1st metatarsal head and 2nd through 5th metatarsal head. The test was positive when at least one area under the foot of a diabetic patient had a pressure of two standard deviations above the corresponding area of the foot in a healthy subject. The results indicated that those type II diabetes patients with elevated foot pressure had 6.3 times the risk of developing ulcers then those with normal foot pressure (RR=6.3 [95% CI 1.2, 33]). Though the result is significant, due to the small sample size the confidence interval is relatively wide indicating that the increase in risk could range from a 12% increased likelihood of ulceration up to a risk nearly 33 times that of those without elevated foot pressure.

The results described above consistently showed that diabetic patients with elevated foot pressure were more likely to develop foot ulcerations than those with a normal foot pressure. Box 13 summarises the body of evidence according to the NHMRC grading criteria.

Box 13 Evidence statement matrix for the predictive value of foot pressure

Component	Rating	Description
Evidence base	A	One level I study with low risk of bias and one level II study with a low risk of bias.
Consistency	A	The studies were consistent.
Clinical impact	B	The results reflect a moderate to substantial clinical impact on the patient. The confidence intervals suggest predominately clinically important effects.
Generalisability	A	All three studies assessed a general diabetic population.
Applicability	B	One study took place in the UK, one in Austria. The UK systematic review included studies mainly undertaken in the USA. The health system in these countries is broadly similar to the Australian situation.

Evidence statement

Diabetic patients with elevated foot pressure, as assessed using peak or mean plantar pressure measurement, have a moderate to substantial increased risk of developing foot ulcer compared to diabetic patients with normal foot pressure (Grade B).

Vibration sensation assessment

Diagnostic accuracy of vibration sensation assessment

Three average quality studies reported the diagnostic accuracy of vibration sensation or perception for the development of ulcerations or lower extremity amputations in patients with diabetes (Table 9)

The good quality cohort study by Ahroni (1997), from the Seattle Diabetic Foot study assessed loss of vibration sensation with a 128Hz tuning fork on the plantar hallux. The author reported a sensitivity of 89% for diagnosing amputation risk in diabetic patients, but poor specificity (51%). The low specificity, in particular, implies that use of a tuning fork has a high false positive rate. The PPV indicates only 5.4% of those with a positive tuning fork result would undergo amputation, which could lead to a very high proportion of patients receiving treatment unnecessarily. The NPV indicates that the test is accurate at ruling out those patients who are not at risk of amputation (NPV= 99%). The authors also reported a positive likelihood ratio (LR^+) of 1.80 and negative likelihood ratio (LR^-) of 0.22. The diagnostic odds ratio of 8, which was calculated by dividing LR^+ by LR^-, indicated that the odds of a positive test in those people who will undergo amputation was 8 times higher than in those people who will not undergo amputation.

For foot ulceration as an outcome, the author reported a lower sensitivity, but a higher specificity for vibration sensation assessment, 77% and 55%, respectively. This indicates that the assessment missed more patients at risk of ulceration, but had a lower false positive rate, compared to amputation as an outcome. Furthermore, the LR^+ and LR^- of 1.70 and 0.42 respectively. The calculated diagnostic odds ratio indicated that the odds of a positive test in those people who will develop foot ulcer 4 times higher than in those people who will not develop foot ulcers (Ahroni 1997). The study seems to suggest that the assessment of vibration sensation to predict amputation was slightly better than for diagnosing risk of foot ulceration, though for both outcomes the assessment had a high proportion of patients that might have an unnecessary change in management, although low rate of at risk patients missed. This is appropriate for a symptomatic population and given the consequences of delayed diagnosis and treatment.

Similarly, Pham et al (2000) reported good test sensitivity (86%) for assessment with vibration perception threshold and lower specificity (56%) at predicting foot ulcer. The PPV of 32% was higher than that reported by Ahroni (1997) presumably because Pham et al included a large proportion of patients with a history of foot ulcer, which could have increased the likelihood of a foot ulcer outcome.

Young et al (1999) provided a more specific risk analysis for vibration sensation assessment. The authors separated the population into three groups; <15Volt, 16-24 Volt and >25 Volt and compared the two highest groups with 15 Volt as the reference group. The vibration sensation assessment for the group with 16 to 14 Volt yielded a low sensitivity (25%), indicating that the test had a high false negative rate. The specificity of 78% suggested that this threshold was much better at correctly identifying those not at risk for foot ulcer. It should be noted that the sample size in the 16-24 Volt group was much smaller than that of the reference group. As a consequence, there were more foot ulcers in the reference group over a 4 year follow up, than in the 16-24 Volt group.

When the group with a threshold higher than 25 Volt was compared with the reference group, the test sensitivity was much higher (87%), whilst the specificity was (56%) increasing the proportion of people that would receive unnecessary treatment but reducing the number of at risk patients who would incorrectly test negative. When a threshold of above 25 Volts was compared to below 25 Volt, the results indicated better overall accuracy. For the sensitivity and specificity, the assessment yielded 83% and 62% respectively, indicating that the detection of a moderate proportion of true positives. These results suggest that vibration sensation assessment with a threshold of 25 Volt has moderate accuracy at predicting those diabetes patients at risk of foot ulceration.

From the results above it seems that there is consistent evidence that the vibration sensation assessment has moderate accuracy at identifying at risk patients for foot ulceration and amputation. It should be noted that, however, all studies had a follow up of 2.5 to 4 years, so there was a time difference between the vibration perception measurement and the observed ulceration or amputation outcome, which may have confounded the outcome as subjects assessed as 'at risk' received standard treatment. Box 14 summarises the body of evidence according to the NHMRC grading criteria.

Box 14 Evidence statement matrix for the diagnostic accuracy of vibration sensation perception testing

Component	Rating	Description
Evidence base	C	Three level II studies with moderate risk of bias.
Consistency	B	The studies provided consistent evidence, reporting that vibration sensation perception testing has moderate accuracy at diagnosing patients at risk of foot ulcers and amputation. The sensitivity was reasonable in identifying those at risk in all three studies (range 76%-89%). The rate of correctly classified true negatives was low in one study, giving a high false positive rate, while the other study reported a low false positive rate.
Clinical impact	C	Some of the results did not provide confidence intervals or had a wide 95% confidence interval, which increased the uncertainty of the result. All studies had a time difference of 2.5 to 4 years between measurement and ulceration/amputation, which could have influenced the outcome as subjects assessed as 'at risk' received treatment. The results have therefore been assessed as having moderate clinical impact. Although this is likely to be a conservative estimate, should the confounding effect of treatment be considered.
Generalisability	B	The studies all included diabetes patients without ulcers. Ahroni's results are mainly based on male patients as the study was undertaken at a veterans' affair hospital. Pham et al had a population that included those with a history of ulceration. These populations are generalisable to the target population of this guideline
Applicability	B	Two studies took place in the US and one in the UK. Both have a similar health care system for diabetes care to the Australian system and are therefore likely applicable for the Australian context.

Evidence statement

The assessment of vibration sensation perception in the diabetes population, with or without a history of foot ulcer, has moderate accuracy at detecting those patients at risk of a subsequent foot ulcer (Grade C).

Table 9 Studies reported on vibration sensation assessment

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Crawford et al 2007) UK	I (systematic review) SIGN SR: Good quality	N = 435 See Kastenbauer et al (2001) and Pham et al (2000)	Vibration perception		Foot ulceration	WMD (pooled estimate)	17 [95%CI14, 20]
(Lehto et al 1996) Finland	II (prospective cohort) SIGN cohort: Good quality	N = 1059 Patients registered by Social Insurance Act for diabetic drug reimbursement Characteristics; IDDM 0%, absence peripheral pulses 80%,	Vibration sensation	Bilateral absence was defined as abnormal	Lower extremity amputation	RR	2.7 [95%CI 1.6, 4.7]
(Ahroni 1997) USA	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Good quality	N = 778, Patients from Seattle Diabetic Foot Study, patients at internal medicine Veterans Affairs Puget Health Care Characteristics: IDDM 6%, NIDDM 92%, male 98%	Vibration sensation	Measured with 128 Hz tuning fork on the plantar hallux	Full thickness cutaneous foot ulcer below the ankle with >14 days until healing or lower extremity	Sensitivity Specificity PPV NPV LR^+ LR^- OR	77% 55% 27% 92% 1.70 0.42 2.0 [95%CI 1.2, 3.6]
					Amputation	Sensitivity Specificity PPV NPV LR^+ LR^- OR	89% 51% 5.4% 99% 1.80 0.22 ns

(Boyko et al 1999) USA	II (prospective cohort) SIGN cohort: Good quality	N = 749, Seattle Diabetic Foot Study Characteristics; Male 98%, DM type II 93.6%	Vibration sensation	Measured with 128Hz Tuning fork on plantar hallux. Absence when patient could not sens vibration while examiner could.	Foot ulceration >14 days until healing	RR	1.3 [95%CI 0.85, 1.91]
(Pham et al 2000) USA	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Good quality	N = 248 Patients from three large primary care diabetic foot centres Characteristics: History of foot ulcer n=87, NSS mean± SD (range)= 3.9±4.1 (0-16), NDS mean± SD (range)= 10±8 (0-28), VPT (Volt) mean± SD (range)= 29±17 (1-51), SWF mean± SD (range)= 5.4±1.4 (1.85-7.00)	Vibration perception threshold	Biothesiometer (biomedical Newbury, Ohio) vibration at 100hz, 0-50volt, mean of three readings. ≥25V risk of foot ulcer	First incidence of foot ulceration after baseline	Sensitivity Specificity PPV OR	86% 56% 32% 3.4 [95%CI 1.7, 6.8]
(Kastenbauer et al 2001) Austria	II (prospective cohort) SIGN cohort: Good quality	N = 187 Outpatients at Diabetes centre at hospital Characteristics: Type II DM, history of ulcers 0% limited ankle joint mobility 51.9%, Hammer/claw toe 21.2%, SWF absence 11.5%	Vibration perception threshold	Biothesiometer (Biomedical, Newbury, Ohio), three times at the pulp of both great toes. Cut off point 25 Volt chosen based on the 90th percentile of the VPT at the great toe of 60 year old healthy subjects.	Foot ulceration defined by full thickness neuropathic plantar or lateral forefoot ulcerations penetrating the curtis and subcurtis.	RR	25 95%CI 3.1, 205]
(Young et al 1994) UK	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Average quality	N = 469 Patients at a Diabetes centre and foot clinic Characteristics: History of ulcer 0%, at least one pedal pulse 100%	Vibration perception threshold	16-24 Volt vs VPT<15Volt (Arnold Horwell, London , UK) Reading at great toe with probe vertically on pulp of the toe. A mean of three readings was used for each foot	First incidence of foot ulceration	Sensitivity Specificity PPV NPV OR	25% [95%CI 44, 64%] 78% [95%CI 72, 82%] 3% [95%CI 1, 13%] 97% [95%CI 93, 99%] 1.2 [95%CI 0.24, 6.2]
				≥25 Volt vs VPT<15Volt		Sensitivity Specificity PPV NPV	87% [95%CI 73, 95%] 56% [95%CI 50, 60%] 20% [95%CI 15, 26%] 3% [95%CI 1, 6]

						OR	7.99 [95%CI 3.7, 18]
				≥25Volt vs <25 Volt		Sensitivity	83% [95%CI 69, 92%]
						Specificity	62% [95%CI 57, 67%]
						PPV	20% [95%CI 15, 26%]
						NPV	3% [95%CI 0.01, 0.06]
						OR	8.2 [95%CI 3.8, 18]

DM= diabetes Mellitus; SWF= Semmes-Weinstein monofilament; NNS= neuropathy symptoms score; NDS= neuropathy disability score; VPT= vibration perception threshold; RR= Relative Risk, OR= Odds Ratio, PPV= Positive Predictive Value, NPV= Negative Predictive Value, LR^+= Positive likelihood Ratio, LR^-= Negative likelihood Ratio, IDDM= insulin dependent diabetes mellitus; NIDDM= non Insulin dependent diabetes mellitus; WMD= weighted mean difference

Predictive value of vibration sensation perception

One good quality systematic review, four good and one average quality cohort study reported on the predictive value of vibration sensation perception in the general diabetic population (Table 9). The good quality articles by Boyko et al and Ahroni are assessed as one study as they both report on the Seattle Diabetes Foot study.

In the evidence base, vibration sensation or perception was assessed with either a biothesiometer, neurothesiometer or a tuning fork. Patients are tested for their perception threshold by gradually increasing the amplitude from zero until the patient feels the vibration. In general a threshold of >25 Volt is considered to be a positive test. In the case of a tuning fork, 128 Hz is generally applied and the patient is asked to notify the examiner if they can sense the vibration on the plantar region of the foot. Crawford et al (2007) included two studies in their systematic review that reported on the predictive role of vibration perception in the development of foot ulcers in diabetic patients. After conducting a meta-analysis, the authors estimated the initial difference in vibration perception in those who later developed foot ulcer and those who did not as being a weighted mean difference of 17.04 Volts [95%CI 13.9, 20.3]. It is difficult to interpret this result as it cannot be directly translated into clinical practice.

In a Finnish study by Lehto et al (1996), the predictive value of vibration perception for the occurrence of a lower extremity amputation was investigated. The authors reported that those patients who had bilateral absence of vibration perception in their legs had almost 3 times the risk of amputation [RR=2.7, 95%CI 1.6, 4.7]. This contrasted with the results of Ahroni (1997) who measured vibration perception with a 128Hz tuning fork placed at the great toe. Ahroni did not find a statistically significant increase in risk for lower extremity amputation in patients with absence of vibration perception at 128Hz. Ahroni reported twice the odds of foot ulcer risk in patients with absence of vibration perception at 128Hz (OR=2.0 [95%CI 1.2, 3.6]) (Ahroni 1997).

Boyko et al (1999) who also reported on the Seattle Diabetic Foot study, did not find a significant increase in foot ulceration when vibration sensation was absent although the confidence interval suggests a lack of power (RR=1.3 [95%CI 0.85, 1.91]). Although Boyko et al (1999) and Ahroni (1999) used data from the Seattle Diabetic Foot study, they reported contradictory evidence for the role of vibration perception in the prediction of foot ulceration. This difference might be explained by the use of different variables in the univariate and multivariate analysis.

Pham et al (2000) measured absence of vibration sensation with the Biothesiometer (Biomedical Newbury, Ohio). Absence of vibration perception was defined by a vibration perception threshold of ≥25 Volt. At this threshold, the authors reported three times the odds of developing ulcers (OR= 3.4 [95%CI 1.7, 6.8]). Kastenbauer et al (2001) used the same equipment and vibration perception threshold and found that diabetes patients above the perception threshold had 25 times the risk of developing foot ulcers than those with a threshold lower than 25V at the hallux (RR=25 [95%CI 3.1, 205]). The population in Pham and Kastenbauer studies included patients with, respectively, a history of foot ulcer, and with foot deformities and limited joint mobility.

Young et al (1994) used the same perception threshold of ≥25 Volts and in their average quality study separated patients in to three categories comparing these with each other.

The results were under powered when comparing diabetic patients with a threshold between 16 and 24 Volts with a threshold <15 Volts (OR=1.2 [95%CI 0.2, 6.2]). Those patients with a threshold above 25 Volts were almost 8 times more likely to develop foot ulcer (OR=8 [95%CI

3.7, 18]). Similar result was reported when the >25 Volts group was compared to the <25 Volts group over a four year follow up period (OR= 8.5 [95%CI 3.8, 18]).

It appears that vibration sensation perception can predict formation of foot ulcers in the general diabetes population. The risk increases with absence of perception at higher thresholds >25 Volts, which could be considered diagnostic. Two studies provided contradictory evidence for the predictive value of vibration perception for lower extremity amputation. However, insufficient information was presented in order to explain the discrepancy. Box 15 summarises the body of evidence according to the NHMRC grading criteria.

Box 15 Evidence statement matrix for the predictive value of vibration sensation perception

Component	Rating	Description
Evidence base	A	One level I study with a low risk of bias, four level II studies with low risk of bias and one level II study with moderate risk of bias.
Consistency	B	The studies provided inconsistent results for lower extremity amputation, although not enough data was provided to ascertain the likely reason. For the primary outcome of foot ulceration, the majority of studies reported an increase in risk with absence of perception at a vibration threshold >25 Volts.
Clinical impact	B	The results suggest substantial impact with 2 to 25 times the risk of foot ulceration. The impact of vibration perception assessment is unclear. Crawford's systematic review found a difference in vibration perception of 17 Hz in those who did or did not subsequently develop foot ulcer.
Generalisability	B	The study included diabetic patients (type I and II) visiting foot or diabetes clinics. The studies by Boyko et al and Ahroni included mainly makes, due to the veterans' affairs setting, which makes the results less directly applicable.
Applicability	B	Two studies took place in the US (one SR), two in the UK, one from Austria and one from Finland. All these countries have a similar health care setting to the system in Australia.

Evidence statement

Vibration sensation perception is a substantial predictor of foot ulceration in the general diabetes population. Absence of vibration perception at a threshold of >25 Volts significantly increases the risk of subsequent foot ulcer development (Grade B).

There was insufficient evidence to determine whether vibration sensation assessment as is a predictor for lower extremity amputation in the diabetes general population.

Semmes-Weinstein Monofilament assessment

Diagnostic accuracy of Semmes-Weinstein monofilaments

Two moderate quality studies included Semmes-Weinstein monofilaments testing to determine what screening techniques identify diabetes patients at risk of foot ulceration and/or amputation (Table 10).

Adler et al (1999) used the SWF test to determine if patients had peripheral sensory neuropathy, which is a risk factor for the occurrence of lower extremity amputation in diabetes patients. By placing the monofilament perpendicular to nine different sites on the plantar foot, the examiner measured if the patient was capable of sensing the applied cutaneous pressure. The assessment commenced with 1 gram followed by 10 gram up to 100 gram if the patient was unable to sense the pressure. A cut-off point of 10 gram or more was used to determine those with peripheral sensory neuropathy. The authors reported that the SWF assessment correctly identified 83% of patients who were identified as being at risk of amputation. This, however, was at the expense of a large proportion of false positive patients (specificity=50.8% [95%CI 47, 55]). As a consequence, this SWF will have a low rate of 'at risk' patients missed, but will have a large proportion of patients who will receive unnecessary treatment for being considered 'at risk' of amputation. Given the low prevalence of lower extremity amputation, the poor PPV (PPV=6.4% [95%CI 4.3, 9.5]) and high NPV (NPV=99% [95%CI 97, 99%]) of SWF is not unexpected. The results provided, indicate that the SWF assessment is an accurate tool for identifying those patients at risk for lower extremity amputation, although, the low specificity means a large proportion of false positive diagnosis and unnecessary treatment.

Pham et al (2000) used SWF to determine the risk of foot ulceration in a general diabetes population. In their assessment the 10 gram monofilament was only tested on the plantar hallux of both feet. The authors found that it correctly classified 91% of patients at risk (sensitivity=91%), but again, at the expense of specificity (specificity=34%). The results are consistent with those of Adler et al (1999).Pham et al included patients with a history of foot ulceration, which is an independent risk factor for future foot ulceration.

The results above suggest that the SWF assessment accurately diagnosis patients at risk of foot ulcers and lower extremity amputations. However, given the low specificity of the test it should be considered a diagnostic, rather than screening tool.

Box 16 summarises the body of evidence according to the NHMRC grading criteria.

Box 16 Evidence statement matrix for the diagnostic accuracy of Semmes-Weinstein monofilament testing

Component	Rating	Description
Evidence base	C	Two level II studies with moderate risk of bias.
Consistency	B	The sensitivity and specificity of the test was fairly similar despite determining risk status for different outcomes (foot ulcer and amputation) and in slightly different populations
Clinical impact	C	The low specificity of SWF (34-51%) means that a large proportion of patients would have incorrectly positive tests for being at risk of foot ulcer or amputation. The test is therefore better used a diagnostic tool in patients with symptoms of peripheral neuropathy, rather than as a screening tool in the general diabetic population.
Generalisability	B	The studies all include diabetes patients without ulcers. Ahroni's results were mainly based on male patients as the study was undertaken at a veteran's affair hospital. Furthermore, Pham et al had a population that included those with a history of ulceration.
Applicability	B	Two studies took place in the US which has a similar health care system for diabetes to the Australian system.

Evidence statement

The use of Semmes-Weinstein monofilament testing to determine patients at risk of foot ulcers or lower extremity amputation in the general diabetes population is not advised, as it's diagnostic accuracy is poor (Grade C).

Predictive value of peripheral sensory neuropathy

Three good and one average quality study investigated the predictive value of peripheral sensory neuropathy measured by SWF testing for foot ulceration and lower extremity amputation in the general diabetes population (Table 10).

The good quality study by Abbott et al (2002) assessed the presence of neuropathy in a large diabetic population (n=9710) by placing a 10g monofilament at three plantar sites of both feet. Over a 2 year follow up, the authors observed that patients with neuropathy had almost twice the risk of developing ulcers than those with a negative result (RR=1.80 [95% CI 1.36, 2.39]). It should be noted that this sample included a reasonable proportion of patients with absent pedal pulses (21%) indicating a peripheral vascular complication, which is itself an independent risk factor for foot ulceration.

Pham et al (2000) reported a similar result when applying SWF to the plantar aspect of the hallux using eight different monofilaments. The authors reported, over a mean follow up of 30 months, that there was approximately 2.5 times the likelihood of developing foot ulcers in patients who were insensitive to the 10g monofilament compared to those who were not insensitive (OR=2.4 [95%CI1.1, 5.3]).

Litzelman et al (1997) found similar results to the above studies for minor foot injuries. The authors separated the outcome according to the Seattle Wound Classification system, where minor foot injury would be defined as a score equal or higher than 1.2 group. The score of 1.2 indicated a superficial or healing lesion with no functional interruption of the protective cutaneous skin. Major foot injury was defined by a score equal or more than 1.3, indicating a non ulcerated lesion with duration less than 4 weeks with clinical evidence of a healing process or blister. The authors reported that patients insensitive to SWF for one or more sites, were almost 3 times more likely to develop a minor foot injury and approximately 5 times more likely to develop a major foot injury, compared to those who were sensitive to SWF (OR=2.8 [95%CI 1.6, 4.9] and OR=5.2 [95%CI 2.3, 12] respectively).

Adler et al (1999) examined the predictive value of the SWF assessment for amputation in diabetic patients. Over a mean follow-up of 3.3 years, the authors found a significantly

increased risk of amputation (RR=2.9 [95%CI 1.1, 7.8]) for those who were classified as insensitive to SWF. When they separated the outcome by minor and major amputation, the results indicated that patients who tested positive had nearly 5.5 times the risk of minor amputation, while there was no statistically significant difference in risk for major amputation (RR=5.4 [95%CI 1.2, 25]; RR=3.4 [95%CI 0.7, 16] respectively). There is reasonable uncertainty around the risk estimate for major amputation as indicated by the wide confidence interval, which might be due to the low incidence of major lower extremity amputation in the study sample.

The evidence provided above suggests that peripheral sensory neuropathy and insensitivity to SWF testing in the general diabetes population is capable of predicting the development of foot ulcers and amputation. Box 17 summarises the body of evidence according to the NHMRC grading criteria.

Box 17 Evidence statement matrix for the predictive value of peripheral sensory neuropathy

Component	Rating	Description
Evidence base	B	Three level II studies with low risk of bias and one level II study with moderate risk of bias
Consistency	A	All studies are consistent.
Clinical impact	B	The results ranged between a relative risk of 1.8 and 5.4 and odds ratios of 2.7 and 5.4, although some of the estimates also had wide confidence intervals. Taking this in to account the results would indicate a substantial clinical impact.
Generalisability	B	The study by Adler et al included mainly males; Litzelman et al had a large proportion of African Americans and socioeconomically disadvantaged patients. Similarly, Abbott et al had a large proportion of patients from a low socio economic class. These groups might be more vulnerable to poor health outcomes.
Applicability	B	Three studies came from the USA and one from the UK, which have a similar health care system for diabetes patients compared to the Australian system.

Evidence statement

Peripheral sensory neuropathy and insensitivity to Semmes-Weinstein monofilament testing is a good predictor of risk of foot ulcer, foot injury and amputation in a general diabetes population (Grade B).

Table 10 Studies reported on Semmes-Weinstein monofilament assessment

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Abbott et al 2002) UK	II (prospective cohort) SIGN cohort: Good quality	N = 9710 Patients from general practice setting in six health districts Characteristics: ≤2 pedal pulses (21.2%); low socio economic class (86%)	Semmes Weinstein monofilament	SWF 1, 10, 75 gram at three validated plantar sites (1st, and 5th metatarsal heads and the heel) on each foot. With eyes closed patient confirms the touch. Commencing with the 1g followed by 10g and 75g if not felt. Insensitivities defined as not feeling ≥10g.	Foot ulceration (>14 days to heal)	RR	1.8 [95%CI 1.4, 2.4]
(Litzelman et al 1997) USA	II (prospective cohort) SIGN cohort: Good quality	N = 395 Patients receiving health care in general practice Characteristics: NIDDM (100%); women (81%); annual income(<$10,000) (70%)	Semmes Weinstein 10g monofilament	SWF touch/ pressure sensation with 10g (5.07log) using standard method. Abnormal pressure sensation was defined as absence at one or more of three sites (great toe, first and fifth metatarsal heads) tested on plantar site of each foot.	Minor foot injury (Seattle Wound Classification system) ≤1.2	OR	2.8 [95%CI 1.6, 4.9]
					Major foot injury (Seattle Wound Classification system) ≥1.3	OR	5.5 [95%CI 2.3, 12.]
(Pham et al 2000) USA	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Good quality	N= 248 Patients from three large primary care diabetic foot centres Characteristics: History of foot ulcer (87%);	Semmes Weinstein 10g monofilament	Set of 8 SWF's 1-100g applied to plantar aspect of hallux. Inability to feel 5.07 SWF (10g) or higher indicated peripheral neuropathy.	First incidence of foot ulceration after baseline	Sensitivity Specificity PPV OR	91% 34% 25% 2.4 [95%CI 1.1, 5.3]
(Adler et al 1999) USA	II (prospective cohort) Quadas:	N = 776 Seattle Diabetic Foot Study Patients at Internal Medicine clinic of Veteran Affairs Puget Sound	Semmes Weinstein 10g monofilament	SWF 10g at nine (eight plantar sites and one dorsal) sites on either foot	First lower extremity amputation	Sensitivity Specificity PPV NPV	83% [95%CI 65, 94%] 51% [95%CI 47, 55%] 6.4% [95%CI 4.3, 9.5%] 99% [95%CI 97, 99%]

	Moderate quality SIGN cohort: Average quality	Characteristics: Type II DM (93%); male (98%); history of ulcer (24%); ≤2 pedal pulses absent (32%)				RR	2.9 [95%CI 1.1, 7.8]
					Minor amputation (distal below the knee)	RR	5.4 [95%CI 1.2, 24]
					Major amputation (below and above the knee)	RR	3.4 [95%CI 0.7, 16.]

RR = Relative Risk, OR = Odds Ratio, PPV = Positive Predictive Value, NPV = Negative Predictive Value; NIDDM = non insulin dependent diabetes mellitus ; DM = Diabetes Mellitus ; SWF = Semmes Weinstein monofilament; VPT = vibration perception threshold; NSS = Neuropathy symptoms score; NDS = neuropathy disability score ; SD= standard deviation

Ankle reflex assessment

Diagnostic accuracy of the ankle reflex assessment

Only the moderate quality study of Ahroni et al (1997) examined the predictive accuracy of ankle reflex assessment for the development of full thickness cutaneous foot ulcers and amputations in the general diabetes population (Table 11).

The Achilles tendon reflex was measured as either present or absent. The authors reported that assessment of the Achilles tendon reflex had both a low sensitivity and specificity (35% and 54% respectively). This suggests that the assessment is unlikely to detect a substantial proportion of patients who are at high risk of ulceration and is also likely to incorrectly identify a large proportion of low risk patients as being at high risk. The uncertainty in these estimates was not reported. The PPV of 13% seems to be reasonable as the prevalence of foot ulcer in the study population was 15%. The estimated NPV (81%) would suggest that there is a reasonable certainty in a negative test result. However, it needs to be noted that no confidence intervals were provided as a consequence the error in this estimate remains unclear. The results appear to indicate that Achilles tendon reflex assessment is a poor technique to identify diabetes patients who are at high risk of foot ulcer. The negative likelihood and positive likelihood ratios, 1.2 and 0.77 respectively, provide a diagnostic odds ratio of 0.65, indicating that the ankle reflex assessment identifies more positive test among patients who do not develop foot ulcer compared to patients who do. Though, this effect is tiny, given the values of LR^+ and LR^- are both close to 1.

For the outcome of amputation, Ahroni et al (1997) reported similar low to moderate sensitivity and specificity, 40% and 56% respectively. The PPV on the other hand was much lower as also the prevalence of amputation in the study sample (2.6%) was much lower than for foot ulcer, indicating that only 2.6% of the positively tested patients could actually subsequently require an amputation and so therefore 98% would likely receive a change in management unnecessarily. Based on these results, it can be concluded that the ankle reflex assessment is a poor technique to identify those at high risk of amputation. This is supported by the negative likelihood value of 1.1 and positive likelihood value of 0.91, indicating that there is a greater chance of a negative test in patients who did undergo amputation and a greater chance of a positive test in patients who did not undergo amputation.

Based on these results, the assessment of ankle reflexes is very poor at identifying patients at high risk of foot ulcer and amputation in a general diabetes population and consequently those who would benefit from effective treatment. Box 18 summarises the body of evidence according to the NHMRC grading criteria.

Box 18 Evidence statement matrix for the diagnostic accuracy of ankle reflex assessment

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Not applicable as there is only one study.
Clinical impact	D	Ahroni et al's results of sensitivity, specificity and PPV of the assessment for risk of foot ulcers and amputation are very poor. Only the NPV seems reasonable for this assessment, indicating that there is a reasonable confidence in a negative result, presumably because the risk of foot ulcer and particularly amputation is low. The clinical impact of the assessment would be slight or restricted as it is a poor tool for screening those who are at high risk.
Generalisability	C	The study sample included mainly male subjects which might restrict generalisation to females or the diabetes population in general.
Applicability	B	The study was conducted in the USA, which has a similar health care system for diabetes patients to the Australian context.

Evidence statement

In the general diabetes population, the assessment of ankle reflexes is a poor screening technique for identifying those at high risk of foot ulceration and lower extremity amputation (Grade C).

Predictive value of ankle reflex assessment

Three good quality studies investigated ankle reflex as a predictor for the development of foot ulcers and amputation (Table 11).

Abbott et al (2002) assessed ankle reflexes using a reflex hammer on the Achilles tendon with the patient in a seated position. The results on both ankles provided the Ankle Reflex Score: present with reinforcement on 1 side (score 1), present with reinforcement on both sides (score 2), absent on 1 side and reinforcement one side (score 3) and the highest score for those with absence on both sides (score 4). The authors found a significantly increased risk of foot ulcer/amputation in those patients with a score of 2, 3 or 4, compared to those with score 0 and 1 (RR=2.0 [95%CI 1.4, 3.1]; RR=2.3 [95%CI 1.2, 4.1]; RR=1.6 [95%CI 1.0, 2.4], respectively), when controlled for history of ulcer, a high neuropathy disability score, previous podiatry treatment, SWF insensitivity, absence of foot pulses, age and foot deformities. It is interesting to note that patients with reflexes absent in both legs, were at a lower risk than those with one side absent/one side reinforced and those with both sides reinforced.

Boyko et al (1999) did not provide additional evidence to support the above result as they were unable to detect a statistically significant difference in risk for diabetes patients with absence of ankle reflex (RR=1.16, [95%CI 0.84, 1.61]) when controlled for increased ankle blood pressure, high ankle arm index, high transcutaneous oxygen tension, Charcot foot, absence of vibration perception, ankle joint immobility and decreased orthostatic blood pressure. It is unclear if the absence of reflex was bilateral or one sided, however as the study indicated that it assessed ulceration per lower limb and not per patient, it is assumed that the absence of reflex was only one sided. The inconsistency between the results presented by Abbott et al (2002) and Boyko et al (1999) might be explained by the different variables for which the studies controlled.

The good quality study by Lehto et al (1996) assessed the ankle reflex test as a dichotomous variable and took bilateral absence of the reflex as the cut off point. Diabetes patients with bilateral absence of the ankle reflex were at 4.3 times the risk of requiring amputation than those with one or two present ankle reflexes (RR=4.3 [95%CI 2.5, 7.3]).

Based on the results presented above, it seems there is some inconsistency and uncertainty regarding the predictive value of ankle reflex assessment for foot ulcers and amputation. Box 19 summarises the body of evidence according to the NHMRC grading criteria.

Box 19 Evidence statement matrix for the predictive value of ankle reflex assessment

Component	Rating	Description
Evidence base	B	Three level II studies with low risk of bias
Consistency	C	Of the two studies that reported results for ulceration in the diabetic foot, one indicated a significant increased risk with absence of ankle reflex, while the other did not find a significant difference in ulceration between those with or without an ankle reflex. This inconsistency might be explained by the different variables that were included in the uni and multivariate analysis of both studies. There was only one study that reported on amputation as an outcome.
Clinical impact	C	The significant result for ulceration suggested a moderate clinical impact (odds between 1.4 and 1.9), given bilateral absence of the reflex as the cut off (similar to other studies). The result from Boyko et al (1999) indicated no significant effect. For amputation as an outcome, the result indicates a substantial clinical impact.
Generalisability	B	Boyko et al (1999) included mainly males, which makes it difficult to generalise to females. Abbott et al (2002) included a sample with a large group of patients with lower socioeconomic status. Overall the samples studied are likely similar to the target group.
Applicability	B	One study came from the USA, one from Finland and one from the UK, which all have a similar health care system for diabetes patients to the Australian context.

Evidence statement

There is inconsistent and inconclusive evidence regarding the role of ankle reflex assessment in predicting foot ulcers in the general diabetes population (Grade C).

Ankle reflex assessment may have a role in predicting risk of amputation in a general diabetes population (Grade C).

Table 11 Studies reporting on ankle reflex assessment

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Abbott et al 2002) UK	II (prospective cohort) SIGN cohort Good quality	N = 9710 Patients from general practice setting in six health districts Characteristics: ≤2 pedal pulses (21.2%); Monofilament insensitive (20.9%); low socio economic class (86%)	Ankle reflex	In sitting position use of a reflex hammer on the Achilles tendon Score 0 if present, 1 if present with reinforcement or 2 if absent.	Foot ulceration (>14 days to heal)	RR reinforcement both sides	2.0 [95%CI 1.3, 3.1]
						RR absent one side/ reinforcement 1 side	2.3 [95%CI 1.2, 4.1]
						RR absent both sides	1.6 [95%CI 1.0, 2.4]
(Lehto et al 1996) Finland	II (prospective cohort) SIGN cohort: Good quality	N = 1059 Patients registered by Social Insurance Act for diabetic drug reimbursement Characteristics: IDDM (0%); absence peripheral pulses (80%)	Ankle reflex	In sitting position, use of a reflex hammer on the Achilles tendon. Abnormal is bilateral absence of reflex.	Lower extremity amputation	RR	4.3 [95%CI 2.5, 7.3]
(Ahroni 1997)) USA	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Good quality	N = 778, Patients from Seattle Diabetic Foot Study, patients at Internal Medicine Veterans Affairs Puget Sound Health Care Characteristics: IDDM (6%); NIDDM (92%); male (98%)	Ankle reflex	In sitting position use of a reflex hammer on the Achilles tendon. Abnormal is absence of reflex.	Full thickness cutaneous foot ulcer below the ankle with >14 days until healing	Sensitivity	35%
						Specificity	54%
						PPV	13%
						NPV	81%
						LR^+	0.77
						LR^-	1.2
					Lower extremity amputation	Sensitivity	40%
						Specificity	56%
						PPV	2.5%
						NPV	97%
						LR^+	0.91

						LR^-	1.1
(Boyko et al 1999) USA	II (prospective cohort) SIGN cohort: Good quality	N = 749 Seattle Diabetic Foot Study Characteristics; Male (98%); DM type II (94%)	Ankle reflex	Achilles tendon reflex tested in seated position	Foot ulceration >14 days until healing	RR	1.2 [95%CI 0.84, 1.6]

RR = Relative Risk, OR = Odds Ratio, PPV = Positive Predictive Value, NPV = Negative Predictive Value; ns = non significant; DM = Diabetes Mellitus; IDDM = Insulin dependent diabetes mellitus; NIDDM = Non insulin dependent diabetes mellitus; LR^+ = positive likelihood ratio; LR^- = negative likelihood ratio

Foot deformity assessment

Predictive value of foot deformity

Two good quality studies reported on the value of foot deformity as a predictor for the development of foot ulcer (Table 12).

Abbott et al (2002) assessed foot deformity with a six point scale which included; small muscle wasting, Charcot foot deformity, bony prominence, prominent metatarsal heads, hammer or claw toes and limited joint mobility. The authors dichotomised the scores based on the amount of deformity present: a low risk group with a score of 0-2 and a high risk group with a score of 3-6. The authors indicated that patients with three or more deformities had approximately one and a half times the risk of developing foot ulcer over a two year follow-up period compared to those with less than three deformities (RR=1.6 [95%CI 1.2, 2.0]). This result is reasonably precise, as demonstrated by the small confidence interval, although it should be noted that this estimate was controlled for absence of ankle reflex, insensitivity to Semmes Weinstein monofilament testing and poor peripheral arterial pulse (all risk factors for foot ulcer in their own right) and may therefore not accurately reflect the ability of foot deformity assessment alone to predict the development of foot ulcers.

Boyko et al (1999) investigated Charcot foot deformity as a predictor of subsequent foot ulcer. The results indicated that those patients with Charcot deformity were three and a half times more likely to develop foot ulcer than those without this particular deformity over a 3.7 year follow-up period (RR=3.5 [95%CI 1.2, 9.9]). This result was controlled for increased ankle blood pressure, high ankle arm index, high transcutaneous oxygen tension, the absence of Achilles reflex, absence of vibration perception and ankle joint immobility. In a similar model which also included decrease in orthostatic blood pressure, Charcot deformity was not found to predict foot ulcer (RR=2.7 [95%CI 0.77, 9.8]), although in this case the wide confidence interval suggests a lack of statistical power. Both results were also adjusted for sensory neuropathy and history of foot ulcer or amputation. Furthermore, the results only accurately reflect foot deformity assessment, as a predictor when other variables stay the same.

These results suggest that the presence of foot deformities is a reasonable predictor for foot ulcer in a diabetes population. Box 20 summarises the body of evidence according to the NHMRC grading criteria.

Box 20 Evidence statement matrix for the predictive value of foot deformity

Component	Rating	Description
Evidence base	A	Two level II studies with low risk of bias
Consistency	B	Both studies found significant results for foot deformity with increased odds of developing foot ulcer of between 1.5 and 3.5.
Clinical impact	C	The result indicate moderate to substantial clinical impact (odds ratios between 1.5 and 3.5 for the development of foot ulcer in those with foot deformities, though the results were very dependent on the included variables in the univariate and multivariate analysis,
Generalisability	B	Boyko et al predominately studied males, which makes it difficult to generalise to females. Abbott et al included a sample with a large group of patients of lower socioeconomic status.
Applicability	B	One study came from the USA and one from the UK, both having a similar approach to treating diabetes patients as in the Australian context.

Evidence statement

The evidence indicates that the presence of foot deformity is a moderate predictor of foot ulcer in the general diabetes population (Grade B).

Table 12 Studies included foot deformity assessment

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Abbott et al 2002) UK	II (prospective cohort) SIGN cohort: Good quality	N = 9710 Patients from general practice setting in six health districts Characteristics: ≤2 pedal pulses (21%); Monofilament insensitivity (20.9%); low socio economic class (86%)	Foot deformity score	Six Point foot deformity score including; small muscle wasting, Charcot foot deformity, bony prominence, prominent metatarsal heads, hammer or claw toes, limited joint mobility. Normal defined as 0-2 and abnormal 3-6 deformities.	Foot ulceration (>14 days to heal)	RR	1.6 [95%CI 1.2, 2.0]
(Boyko et al 1999) USA	II (prospective cohort) SIGN cohort: Good quality	N = 749, Seattle Diabetic Foot Study Characteristics; Male (98%); DM type II (94%)	Charcot deformity		Foot ulceration (>14 days to heal)	RR	2.7 [95%CI 0.77, 9.8]
						RR*	3.5 [95%CI 1.2, 9.9]

*multivariate analysis with decreased orthostatic blood pressure; RR= Relative Risk; DM= Diabetes Mellitus

Gait assessment

Diagnostic accuracy of gait assessment

The average quality study by Ahroni et al (1997) was the only study which assessed gait to diagnose foot ulcer risk (Table 13). Patient's gait was observed over 50 feet of ambulation, with particular focus on the presence of genu varum (knock-kneed), genu vagus (pigeon-toed), visible limp and extensive heel pronation (turned down and out) or supination (turned up and in). The presence of one or more of the above conditions was defined as abnormal gait. For the outcome of foot ulcer, gait assessment yielded a sensitivity of 17% and specificity of 74%, indicating that there was a high proportion of high risk patients who remained undetected, but a large proportion of patients who did not develop foot ulcer who were correctly identified as low risk. The test had reasonable specificity and thus could have potential as a screening testing, as there is a low false positive rate. However, the very poor sensitivity would mean that the yield from doing gait assessment would probably not warrant the resources put in to doing the testing.

For the outcome of amputation, the author reported an even lower sensitivity although similar specificity (75%). Gait assessment had a 97% NPV, indicating that the test performs well in ruling out risk of amputation presumably because amputation risk is a rare outcome.

From these results it appears that gait assessment does not perform well as a screening test in diabetes patients to diagnose risk of foot ulcer and amputation. Box 21 summarises the body of evidence according to the NHMRC grading criteria.

Box 21 Evidence statement matrix for the diagnostic accuracy of gait assessment

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study provided evidence.
Clinical impact	D	The sensitivity of the test is extremely poor (17%), meaning that an unacceptable proportion of 'at risk' patients would be missed. In contrast the specificity and NPV was moderate to high, indicating that the assessment is better at detecting those not at high risk.
Generalisability	C	The study sample included mainly male subjects therefore there may be some limitations in generalising to the female or general diabetes population
Applicability	B	The study came from the USA, which has a similar health care system for diabetes care as the Australian system.

Evidence statement

Based on a single study, the assessment of gait in the general diabetes population is a poor screening technique for identifying those patients at high risk of foot ulcer and amputation (Grade D).

Table 13 Study reported on gait assessment

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Ahroni 1997) USA	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Good quality	N = 778, Patients from Seattle Diabetic Foot Study, patients at Internal Medicine Veterans Affairs Puget Sound Health Care Characteristics: IDDM (6%); NIDDM (92%); male (98%)	Gait	Observation of gait over 50 feet. Absence or presence of genu varum (knock-kneed), genu vagus (pigeon-toed), visible limp and extensive heel pronation (turned down and out) or supination (turned up and in) Abnormal gait was defined by having one or more of the above conditions.	Full thickness cutaneous foot ulcer below the ankle and >14 days to heal	Sensitivity Specificity PPV NPV LR^+ LR^-	17.0% 74.2% 11.2% 82.3% 0.66 1.12
					Lower extremity amputation	Sensitivity Specificity PPV NPV LR^+ LR^-	9.5% 75.2% 1.1% 96.6% 0.38 1.20

IDDM= Insulin dependent diabetes mellitus; NIDDM= non insulin dependent diabetes mellitus; PPV= positive predictive value; NPV= negative predictive value; LR^+= positive likelihood ratio; LR^-= negative likelihood ratio

Peripheral arterial pulse assessment

Diagnostic accuracy of peripheral arterial pulse assessment

One study by Adler et al (1999) assessed peripheral arterial pulses by palpating the dorsal pedis artery and posterior tibialis artery (Table 14)

The assessment was considered negative if either pulse was normal or one pulse was absent or diminished in both limbs. A positive result was defined by the absence of both pulses or diminished pulses in one or both legs. The assessment yielded a sensitivity of 48%, indicating that more than half of the patients at high risk of amputation were not identified by arterial pulse assessment [95% CI 30, 67%]. Of the patients that were at low risk of amputation, the assessment was able to identify 77% (specificity = 77% [95% CI 73, 80%]). The NPV showed that a negative result can rule out the risk of amputation (NPV = 97% [95% CI 95, 98%]). The PPV was reasonable as the prevalence of lower extremity was 3.8%, indicating that the majority of those identified as high risk would not require amputation (PPV = 8.4% [95% CI 4.8, 14%]) (Adler et al 1999). It should be noted that a number of patients in this study were known to have peripheral sensory neuropathy, which is another risk factor for amputation. Furthermore, the patients were predominantly male, who generally have a higher incidence and prevalence of vascular disease than females.

The evidence provided by Adler et al (1999) suggests that peripheral arterial pulse assessment is of limited value for the identification of those at high risk of amputation in the general diabetes population. However, it appears to perform well at identifying those who are at low risk of amputation. Box 22 summarises the body of evidence according to the NHMRC grading criteria.

Box 22 Evidence statement matrix for the diagnostic accuracy of peripheral arterial pulse assessment

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study provided evidence.
Clinical impact	D	This study provides evidence that peripheral arterial pulse assessment is useful in ruling out risk of amputation as indicated by the low level of false negatives. However, this is primarily because the risk of amputation is uncommon. Test sensitivity was low to moderate.
Generalisability	C	The study sample included predominantly male subjects. Therefore it may be hard to generalise to females or the general diabetes population
Applicability	B	The study came from the USA, which has a similar health system for diabetes care as the Australian system.

Evidence statement

Evidence suggests that peripheral arterial pulse assessment alone is a poor screening technique to identify those patients in the general diabetes population at high risk of amputation (Grade C).

Table 14 Studies reported on peripheral arterial pulse assessment

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Abbott et al 2002) UK	II (prospective cohort) SIGN cohort: Good quality	N = 9710 Patients from general practice setting in six health districts Characteristics: ≤2 pedal pulses (21%); Monofilament insensitivity (20.9%); Low socio economic class (86%)	Peripheral arterial pulse	Palpation of the dorsal pedis artery and posterior tibialis artery on both feet. Absence defined as only having 0 or 2 pulses present. Normal when more than 2 pulses are present.	Foot ulceration (>14 days to heal)	RR	1.8 [95%CI 1.4, 2.3]
(Lehto et al 1996) Finland	II (prospective cohort) SIGN cohort: Good quality	N = 1059 Patients registered by Social Insurance Act for diabetic drug reimbursement Characteristics: IDDM (0%); absence of vibration perception (24%); absence of Achilles reflex (29%)	Peripheral arterial pulse	Palpation of the dorsal pedis artery and posterior tibialis artery on both feet. Negative result if both pulses were normal or one pulse absent or diminished in both limbs. A positive result defined as if both pulses absent or diminished in one or both legs	Lower extremity amputation due to arteriosclerotic vascular disease	RR	3.9 [95%CI 2.3, 6.8]
(Adler et al 1999) USA	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Average quality	N = 776 Seattle Diabetic Foot Study Patients at Internal Medicine clinic of Veteran Affairs Puget Sound Health Care Characteristics: Type II DM 93%, male 98%, history of ulcer 24%, ≤2 pedal pulses absent 32%	Peripheral arterial pulse	Palpation of the dorsal pedis artery and posterior tibialis artery on both feet. Negative result if both pulses were normal or one pulse absent or diminished in both limbs. A positive result was if both pulses were absent or diminished in one or both legs	First lower extremity amputation	Sensitivity Specificity PPV NPV	48% [95%CI 30, 67%] 77% [95%CI 73, 80%] 8.4% [95%CI 4.8, 14%] 97% [95%CI 95, 98%]

IDDM = Insulin dependent diabetes mellitus; NIDDM = non insulin dependent diabetes mellitus; PPV = positive predictive value; NPV = negative predictive value; RR = Relative risk

Predictive value of peripheral arterial pulse

Two good quality cohort studies investigated the value of peripheral arterial pulse as a predictor of foot ulcers in the general diabetes population (Table 14).

Abbott et al (2002) examined the peripheral arterial pulse by palpation of the dorsal pedis and posterior tibialis on both feet. For those patients with absence of peripheral arterial pulses, the results indicated a 1.8 times higher risk for the development of foot ulcer over a 2 year follow up, compared to those with more than three palpable pulses (RR=1.8, [95% CI 1.4, 2.3]). The analysis controlled for a history of foot ulcer, a high neuropathy disability score, previous podiatric treatment, SWF insensitivity, foot deformity and absence of ankle reflex, therefore the result might not accurately reflect the ability of peripheral arterial pulse assessment alone to predict the development of foot ulcer. Given that the additional predictive effect of peripheral arterial pulse is most likely of relevance in clinical practice, the uncertainty regarding its singular effect is not of great consequence.

Lehto et al (1996) found that those patients with absence of two or more peripheral arterial pulses had almost 4 times the risk of amputation over a 7 year follow up period than those with 'normal' pulses (RR=3.9 [95%CI 2.3, 6.8]). It has to be noted that the authors included patients with peripheral sensory neuropathy, for which the result was not adjusted. Therefore these results are indicative of peripheral arterial pulse assessment as a predictor of amputation in the presence of other potential confounders. This may, therefore explain the higher risk estimate in Lehto et al compared to Abbott et al.

From the evidence identified, it appears that the assessment of peripheral arterial pulses may be useful in predicting the occurrence of amputation and development of foot ulcer. Box 23 summarizes the body of evidence according to the NHMRC grading criteria.

Box 23 Evidence statement matrix for the predictive value of peripheral arterial pulse

Component	Rating	Description
Evidence base	A	Two level II studies with low risk of bias
Consistency	B	Both studies found significant results for peripheral arterial pulse as a predictor of foot ulcer and amputation.
Clinical impact	C	The significant result for ulceration indicates a moderate clinical impact with an odds ratio of 1.80. For amputation as an outcome, the result indicated a substantial clinical impact, although this result was likely confounded.
Generalisability	B	Abbott et al included a sample with a large group of patients of low socioeconomic status, while Lehto et al had a population that was generalisable to the target population.
Applicability	B	One study came from the USA and one from the Finland and both have similar health care for diabetes patients as in Australian.

Evidence statement

Peripheral arterial pulse is a moderate predictor of subsequent foot ulcer or amputation in the general diabetes population (Grade B).

Ankle arm index assessment

Diagnostic accuracy of ankle arm index assessment

The average quality study by Adler et al (1999) examined the diagnostic accuracy of the ankle arm index (AAI or also called Ankle Brachial Index) in identifying the risk of lower extremity amputation (Table 15).

The AAI was calculated as the ratio of the ankle systolic pressure (defined as the higher of the posterior tibialis or the dorsalis pedis measurement divided by the higher brachial systolic pressure. Abnormal AAI was defined as a having an index score below 0.8. At this cut off point, Adler et al found that the test yielded a sensitivity and specificity of 52% and 74% respectively, indicating a high false negative and moderate false positive rate (sensitivity= 52% [95%CI 33, 70%], specificity= 74% [95%CI 70, 77%], respectively). Given the low sensitivity, this test is unable to adequately identify those who will subsequently require amputation. The NPV (97% [95%CI 95, 98]), indicated that negative test result could accurately rule out risk of amputation, presumably because the risk of amputation was only 3.8% in the study sample. This study included a large proportion of patients with sensory neuropathy (53%) and a history of ulcer and thus not reflects test performance in a general diabetes population, where in fact it may be poorer.

The evidence it suggests that AAI assessment is not very accurate at diagnosing risk of lower extremity amputation in the general diabetes population. Box 24 summarises the body of evidence according to the NHMRC grading criteria.

Box 24 Evidence statement matrix for the diagnostic accuracy of ankle arm index assessment

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study provided evidence.
Clinical impact	D	This study shows that AAI has low sensitivity and moderate specificity at identifying those patients at high risk.
Generalisability	C	The study sample included mainly male subjects.Therefore there may be limited generalisability to females with diabetes .
Applicability	C	The study was conducted in the USA, which has similar health care for diabetes patients as in Australian.

Evidence statement

On the bases of limited evidence, Ankle Arm Index assessment would appear to be a poor screening technique to predict lower extremity amputation in the general diabetes population (Grade C).

Table 15 Studies reported on ankle arm index

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Adler et al 1999) USA	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Average quality	N = 776 Seattle Diabetic Foot Study Patients at Internal Medicine clinic of Veteran Affairs Puget Sound Health Care Characteristics: Type II DM (93%); male (98%); history of ulcer (24%); ≤2 pedal pulses absent (32%); neuropathy (53%)	Ankle Arm Index	AAI was calculated as the ratio of the ankle systolic pressure (defined as the higher of the posterior tibialis or the dorsalis pedis measurement) divided by the higher brachial systolic pressure. The arm ankle index was defined as abnormal when the index was below 0.8.	First lower extremity amputation	Sensitivity Specificity PPV NPV	52% [95%CI 33, 70%] 74% [95%CI 70, 77%] 8% [95%CI 4.6, 13%] 97% [95%CI 95, 98%]
					Minor amputation	RR	2.6 [95%CI 0.7, 9.3]
					Major amputation	RR	5.8 [95%CI 1.6, 20.]
(Boyko et al 1999) USA	II (prospective cohort) SIGN cohort: Good quality	N =749 Seattle Diabetic Foot Study Characteristics; Male (98%), DM type II (93.6%)	Ankle Arm Index	AAI was calculated as the ratio of the ankle systolic pressure (defined as the higher of the posterior tibialis or the dorsalis pedis measurement) divided by the higher brachial systolic pressure. AAI >0.8 is the reference group, other categories were ≤0.5 and > 0.5 – ≤0.8.	Foot ulceration (>14 days to heal)	RR ≤0.5	1.9 [95%CI 1.0, 3.5]
						RR >0.5 to ≤0.8	1.7 [95%CI 1.1, 2.5]

AAI = ankle arm index; PPV = positive predictive value; NPV = negative predictive value; RR = relative risk; DM = diabetes mellitus.

Predictive value of ankle arm index

One average and one good quality cohort study investigated the value of AAI at predicting foot ulcer and major or minor amputation (Table 15). Both studies used data from the Seattle Diabetic Foot study, indicating that the study population, measurements and management are similar for both. Therefore, these studies will be graded as one study.

The good quality study by Boyko et al (1999) categorised patients, based on their AAI measurement into three groups; AAI ≤0.5, >0.5 to ≤0.8 and using the >0.8 group as the reference. Multivariate analysis, which adjusted for history of foot ulcer and sensory neuropathy, indicated that patients with an AAI ≤0.5 had almost twice the risk of developing foot ulcer over a 3.7 year follow-up, than those with AAI >0.8 (RR = 1.94 [95%CI 1.07, 3.52]). The category >0.5 – 0.8 had 1.7 times the risk of developing foot ulcer over the same period (RR = 1.7 [95%CI 1.1, 2.5]) controlled for confounders including sensory neuropathy, history of foot ulcer/amputation, insulin use, high transcutaneous oxygen tension, weight, Charcot deformity and decreased vision. Some caution is advised when interpreting these results as the study sample had 23% attrition in a sample size of 749 veterans.

Adler et al (1999) reported that over a mean 3.3 year follow-up, patients with an AAI of 0.8 or lower had an almost 6 times the risk of major amputation compared to those with AAI above 0.8 (RR = 5.8 [95%CI 1.6, 20.4]). The confidence interval is rather large, indicating some uncertainty around the estimate. Conversely, the authors did not find a significant relative risk of minor amputation in patients with an AAI of 0.8 or lower (RR = 2.5 [95%CI 0.7, 9.3]).

The results seem to suggest that the AAI assessment is a moderate predictor of foot ulcer and major amputation in male diabetic patients, although again the confidence interval was wide so it is possible that the analysis lacked power for this particular outcome. Box 25 provides an overview of the body of evidence for the ankle arm index according to the NHMRC criteria.

Box 25 Evidence statement matrix for the predictive value of ankle arm index

Component	Rating	Description
Evidence base	B	One level II study with low risk of bias
Consistency	N/A	Only one study.
Clinical impact	B	The results presented by Boyko et al indicate that the ankle arm index may have a moderate clinical impact as the adjusted odds ratios were between 1.4 and 1.9. Adler et al presented a rather large relative risk, which had a wide confidence interval for major amputation. Both studies used data from the Seattle Diabetes Foot study.
Generalisability	C	Both studies used data from the same sample that included mainly male. Therefore it will be hard to generalise to females or the general diabetes population.
Applicability	C	The study came from the USA, which has similar health care for diabetes patients as in Australian.

Evidence statement

The Ankle Arm Index may be a moderate predictor of foot ulceration and substantial predictor of major amputation in the male diabetes population (Grade C).

Ankle blood pressure assessment

Predictive value of ankle blood pressure assessment

Boyko et al (1999) measured ankle blood pressure in male diabetic patients to determine its value as a predictor of foot ulceration (Table 16).

In the first multivariate model, uncontrolled for decrease in orthostatic blood pressure, the authors reported an increased risk of foot ulcer in patients with an ankle blood pressure above 200mmHg compared to those with a normal ankle blood pressure (RR=2.2 [95%CI 1.5, 23]). Given the wide confidence interval there is uncertainty regarding this estimate. In the second multivariate model, ankle blood pressure was controlled for orthostatic blood pressure, resulting in a slightly lower relative risk of 2.0 [95%CI 1.4, 2.8]. Both risk estimates also controlled for assessment of sensory neuropathy, history of foot ulcer/amputation, insulin use, high transcutaneous oxygen tension, weight, Charcot deformity and decreased vision. Once again, there are potentially some limitations as to the generalisability of this study as it suffered attrition of 23% and consisted of a mainly male population.

The evidence provided suggests that ankle blood pressure assessment is a moderate predictor for the development of foot ulcer in a male diabetic population. Box 26 summarises the body of evidence according to the NHMRC grading criteria.

Box 26 Evidence statement matrix for the predictive value of ankle blood pressure

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study provided evidence.
Clinical impact	C	The results presented by Boyko et al indicate that ankle blood pressure assessment may have a moderate clinical impact with a relative risk of 2.0
Generalisability	C	The study sample included mainly male subjects. Therefore it may be difficult to generalise to females or the general diabetes population
Applicability	C	The study came from the USA, which has similar health care for diabetes patients as in Australian.

Evidence statement

Ankle blood pressure may be a moderate predictor of foot ulceration in male diabetes patients. However, further research is required to confirm this association (Grade C).

Orthostatic blood pressure drop assessment

Predictive value of orthostatic blood pressure drop assessment

Boyko et al (1999) also included orthostatic blood pressure in their multivariate analysis to determine its predictive value for foot ulcer in the male diabetic population (Table 16). Systolic blood pressure was measured immediately after the patient stood up from a supine position. The authors reported a slight increase in risk of foot ulcer for those patients with a blood pressure drop (RR = 1.23 [95%CI 1.05, 1.45]). In considering these results it is important to note it was not clear as to what was considered as a blood pressure drop i.e. 1 mmHg or 10mmHg. Hence, this evidence would be difficult to translate into clinical practice. Again, previously stated concerns regarding attrition in this study may limit its interpretability.

The evidence provided seems to indicate that orthostatic blood pressure drop is not a strong predictor of foot ulcer in the male diabetic population. Box 27 provides an overview of the body of evidence for orthostatic blood pressure according to NHMRC criteria.

Box 27 Evidence statement matrix for the predictive value of orthostatic blood pressure drop assessment

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study provided evidence.
Clinical impact	D	The results indicate that orthostatic blood pressure has a likely slight to restricted clinical impact with a relative risk of 1.23. More importantly, the study did not describe the level of orthostatic blood pressure which would indicate a high risk of foot ulcer.
Generalisability	C	The study sample included mainly male subjects.Therefore it could be difficult to generalise to females or the general diabetes population
Applicability	C	The study came from the USA, which has similar health for diabetes patients as in Australian.

Evidence statement

There is limited evidence suggesting that orthostatic blood pressure is a poor predictor for the development of subsequent foot ulcer in male diabetes patients (Grade D).

Table 16 Studies reported on the assessment of Ankle blood pressure

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Boyko et al 1999) USA	II (prospective cohort) SIGN cohort: Good quality	N = 749 Seattle Diabetic Foot Study Characteristics: Male (98%); DM type II (93.6%)	Ankle blood pressure	Measured with Doppler blood pressure. Cut off point at 200mmHg	Foot ulceration (>14 days to heal)	RR	2.17 [95%CI1.52, 23.08]
						RR*	1.96 [95%CI 1.36, 2.83]

*= controlled for orthostatic blood pressure drop; DM= diabetes mellitus; RR= relative risk

Transcutaneous oxygen tension assessment

Diagnostic accuracy for transcutaneous oxygen tension assessment

The average quality study by Adler et al (1999) examined the accuracy of the transcutaneous oxygen tension ($TcPO_2$) assessment to identify patients at high risk of lower extremity amputation in a general diabetes population (Table 17).

The authors used 50mmHg as a cut-off point. A positive test result was defined by a $TcPO_2$ of 50mmHg or lower, while a negative test result was defined as higher than 50mmHg. The authors reported test sensitivity of 76% [95% CI 56, 89%] and specificity of 52% [95% CI 48, 56%] at this threshold. Thus, the test identified a reasonable proportion of people who require a lower extremity amputation on the bases of abnormal $TcPO_2$ levels. The results indicate that the $TcPO_2$ assessment has a moderate value as a tool to determine which diabetic patients are at high risk of amputation. However, to be of use in a general diabetes population, higher test specificity is warranted. A false positive rate of 48% would result in a considerable amount of unnecessary treatment. As $TcPO_2$ is a measure of peripheral vascular disease its use is unlikely to identify those with neuropathy who are also at high risk of amputation, which might explain its moderate test accuracy.

The evidence provided by Adler et al (1999) suggests that $TcPO_2$ assessment may have a place as a diagnostic tool in symptomatic patients, but would be of limited value as a predictor of amputation in a general diabetes population. Box 28 summarises the body of evidence according to the NHMRC grading criteria.

Box 28 Evidence statement matrix for the diagnostic accuracy of transcutaneous oxygen tension assessment

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study provided evidence.
Clinical impact	C	The results presented by Adler et al indicate that $TcPO_2$ assessment had low specificity and therefore had a high proportion of false positives receiving unnecessary treatment. The sensitivity was reasonable at identifying true positives, but had a rather wide confidence interval. Overall this results in a poor screening tool of a moderate clinical impact.
Generalisability	C	The study sample included mainly male subjects. Therefore it may be difficult to generalise the results to females or the general diabetes population
Applicability	C	The study was conducted in the USA, which has a similar health care for diabetes patients as in Australian.

Evidence statement

Transcutaneous oxygen tension assessment is of limited value as a screening tool for identifying those at high risk of lower extremity amputation in a general diabetic population. However, it has moderate value as a diagnostic tool. Further research is required to confirm this association (Grade C).

Predictive value of transcutaneous oxygen tension

One average and one good quality study evaluated $TcPO_2$ as a predictor for the occurrence of foot ulcer and lower extremity amputation (Table 17). As both studies used data from the Seattle Diabetic Foot study, and study population, measurements and management were similar for both. They will be considered as one study. After measuring the $TcPO_2$ of both legs at 44 degrees at the dorsum of the foot, patients were then followed for a mean of 3.3 years (range 0–5.8 years) (Adler et al 1999). The authors reported that patients with a $TcPO_2$ of less

than 50mmHg had three times the risk of amputation than those with higher $TcPO_2$ (RR=3.0 [95%CI 1.3, 7.1]). Boyko et al (1999) confirmed this with a follow-up over a mean of 3.7 years observing the development of foot ulcer in the same male population. The authors found that patients with an increased $TcPO_2$ of more than 15mmHG were less likely to develop foot ulcer (RR=0.77 [95%CI 0.73, 0.97]). There was no reference standard provided by the authors.

The results suggest that $TcPO_2$ is a moderate predictor for the development of foot ulcer and the occurrence of lower extremity amputation. Box 29 summarises the body of evidence according to the NHMRC grading criteria.

Box 29 Evidence statement matrix for the predictive value of transcutaneous oxygen tension

Component	Rating	Description
Evidence base	B	One level II sub-study with low risk of bias and one level II sub- study with moderate risk of bias
Consistency	N/A	Only one study.
Clinical impact	C	Adler et al's reported relative risk of 3 with a confidence interval that generally included clinically important effects. The results presented by Boyko et al suggested that those with an increased $TcPO_2$ of 15 mmHg did not develop foot ulcer.
Generalisability	C	The study sample included mainly male subjects and thus it is difficult to females or the general diabetes population
Applicability	C	The study was conducted in the USA, which has similar health care for diabetic patients as in Australian.

Evidence statement

Transcutaneous oxygen tension may be a moderate predictor for the development of foot ulcer and the occurrence of amputation in male diabetic patients (Grade C)

Table 17 Studies included transcutaneous oxygen tension assessment

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Adler et al 1999) USA	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Average quality	N = 776 Seattle Diabetic Foot Study Patients at Internal Medicine clinic of Veteran Affairs Puget Sound Health Care Characteristics: Type II DM (93%); male (98%); history of ulcer (24%); ≤2 pedal pulses absent (32%)	Transcutaneous oxygen tension	TCPO2 measured in either foot at 44º on the dorsum of the foot. Cut off point is 50mmHg	First lower extremity amputation	Sensitivity Specificity PPV NPV RR	76% [95%CI 56, 89%] 52% [95%CI 48, 56%] 6.4% [95%CI 4.8, 9.6%] 98% [95%CI 96, 99] 3.0 [95%CI 1.3, 7.1]
(Boyko et al 1999) USA	II (prospective cohort) SIGN cohort: Good quality	N = 749 Seattle Diabetic Foot Study Characteristics: Male (98%); DM type II (94%)	Transcutaneous oxygen tension	An increase of >15mmHg TcPO2 at the dorsal foot. No cut off point mentioned.	Foot ulceration (>14 days to heal)	RR RR*	0.80 [95%CI 0.69, 0.93] 0.77 [95%CI 0.66, 0.90]

*= controlled for orthostatic blood pressure drop; RR= Relative Risk; DM= Diabetes Mellitus; AAI= ankle arm index; PPV= positive predictive value; NPV= negative predictive value

Glycaemic control assessment

Diagnostic accuracy of glycaemic control assessment

Two average quality studies investigated the predictive accuracy of glycosylated haemoglobin (HbA1c) for foot ulcer and lower extremity amputation (Table 18). As both studies used the same population data available from the Seattle Diabetic Foot study, the studies will be graded as one study according to the NHMRC grading criteria.

Ahroni et al (1997) used an HbA1c level of 10% or more as the cut off point to identify high risk of foot ulcer and amputation. This yielded a sensitivity and specificity of 31% and 57%, while the PPV and NPV were 12% and 81% respectively. This suggests that HbA1c assessment is a poor test for predicting foot ulcer in the general diabetes population.

Ahroni et al (1997) found similar results for determining the likelihood of amputation. HbA1c assessment was found to have sensitivity, specificity, PPV and NPV of 43%, 59%, 3% and 97% respectively for detecting risk of amputation. It should be noted that the sample included patients with other risk factors for foot ulcer and amputation, like sensory neuropathy, which may explain the poor diagnostic performance of HbA1c. Furthermore, the results are only generalisable to the male diabetic population, as the study sample did not include female subjects and gender may be an effect modifier.

The average quality study by Adler et al (1999) were considered with the results of the above study, indicating that HbA1c assessment, even with a higher cut off point of 12.6%, yielded a sensitivity and specificity of 56% [95%CI 31, 79%] and 53% [95%CI 48, 57%] respectively.

The results suggest that the assessment of blood sugar level (HbA1c) performance poorly at accurately identifying those at risk of foot ulcer and lower extremity amputation. Box 30 summarises the body of evidence according to the NHMRC grading criteria.

Box 30 Evidence statement matrix for the diagnostic accuracy of glycaemic control assessment

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study.
Clinical impact	D	The results suggest that the assessment of HbA1c has little clinical use in predicting either foot ulcer or amputation. Therefore, the overall clinical impact of the assessment can be stated as slight to restricted.
Generalisability	C	The study samples included mainly male subjects , thus making it difficult to generalise to females or the general diabetes population.
Applicability	C	The study came from the USA, which has a similar health care system for diabetes patients to the Australian context and is therefore applicable with few caveats.

Evidence statement

Limited evidence suggests that the assessment of glycaemic control has poor accuracy at identifying those at risk of foot ulcer or lower extremity amputation (Grade C).

Predictive value of glycaemic control

The good quality study by Lehto et al (1996) examined glycaemic control as a predictor for the occurrence of lower extremity amputation due to arteriosclerotic vascular disease (Table 18). After measuring the HbA1c level, the authors divided the groups into high and low risk groups based on a cut-off point of 10.7%. Those patients with a 10.7% HbA1c level or above, were found to have almost 2.5 times the risk of amputation than those with a normal HbA1c level over a 7 year follow up (RR=2.4 [95%CI 1.4, 4.0]). Furthermore, the authors measured fasting

plasma glucose and reported that patients with a level above 13.4 mmol/l were 2.2 times more likely to be amputated than those with levels below (RR=2.2 [95%CI 1.2, 3.9]). Both results were adjusted for age and gender.

This result suggests that glycaemic control is a moderate predictor of lower extremity amputation resulting from arteriosclerotic vascular disease. Patients with sensory neuropathy were included in the study and the effect of this confounder on the relative risk was not controlled for, so the estimate should be interpreted with some caution as it might be an overestimation. Box 31 summarises the body of evidence according to the NHMRC grading criteria.

Box 31 Evidence statement matrix for the predictive value of glycaemic control assessment

Component	Rating	Description
Evidence base	B	One level II study with low risk of bias
Consistency	N/A	Only one study provided evidence.
Clinical impact	C	Lehto et al reported a 2.4 RR for the assessment of HbA1 and 2.2 for fasting plasma glucose, which can be seen as potentially having substantial impact. However, the study did include patients with other risk factors for lower extremity amputation, which were not controlled for.. Therefore, the clinical impact is stated as moderate.
Generalisability	B	The study sample was a good representation of the target population.
Applicability	B	The study came from Finland, which has a similar health care system for diabetes patients to the Australian context and is therefore applicable with some caveats.

Evidence statement

Limited evidence suggests that glycaemic control may be a moderate predictor of lower extremity amputation as a consequence of arteriosclerotic vascular disease in a general diabetes population (Grade C)

Table 18 Studies included glycaemic control assessment

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Lehto et al 1996) Finland	II (prospective cohort) SIGN cohort: Good quality	N = 1059 Patients registered by Social Insurance Act for diabetic drug reimbursement Characteristics: IDDM (0%); absence of vibration perception (24%); absence of Achilles reflex (29%)	HbA1c	High HbA1c defined as ≥10.7%	Lower extremity amputation due to arteriosclerotic vascular disease	RR	2.4 [95%CI 1.4, 4.0]
			Fasting plasma glucose	>13.4 mmol/l		RR	2.2 [95%CI 1.2, 3.9]
(Ahroni 1997) USA	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Good quality	N = 778 Patients from the Seattle Diabetic Foot Study, patients were attending internal medicine clinic at the Veterans Affairs Puget Health Care Characteristics: IDDM (6%); NIDDM (92%); male (98%)	HbA1c	High HbA1c defined as ≥10%	Full thickness cutaneous foot ulcer below the ankle and >14 days to heal.	Sensitivity Specificity PPV NPV LR^+ LR^-	31.4% 57.1% 12.4% 81.1% 0.73 1.20
					Lower extremity amputation	Sensitivity Specificity PPV NPV LR^+ LR^-	42.9% 59.0% 3.0% 97.2% 1.05 0.97
(Adler et al 1999) USA	II (prospective cohort) Quadas:	N = 776 Seattle Diabetic Foot Study Patients at Internal Medicine clinic of Veteran Affairs Puget Sound	HbA1c	High HbA1c defined as 9.4–12.6%	First lower extremity amputation	Sensitivity Specificity PPV NPV	67% [95%CI 43, 85%] 51% [95%CI 46, 55%] 5.3% [95%CI 3.0, 8.9%] 97% [95%CI 94, 99%]

	Moderate quality SIGN cohort: Average quality	Health Care Characteristics: Type II DM (93%); male (98%); history of ulcer (24%); ≤2 pedal pulses absent 3(2%)		High HbA1c is defined as ≥12.6%		Sensitivity Specificity PPV NPV	56% [95%CI 31. 79%] 53% [95%CI 48, 57%] 3.8% [95%CI 1.8, 7.2%] 97% [95%CI 94, 99%]

PPV = Positive Predictive Value, NPV = Negative Predictive Value; DM = Diabetes Mellitus; IDDM = Insulin dependent diabetes mellitus; NIDDM = Non insulin dependent diabetes; LR^+= positive likelihood ratio; LR^-= negative likelihood ratio

Laboratory assessments

Diagnostic accuracy of laboratory creatinine assessment

The average quality study by Adler et al (1999) measured the level of creatinine and its accuracy at correctly identifying foot ulcer risk over a mean of 3.3 years (Table 19).

The authors used a cut off point of 1.3 mmol/l which yielded 50% sensitivity and 62% specificity. Thus a creatinine level above 1.3 mmol/l correctly identified half of the patients who later went on to develop foot ulcer, while 62% of the patients who did not receive amputation were classified as having a normal creatinine level (sensitivity= 50% [95%CI 32, 68%; specificity= 62% [95%CI 59, 66%], respectively). This indicates that the test is poorer at detecting risk of amputation, than at identifying true negatives. The likely consequence of this is that patients who are at risk would be missed.

Creatinine testing appears to have limited accuracy at diagnosing risk of amputation in the general diabetes population. Box 32 summarises the body of evidence according to the NHMRC grading criteria.

Box 32 Evidence statement matrix for the diagnostic accuracy of creatinine testing

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study provided evidence.
Clinical impact	D	This study shows that the creatinine test has low sensitivity and moderate specificity at identifying those patients at high risk of amputation.
Generalisability	C	The study sample included mainly male subjects.Therefore there may be limited generalisability to females with diabetes .
Applicability	C	The study was conducted in the USA, which has similar health care for diabetes patients as in Australia.

Evidence statement

On the basis of limited evidence, creatinine testing would appear to be a poor test for predicting amputation in a general diabetes population (Grade C).

Predictive value of laboratory HDL cholesterol assessment

Two good quality studies investigated the value of HDL cholesterol as a predictor for lower extremity amputation and foot injury (Table 19).

Lehto et al (1996) found for those patients with HDL cholesterol above 0.9 mmol/l had 1.3 times the risk for lower extremity amputation than those patients with normal HDL cholesterol (RR=1.3 [95%CI 0.7, 2.5]). The authors also found a moderate increase in risk for patients with total cholesterol above 6.2 mmol/l (RR=1.8 [95%CI 1.1, 3.2]).

Litzelman et al (1997) reported that patients with a decreasing change in HDL cholesterol of 386.9 mmol/l were 1.6 times more likely to develop a major foot injury as defined by the Seattle Wound Classification system (OR=1.6 [95%CI 1.1, 2.4]). The cut offs different considerable which could not be explained due to insufficient information given by the study of Litzelman et al.

The results suggest that there is contradictory evidence that HDL cholesterol might be predictor for lower extremity amputation and major foot injury. Box 33 summarises the body of evidence according to the NHMRC grading criteria.

Box 33 Evidence statement matrix for the predictive value of HDL cholesterol

Component	Rating	Description
Evidence base	B	Two level II studies with low risk of bias
Consistency	C	The evidence provided by both studies was contradictory.
Clinical impact	D	Both results presented, suggest a slight to moderate clinical impact.
Generalisability	B	Litzelman et al's study samples included a large proportion of females and patients with a low socio economic status. Therefore it may be hard to generalise to males or the general diabetes population. Lehto et al had a population that was generalisable to the target population.
Applicability	B	One study came from the USA and one from Finland, which have similar health care diabetes patients as to Australian.

Evidence statement

There is insufficient evidence regarding HDL cholesterol as a predictor of lower extremity amputation and major foot injury (Grade C).

Table 19 Studies included laboratory assessment

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Lehto et al 1996) Finland	II (prospective cohort) SIGN cohort: Good quality	N=1059 Patients registered in Social Insurance Act for diabetic drug reimbursement Characteristics; IDDM 0%, absence vibration perception 24%, absence Achilles reflex 29%	Total cholesterol	>6.2 mmol/l	Lower extremity amputation defined due to arteriosclerotic vascular disease	RR	1.8 [95%CI 1.1, 3.2]
			HDL cholesterol	>0.9 mmol/l		RR	1.3 [95%CI 0.7, 2.5]
(Litzelman et a 1997) US	II (prospective cohort) SIGN cohort: Good quality	N= 395 Patients receiving health care from general practice Characteristics: NIDDM 100%, women 81%, annual income(<&10000) 70%	HDL cholesterol	Decreasing change in HDL of 386.7mmol/l (10mg/dl)	Major foot injury (Seattle Wound Classification system) ≥1.3	OR	1.6 [95%CI 1.1, 2.4]
(Adler et al 1999) US	II (prospective cohort) Quadas: moderate SIGN cohort: Average quality	N= 776 Seattle Diabetic Foot Study Patients at Internal medicine clinic of Veteran Affairs Puget Characteristics: Type II DM 93%, male 98%, history of ulcer 24%, ≤2 pedal pulses absent 32%	Creatinine	> 1.3 mg/dl	First lower extremity amputation	Sensitivity Specificity PPV NPV	50% [95%CI 32, 68%] 62% [95%CI 59, 66%] 5.0% [95%CI 2.9, 8.4%] 97% [95%CI 95, 98%]

PPV= Positive Predictive Value, NPV= Negative Predictive Value; ns= non significant; DM= Diabetes Mellitus; IDDM= Insulin dependent diabetes mellitus; NIDDM= Non insulin dependent diabetes mellitus;

Neuropathic diabetes population

Foot Pressure assessment

Diagnostic accuracy of foot pressure assessment in the neuropathic diabetes population

Two average quality studies reported on the accuracy of foot pressure assessment at identifying risk of foot ulcer in diabetes patients with neuropathy (Table 20).

The average quality study by Lavery et al (2003) used Novel's EMED force plait gait analysis system© (Novell, Minneapolis, MN) to measure plantar pressure over the entire foot surface. The authors found baseline peak plantar pressure (PPP) to be significantly higher in those patients that developed an ulcer, than in those who did not (95.5±26.4 vs 85.1±27.3 N/cm^2, p<0.01). Also, the authors found a trend for elevated PPP in neuropathic patients compared to those without neuropathy. Consequently, patients without neuropathy were excluded from the remainder of the analysis. Using a cut-off value of 88 N/cm^2, the sensitivity, specificity, PPV and NPV of foot pressure assessment was 64%, 46%, 17% and 90% respectively. These results would suggest that foot pressure assessment is not a valuable assessment for predicting foot ulcer in diabetes patients with neuropathy. The authors also provided data on area under the curve, which suggests that this assessment of foot pressure performs poorly in discriminating between those at high risk of foot ulcer and those at low risk (AUC=0.57 [95%CI 0.51, 0.62]).

Veves et al (1992) measured peak plantar pressure (PPP) with optical pedobarography under the metatarsal heads; heel; great toe and any other area expected to have high pressure in the neuropathic diabetes subjects included in the study. Patients were required to take three footsteps and the authors used the measurement of the footstep which was closest to a normal gait. Using a cut-off point of 12.3 kg/cm^2 yielded a sensitivity of 93% [95CI% 66, 99%] and specificity of 39% [95%CI 22, 59%]. Based on these estimates, this type of foot pressure would accurately identify 'at risk' patients, but at the expense of a high false positive rate. At peak pressures higher than 12.3 kg/cm^2, the PPV was 45% [95%CI 28, 64%] and the NPV 92% [95%CI 60, 99%]. The PPV is moderate as the prevalence of foot ulcer in the study population was 17%. In this study, the PPP assessment was a reasonable predictor of the development of ulcers in neuropathic diabetic patients over a follow up of 30 months. Still, caution is advised as the results are based on a small sample size which had high attrition.

The results lack some consistency particularly with regard to the estimates of sensitivity and positive predictive value. This might be explained by the small sample size used by Veves et al (1992). As it is, the evidence would suggest that in a diabetes population with neuropathy, the foot pressure assessment might not be very accurate at discriminating those at high and low risk of foot ulcer. The best use of this test may be for ruling out those at very low risk of foot ulcer. Box 34 summarises the body of evidence according to the NHMRC grading criteria.

Box 34 Evidence statement matrix for the diagnostic accuracy of foot pressure assessment in neuropathic diabetes population

Component	Rating	Description
Evidence base	C	Two level II studies with moderate risk of bias
Consistency	B	The evidence provided by both studies was inconsistent, which might be explained by or the small sample size of Veves et al.
Clinical impact	C	The moderate to poor performance of foot pressure assessment would suggest that it would have little clinical impact for predicting foot ulcer in neuropathic diabetic patients, with the exception of potentially ruling out those at low risk.
Generalisability	B	Veves et al (1992) included patients visiting a Manchester diabetes centre, while Lavery et al (2003) included patients from an urban managed care outpatient clinic. The samples were only diabetes patients with peripheral neuropathy.
Applicability	C	Both studies came from the USA, which has a similar health care system for diabetes patients to the Australian context.

Evidence statement

Despite some inconsistencies, the evidence suggests that foot pressure assessment in a neuropathic diabetes population is not accurate at predicting foot ulcer. However, optical pedobarography may only be of value at ruling out those at risk of foot ulcer. (Grade C).

Predictive value of foot pressure assessment in the neuropathic diabetes population

Only Lavery et al (2003) reported results regarding foot pressure as a predictor. This study found that patients with peak plantar foot pressures higher than a cut-off point of 87.5 N/cm^2 were twice as likely to develop an ulcer than those who had foot pressures lower than 87.5 N/cm^2 (OR=2.0 [95%CI 1.4, 2.9]). Box 35 summarises the body of evidence according to the NHMRC grading criteria.

Box 35 Evidence statement matrix for the predictive value of foot pressure assessment in neuropathic diabetes population

Component	Rating	Description
Evidence base	C	One level II study with low risk of bias
Consistency	N/A	Only one study.
Clinical impact	C	The odds ratio shows a moderate clinical effect for predicting foot ulcer.
Generalisability	B	Lavery et al included patients from an urban managed care outpatient clinic. The sample included only diabetes patients with neuropathy.
Applicability	C	The study came from the USA, which has a similar health care system for diabetes patients to the Australian context.

Evidence statement

The evidence suggests that foot pressure assessment in a diabetes population with neuropathy is a moderate predictor for the development of foot ulcer (Grade C).

Table 20 Studies included foot pressure assessment in neuropathic diabetes population

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Lavery et al 2003) USA	II (prospective cohort) SIGN cohort: Average quality	N = 1666 Diabetes patients at large urban managed care based outpatient clinic Characteristics: VPT = 22.5±11.7 Volts, patients all had neuropathy and/or deformities	Peak Plantar Pressure	Cut off ≥87.5 N/cm², measured with EMED force plate gait system© over entire foot surface	Foot ulceration	Sensitivity Specificity PPV NPV OR AUC	63% 46.3% 17.4% 90.4% 2.0 [95%CI 1.4, 2.9] 0.57 [95%CI 0.51, 0.62]
(Veves et al 1992) UK	II (prospective cohort) Quadas: Moderate quality SIGN cohort: Good quality	N = 86 Patients attending clinics at Manchester Diabetes Centre with neuropathy Characteristics: Neuropathy (100%); history of ulceration (0%); active foot ulcers (0%); unable to walk without aid (0%)	Peak Plantar pressure:	Measured with optical pedobarography under the metatarsal heads, heel, the great toe and any other high area of pressure. >12.3kg/cm² is seen as abnormal Footstep with most normal gait of three footsteps was measured	First incidence of foot ulceration	Sensitivity Specificity PPV NPV	93% [CI95% 66, 99%] 39% [95%CI 22, 59%] 45% [95%CI 28, 64%] 92% [95%CI 60, 99%]

VPT= vibration perception threshold; PPV= positive predictive value; NPR= negative predictive value; OR= odds ratio; AUC; area under the curve

Indigenous Diabetes population

Risk categorisation assessment scheme

Predictive value of risk categorisation assessment scheme

The average quality study by Rith-Najarian et al (1992) investigated the predictive value of risk categorisation for the development of foot ulcer and amputation (Table 21).
Risk categorisation in this study included assessment of history of a lower extremity event (foot ulcer or amputation), use of Semmes-Weinstein monofilament and a foot deformity assessment. Foot deformities included hallux valgus or varus, claw or hammer toe, bony prominence or Charcot foot on either foot. The study sample consisted of residents from a Native American reservation who visited the Indian Hospital Service in Red Lake, Chippewa.

After the assessment patients were categorised as either 0 defined by being sensate for SWF; 1, defined by being insensate to SWF; 2, defined by being insensate for SWF with a foot deformity; or 3, defined as having a history of lower extremity events. The authors reported that with respect to the 0 reference group, those patients categorised as 1 were 15 times more likely to develop foot ulcers (OR=15 [p<0.01]), whilst those patients categorised as 2 or 3 were 32 or 78 times more likely to develop foot ulcer (OR=32 [p<0.01], OR= 78 [p<0.01], respectively). The results were only supported by the p value, when no confidence intervals reported. The rather large odds ratios may be explained by the small sample size, or alternatively the population group. Box 36 summarises the body of evidence according to the NHMRC grading criteria.

Box 36 Evidence statement matrix for the predictive value of risk categorisation assessment scheme in indigenous diabetes population

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study.
Clinical impact	A	The odds ratio showed a large clinical effect for the prediction of foot ulcer.
Generalisability	B	The population included only residents of a Native American reservation, who visited a Hospital Service. The population is generalisable to the indigenous target population in Australia with some caveats.
Applicability	C	The study came from the US, which has a similar health care system for diabetes patients to the Australian context.

Evidence statement

Limited evidence suggests that indigenous diabetes patients with a risk categorisation indicating insensitivity to Semmes-Weinstein monofilaments (SWF) or SWF combined with foot deformity or a history of a lower extremity event may be more likely to develop foot ulcers than those with normal sensation (Grade C).

Semmes - Weinstein monofilament assessment

Predictive value of Semmes – Weinstein monofilament assessment

Rith-Najarian et al (1992) also investigated the predictive value of Semmes-Weinstein monofilament assessment on its own (see Table 21). The authors found 9.9 times the odds ratio of foot ulcer in those patients insensitive to SWF 10g compared to those patients who retained sensitivity over a 32 month follow up (OR= 9.9 [95%CI 4.8, 21.0]). For amputation, the authors found an odds ratio of 17 for patients with insensitivity (OR= 17 [95%CI 4.5, 95]). The

results are provided with rather wide confidence intervals, which reflect uncertainty around the estimates and which can be explained by the small sample size. Box 37 summarises the body of evidence according to the NHMRC grading criteria.

Box 37 Evidence statement matrix for the predictive value of Semmes-Weinstein monofilament assessment in indigenous diabetes population

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study.
Clinical impact	A	The odds ratio showed a large clinical effect for the prediction of foot ulcer and an even larger odds ratio for amputation. The precision of the results could not be ascertained.
Generalisability	B	The population included only residence of a Native American reservation, who visited a Hospital Service. The population is generalisable to the indigenous target population in Australia with some caveats.
Applicability	C	The study came from the US, which has a similar health care system for diabetes patients to the Australian context and is therefore applicable with some caveats..

Evidence statement

Limited evidence suggests that indigenous diabetes patients who are insensate to the Semmes-Weinstein monofilament assessment are more likely to develop foot ulcers and undergo amputation compared to those patients with normal sensation (Grade C).

Table 21 Studies reported on risk categorisation assessment in an indigenous diabetes population

Author Country	Level and quality of study	Population	Assessment		Outcome	Outcome data	
(Rith-Najarian et al 1992) USA	II (prospective cohort) SIGN cohort: Average quality	N = 358 Native American Diabetes patients visiting the Indian Hospital Service.	Risk categorisation assessment scheme	The assessment included history of lower extremity event (foot ulcer or amputation) and Semmes-Weinstein monofilament and foot deformity assessment. Categories as: 0= sensate for SWF, 1= insensate to SWF, 2= insensate with deformity and 4= history of lower extremity event.	Foot ulceration defined by full thickness penetration of the dermis on the plantar aspect of the foot.	Category 1 vs 0	
						OR	15 [p<0.01]
						Category 2 vs 0	
						OR	32 [p<0.01]
						Category 3 vs 0	
						OR	78 [p<0.01]
			Semmes Weinstein monofilament	10g monofilament tested at eight sites on the plantar aspect of each foot while the patient was blinded. Insensitivity was defined as not being able to sense the 10g monofilament at one or more sites of the foot.	Foot ulcer (as above)	SWF insensitivity	
						OR	9.9 [95%CI 4.8, 21.0]
					Amputation	SWF insensitivity	
						OR	17 [95%CI 4.5, 95]

OR= odds ratio; SWF= Semmes Weinstein Monofilament

Summary of diagnostic and predictive performance

Based on one systematic review and 11 cohort studies, 17 assessments have been reported for the general diabetes population, 1 for the neuropathic diabetes population and 2 for an Indigenous diabetes population. These are outlined in Table 22 according to their diagnostic accuracy, followed by the NHMRC evidence grade for diagnostic accuracy, then the predictive value and the respective NHMRC evidence grade.

The Neuropathy Disability Score (NDS) performed best in identifying patients at risk of foot ulcer and lower extremity amputation in the general diabetes population, as did the Risk Assessment Tool. Two additional assessments (HDC risk assessment and combined NDS) might be of value to rule out risk of foot ulcer and lower extremity amputation.

There was limited evidence in the neuropathic and Indigenous sub populations, therefore it is difficult to determine which assessments are the best predictor of risk in these populations.

Table 22 Summary of diagnostic and predictive performance of included assessments.

Assessment	Diagnostic performance	Predictive performance
General Diabetic Population		
NDS	Good (Grade C)	Good (Grade B)
Risk assessment tool	Good (Grade C)	Good (Grade C)
HDC risk assessment	Poor at screening, good for ruling out (Grade C)	No evidence
NDS combined	Poor at screening, good for ruling out (Grade C)	No evidence
Vibration sensation	Moderate (Grade C)	Foot ulcer – substantial (Grade B) Amputation – insufficient evidence
$TCPO_2$	Moderate (Grade C)	Moderate (Grade C)
Seattle risk assessment	Moderate (Grade C)	No evidence
Glycaemic control	Moderate (Grade C)	No evidence
SWF	Poor (Grade C)	Good (Grade B)
Foot pressure assessment	Poor (Grade C)	Moderate to substantial (Grade B)
Arterial pulse assessment	Poor (Grade C)	Moderate (Grade B)
Ankle – Arm Index	Poor (Grade C)	Moderate (Grade C)
Ankle blood pressure	No evidence	Moderate (Grade C)
Foot deformity	No evidence	Moderate (Grade B)
Orthostatic blood pressure	No evidence	Poor (Grade D)
Ankle reflex assessment	Poor (Grade C)	Inconclusive (Grade C)
Gait assessment	Poor (Grade D)	No evidence
Neuropathic Diabetic Population		
Foot pressure assessment	Moderate – ruling out (Grade C)	Moderate (Grade C)
Indigenous populations		
Risk Categorisation Assessment Scheme	No evidence	Moderate (Grade C)
SWF	No evidence	Moderate (Grade C)

NDS = neuropathic disability score; SWF = Semmes Weinstein filaments; $TCPO_2$ = transcutaneous oximetry; HDC = Hansen's Disease Center

Research question 3: Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer?

Box 38 Inclusion criteria for the evaluation of clinical assessments which predict foot ulcer severity and outcomes in people with foot ulcer.

Research Question	
Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer?	
Parameter	Inclusion criteria
Population	Adults with type 1 or type 2 diabetes mellitus with foot ulcer, including a) people with Charcot's neuroarthropathy; or b) Indigenous populations
Intervention	Clinical examinations or assessments to grade the severity of foot ulcer, such as the Wagner and Texas grading systems.
Comparator (if available)	Other types of clinical examinations or assessment tools to grade the severity of foot ulcer, including more invasive methods
Outcomes	*Prognostic outcomes:* Observed risk of clinical outcomes (eg mortality/survival; ulcer healing; time to healing; amputation (major, transmetatarsal, transtibial, ray or toe); time to amputation; mobility restriction; general functioning; quality of life; independence). *Diagnostic outcomes:* Sensitivity and specificity (and therefore rates of false positives and negatives), positive and negative likelihood ratios, positive and negative predictive values, diagnostic odds ratios, receiver operator characteristic curves, area under the curve, accuracy.
Study design	For prognosis: Prospective cohort studies; all or none; analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial; a retrospective cohort study; case series or cohort study of persons at different stages of disease. For diagnosis: Cross-classification studies where subjects are cross-classified on the test and comparator; or systematic reviews of cross-classification studies. Case-control diagnostic studies, or uncontrolled studies are only acceptable if cross-sectional studies are not available
Language	Non-English language articles were excluded unless they appeared to provide a higher level of evidence than the English language articles identified.
Publication date	1966 – 11/2009
Limitations	Human

The relevant studies have been presented below in sections which assess single clinical or laboratory assessments and multiple assessments in the form of classification systems or scores which predict foot ulcer outcomes. Essentially, the single assessments are univariate analyses of measurements to predict outcomes and have not been controlled or adjusted for potential confounders. The multiple assessments however, consist of multivariate analyses which combine a number of relevant clinical or laboratory assessments to predict outcomes of foot ulcer. It should be noted when reading this review that very few, if any, studies adjusted for the treatment received by patients. However, in a clinical sense, the use of predictive models for foot ulcer outcomes would be to identify patients who are at higher risk of poor outcomes and whose management should therefore change. As causation of the outcome is not being sought, it may not be as important to control for treatment however, generalisability and applicability to the Australian healthcare context would remain fundamental to ensure that the predictive ability of measurements/scores would be reproducible in an Australian clinical setting.

Single clinical or laboratory assessments

Bone scans for osteomyelitis

Diagnostic accuracy of bone scans for osteomyelitis

The presence of osteomyelitis in people with diabetic foot ulcers can often lead to worse health outcomes hence, the accurate assessment of its presence is useful in predicting the severity of foot ulcers.

A poor quality study by Balsells et al (1997) considered the use of combining radiographic x-ray and radiolabelled bone and leukocyte scans to determine the presence of osteomyelitis and hence the likely outcome for people with diabetic foot ulcers (Table 23). Patients were hospitalised with foot ulcers that had failed to heal and were suspected of further complications. All patients receive standard wound care and underwent plain x-ray as well as scintigraphic evaluation with bone and leukocyte scans, which were used to determine the presence of osteomyelitis. Osteomyelitis was diagnosed by either the presence of characteristic changes on plain x-ray or by the combined results of the bone or leukocyte scans. Patients were followed for at least 12 months and were classified as having a good or bad outcome depending on their requirement for amputation. The authors reported the sensitivity and specificity of the combined bone and leukocyte scan as 75% and 59% respectively for predicting amputation using the observed risk as the reference standard. The respective sensitivity and specificity for plain x-ray was 69% and 88%. However the diagnostic accuracy of using the combined results of bone and leukocyte scan, and plain x-ray (as used in the study) were not reported. Once osteomyelitis was diagnosed the likelihood of amputation was 11 times that for patients without osteomyelitis (OR=11, [95%CI 1.65, 74.2]).

Given the lack of information regarding the diagnostic accuracy of the combination of bone and leukocyte scans and plain x-ray, it is not possible to evaluate its use in identifying those at higher risk of amputation. However, this study does suggest that the presence of osteomyelitis may be a predictor of amputation in people with severe diabetic foot ulcers. The evidence presented here is summarised in the evidence statement matrix (Box 39).

Box 39 Evidence statement matrix for the diagnostic accuracy of bone scans for osteomyelitis

Component	Rating	Description
Evidence base	D	One level II study with a high risk of bias.
Consistency	N/A	Only one study available
Clinical impact	D	The results are difficult to interpret as the diagnostic accuracy of the combined use of plain x-ray and combined bone and leukocyte scans are not reported.
Generalisability	B	The study would be generalisable to diabetic patients hospitalised with severe foot ulcers.
Applicability	C	The study was conducted in Spain which is probably applicable to the Australian healthcare context with some caveats.

Evidence statement

There is weak evidence to support the use of bone scans to identify higher risk of amputation in patients with severe diabetic foot ulcers (Grade D).

Table 23 Evaluation of bone scans for the prediction of amputation

Author Country	Level and quality of study	Population	Assessment	Outcome	Outcome data	
(Balsells et al 1997) Spain	II (Prognosis) Cohort study SIGN: Poor quality QUADAS: Poor quality	28 patients with type II diabetes and foot ulcer, who were admitted to hospital with suspected complications such as osteomyelitis or vascular impairment. Patient characteristics: Age = 65 ± 12 years; male = 12 (43%); ABI <0.6 = 36%; Neuropathy (VPT >30V) = 29%; mixed vasculopathy and neuropathy = 36%; previous amputation = 25%	Plain radiographs, Tecnetium-99 methilen diphosphate bone scan (at 5 min and 4h after isotope injection) and Tecnetium-99 HMPAO autologous leukocyte scan. These scans were performed within a one week interval	Amputation	Combined bone and leukocyte scan Radiographic x-ray Osteomyelitis	Sensitivity = 75% Specificity = 59% Sensitivity = 69% Specificity = 88% M-H OR = 11 [95% CI 1.65, 74.2]

VPT = vibration perception threshold; ABI = ankle brachial index; MH = Mantel-Hanzel; OR = odds ratio; CI = confidence intervals.

Predictive ability of bone scans for osteomyelitis

Balsells et al (1997) also reported the ability of a diagnosis of osteomyelitis to predict amputation in patients with severe diabetic foot ulcers (Table 23). The results of the study suggest that the presence of osteomyelitis (as diagnosed by x-ray and bone and leukocyte scans) is a predictor of amputation (OR = 11 [95% CI 1.65, 74.2]) when adjusting for the presence of severe peripheral vasculopathy. The wide confidence intervals around this estimate suggest there is substantial uncertainty with these results and they should be considered with some caution. Again, the poor quality of the study would suggest that little weight should be given to these results.

The evidence of predictive ability as presented here is summarised in the evidence statement matrix (Box 40).

Box 40 Evidence statement matrix for the predictive ability of bone scans for osteomyelitis

Component	Rating	Description
Evidence base	D	One level II study with a high risk of bias.
Consistency	N/A	Only one study available
Clinical impact	C	The results suggest that osteomyelitis is a strong predictor of amputation however there is considerable uncertainty around the point estimate.
Generalisability	B	The study would be generalisable to diabetic patients hospitalised with severe foot ulcers.
Applicability	C	The study was conducted in Spain which is probably applicable to the Australian healthcare context with some caveats.

Evidence statement

There is some evidence to suggest that osteomyelitis is a strong predictor of amputation in patients with severe diabetic foot ulcers (Grade C).

Ankle peak systolic velocity

Diagnostic accuracy of ankle peak systolic velocity

Ankle peak systolic velocity (APSV), which is not affected by the presence of arterial wall calcification, provides a measure of the extent of peripheral ischaemia. It may be useful to perform this measurement instead of the toe–brachial index particularly in the presence of ulcers, gangrene or amputation of toes (Bishara et al 2009).

A poor quality prospective cohort study reported by Bishara et al (2009) measured APSV in diabetic patients with absent pedal pulses and either foot ulcer or gangrene (Table 24). These measurements were taken at baseline, after which patients received standard wound care and were followed until an end point was reached. The end points for the study were a completely healed wound; a healing wound; revascularisation; major amputation or death. A wound was considered non-healed if after one month the lesion showed no sign of healthy granulations or there were signs of critical limb ischaemia. The authors also reported that if a patient was entered into the study once and required revascularisation (a defined endpoint), they re-entered that study from baseline after the procedure. Of the 100 patients who were reported as entering the study, 84 required revascularisation and would therefore have been re-entered into the study.

Using a cut-off value for APSV of 35cm/s, the sensitivity and specificity were 93% [95% CI 82, 97] and 91% [95%CI 76, 96] respectively. In addition, the positive predictive value (PPV) and negative predictive value (NPV) were 93% and 91% respectively. This cut-off value for APSV resulted in an area under the curve (AUC) of 0.97 [95%CI 0.59, 1.0]. The results of APSV

measurement indicate that this method is able to accurately discriminate between those who are at risk and those who are not however, the questionable practice of re-entering patients into the study after treatment introduces significant uncertainty into the validity of the results.

The evidence of predictive ability here is summarised in the evidence statement matrix (Box 41).

Box 41 Evidence statement matrix for the diagnostic accuracy of APSV

Component	Rating	Description
Evidence base	D	One level II study with a high risk of bias.
Consistency	N/A	Only one study available
Clinical impact	D	The results suggest that measurement of APSV has high discriminatory ability for identifying those at risk of non-healing. However, these results are likely to be unreliable given the questionable methods regarding patient entry into the study.
Generalisability	B	The study would be generalisable to diabetic people with foot ulcers and absence of pedal pulses. Furthermore, it may also be generalisable to people who have undergone revascularisation.
Applicability	D	It is likely that the study was conducted in a teaching hospital in Egypt which may restrict the applicability of these results to the Australian healthcare context.

Evidence statement

APSV measurements may be useful in identifying diabetic patients with foot lesions or gangrene, who are at risk of not healing. (Grade D).

Table 24 Evaluation of APSV for the prediction of amputation

Author Country	Level and quality of study	Population	Assessment	Outcome	Outcome data
(Bishara et al 2009) Egypt	II (Prognosis) Prospective cohort study SIGN: Poor quality QUADAS: Poor quality	100 limbs in 62 patients. Patients were diabetic with absent dorsalis pedis and posterior tibial pulses in the affected leg, and had foot lesions in the form of ulcers, gangrene or tissue necrosis. Patient characteristics: Age = 63 years (range = 42–78 years); male = 42 (68%); IHD = 30 (49%); hypertension =29 (47%); smoking = 15 (24%); stoke = 6 (10%); renal impairment = 6 (10%); dyslipidaemia = 6 (10%)	APSV – mean of the peak systolic velocities of the anterior and posterior tibial arteries measured at the ankle level. Measurements were taken as part of the duplex scan.	Non-healing defined as no signs of healthy granulations after 1 month of follow-up or if patient developed manifestations of critical limb ischaemia	Using cut-off value of 35 cm/s: Sensitivity 92.9% [95%CI 82, 97] Specificity 90.6% [95%CI 76, 96] PPV 92.9% NPV 90.6% AUC 0.9723 [95%CI 0.59, 1.0]

IHD = ischaemic heart disease; APSV = ankle peak systolic velocity; PPV = positive predictive value; NPV = negative predictive value; AUC = area under the curve; CI = confidence intervals.

Predictive ability of ankle peak systolic velocity

Bishara et al (2009) also reported a logistic regression model that was developed based on the results of their study. Although no estimates for the strength of the relationships between predictor and outcome variables were provided, the authors indicated that the only variable which was an independent predictor of non-healing was APSV. The other variables considered were age; gender; diabetes mellitus; hypertension; ischaemic heart disease; renal impairment; cerebrovascular accident and dyslipidaemia. It is uncertain as to why diabetes mellitus was considered in the regression model as this was a requirement for entry into the study. Again, the re-entry of patients into the study is likely to have significantly biased the results in favour of APSV particularly as the model was not adjusted for treatment.

Box 42 summarises this evidence according to the NHMRC body of evidence matrix.

Box 42 Evidence statement matrix for the predictive ability of APSV to predict non-healing

Component	Rating	Description
Evidence base	D	One level II study with a high risk of bias.
Consistency	N/A	Only one study available
Clinical impact	D	The results suggest that APSV measurement is an independent predictor of non-healing however, it is unlikely that these results can be relied upon.
Generalisability	B	The study would be generalisable to diabetic people with foot ulcers and absence of pedal pulses. Furthermore, it may also be generalisable to people who have undergone revascularisation.
Applicability	D	It is probable that the study was conducted in a teaching hospital in Egypt which may restrict the applicability of these results to the Australian healthcare context.

Evidence statement

It is possible that APSV is an independent predictor of non-healing in diabetic patients with foot lesions or gangrene (Grade D).

Skin perfusion pressure

Diagnostic accuracy of skin perfusion pressure

A poor quality study conducted in Adelaide, Australia evaluated the use of skin perfusion pressure to identify those patients, with diabetic foot ulcer, who are likely to heal without arterial surgery or major amputation (Faris & Duncan 1985). Although the study was poorly reported, skin perfusion pressure was measured using a radioisotope clearance method with an intradermal injection of ^{99m}Tc-pertechnetate with histamine to ensure maximum dilation of local vessels. The study enrolled 61 subjects with diabetic foot ulcer or gangrene but little information regarding baseline characteristics, length of follow-up after assessment or details of conservative treatment were provided (Table 25). The outcomes recorded were healing (including healing with conservative treatment, local surgery or transmetatarsal amputation); arterial surgery; or below the knee amputation. Using the raw data reported, the sensitivity, specificity and positive and negative predictive values were calculated to be 97.2% [95% CI 85.8, 99.5], 80% [95% CI 60.9, 91.1], 87.5% and 95.2% respectively. These results are based on using a cut-off value of 40mmHg and an outcome of healing which also included local surgery or amputation.

The high sensitivity of using skin perfusion pressure suggests that it would perform well at identifying those who would heal and subsequently, be able to rule out healing in those patients with a low skin perfusion pressure due to the low number of false negative results. However,

the poor quality of reporting in this study and the likely biases which have been introduced, indicate that this study provides very weak evidence in this regard.

Box 43 summarises this evidence according to the NHMRC body of evidence matrix.

Box 43 Evidence statement matrix for the predictive ability of skin perfusion pressure to predict non-healing

Component	Rating	Description
Evidence base	D	One level II study with a high risk of bias.
Consistency	N/A	Only one study available
Clinical impact	D	The results suggest that skin perfusion pressure is a good diagnostic tool to predict healing (including local surgery or amputation) and in particular, to rule out the likelihood of healing in patients with low skin perfusion pressure. However, the potential for introduced biases ensures that the evidence for this is weak.
Generalisability	A	The study would be generalisable to diabetic people with foot ulcers or gangrene.
Applicability	A	This study is directly applicable to the Australian healthcare context.

Evidence statement

It is possible that skin perfusion pressure is able to predict healing in diabetic patients with foot lesions or gangrene. In particular, it is possible that skin perfusion pressure may rule out the likelihood of healing in patients with low skin perfusion pressure (Grade C).

Table 25 Evaluation of skin perfusion pressure for identifying risk of healing

Author Country	Level and quality of study	Population	Assessment	Outcome	Outcome data
(Faris & Duncan 1985) Australia	II (Prognosis) Prospective cohort study SIGN: Poor quality QUADAS: Poor quality	61 diabetic patients with foot ulcer or gangrene. Patient characteristics: Age = 72 years (range = 38–86 years); male = 37 (61%); duration of diabetes 10 years (range = 0.5–40 years); ulcer = 35 (57%); gangrene = 26 (43%).	Skin perfusion pressure measured by radioisotope clearance method.	Healing (including healing with conservative treatment, local surgery, transmetatarsal amputation)	Using cut-off value of 40 mmHg: Sensitivity 97.2% [95%CI 86, 100] Specificity 80.0% [95%CI 61, 91] PPV 87.5% NPV 95.2%

PPV = positive predictive value; NPV = negative predictive value; CI = confidence intervals.

Capillary circulation with macro-aggregated albumin

Predictive accuracy of capillary circulation

A poor quality study by Moriarty et al (1994) assessed the use of macro-aggregated perfusion scanning for evaluating capillary circulation in a population of diabetics with foot ulcers and impalpable pedal pulses (Table 26). Patients underwent scanning and the results were then assessed by a radiologist and medical physicist who were blinded to the location of the ulcers. Perfusion was graded as either poor, adequate or increased after which, patients were treated by their physician without knowledge of the results of the scan. After 3 months, ulcers were classified as healed or not healed although the criteria for a healed outcome were not described.

The simple analysis provided by the investigators indicated that compared to normal perfusion, there was a significant association between increased perfusion and ulcer healing (18% and 82% respectively, $p = 0.047$) and poor perfusion and non-healing (33% and 100% respectively, $p < 0.005$). The analysis however, did not consider the effect that treatment had on the outcome of patients. Many patients underwent angioplasty or surgery which would be expected to have had a direct impact on whether the ulcers healed.

Box 44 summarises this evidence according to the NHMRC body of evidence matrix.

Box 44 Evidence statement matrix for the ability of capillary circulation to predict healing

Component	Rating	Description
Evidence base	D	One level II study with a high risk of bias.
Consistency	N/A	Only one study available
Clinical impact	D	The impact of this evidence is likely to be restricted as the grades and outcome of healing were poorly defined and furthermore, the association between capillary circulation and healing was not adjusted for treatments received by patients.
Generalisability	A	The study would be generalisable to diabetic people with ischaemic foot ulcers.
Applicability	B	The study was conducted in the United Kingdom and is applicable to the Australian healthcare context with few caveats.

Evidence statement

There is likely to be an association between poor capillary circulation and non-healing, as well as between increased perfusion and healing of foot ulcers (Grade C).

Table 26 Evaluation of capillary circulation for the prediction of healing

Author Country	Level and quality of study	Population	Assessment	Outcome	Outcome data			
(Moriarty et al 1994) United Kingdom	II Prospective cohort study SIGN: Poor quality	23 diabetic patients with 41 foot ulcer and impalpable foot pulses. Patient characteristics: Age = 68 ± 2 years (range = 44–82 years); male = 78%; type 2 diabetes = 74%; current smokers = 13%; ex-smokers = 61%; never smoked = 26%; mean ankle-brachial index = 0.46 ± 0.07.	Capillary circulation measured by ^{99m}Tc-macroaggregated albumin perfusion scanning.	Healing	Perfusion Poor Normal Increased Total[c]	Healed 0 (0%) 12 (66%) 14 (82%) 26 (65%)	Not healed 5 (100%) 6 (33%) 3 (18%) 14 (35%)	Fisher's exact test p = 0.0005[a] – p = 0.047[b]

[a] Comparison of poor versus normal perfusion; [b] comparison of increased versus normal perfusion; [c] one patient died therefore the outcomes of 40 ulcers were available at end of follow-up.

Transcutaneous oxygen pressure ($TcPO_2$) and toe blood pressure

Diagnostic accuracy of $TcPO_2$ and toe blood pressure

In a poor quality prospective cohort study,$TcPO_2$ and toe blood pressure (TBP) were assessed for their ability to predict healing in diabetic patients with chronic foot ulcers (Kalani et al 1999). Fifty patients were referred to a microcirculatory laboratory with diabetic foot ulcers of more than two months duration. Measures of $TcPO_2$ and TBP were conducted at baseline, and patients received standard wound care from a multidisciplinary foot care team during a follow-up period of 12 months. Ulcer area was measured at baseline and again at 12 months, and patients were then classified as having impaired or improved ulcer healing. The exact definitions which were applied to these groups is unclear however, it is possible that improved or impaired ulcer healing was considered as an increase or decrease in ulcer area of 25% respectively.

Kalani et al (1999) reported the diagnostic accuracy of the two measurements in identifying patients with ulcer healing. The outcome of ulcer healing in this analysis has included those patients with improved ulcer healing, as well as those with complete healing. The sensitivity and specificity of $TcPO_2$ was 85% [95%CI 57, 96] and 92% [95% CI 79, 97] respectively. The PPV and NPV were 79% and 94% respectively. Given the excellent specificity, these results suggest that $TcPO_2$ would be useful in ruling in those people who were likely to heal. That is, given the unlikelihood of a false positive (due to the high specificity); those with a positive result are likely to heal. However, given the uncertainty regarding the definition of healing it may be difficult to translate this evidence into clinical practice.

The sensitivity and specificity of TBP was also reported for two different cut-off values, 30mmHg and 45mmHg. Better diagnostic accuracy was achieved with the 45mmHg cut-off value with a sensitivity, specificity and PPV of 46%, 84% and 50% respectively. Although the lower cut-off value achieved an excellent specificity, this was associated with a significant reduction in sensitivity (Table 27).

Box 45 summarises this evidence according to the NHMRC body of evidence matrix.

Box 45 Evidence statement matrix for the ability of $TcPO_2$ and TBP to predict healing

Component	Rating	Description
Evidence base	D	One level II study with a high risk of bias.
Consistency	N/A	Only one study available
Clinical impact	C	The impact of this evidence is likely to be restricted as the outcome of healing was poorly defined and is likely to have included patients with improved rather than complete healing. $TcPO_2$ appears to have greater ability to identify those with healing compared to TBP but given the uncertainty regarding the definitions of outcomes, it would be more appropriate to suggest that it identifies improvement rather than ulcer healing.
Generalisability	A	The study would be generalisable to diabetic people with chronic foot ulcers.
Applicability	B	This study was conducted in Sweden and would be applicable to the Australian healthcare context with few caveats.

Evidence statement

It is possible that $TcPO_2$ measurement can better identify those ulcers which will improve compared with TBP (Grade C).

Table 27 Evaluation of $TcPO_2$ and TBP for the prediction of healing

Author Country	Level and quality of study	Population	Assessment	Outcome	Outcome data
(Kalani et al 1999) Sweden	II (Prognosis) Prospective cohort study SIGN: Poor quality QUADAS: Poor quality	50 diabetic patients referred to microcirculatory laboratory with chronic foot ulcers of > 2 months duration. Patient characteristics: Age = 61± 22 years; male = 74%; diabetes duration = 26 ± 14 years; ankle-brachial index < 0.6= 64%; reconstructive vascular surgery = 2%; smokers = 20%; ex-smokers = 20%; insulin therapy = 68%; oral antidiabetics = 32%.	$TcPO_2$ measured by electrochemical transducer at the dorsum of the foot in the first intertarsal space.	Healing (which may include improved healing)	Using a cut-off value of 25 mmHg: Sensitivity 84.6% [95%CI 57, 96] Specificity 91.8% [95%CI 79, 97] PPV 79% NPV 94%
			Toe blood pressure (TBP) measured as systolic TBP using a miniature cuff placed around the base of the great toe.	Healing (which may include improved healing)	Using a cut-off value of 30 mmHg[a]: Sensitivity 15% Specificity 97% PPV 67% NPV 77% Using a cut-off value of 45 mmHg[a]: Sensitivity 46% Specificity 84% PPV 50%

$TcPO_2$ = transcutaneous oxygen tension; TBP = toe blood pressure; PPV = positive predictive value; NPV = negative predictive value CI = confidence interval.
[a] Raw data were not provided for these outcomes hence, confidence intervals could not be calculated.

Systolic ankle and toe blood pressure

No evidence was available regarding the predictive ability per se, of systolic ankle and toe pressure in regard to primary healing of foot ulcers. However, a poor quality study by Apelqvist et al (1989) which met the inclusion criteria of this review, provided evidence that there was a significant difference between the ankle and toe pressure indices of people with foot ulcers, who achieved primary healing or amputation.

In this prospective cohort study, 314 consecutive patients were assessed every 6 months when the systolic ankle and toe blood pressure were measured. The ankle and toe indices were calculated by the ratio of systolic ankle or toe blood pressure (using the mean of three measurements), with brachial artery systolic pressure, respectively. Although not stated by the authors, the last calculated index was presumably used in the analysis. Apelqvist et al (1989) reported that the mean ischaemic ankle index in primary healed and amputated patients was 0.87 ± 0.29 and 0.55 ± 0.28 ($p < 0.001$), respectively. In comparison, the mean systolic toe pressure index for primary healed and amputated patients was 0.55 ± 0.30 and 0.20 ± 0.18 ($p < 0.001$), respectively.

With regard to predicting ulcer healing, this study does not provide evidence that these measurements can be used for this purpose however it does suggest that there are differences in these indices between patients who heal and those who undergo amputation. With further research, these measurements may be of some use in identifying those who are likely to achieve these outcomes.

Box 46 summarises this evidence according to the NHMRC body of evidence matrix.

Box 46 Evidence statement matrix for the ability of toe or ankle blood pressure to predict healing

Component	Rating	Description
Evidence base	D	One level II studies with a high risk of bias.
Consistency	N/A	Only one study available
Clinical impact	D	There is likely to be restricted use of this evidence in the prediction of ulcer healing.
Generalisability	A	The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.
Applicability	B	This study was conducted in Sweden and is applicable to the Australian healthcare context with few caveats.

Evidence statement

There is evidence to indicate that the toe and ankle systolic pressure indices are likely to be higher in patients who achieve primary healing than those who are amputated (Grade C).

Hyperspectral imaging of oxyhaemoglobin and deoxyhaemoglobin

Diagnostic accuracy of hyperspectral imaging for predicting ulcer healing

Two studies provided diagnostic accuracy outcomes for measurement of tissue oxygenation for the prediction of ulcer healing (Khaodhiar et al 2007; Nouvong et al 2009). The initial study by Khaodhiar et al (2007) was an average quality pilot study conducted with ten patients with diabetic foot ulcer recruited from a number of diabetic practices (Table 28). Hyperspectral imaging was used to assess the extent of tissue oxygenation surrounding ulcers and consequently to predict the likelihood of healing after six months. Patients continued to receive regular care from their physicians who were blinded to the results of the hyperspectral imaging.

Based on the assumption that the measure of tissue oxygenation is normally distributed, linear discriminant analysis was used to predict the likelihood of ulcer healing. A healing index was generated by the distance between the relative value oxy/deoxyhaemoglobin to the linear discriminant decision line which best separated healed and nonhealed ulcers. The reported sensitivity, specificity, PPV and NPV of the index was 93% [95% CI 66, 100]; 86% [95% CI 42, 100]; 93% [95% CI 66, 100] and 86% [95% CI 42, 100] respectively.

Nouvong et al (2009) also conducted a study to evaluate the use of hyperspectral imaging to assess the extent of tissue oxygenation surrounding ulcers and consequently predicting the likelihood of healing. In this study 66 patients were enrolled after applying extensive exclusion criteria. After receiving standard wound care, including offloading and debridement, complete data were available for 54 patients with 73 ulcers after a one year period. The definition of healing used in this study was complete epithelialisation after 24 weeks with no exudates.

After data collection, linear discriminate analysis was used to determine the best separation of healed and nonhealed ulcers based on the tissue oxygenation values. A healing index was then generated and used to predict healing. A positive healing index had a greater likelihood of healing than a negative healing index. The authors reported that the sensitivity, specificity and PPV of the index were 80% [95%CI 67, 88], 74% [95%CI 51, 88] and 90% respectively. Diagnostic accuracy appeared to improve when patients with surrounding calluses and underlying osteomyelitis were excluded from the analysis with the sensitivity, specificity and PPV increasing to 86%, 88% and 96% respectively.

Although these results suggest that hyperspectral imaging and the generation of a healing index are accurate in identifying both ulcer healing and non-healing some caution should be used in applying it directly to a clinical setting. Both studies reported that the discriminant line was produced after the outcome had been ascertained, which would not be of any use in a clinical setting. Therefore, it would be recommended that the model produced by Nuovong et al (2009) be applied to an external data set to validate the linear discriminant decision line used in the study, particularly as treatment may have had an impact on the ulcer outcome.

Box 47 summarises this evidence according to the NHMRC body of evidence matrix.

Box 47 Evidence statement matrix for the ability of hyperspectral imaging to identify likelihood of healing.

Component	Rating	Description
Evidence base	C	Two level II studies with a moderate risk of bias.
Consistency	B	The differences in diagnostic accuracy are likely to be attributable to the greater statistical power of the larger study.
Clinical impact	C	The results of this study provide evidence that tissue oxygenation as measured by hyperspectral imaging could identify both healing and to a lesser extent, non-healing ulcers. However, some caution should be used with these results as they ought to be validated in an external data set to confirm the accuracy of the model in identifying ulcer healing.
Generalisability	A	The study would be generalisable to people with diabetic foot ulcers attending diabetic foot clinics.
Applicability	B	This study is applicable to the Australian healthcare context with few caveats.

Evidence statement

There is some evidence to suggest that hyperspectral imaging of tissue oxygenation can identify healing of diabetic foot ulcers (Grade C).

Table 28 Evaluation of hyperspectral imaging for identifying ulcer healing

Author Country	Level and quality of study	Population	Assessment	Outcome	Outcome data
(Khaodhiar et al 2007) USA	II (Prognosis) Prospective cohort study SIGN: Average quality QUADAS: Poor quality	10 type I diabetic patients with foot ulcer without peripheral arterial occlusive disease requiring surgery, heart failure resulting in oedema, stroke or TIA with residual nerve dysfunction, uncontrolled hypertension, end stage renal disease, severe peripheral oedema, other serious chronic diseases that affect healing, treatment with steroids or chemotherapy, pregnant or lactating women. Patient characteristics: Age = 51 years (range = 38–64 years); Male = 60%; BMI (kg/m^2) = 29 ± 7; duration of diabetes = 31 ± 12 years; systolic BP (mmHg) = 133 ± 20; diastolic BP (mmHg) = 76 ± 8; ankle-brachial pressure index = 1.14 ± 0.19; $TcPO_2$ (mmHg) = 46 ± 16; Neuropathy Symptoms Score = 5 ± 3; Neuropathy Disability Score = 15 ± 8; VPT = 44 ± 10; SWF = 6.2 ±0.9	Healing Index (based on oxyhaemoglobin and deoxyhaemoglobin as measured by hyperspectral technology cutaneous oxygenation monitoring, and the distance to the discriminate line between healing and nonhealing ulcers).	Healing at 6 months	Sensitivity 93% [95%CI 66, 100][a] Specificity 86% [95%CI 42, 100] PPV 93% [95%CI 66, 100] NPV 86% [95%CI 42, 100]
(Nouvong et al 2009) USA	II (Prognosis) Prospective cohort study SIGN: Average quality QUADAS: Poor quality	66 diabetic patients although only 54 completed follow-up. Exclusion criteria: Peripheral arterial occlusive disease requiring surgery, heart failure resulting in oedema, stroke or TIA with residual nerve dysfunction, uncontrolled hypertension, end stage renal disease, severe peripheral oedema, other serious chronic diseases that affect healing, treatment with steroids or chemotherapy, pregnant or lactating women. Patient characteristics:	Healing Index (a measurement requiring oxyhaemoglobin and deoxyhaemoglobin measured at 0.5 or 1cm radius around the ulcer (depending upon ulcer size), as well as the value of oxy and deoxy that best discriminates healed and non healed ulcers).	Healing at 12 months	Sensitivity 80% [95%CI 67, 88][a] Specificity 74% [95%CI 51, 88] PPV 90% Excluding ulcers with callus or osteomyelitis: Sensitivity 86% [b] Specificity 88% PPV 96%

		Male (n) Age (median (range)) Diabetes (type1 / type2) Diabetes Duration (years) A1C (%) BMI (kg/m^2) Systolic BP (mm/Hg) Diastolic BP (mm/Hg) Neuropathy Symptoms Score Neuropathy Disability Score	Healed 35 51 (34-68) 15 / 23 13 (±10) 9.7 (±2.6) 34 (±10) 135 (±24) 76 (±13) 5.3 (±3.3) 7.7 (±3.4)	Non-healed 14 52 (25-63) 8 / 8 12 (±8) 9.5 (±2.4) 31 (±12) 142 (±21) 79 (±9) 4.9 (±3.0) 6.7(±4.9)			

[a] confidence intervals calculated from raw data; [b] raw data unavailable to calculate confidence intervals

PPV = positive predictive value; NPV = negative predictive value; BMI = body mass index; BP = blood pressure; TIA = transient ischaemic attack; VPT = vibration perception threshold; SWF = Semmes-Weinstein filament

Plasma fibrinogen

Plasma fibrinogen as a measure of oxidative stress, was assessed by Rattan and Nayak (2008) to determine its ability to identify who would undergo amputation in those patients with diabetic foot ulcers. Sixty one patients with diabetic foot ulcers (Wagner grade 1 = 41(68%), Wagner grade 2 = 20 (33%)) in India were enrolled in this poor quality study. The potential for confounders was minimised by restrictive exclusion criteria including history of lower extremity vascular surgery, amputation, atherosclerosis, renal impairment, cardiovascular disease or impaired renal function. Plasma fibrinogen levels were determined by immunoturbimetric assay and the mean plasma fibrinogen levels for subjects with Grade 1 and Grade 2 ulcers were 273.88 ± 14.1 mg/dL and 313 ± 5.66 mg/dL respectively ($p < 0.01$).

A receiver operating characteristic (ROC) curve was used to determine the optimal cut-off value of plasma fibrinogen to discriminate between those with and without amputation at the end of follow-up. The optimal cut-off value was ascertained to be 300.4mg/dL which was associated with an area under the curve of 0.976 ($p < 0.001$), sensitivity of 100% and specificity of 92%.

It is unclear from the authors' description what treatment was received by the patients during the eight month follow-up, or whether the treating physician was blinded to these results. Given these limitations, it is difficult to determine whether these results can be directly attributed to plasma fibrinogen levels.

Box 48 summarises this evidence according to the NHMRC body of evidence matrix.

Box 48 Evidence statement matrix for the ability of plasma fibrinogen levels to identify the likelihood of amputation.

Component	Rating	Description
Evidence base	D	One level II studies with a high risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	C	The results of this study suggest that plasma fibrinogen levels are a good discriminator of those at high and low risk of amputation in people with diabetic foot ulcers. However, due to the potential confounding by treatment and possible lack of blinding by treating physician, it is difficult to determine whether these results would be useful in a clinical setting.
Generalisability	A	The study would be generalisable to people with Wagner grade 1 and 2 diabetic foot ulcers.
Applicability	C	Conducted in India, this study is probably applicable to the Australian healthcare context with some caveats.

Evidence statement

There is some evidence to suggest that plasma fibrinogen levels may identify those at risk of amputation in people with Wagner grade 1 or 2 diabetic foot ulcers (Grade C).

Multiple clinical or laboratory assessments

Measures of predictive ability have been described in a number of ways in the studies included in this review. A number of studies reported the strength of the relationship between the predictor variable and the outcome, while others have assessed the discriminatory ability of models to ascertain those at risk of particular outcomes. In order to determine which clinical assessments are the best predictors of foot ulcer outcomes it is necessary to be informed of the discriminatory power of predictive models rather than just the strength of the relationship between the two variables. Studies which provide either measures have been included as they all meet the inclusion criteria for this review, however the usefulness in answering the research question will differ.

DEPA score

(Table 165 and Table 166). The average quality study enrolled 84 consecutive patients with type 1 or 2 diabetes and foot ulcer which were graded either low, moderate of high based on the scoring system. Patients received treatment according to the grade of ulcer, low grade ulcers were managed on an outpatient basis. Only those who showed clinical signs of infection received oral antibiotics, while the remainder received sharp debridement and therapy to maintain blood-sugar control. Moderate grade ulcers received intravenous antibiotics in the presence of infection, underwent blood-sugar control and sharp debridement as well as off-loading methods and healing promoting agents. High grade ulcers were treated as for moderate grade ulcers with the addition of vascular reconstruction where indicated.

The mean follow-up period was 20 weeks (range, 4–24 weeks) and the outcomes were classified as excellent (complete healing of ulcer in < 10 weeks); good (complete healing of ulcer in 10–20 weeks); poor (no healing at 20 weeks); or amputation. The analysis of the raw data consisted of calculating the correlation between the DEPA score and the ulcer outcome. No effect sizes were reported however, the Spearman's correlation coefficient was 0.78 [95% CI 0.68, 0.86] p<0.0001 suggesting a strong linear association between ulcer score and the outcome.

With only the strength of the linear relationship between the DEPA score and ulcer outcome reported, this study provides little value in assessing the predictive ability of the score in relation to foot outcomes.

Box 49 summarises this evidence according to the NHMRC body of evidence matrix.

Box 49 Evidence statement matrix for the ability of DEPA score to predict healing of foot ulcers.

Component	Rating	Description
Evidence base	C	One level II studies with a moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	D	The results of the study indicate a strong linear association between DEPA score and ulcer outcome however, no measures are provided of its diagnostic or predictive performance.
Generalisability	A	The study would be generalisable to people with diabetic foot ulcers.
Applicability	C	Conducted in Jordan, this study is probably applicable to the Australian healthcare context with some caveats.

Evidence statement

There is some evidence to suggest that there is a strong linear relationship between DEPA score and foot ulcer outcome. (Grade C).

University of Texas classification

Armstrong et al (1998) evaluated the University of Texas (UT) wound classification of ulcers in an average quality retrospective cohort study. In this study, Armstrong et al (1998) considered the benefit of evaluating infection and ischaemia in addition to the depth of the wound for determining the severity of the foot ulcer.

Due to the retrospective nature of the study, medical records were relied upon to provide data regarding the baseline status of 360 patients attending a multidisciplinary tertiary care diabetic foot clinic. The authors indicated that all patients who attended the clinic underwent a standardised foot evaluation which included assessment of wound depth, sensory neuropathy, vascular insufficiency and infection. Sensory neuropathy was evaluated with 10g Semmes-Weinstein monofilament and a biothesiometer. Infection was determined using clinical criteria and wound depth was assessed using a sterile blunt probe. If the wound probed to the bone, a biopsy was taken to diagnose osteomyelitis. Ischaemia was assessed by the absence of one or more foot pulses and/or an abnormal ankle-brachial index (< 0.8). Once, patients were classified according to the UT classification (Appendix G), the incidence of amputation after 6 months was determined from the medical records.

The basic analyses consisted of assessing the association between increasing grade or stage of ulceration and the incidence of lower extremity amputation where the authors found a significant trend for increasing amputation at 6 months by both wound depth (grade) (143.1, p<0.001) and stage (91.0, p<0.001). Patients were more than 11 times more likely to receive a midfoot or higher level amputation if their ulcer was classified as grade 3 (OR = 11.1 [95% CI 4.0, 30.3], 31.5, p<0.001) presumably compared to grade 0-2 ulcers. For patients with infection and ischaemia (stage D) the likelihood of midfoot or higher amputation was 90 times greater (OR = 89.6 [95% CI 25, 316], 133.5, p<0.001). Large confidence intervals were associated with these estimates but it is possible that this is a result of no amputation being performed on patients with stage A lesions hence, the authors' may have made adjustments in order to conduct the analyses.

The results of this study show that the consideration of wound depth and the presence of ischaemia and infection are able to classify the severity of the foot ulcer. It also indicates that patients with severe wounds are more likely to require amputation. However, the study did not provide information regarding calibration or the discriminatory ability of the classification system, it is therefore difficult to assess predictive ability and the likely clinical impact.

Box 50 summarises this evidence for the UT system according to the NHMRC body of evidence matrix.

Box 50 Evidence statement matrix for the ability of UT classification with infection and ischaemia, to predict foot ulcer outcomes.

Component	Rating	Description
Evidence base	C	Level III-3 study with moderate risk of bias
Consistency	N/A	Only one study available
Clinical impact	C	The evidence provided suggests that there is a strong association between grade 3 and/or stage D foot ulcers and midfoot or higher amputations.
Generalisability	B	The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care. It should be noted that the majority of patients were Mexican Americans.
Applicability	B	Conducted in the USA, this study is probably applicable to the Australian healthcare context with few caveats.

Evidence statement

There is evidence that there may be a strong association between stage and grade of ulcer, and midfoot or higher amputation in the short term (6 months) (Grade C).

Wagner classification

Apelqvist et al (1989) evaluated the Wagner classification to determine if it were of value in predicting the healing of foot ulcers in a general diabetic population referred to an outpatient clinic in Sweden. The evaluation involved the comparison of the incidence of healing between the Wagner grades and is therefore of limited usefulness in regard to predicting the absolute risk of healing.

The average quality prospective cohort study enrolled consecutive patients referred to an outpatient clinic as a result of foot ulcer. Lesions were classified using the Wagner classification, in addition necrosis through the full thickness of the dermis was included as Grade 1 ulcers, and grade 4 also included continuous necrosis of the skin and underlying tissues mainly on the forefoot. Grade 5 was further defined by continuous necrosis involving the majority of the foot. Ulcers were also defined by their location – digit I; digit II–V; metatarsal heads; heal and mid-foot; and the dorsal surface of the foot. Multidisciplinary care was provided to patients and may have included improved metabolic control or antibiotics for infection. Moist wound dressings were applied and absorptive dressings in the case of exudative wounds. Pressure off-loading and preventive education were also provided to patients. Surgical debridement of lesions and amputation were performed as required.

The primary healing rate was reported by Wagner grade and also the location of ulcer, although the period of follow-up was not defined by the authors. Due to the lack of healing in lesions classified as Wagner grade 5, these lesions have been combined with those of Wagner grade 4. Compared to Wagner grade 1, the risk of not achieving primary healing was 2.17 (95% CI 1.15, 4.10] for those with a lesion classified as Wagner grade 2. For Wagner grade 3 and grades 4 and 5, the relative risk of not achieving primary healing was 3.62 [95% CI 2.10, 6.24] and 8.09 [95% CI 5.23, 12.5] respectively, compared to Wagner grade 1.

With regard to primary healing by location of the ulcer, a significant difference was seen only between ulcers localized to the first metatarsal head compared to other metatarsal heads (91% v 63 % respectively, $p < 0.05$).

Box 51 summarises this evidence for the Wagner classification system according to the NHMRC body of evidence matrix.

Box 51 Evidence statement matrix for the ability of Wagner classification to predict foot ulcer outcomes.

Component	Rating	Description
Evidence base	C	Level II study with moderate risk of bias
Consistency	N/A	Only one study available
Clinical impact	C	The evidence provides relative measures of risk and indicates that the risk of not achieving primary healing increases with increasing Wagner grade.
Generalisability	A	The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.
Applicability	B	Conducted in Sweden, this study is probably applicable to the Australian healthcare context with few caveats.

Evidence statement

With regard to non-primary healing, there is evidence that there is an increase in relative risk with increasing Wagner grade (Grade C).

Baseline characteristics

Two studies reported on similar baseline characteristics as predictors of foot ulcer outcomes. Although both studies met the inclusion criteria for the systematic review, neither provided meaningful information for predicting the risk of foot ulcer outcomes. The purpose of the studies was to identify independent predictors of foot ulcer healing however; the model was not evaluated with regard to estimating risk. Only the higher quality study has been discussed below although the results of both are provided in Table 29.

Ince et al (2007) reported the association of numerous baseline characteristics with time to healing. The average quality retrospective cohort study reviewed the medical records of 449 consecutive patients attending a single specialist foot clinic in the UK. Ulcers were classified using the S(AD)SAD system although it is unclear whether this occurred prospectively or retrospectively. Data for other characteristics including age, gender, type of diabetes and duration were also extracted from the medical records.

Analysis of the data used Cox regression modeling to identify the independent predictors of healing after testing that the assumption of proportional hazards had been met. Multivariate analysis produced a model which included ulcer area, arteriopathy, ulcer site and duration of diabetes as independent predictors of time to healing. Each of these variables showed a dose response relationship with healing which further supports the argument that they contribute to this outcome.

Although this study provides sound evidence for these variables as independent predictors of time to healing and quantifies the strength of this relationship (Table 29), it does not indicate the ability of the model to discriminate between those who are likely to heal and those who are not. Additionally, the study does not provide evidence that this model can be used to predict the risk of ulcer healing therefore, its use in a clinical setting is likely to be moderate.

Box 53 summarises the evidence provided by both studies according to the NHMRC body of evidence matrix.

Box 52 Evidence statement matrix for the ability of baseline characteristics to predict foot ulcer outcomes.

Component	Rating	Description
Evidence base	C	Level II and III-3 study with moderate risk of bias
Consistency	B	There are some inconsistencies which may be explained by the smaller sample size in the study by Obiyo et al (2001).
Clinical impact	C	The evidence provided is likely to have a moderate clinical impact as the studies do not provide sufficient information to estimate risk, nor do they provide adequate information regarding its ability to discriminate between those who are likely to heal and those who are not. However, they do show a relationship between these baseline characteristics and time to healing.
Generalisability	A	The studies would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.
Applicability	B	Conducted in the United Kingdom and the USA, these studies are probably applicable to the Australian healthcare context with few caveats.

Evidence statement

There is evidence that ulcer area, arteriopathy, ulcer site and duration of diabetes are strong independent predictors of time to healing (Grade C).

Table 29 Evaluation of baseline characteristics for the prediction of ulcer healing

Author Country	Level and quality of study	Population	Assessment	Outcome	Outcome data			
(Oyibo et al 2001a) United Kingdom and USA	II Prospective cohort study SIGN: Average quality	194 patients presenting with a new foot ulcer to a diabetic foot clinic. Patient characteristics: Age = 57 ± 13 years; Male = 77%; duration of diabetes = 15 ± 10 years; type II diabetes = 89%.	Clinical and physical examination of: Age Sex Diabetes type Diabetes duration Ulcer size Ulcer depth Presence of infection Presence of ischaemia	Non-healing	**Final model:**		**HR**	**[95% CI]**
					Age		0.99	[0.97, 1.01]
					Sex		0.78	[0.51, 1.18]
					Diabetes type		1.49	[0.74, 3.03]
					Diabetes duration		1.02	[0.99, 1.04]
					Ulcer size*		1.08	[1.01, 1.14]
					Ulcer site		0.98	[0.72, 1.33]
					Ulcer depth		1.04	[0.74, 1.49]
					Presence of infection		1.01	[0.60, 1.72]
					Presence of ischaemia*		1.69	[1.06, 2.70]
(Ince et al 2007) United Kingdom	III-3 Retrospective cohort study SIGN: Average quality	449 patients referred to a specialist foot clinic in the United Kingdom. Patient characteristics: Age = 67 ± 13 years; Male = 64%; duration of diabetes = 13 years (range, 8–21 years); duration of ulcer to first presentation = 29 days (range, 11–61 days); type II diabetes = 86%.	Clinical and physical examination of: S(AD)SAD components including ulcer area; ulcer depth; sepsis; arteriopathy and denervation. Age Duration of diabetes Duration of ulcer Sex Diabetes type Socio-economic status Ulcer site (toe, MTP joint, mid and hind foot)	Time to healing	**Final model:**		**HR**	**[95% CI]**
					Ulcer Area	1	1.0	(Reference)
						2	0.75	[0.54, 1.04]
						3	0.40	[0.24, 0.67]
					Arteriopathy	0	1.0	(Reference)
						1	0.76	[0.54, 1.06]
						2 & 3	0.50	[0.37, 0.67]
					Ulcer Site	Toe	1.0	(Reference)
						MTP	0.73	[0.51, 1.05]
						Mid and hind foot	0.68	[0.49, 0.96]
					Duration of Diabetes	<10 years	1.0	(Reference)
						10-19 years	0.72	[0.53, 0.98]
						≥20 years	0.66	[0.48, 0.92]

MTP = metatarsophalangeal joint; HR = hazard ratio; CI = confidence interval; * statistically significant at the α=0.05 level

Comparison of Wagner, University of Texas and S(AD)SAD classification of foot ulcers

Two average quality studies prospectively evaluated the use of the Wagner wound classification system in predicting foot ulcer outcomes and compared it to either the University of Texas (UT) system and/or the S(AD)SAD score (Oyibo et al 2001b; Parisi et al 2008). Details of the grading systems can be found in Appendix G.

Oyibo et al (2001) compared the Wagner and UT systems in a cohort of diabetic patients with newly presented diabetic foot ulcers. Patients attended one of two specialist diabetic foot clinics in the United Kingdom or Texas. After ulcer assessment and grading, using both classification systems, patients made weekly visits to the clinics where they received care such as debridement, pressure relief with either scotchcast boot or total contact cast. Antibiotics were administered if there were signs of infection; and where there were clinical signs of ischaemia, ultrasound and consultation with a vascular surgeon were provided. Patients were followed for a minimum of 6 months if the ulcer had not healed. Those patients with complete healing or who underwent amputation were recorded, and then exited the study.

The analysis of the data involved assessing the association between ulcer grade or stage and amputation. The evidence of association between grade of ulcer and amputation was slightly stronger with the UT classification system (= 23.7 versus = 21.0) (Table 30). Additionally, the stage of ulcer was also significantly associated with median healing time for the UT scoring system, but not so for the grade in both UT and Wagner systems.

Parisi et al (2008) evaluated both Wagner and UT systems as well as the (S(AD)SAD) classification system in a cohort of 94 consecutive patients who presented at a multidisciplinary diabetes clinic in Brazil. Patients were assessed for neuropathy using vibration perception and Semmes-Weinstein filaments; ulcer depth was assessed by visual inspection; and infections were determined by clinical signs and a positive probe to bone test. Patients received care including sharp debridement, pressure off-loading and revascularisation if appropriate at regular visits to the clinic every 1 to 4 weeks. The primary outcome of interest was ulcer healing (with or without minor amputation) after a minimum 6 month follow-up.

The authors reported two measures of discriminate ability for these classification systems. The odds ratio was reported to describe the likelihood of healing between the stages and/or grades within a classification system. Also, they reported the AUC to describe the ability of the classification systems to appropriately discriminate between those with a higher probability of healing and those with a lower probability. These results are described in Table 30 and show that all three classification systems discriminate well, although based on the AUC, the UT system has the greatest discriminatory power. This is likely to be as a result of the inclusion of the infection and ischaemic variables in the classification system, which is further supported by the absence of infection being the only independent predictor of healing when considered in the regression analysis of the S(AD)SAD system component variables.

It is difficult to directly compare the results of the Parisi et al (2008) study with those of the Obiyo et al (2001) as the outcomes differed, as well as some of the reported measures of effect. However, the studies did show that Wagner and UT systems perform well in predicting the likelihood of healing and that there is a strong association between grade of ulcer and risk of amputation in patients with diabetic foot ulcer. It could be argued, based on the results provided, that the UT classification system is superior at predicting these outcomes than the Wagner system. The S(AD)SAD system has also been shown to perform well in predicting healing of foot ulcers at 6 months although the confidence intervals were reasonably wide suggesting some uncertainty around the point estimate.

Box 53 summarises this evidence for the comparison of Wagner and UT system according to the NHMRC body of evidence matrix.

Box 53 Evidence statement matrix for the comparison of Wagner and UT classification.

Component	Rating	Description
Evidence base	C	Two level II studies with a moderate risk of bias.
Consistency	C	Both studies provide evidence that the UT classification is likely to be superior in predicting amputation and healing of foot ulcers
Clinical impact	B	This evidence would likely have a substantial impact on clinical practice.
Generalisability	A	The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.
Applicability	B	Conducted in Brazil, UK and USA, these studies are probably applicable to the Australian healthcare context with few caveats.

Evidence statement

The evidence provided suggests that the UT classification would better predict the outcome of ulcers and healing compared to Wagner grading (Grade C).

Box 54 summarises this evidence for the UT system according to the NHMRC body of evidence matrix.

Box 54 Evidence statement matrix for the comparison of Wagner, UT and S(AD)SAD classification.

Component	Rating	Description
Evidence base	C	One level II studies with a moderate risk of bias.
Consistency	N/A	Only one study available
Clinical impact	B	This study suggests that all three classifications are likely to predict the outcome of healing although with regard to discriminatory ability, the UT system is superior (no measure of discrimination was provided for S(AD)SAD)
Generalisability	A	The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.
Applicability	B	Conducted in Brazil, UK and USA, these studies are probably applicable to the Australian healthcare context with few caveats.

Evidence statement

There is reasonable evidence to suggest that the UT classification of diabetic foot ulcer is better able to predict the likelihood of healing or amputation than the Wagner and S(AD)SAD classification systems (Grade C)

Table 30 Predictive performance of Wagner, University of Texas and S(AD)SAD classification systems

Author Country	Level and quality of study	Population	Assessment	Outcome	Outcome data
(Oyibo et al 2001b) UK and USA	II Prospective cohort study SIGN: Average quality	194 diabetic patients with newly presenting foot ulcers Patient characteristics: Age = 56 ± 12.6 years; male/female = 149/45; type 1 / type 2 diabetes = 21 / 173; ulcer size = 1.48 cm^2 (range, 0.68–4.0); type of ulcer: neuropathic (67%), neuroischaemic (26%), ischaemic (1%), non-neuropathic non-ischaemic (6%); site of ulcer: forefoot (78%), midfoot (12%), hindfoot (10%).	Wagner classification[a]	Amputation	= 21.0 p<0.0001
				Median healing time	Grade 1: 8 weeks Grade 2: 16 weeks Grade 3: 11 weeks 5.68, df = 3 p = 0.13
			University of Texas classificiation[b]	Amputation	Grade: = 23.7, p < 0.0001 Stage: = 15.1, p = 0.0001 Stage B v Stage A OR = 11.1 [95% CI 3.0, 41.0] p < 0.0001 Stage C v Stage A OR = 4.6 [95% CI 0.9, 24.7] p = 0.09 Stage D v Stage A OR = 14.7 [95%CI 3.7, 58.2] p < 0.0001 Stage C & D v Stage A & B OR = 2.8 [95%CI 1.2, 6.5] p < 0.05
				Median healing time	Grade 1: 8 weeks Grade 2: 12 weeks Grade 3: 16 weeks 5.47, df=2, p=0.07 Stage A: 7 weeks Stage B: 11 weeks Stage C: 16 weeks Stage D: 20 weeks 10.24, df=3, p=0.02
(Parisi et al 2008) Brazil	II Prospective cohort study	94 consecutive patients presenting with diabetic foot ulcer at multidisciplinary clinic.	Wagner classification[a]	Healing at 6 months (with or without minor amputation)	Grade 1 OR = 3.48 [95% CI 1.38, 8.76] 2–3 OR = 1 (reference) AUC = 0.631

	SIGN: Average quality	Patient characteristics: Age = 57.6 ± 12.4years; male = 61%; duration of diabetes = 16.9 ± 8.2 years; smoking = 41%; hypertension = 81%; cardiovascular disease = 33%; stroke = 7%; neuropathy = 59%; ischaemia = 36%; plantar ulcer = 95%; dorsal ulcer = 5%.	University of Texas classificiation[b]	Healing at 6 months (with or without minor amputation)	Grade	1	OR = 2.87	[95% CI 1.08, 7.64]
						2–3	OR = 1	(reference)
					Stage	A	OR = 4.6	[95% CI 1.37, 15.49]
						B	OR = 1.68	[95% CI 0.46, 6.11]
						C	OR = 2.26	[95% CI 0.62, 8.32]
						D	OR = 1	(reference)
							AUC = 0.723	
			S(AD)SAD classification [c]	Healing at 6 months (with or without minor amputation)	Score	≤9	OR = 7.64	[95% CI 2.72, 21.45]
						>9	OR = 1	(reference)
					Using the above cut-off scores to predict healing:			
					Sensitivity		87.5%	
					Specificity		52.2%	
					Accuracy		70.2%	
					In a multivariate logistic regression, infection was an independent predictor of healing at 6 months:			
					No infected lesions		OR = 4.26 [95% CI 1.77, 10.26]	
					Cellulitis/Osteomyelitits		OR = 1	(reference)

[a] details of Wagner classification are in Appendix G; [b] details of University of Texas classification are inAppendix G; [c] = details of S(AD)SAD classification are inAppendix G; OR = odds ratio; AUC = area under the curve.

Comparison of Wagner and Van Acker/Peter classification

The poor quality study by Van Acker et al (2002) compared the Van Acker/Peter (VA/P) classification of foot ulcers (based on the University of Texas classification), with the Wagner system. In this retrospective study design, 121 patients with 253 ulcers were classified by the Wagner and the VA/P classification systems (Appendix G) and followed to determine whether amputation was required to achieve healing. It is uncertain how long the patients were followed or what treatments were received. The VA/P system is based on the University of Texas classification and includes grades of foot pathology and type of lesion. A simple analysis determined if there were significant associations between components of the VA/P classification and amputation, and also the correlation between the two scores. The results of the study indicate that there was a significant association between the VA/P classification and the need for amputation by both vertical (foot pathology) and horizontal (type of lesion) axes ($p < 0.05$). Additionally, the analysis showed that the VA/P was statistically correlated with the Wagner classification (Spearman's rho = 0.473, $p < 0.05$), although the strength of this correlation was noticeably stronger for the vertical (Spearman's rho = 0.665) than the horizontal axis (Spearman's rho = 0.274), $p > 0.05$.

The information provided in this study suggests that there is a significant correlation between the two grading systems but does not provide any data to suggest that either is superior in predicting ulcer outcomes or for discriminating between risk levels.

Box 55 summarises the evidence for the comparison of the VA/P and Wagner grading of foot ulcers according to the NHMRC body of evidence matrix.

Box 55 Evidence statement matrix for the comparison of VA/P and Wager grading systems.

Component	Rating	Description
Evidence base	D	One level III-3 studies with a high risk of bias.
Consistency	N/A	Only one study available
Clinical impact	C	The study provides evidence that there is an association between VA/P classification and amputation, and that the grading of patients is significantly correlated between the two systems.
Generalisability	A	The study would be generalisable to people with diabetic foot ulcers.
Applicability	B	Conducted in Belgium the study is probably applicable to the Australian healthcare context with few caveats.

Evidence statement

There is evidence that the VA/P classification is moderately correlated with the Wagner grading of foot ulcers (Grade C).

Diabetic ulcer severity score (DUSS) and M.A.I.D[1]

Two studies evaluated very similar prognostic scoring systems in chronic lower extremity ulcers (Beckert et al 2006; Beckert et al 2009). Using similar populations, the studies evaluated the use of probing to bone; location of foot ulcer; pedal pulses; multiple ulcers; wound are and wound duration to predict the probability of healing (Table 31). As the earlier study was specifically for diabetic ulcers, only this study will be discussed.

[1] M.A.I.D. refers to presence of multiple ulcerations (M); wound area (A); palpable pedal pulses (I); and ulcer duration (D).

The severity of foot ulcers using ischaemia, infection, site and number was evaluated by Beckert et al (2006) in a large average quality cohort study. Patients attended a wound care unit where they received appropriate multidisciplinary care including sharp debridement, surgery, moist wound therapy and pressure off-loading. Baseline evaluation of patients included assessment of wound depth with a sterile blunt probe; clinical signs of infection; peripheral vascular disease as defined by the absence of both pedal pulses; and the number and location of ulcers. A wound score was calculated according to the scoring system described in Appendix G. Patients were then followed for one year or until healing or amputation had occurred.

Cox regression was used to determine the risk of healing according to DUSS and then to assess which variables contributed most to the outcome. Healing was defined as complete epithelialisation which differs slightly from other studies which included minor amputations as part of the definition. According to Beckert et al (2006) the risk ratio of healing according to DUSS was 0.65 [95%CI 0.59, 0.71] ($p < 0.001$) indicating that for every increase in DUSS of one point, there was a 35% decrease in the probability of healing. Further analysis suggested that all of the components measured by DUSS were independent predictors of healing which had a significant influence on the outcome (data not shown).

The results of this study suggest that DUSS may indicate those with a high probability of healing and those with low probability however, no further analyses regarding the goodness of fit, discrimination or calibration of the scoring system were provided. As a consequence of this lack of information regarding the usefulness of the scoring system, it is difficult to determine the clinical impact of the DUSS.

Box 56 summarises this evidence for the DUSS and M.A.I.D. according to the NHMRC body of evidence matrix.

Box 56 Evidence statement matrix for the ability of the DUSS to predict foot ulcer outcomes.

Component	Rating	Description
Evidence base	C	Two level II studies with a moderate risk of bias.
Consistency	B	Inconsistencies are likely to be explained by the additional population in the later study.
Clinical impact	C	The evidence provided suggests that there is a decreasing likelihood of healing with an increase in DUSS or M.A.I.D. however no information was provided regarding the accuracy of the scores to predict healing in people with foot ulcer
Generalisability	B	The studies should be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.
Applicability	B	Conducted in Germany, the studies is probably applicable to the Australian healthcare context with few caveats.

Evidence statement

The evidence provided suggests that an increase in DUSS or M.A.I.D score is associated with a decreased probability of foot ulcer healing (Grade C).

Table 31 M.A.I.D and DUSS classification of foot ulcers to predict healing

Author Country	Level and quality of study	Population	Assessment	Outcome	Outcome data		
(Beckert et al 2006) Germany	II Prospective cohort study SIGN: Average quality	1000 consecutive diabetic patients presenting with foot ulcer(s) to an outpatient wound care unit in Germany. Patient characteristics: Age = 69 years (range, 26–95 years); male = 68%; number of visits = 5 (range, 2–60).	DUSS score[a]: Multiple ulcers Probing to bone Location (foot or toe) Non-palpable pulses	Time to healing		HR	[95% CI]
					DUSS	0.65	[0.59, 0.71]
					DUSS components:		
					Multiple ulcers	0.65	[0.54, 0.78]
					Probing to bone	0.78	[0.62, 0.97]
					Location	0.48	[0.40, 0.58]
					Non-palpable pulses	0.72	[0.60, 0.87]
(Beckert et al 2009) Germany	II Prospective cohort study SIGN: Average quality	2019 consecutive patients presenting with a chronic lower extremity ulcer to an outpatient clinic in Germany. Patient characteristics: Age = 70 years (range, 15–98 years); male = 58%; number of visits = 5 (range, 2–96).	M.A.I.D score[b]: Multiple ulcers Wound size (> 4 cm^2) Wound history (> 130 days) Non-palpable pulses	Time to healing		HR	[95% CI]
					M.A.I.D.	0.63	[0.58, 0.67]
					M.A.I.D components:		
					Multiple ulcers	0.73	[0.70, 0.84]
					Wound size	0.46	[0.39, 0.54]
					Wound history	0.64	[0.55, 0.75]
					Non-palpable pulses	0.83	[0.72, 0.95]

[a] Details for DUSS scoring system are found in Appendix G; [b] details for M.A.I.D scoring are found in Appendix G.

Scottish foot ulcer risk score

Leese et al (2007) reported on the use of a foot screening tool in a multidisciplinary diabetic foot clinic to predict the outcome of foot ulcer in a poor quality retrospective cohort study. Initially, patients without foot ulcer and who were attending hospital or general practice-based diabetes clinics were screened for risk of foot ulcer with the tool (Appendix G) and the information was stored in shared electronic health records. This study performed a retrospective analysis on the patients who were attending specialist diabetic foot clinics and determined the association between the original foot risk score and the probability of ulcer healing in those who subsequently developed foot ulcer and attended the foot clinic. It should be noted that not all patients who were originally screened were referred to the foot clinic, with the potential for more people who were at high risk being referred to the clinic than people considered at low risk of foot ulcer.

With regard to the ability of the foot risk score to predict ulcer outcomes, little information is provided. The authors reported that people who were at high risk of ulceration were less likely to heal than those at low- or moderate risk of ulceration (68% versus 93%, $p < 0.0001$). Whilst a significant association between the risk score and ulcer outcome has been reported, this study is likely to be substantially affected by selection bias due to differences in referral rates between risk categories. Hence, little weight should be given to the results of the study.

Box 57 summarises the evidence for the Scottish foot risk score according to the NHMRC body of evidence matrix.

Box 57 Evidence statement matrix for the ability of the Scottish foot risk score to predict foot ulcer outcomes.

Component	Rating	Description
Evidence base	D	One level II studies with a high risk of bias.
Consistency	N/A	Only one study available
Clinical impact	D	This poor quality evidence and lack of information regarding the predictive ability of the foot risk score prevent the evaluation of the potential clinical impact.
Generalisability	B	The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care. There is likely to be substantial selection bias which would decrease the generalisability.
Applicability	B	Conducted in Scotland, the study is probably applicable to the Australian healthcare context with few caveats.

Evidence statement

The evidence for the association between foot risk score and outcomes is poor (Grade D).

Prediction of non-healing in diabetic neuropathic foot ulcers

Three studies provided evidence regarding the prediction of non-healing in diabetic neuropathic foot ulcers (Margolis et al 2002; Margolis et al 2003; Margolis et al 2005). These three studies are likely to have been conducted in the same population, with the 2002 and 2005 studies reporting the predictor variables and their association with the outcome, and the 2003 study providing evidence of the relative predictive ability of the model. As little information is provided in the first and last study with regard to predictive ability, only the second study will be discussed however, the results of all studies are reported in Table 32.

In the average quality study by Margolis et al (2003), three predictive models were evaluated for their accuracy in terms of discrimination and calibration using a large dataset to develop the models. The cohort was randomly divided into modeling (70%) and validation (30%) data sets

however, potential confounders such as treatment regimen are likely to apply equally to both data sets. Additionally, the validation dataset is unlikely to differ greatly from the modeling dataset as they are derived from the same source population and it would be expected that they are subject to the same referral patterns and be comprised of similar demographic and baseline characteristics.

Calibration, or the ability of the model to accurately predict the risk of non-healing, was assessed by visually appraising the observed and expected risk of non-healing for each model. The authors did not report a statistical analysis of the models in this regard although they did indicate that the risks were similar for all prognostic factors. Discrimination was assessed by calculating the area under the receiver operating characteristic (ROC) curve (AUC) for each of the models considered using both the modeling data and the validation data. Of the four models, the first model which included all prognostic factors (sex, number of wounds, duration of wounds, size of wounds and wound grade) showed the best discrimination, this was followed by the three variable model (model 2, Table 32). Dichotomising the variables or simplifying the scoring method saw a loss in discriminatory ability as seen by model 3 and 4. It is unknown if there is significant uncertainty around these estimates as no confidence intervals were reported.

Box 58 summarises the evidence for the Curative Health Services predictive models according to the NHMRC body of evidence matrix.

Box 58 Evidence statement matrix for the ability of the Curative Health Services predictive models to predict non-healing.

Component	Rating	Description
Evidence base	C	One level III studies with a moderate risk of bias.
Consistency	N/A	Only one study available which reported outcomes of predictive ability
Clinical impact	B	The study provided evidence that the models were able to discriminate and satisfactorily identify those patients who were unlikely to heal. Greater discrimination was seen in the model with the most predictor variables. Basic evaluation of the calibration of the models indicated that the predicted risk was similar to the observed risk of non-healing.
Generalisability	B	The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.
Applicability	B	Conducted in the USA, the study is probably applicable to the Australian healthcare context with few caveats.

Evidence statement

There is some evidence to suggest that the predictive model developed by the Curative Health Services is able to discriminate and accurately predict the risk of non-healing in people with diabetic foot ulcers attending specialist wound care centres (Grade C).

Table 32 Prediction of non-healing in diabetic neuropathic foot ulcers by the Curative Health Services

Author Country	Level and quality of study	Population	Assessment	Outcome	Outcome data
(Margolis et al 2005) USA	III-3 Retrospective cohort study SIGN: Average quality	24,616 patients attending Curative Health Services wound care facilities. Patient characteristics: Age = 63.6 ± 43.9 years; male = 56%; duration of wound = 2.75 ± 3.75 months.	Sex Ulcer grade [a] Age Count (number of wounds) Wound duration Wound size	Amputation at 20 weeks	OR [95% CI] Sex (male) 1.33 [1.19, 1.48] Grade 1 Reference 2 1.28 [0.88, 1.86] 3 2.71 [1.83, 4.01] 4 6.30 [4.31, 9.21] 5 7.33 [4.93, 10.90] 6 31.57 [20.15, 49.47] Age 1.01 [1.01, 1.01] Count 1.32 [1.27, 1.38] Wound duration 0.97 [0.93, 1.01] Wound size 0.97 [0.94, 1.00]
(Margolis et al 2002) USA	III-3 Retrospective cohort study SIGN: Average quality	75, 525 wounds in 31, 106 individuals attending Curative Health Services wound care facilities. Patient characteristics: Age = 63.8 years; male = 53.9%; previous care at wound care centre = 20.5%; duration of wound = 5.39 months (mean), 1.0 months (median).	Sex Prior wounds Ulcer grade [a] Age Count (number of wounds) Wound duration Wound size	Non-healing	OR [95% CI] Sex (male) 1.07 [1.03, 1.12] Prior wounds 0.92 [0.89, 0.96] Grade 2.05 [1.98, 2.13] Age 1.00 [1.00, 1.01] Count 1.12 [1.11, 1.14] Wound duration 1.23 [1.21, 1.24] Wound size 1.31 [1.23, 1.32]
(Margolis et al 2003) USA	III-3 Retrospective cohort study SIGN: Average quality	27, 630 patients attending Curative Health Services wound care facilities.	Size Duration Ulcer grade [a]	Non-healing	AUC Model data / Validation data Model 1[c] 0.69 / 0.70 Model 2[d] 0.68 / 0.69 Model 3[e] 0.66 / 0.66 Model 4[f] 0.65 / 0.66

[a] Wounds were graded according to the Curative Health Center (classification) (Table 173);
[b] count refers to the number of dichotomous prognostic factors;
[c] Model 1 = -2.64 + (0.01 x age) + (0.01 x male) + (0.18 x number of wounds) + (0.25 x ln(wound size in mm^2)) + (0.32 x wound grade 2) + (0.72 x wound grade 3) + (0.97 x wound grade 4) + (1.31 x wound grade 5) + (2.47 x wound grade 6)
[d] Model 2 = -1.71 + (0.26 x ln(duration in months)) + (0.28 x ln(wound size in mm^2)) + (0.63 x wound grade)
[e] Model 3 = -0.70 + (0.57 x wound duration) + (0.73 x wound size) + (0.71 x wound grade), Note: these variables are dichotomised as follows: wound duration 0.695 ln(months), wound size 5.30 ln (mm^2), wound grade ≥ 3
[f] Model 4 = count model where sum of 1 point each if wound is older than 2 months, larger than 2 cm^2, and grade ≥ 3.
OR = odds ration; CI = confidence interval.

Clinical history, physical examination and MRI

Edelman et al (1997) reported the assessment of a model to predict non-healing of diabetic foot ulcer in an average quality prospective cohort study. The authors wished to evaluate the discriminatory ability of clinical history, physical examination and magnetic resonance imaging (MRI) for the diagnosis of osteomyelitis, to predict complete wound closure in a population of diabetics with one or more foot ulcers, regardless of their severity. Patients were excluded if they had previously been diagnosed with osteomyelitis or had a bone biopsy for the current ulcer. A total of 64 patients with 78 ulcers were enrolled from outpatient, inpatient and emergency department settings and followed for 6 months.

Patients received a 13 item structured clinical history and a 16 item structured physical examination (Appendix G). Correlation for continuous variables, and kappa score for discrete variables, was calculated to determine the inter-observer agreement between the study physician and the referring physician. This was used to assess whether the clinical examination was adequately reproducible to use as a prognostic tool. Agreement ranged from very good for smoking status ($\kappa = 0.86$, [95% CI 0.79, 0.94]) to very poor for physician estimate of the likelihood of osteomyelitis ($\kappa = 0.13$, [95% CI -0.13, 0.30]). Patients also received MRI to determine the presence of osteomyelitis. The results of this assessment were relayed to the referring doctor by the study physician, with the former always responsible for the patient's treatment plan.

Multiple logistic regression was used to build a model for the prediction of ulcer non-healing after considering the relationship with all the variables measured for clinical history, physical examination and MRI diagnosis of osteomyelitis. The final model included only the absence of an audible posterior tibial pulse on Doppler examination (OR = 8.46 [95%CI 1.54, 46.5]) and the presence of pain at the site of the ulcer (OR = 3.69 [95%CI 1.03, 13.2]). This model showed good discriminatory ability with an AUC of 0.742. When elements of the examination which required use of a Doppler were excluded, the significant predictor elements were prior amputation (OR = 6.45 [95%CI 1.86, 22.4]) and pain (OR = 2.85 [95%CI 1.04, 7.81]). This model also had good discriminatory ability with an AUC of 0.741. Interestingly, MRI diagnosis of osteomyelitis did not prove to be an independent predictor of non-healing.

Unfortunately the study did not define the entire risk equation and therefore it would not be possible to calculate the expected risk of non-healing in a patient with foot ulcer. It is therefore difficult to evaluate the likely impact of using this model in predicting foot ulcer severity.

Box 59 summarises the evidence for the clinical and physical examination to predict non-healing according to the NHMRC body of evidence matrix.

Box 59 Evidence statement matrix for the predictive ability of clinical and physical examination, and MRI

Component	Rating	Description
Evidence base	C	One level II studies with a moderate risk of bias.
Consistency	N/A	Only one study available
Clinical impact	C	The study provided evidence that the absence of an audible posterior tibial pulse on Doppler examination and the presence of pain at the site of the ulcer were strong predictors of non-healing. However, the ability of model to accurately predict the risk of this outcome was not assessed.
Generalisability	A	The study would be generalisable to people with diabetic foot ulcers.
Applicability	B	Conducted in the USA, the study is probably applicable to the Australian healthcare context with few caveats.

Evidence statement

There is evidence to suggest that audible posterior tibial pulse on Doppler examination and the presence of pain at the site of the ulcer are strong predictors of non-healing in people with diabetic foot ulcers (Grade C).

International consensus on the diabetic foot wound classification

Widatalla et al (2009) reported the use of the wound classification criteria of the International Working Group on the diabetic foot as predictors of amputation. In this average quality prospective cohort study 2321 patients attending the diabetic foot centre in Khartoum were assessed for ischaemia; neuropathy; depth of wound; infection; and linear measures of wound surface and classified according to the criteria described in Table 22 (Appendix G). Renal impairment was also used to classify patients although the exact criteria for this were not described. The majority of patients who enrolled had type II diabetes (71%) and a foot ulcer (84%). Patients were followed for up to two years and the incidence of amputation was recorded, and the association between the variable and the outcome calculated. No description of the statistical analysis was provided by the authors so it is unclear whether the odds ratios reported were adjusted or crude estimates.

Statistically significant predictors of major amputation were neuropathy (OR = 2.43 [95% CI 1.08, 5.45]), end stage renal disease (OR = 4.39 [95% CI 1.53, 12.61]) and ischaemia (grade 1 or 2 versus grade 3) (OR = 5.08 [95% CI 2.56, 10.07]). For predicting toe amputation the significant predictors were neuropathy (OR = 2.16 [95% CI 1.32, 3.5]), grade of infection (Grade 1 or 2 versus grade 3 or 4) (OR = 2.4 [95% CI 1.55, 3.7]).

No meaningful data was reported in the study to provide evidence of the predictive ability of this classification in predicting amputation however; it does establish a relationship between the individual criteria and amputation.

Box 60 summarises the evidence according to the NHMRC body of evidence matrix.

Box 60 Evidence statement matrix for the International Working Group on the diabetic foot criteria

Component	Rating	Description
Evidence base	C	One level II studies with a moderate risk of bias.
Consistency	N/A	Only one study available
Clinical impact	C	This study only provides evidence that the criteria are predictors of amputation. It remains unclear whether the results were crude or adjusted estimates of association.
Generalisability	B	The study may be generalisable to people with diabetic foot ulcers.
Applicability	C	Conducted in the Sudan, the study is probably applicable to the Australian healthcare context with some caveats.

Evidence statement

This study provides evidence that neuropathy, end stage renal disease, ischaemia and infection are strong predictors of amputation (Grade C).

Summary

Of the studies included in this review 23 provided evidence for multiple clinical assessments or scores; while 9 provided evidence for single assessments. The studies have been summarised below in terms of the diagnostic and predictive performance. With regard to reporting the predictive ability of assessments, studies only reported relative measures of association that is,

odds ratios, relative risks and hazard ratios. As a result, it is difficult to evaluate the ability of an assessment to predict the absolute risk of a foot outcome, only the ability to do so relative to a reference group. Additionally, a number of assessments reported the strength of association between a variable (as part of a multivariate risk model) and the outcome, rather than the strength of association with the model as a whole. Consequently, the diagnostic performance is likely to provide the most valuable information regarding predictive ability. Good diagnostic accuracy was reported in a number of single and multiple assessments (Table 33). Comparatively, there was evidence that the UT classification has better diagnostic performance than the Wagner grading system

Table 33 Summary of diagnostic and predictive performance of assessments.

Assessment	Diagnostic performance	Predictive performance[a]
Single clinical or laboratory assessments		
Skin perfusion pressure	Good (Grade C) –healing	No evidence
Hyperspectral imaging	Good (Grade C)–healing	No evidence
Plasma fibrinogen levels	Good (Grade C)–amputation	No evidence
$TcPO_2$	Good – improved healing (Grade C)	No evidence
Toe Blood pressure	Good, ruling in – improved healing (Grade C)	No evidence
Ankle peak systolic velocity	Good (Grade D) – non-healing	No measures of predictive performance[b].
Bone scans for osteomyelitis	Moderate (Grade D)– amputation	Good (Grade C)
Capillary circulation with macro-aggregated albumin	No evidence	No measures of association reported
Systolic ankle and toe blood pressure	No evidence	No evidence[c]
Multiple clinical or laboratory assessments		
University of Texas	Good discrimination (Grade C) – healing	Good (Grade C)
Clinical history, physical examination, MRI	Good discrimination (Grade C) – non-healing	Good (Grade C)
Wagner classification	Moderate discrimination (Grade C) – healing	Good (Grade C)
S(AD)SAD classification	Moderate (Grade C) - healing	Good (Grade C)
CHS (Curative Health Services)	Moderate discrimination (Grade C) – non-healing	Moderate (Grade C)
DEPA score	No evidence	Strong correlation (Grade C)
International consensus on diabetic foot wound classification	No evidence	Good (Grade C)
Baseline characteristics	No evidence	Moderate (Grade C)
DUSS	No evidence	Moderate (Grade C)
M.A.I.D.	No evidence	Moderate (Grade C)
Van Acker/Peter classification	No evidence	Poor (Grade C)
Scottish foot risk score	No evidence	No measures of association reported

[a] Only relative measures of association were reported in the included evidence; [b] Logistic regression indicated that ankle peak systolic velocity was an independent predictor of non-healing but no estimates of the strength of the relationship were reported; [c] Evidence was reported of a significant difference in ankle and toe blood pressure between those who healed and those who undergo amputation.

Research Question 4: How often, and by whom, should foot assessment be carried out in people with or without foot ulceration

Box 61 Inclusion criteria for the evaluation of foot assessment frequency

Research Question	
How often, and by whom, should foot assessments be carried out in people with or without foot ulceration?	
Parameter	Inclusion criteria
Population	Adults with type 1 or type 2 diabetes with or without a foot ulcer Subgroups- a) who have potentially elevated risk of ulceration (eg long duration of diseae, injury, smoking, uncontrolled glucose levels for extended periods, age); or b) with the presence of a risk factor eg PVD, peripheral neuropathy or foot deformity; or c) people with a history of foot ulcer; or d) In indigenous populations
Intervention	*This will depend on the assessments identified in question 1* eg Semmes-Weinstein monofilaments; plantar foot pressure measurements; vibration perception threshold; joint mobility; or pedal pulse
Outcomes	Clinical outcomes including mortality/survival; pre-ulcer lesions; time to foot ulcer; foot ulceration; amputation (major, transmetatarsal, transtibial, ray or toe); time to amputation; mobility restriction; general functioning; quality of life; independence; frequency of assessment.
Study design	Randomised, pseudo-randomised or non-randomised controlled trials, cohort studies, or systematic reviews of these study designs. For studies reporting diagnostic accuracy outcomes, cross-sectional studies where subjects are cross-classified on the test and comparator(s)and/or reference standard; or systematic reviews of cross-sectional studies. *In the absence of evidence regarding foot assessment as an intervention (Q1) then frequency of assessment as a predictor of foot ulcer will be considered using the study design criteria below:* Prospective cohort studies[a]; all or none study; analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial; retrospective cohort study; case series or cohort study of persons at different stages of disease; or systematic reviews of these study designs.
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified. Translation of such articles will significantly increase the timeframe of the review.
Publication date	1966 – 11/2009
Limitations	Human

Based on the evidence found in questions 1 to 3, five articles were identified that fulfilled the inclusion criteria as per Box 61. Four articles reported on foot assessment in a diabetic population without foot ulceration and one article on a diabetic population with foot ulceration.

Furthermore, a section on assessments for the prediction of foot ulceration or lower extremity amputation has been included, to provide an overview of follow-up periods over which the predictive ability of assessments has been assessed. A detailed discussion is provided below.

Diabetic population without foot ulceration

Home-Based Foot Temperature Monitoring

There were a total of three good quality studies identified that reported on home based foot temperature monitoring as an assessment tool. One study was a pilot study that was followed by an extension phase. The results of the pilot study (6 month follow-up) and extension phase (15 month follow-up) the randomised controlled trial with 18 month follow-up demonstrate that

home-based skin temperature monitoring with the TempTouch© in addition to standard care reduced the incidence of foot ulcer in high risk diabetic patients. The studies indicated that screening should be applied twice daily on six sites on both feet. The screening was done by the patients themselves after being instructed by a nurse how to apply the infrared skin thermometer. As soon as the patient measured a temperature difference of more than 4º F (2.2ºC) between the two feet, they were to contact the study coordinator and reduce activity until temperatures normalised (Armstrong et al 2007; Lavery et al 2004; Lavery et al 2007).

The results suggest that twice daily assessment of foot temperature by the patient in the home-based setting reduces the incidence of foot ulcer in high risk patients. However, this result is dependent on patients complying with the monitoring frequency, which might taper off during or after 18 months if patients are not participating in a trial and receiving support and reminders. Box 62 summarises the body of evidence according to the NHMRC grading criteria.

Box 62 Evidence statement matrix for the frequency of home based temperature monitoring in addition to standard wound care

Component	Rating	Description
Evidence base	B	Two level II studies with a low risk of bias.
Consistency	A	The studies provided consistent results.
Clinical impact	B	The results on the prevention of foot ulceration or lower extremity amputation reflect a substantial clinical impact The absolute reduction in risk of foot ulcer varied from 7-22% when patients complied with the program.
Generalisability	B	The study included diabetic patients at high risk of foot complications, able to apply the intervention by themselves in their home situation.
Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.

Evidence statement

The evidence indicates that home based foot temperature monitoring in addition to standard care should be applied twice daily by the patient to prevent diabetic foot ulceration and lower extremity amputation (Grade B).

Diabetic foot screening program

The average quality study by McCabe et al assessed a foot screening program for the prevention of foot ulceration and amputation in diabetic patients (McCabe et al 1998a).

The screening program consisted of two stages. In the first stage, 1001 patients, recruited from a weekly general diabetes clinic, were measured with Semmes-Weinstein monofilament, biothesiometer and palpation of pedal pulse by registrars. Patients that were found to have a major deficit in one of the measurements above (n=259) were immediately screened for a second time (second stage), which included ankle brachial index calculation, subcutaneous oxygen levels, foot pressure measurements and x-rays in addition to the original screening tests. Patients that were found to be at high risk of foot ulceration or amputation after the second screening followed a weekly protection program involving foot care (chiropody and hygiene maintenance), support hosiery and protective foot wear over a 2 year follow up period.

The study reported a reduction in ulcer or amputation incidence over a 2 year follow up period, however the assessment was only conducted at baseline and no information was reported to suggest that it was performed more frequently. Additionally it was unclear over what duration the protection program was conducted. As such, only an evidence statement regarding who should conduct the assessment has been provided.

Box 63 Evidence statement matrix for the frequency of diabetic foot screening and protection program

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study.
Clinical impact	D	As the study did not provide information on the frequency of screening or the duration of the protection program, the clinical impact is uncertain.
Generalisability	B	The study included patients from a general diabetes clinic in the UK. There are no patient characteristics presented.
Applicability	B	The study was performed in the UK which has a similar healthcare context to the Australian health care system.

Evidence statement

The evidence suggests that foot screening, performed by a registrar, should take place in two direct sequential stages to identify those patients at high risk of lower extremity amputation, followed by a protection program to prevent amputation. (Grade C).

Assessments for the prediction of foot ulceration and lower extremity amputation

Two tables, for a population without foot ulcer (Table 34) and with foot ulcer (Table 35) at baseline, have been included in this section to provide an overview of the follow-up periods for which particular foot assessments may be able to predict foot ulceration or lower extremity amputation.

Only one study reported that a foot assessment was conducted regularly. Apelqvist et al (1989) reported that systolic ankle and toe blood pressure was assessed every 6 months. However, at the end of 18 months, they only reported that there was a statistically significant difference in blood pressure measurements between those who required amputation and those who did not. This evidence therefore, does not provide information regarding the frequency of assessment for predictors of foot ulcer outcomes

Due to the lack of information on the frequency of assessment, no evidence statement has been provided.

Table 34 Summary of diagnostic and predictive performance of included assessments in a diabetes population without foot ulcer

Assessment	Diagnostic performance	Predictive performance	Follow-up period
General Diabetic Population			
NDS	Good (Grade C)	Good (Grade B)	30 months
Risk assessment tool	Good (Grade C)	Good (Grade C)	30 months
HDC risk assessment	Poor at screening, good for ruling out (Grade C)	No evidence	2.5 years (yearly re-examination)
NDS combined	Poor at screening, good for ruling out (Grade C)	No evidence	30 months
Vibration sensation	Moderate (Grade C)	Foot ulcer – substantial (Grade B) Amputation – insufficient evidence	2.5 to 7 year (yearly re-examination)
$TCPO_2$	Moderate (Grade C)	Moderate (Grade C)	3.3 years
Seattle risk assessment	Moderate (Grade C)	No evidence	2.5 years (yearly re-examination)
Glycaemic control	Moderate (Grade C)	No evidence	2.5 to 7 years(yearly re-examination)
SWF	Poor (Grade C)	Good (Grade B)	12 to 39 months
Foot pressure assessment	Poor (Grade C)	Moderate to substantial (Grade B)	24 to 30 months
Arterial pulse assessment	Poor (Grade C)	Moderate (Grade B)	2 to 7 years
Ankle – Arm Index	Poor (Grade C)	Moderate (Grade C)	3.3 to 3.7 years
Ankle blood pressure	No evidence	Moderate (Grade C)	3.4 years
Foot deformity	No evidence	Moderate (Grade B)	2 to 3.7 years
Orthostatic blood pressure	No evidence	Poor (Grade D)	3.4 years
Ankle reflex assessment	Poor (Grade C)	Inconclusive (Grade C)	2.5 years (yearly re-examination) to 3.4 years
Gait assessment	Poor (Grade D)	No evidence	2.5 years (yearly re-examination)
Neuropathic Diabetic Population			
Foot pressure assessment	Moderate – ruling out (Grade C)	Moderate (Grade C)	24 months
Indigenous populations			
Risk Categorisation Assessment Scheme	No evidence	Moderate (Grade C)	32 months
SWF	No evidence	Moderate (Grade C)	32 months

NDS = neuropathic disability score; SWF = Semmes Weinstein filaments; $TCPO_2$ = transcutaneous oximetry; HDC = Hansen's Disease Center

Table 35 Summary of clinical assessments for the prediction of ulcer outcomes in a diabetes population with foot ulcer

Assessment	Diagnostic performance	Predictive performance[a]	Follow-up period
Single clinical or laboratory assessments			
Skin perfusion pressure	Good (Grade C) –healing	No evidence	Not reported
Hyperspectral imaging	Good (Grade C)–healing	No evidence	6 months or at least 12 months
Plasma fibrinogen levels	Good (Grade C)–amputation	No evidence	8 months
$TcPO_2$	Good – improved healing (Grade C)	No evidence	12 months
Toe Blood pressure	Good, ruling in – improved healing (Grade C)	No evidence	12 months
Ankle peak systolic velocity	Good (Grade D) – non-healing	No measures of predictive performance[b].	Uncertain
Bone scans for osteomyelitis	Moderate (Grade D)–amputation	Good (Grade C)	12 months
Capillary circulation with macro-aggregated albumin	No evidence	No measures of association reported	3 months
Systolic ankle and toe blood pressure	No evidence	No evidence[c]	Assessment every 6 months
Multiple clinical or laboratory assessments			
University of Texas	Good discrimination (Grade C) – healing	Good (Grade C)	6 months
Clinical history, physical examination, MRI	Good discrimination (Grade C) – non-healing	Good (Grade C)	6 months
Wagner classification	Moderate discrimination (Grade C) – healing	Good (Grade C)	6 months
S(AD)SAD classification	Moderate (Grade C) - healing	Good (Grade C)	6 months
CHS (Curative Health Services)	Moderate discrimination (Grade C) – non-healing	Moderate (Grade C)	20 weeks
International consensus on diabetic foot wound classification		Good (Grade C)	Up to 2 years
Baseline characteristics	No evidence	Moderate (Grade C)	At least 1 year
DUSS	No evidence	Moderate (Grade C)	At least 1 year
M.A.I.D.	No evidence	Moderate (Grade C)	At least 1 year
Van Acker/Peter classification	No evidence	Poor (Grade C)	Not reported
DEPA score	No evidence	Strong correlation (Grade C)	20 weeks
Scottish foot risk score	No evidence	No measures of association reported	Up to 2 years 9 months

Research Question 5: When should a patient be referred to a high risk foot clinic?

(What are the risk factors for a poor foot-related outcome for people in a primary care setting?)

Box 64 Inclusion criteria for the evaluation of when a people should be referred to a high risk foot clinic

Research Question	
What are the risk factors for a poor foot-related outcome for people in a primary care setting?	
Parameter	Inclusion criteria
Population	Adults with type 1 or type 2 diabetes managed in a primary care setting, including • In indigenous populations
Intervention [a]	For people without foot ulcer: Risk factors for foot ulcer and amputation which may include severity of peripheral neuropathy; peripheral vascular disease; or previous history of ulcer. For people with foot ulcer: Risk factors for poor outcomes may include size or severity of foot ulcer; or infection.
Outcomes	Poor clinical outcomes including mortality; foot morbidity (which may include ulceration or worsening foot ulceration; amputation (major, transmetatarsal, transtibial, ray or toe) osteomyelitis; Charcot's neuroarthropathy); mobility restriction; poor general functioning; poor quality of life; lack of independence.
Study design	Prospective cohort studies [b]; all or none study; analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial; retrospective cohort study; case series or cohort study of persons at different stages of disease; or systematic reviews of these study designs.
Language	Non-English language articles will be excluded unless they appear to provide a higher level of evidence than the English language articles identified. Translation of such articles will significantly increase the timeframe of the review.
Publication date	1966 – 11/2009
Limitations	Human

The question of when a person should be referred to a high risk foot clinic can be answered by identifying risk factors for poor foot-related outcomes in people being managed in a primary care setting. Inclusion criteria for studies in this review are outlined in Box 64.

Twenty eight studies were assessed and met the inclusion criteria and were consequently included in this review. Risk factors for the outcome of mobility and/or falls (as an indicator of general functioning) were also reported. Descriptions of all the variables included in the models are provided in Appendix H.

The results of this review will be reported according to the risk factor evaluated and then by the outcome.

Neuropathy

Sensory neuropathy

Ten studies reported sensory neuropathy as a risk factor for poor foot outcomes in people with diabetes managed in a primary care setting (Table 36). Assessment of this risk factor was undertaken using a number of different methods – vibration perception threshold (VPT); Semmes Weinstein filaments (SWFs) and the Michigan Neuropathy Screening Instrument.

For the outcome of amputation, three studies reported neuropathy as a risk factor. In the average quality study by Davis et al (2006), neuropathy was defined as a score of two or more in the clinical portion of the Michigan Neuropathy Screening Instrument. Subjects in this study were recruited from a hospital catchment area in Fremantle, WA therefore it is possible that the population included people receiving higher levels of care than they would be received in a primary care setting.

The average quality study by Hamalainen et al (1999) reported a strong relationship between neuropathy and lower extremity amputation. The investigators defined neuropathy as a VPT greater than two standard deviations from age-specific reference values however, they did not consider the presence of foot ulcer at baseline in their analysis.

One study reported neuropathy as a risk factor for amputation in an Indigenous population in the United States of America (Nelson et al 1988). This average quality study reported a strong association between increasing VPT and amputation in a large cohort of Native American Indians in a community setting. It is unclear whether all subjects were being managed in a primary care setting.

Foot ulcer was reported to be statistically significantly associated with neuropathy in one good quality and two average quality studies (Abbott et al 1998; Litzelman et al 1997; Pham et al 2000).

Litzelman et al (1997), in a good quality study, reported risk factors for foot lesions in a sample of patients who were enrolled in a randomised controlled trial assessing patient education and provision of guidelines for foot care to primary care physicians. The outcome of foot lesions was considered according to the severity of the lesion as determined by the Seattle Wound Classification system. Risk factors for lesions graded as 1.2 (superficial or healing minor lesions without functional interruption of the protective cutaneous barrier) or higher were reported, as well as for those graded as 1.3 (non-ulcerated minor lesions) or higher. Both abnormal SWF testing and thermal sensitivity were moderate risk factors for the development minor foot lesions (OR = 2.75, [95%CI 1.55, 4.88] and OR = 2.18, [95%CI 1.13, 4.21] respectively). However, for the more severe foot lesions, only abnormal SWF testing was found to be an independent risk factor (OR = 2.23 [95% CI 2.26, 12.13]).

The study by Abbott et al (1998) included patients who were originally involved in a randomised controlled trial. The trial was discontinued after failing to demonstrate efficacy of a drug aimed at reducing incident foot ulcers in people with diabetic neuropathy. This subsequent study found that a one unit increase in VPT measurement increased the risk of first ulcer by 5.6%. Similarly, for every one unit increase in the clinical portion of the Michigan Neuropathy Screening instrument, there was a 5.0% increase in the risk of foot ulcer.

A summary of the evidence for neuropathy as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 7.

Box 65 Evidence statement matrix for sensory neuropathy as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Ten level II study with low to moderate risk of bias.
Consistency	B	Most studies consistently showed that neuropathy is a risk factor for poor foot outcomes in people with and without foot ulcer. Any inconsistencies can be explained.
Clinical impact	C	The evidence suggests that neuropathy is a weak to moderate risk factor for poor foot outcomes. Although some studies show a moderate strength of relationship, the confidence intervals around the estimate would suggest a lesser clinical impact.
Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	B	Studies were undertaken in Australia, UK, Finland and the USA therefore, overall the evidence is likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is good evidence to show that sensory neuropathy, as measured by VPT, SWF and the Michigan Neuropathy Screening Instrument, is an independent risk factor for amputation, foot ulceration and general functioning (mobility/falls) in people with diabetes managed in a primary care setting (Grade B).

Table 36 Value of sensory neuropathy as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association + [95% CI]	Outcome
(Davis et al 2006) Western Australia	II Prospective cohort study Average quality	People (n = 1294) with type I or type II diabetes residing in the Fremantle Hospital catchment area.	Peripheral sensory neuropathy *Measurement*: Michigan Neuropathy Screening Instrument, a score of > 2/8 on the clinical portion was considered to indicate peripheral sensory neuropathy.	HR 2.65 [1.30, 5.44]	First diabetes-related lower extremity amputation.
(Hamalainen et al 1999) Finland	II Prospective cohort study Average quality	People with type I or type II diabetes (n = 733)	Neuropathy *Measurement*: Vibration perception threshold, > than 2 standard deviations from age-specific reference values was considered to indicate neuropathy.	OR 14.5 [3.6, 57.8]	Lower extremity amputation
(Nelson et al 1988) USA	II Prospective cohort study Average quality	Residents (n = 4,399) with diabetes of Gila River Indian community, Arizona.	Neuropathy *Measurement:* Mean voltage estimate from the median voltage threshold (3 measurements) for each great toe.	Crude incidence (cases per 1000 person-years) < 10V 4.7 10 – 19V 8.0 ≥ 20V 29.6 = 12.8, p<0.001	Amputation
(Lehto et al 1996) Finland	II Prospective cohort study Average quality	People (n = 1044) with type II diabetes aged between 45 and 64 years receiving reimbursement for diabetic medications.	Absence of vibration sense *Measurement:* Not reported	OR 2.7 [1.6, 4.7]	Amputation as a result of atherosclerotic vascular disease.
(Litzelman et al 1997) USA	II Prospective cohort study	Patients (n = 395) receiving primary care at a university	Neuropathy *Measurement:*	Seattle Wound Classification ≥ 1.2 SWF:	Foot ulcer

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association + [95% CI]	Outcome
	(RCT) Good quality	affiliated general medicine practice serving socioeconomically disadvantaged people.	10g SWFs applied to great, first and fifth metatarsal heads. Abnormality detected if sensation absent on one or more sites. Thermal sensitivity evaluated using Sensortek apparatus. Abnormality detected if temperature change > 2 standard deviations from reference (25°C) mean for sample of healthy people without diabetes.	OR 2.75 [1.02, 3.34] Thermal: OR 2.18 [1.13, 4.21] Seattle Wound Classification ≥ 1.3 SWF: OR 5.23 [2.26, 12.13] Thermal: Not in model	
(Ledoux et al 2005) USA	II Prospective cohort study (RCT) Good quality	People (n = 400) with diabetes with a history of full thickness foot lesion.	Neuropathy *Measurement:* Response to 5.07 SWF	OR 6.28 [1.88, 21.0]	First new ulcer
(Pham et al 2000) USA	II Prospective cohort study Average quality	Patients (n=248) attending both primary and tertiary care clinics.	Neuropathy *Measurement:* Mean VPT estimate of three readings with hand held biothesiometer. A VPT ≥ 25V was considered to indicate neuropathy. SWF was considered abnormal if plantar aspect of hallux was insensate to 10g SWF.	VPT: OR 3.4 [1.7, 6.8] SWF: OR 2.4 [1.1, 5.3]	Foot ulcer
(Abbott et al 1998) UK, USA and Canada	II Prospective cohort study Average quality	People (n = 1,035) with peripheral neuropathy (VPT ≥ 25V on at least one foot, ≤ 50V on both feet and at least one palpable	Neuropathy *Measurement:* Mean VPT measured in triplicate at the great toe of	VPT: HR 1.056 p < 0.001 MNSI: HR 1.050 p < 0.001	Foot ulcer

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association + [95% CI]	Outcome
		pedal pulse).	both feet. Clinical portion of Michigan Neuropathy Screening Instrument.		
(Bruce et al 2005) Western Australia	II Prospective cohort study Average quality	People with type II diabetes (n = 1752) residing in the Fremantle Hospital catchment area.	Peripheral sensory neuropathy *Measurement*: Clinical portion of Michigan Neuropathy Screening Instrument.	HR 1.40 [1.04, 1.88]	Mobility impairment
(Wallace et al 2002) USA	II Prospective cohort study Average quality	People (n = 400) with diabetes and without foot deformities which require customised footwear or history of foot ulcer.	Neuropathy – foot sensation *Measurement*: 10g SWF (no further details provided)	OR 1.39 [1.28, 3.44] OR 1.87 [1.1, 3.2]	Any falls Multiple falls

SWF = Semmes Weinstein filaments; VPT = vibration perception threshold; MNSI = Michigan Neuropathy Screening Instrument; RCT = randomised controlled trial

Neuropathic symptom score / neuropathic disability score

Only one study reported on the Neuropathic symptom score (NSS) and the Neuropathic disability score (NDS) as risk factors for poor foot outcomes. The average study by Pham et al (2000) assessed whether either of these instruments were predictive of foot ulcer in a population of people with diabetes attending a number of primary foot care clinics as well as a tertiary care clinic in the USA.

Each patient provided responses to the modified NSS with regard to the presence of nocturnal muscular cramps, numbness, abnormal thermal sensations, tingling, burning, aching and irritation from bed clothes in the lower legs and feet. If the patient did not report a symptom they received a score of zero, otherwise they received a score of one or two if the symptom was exacerbated nocturnally. An NSS score greater than or equal to three was considered to be abnormal.

The NDS quantified the assessment of tendon reflexes and sensory modalities. Both patellar and Achilles tendon reflexes were examined and the patient received a score of zero if the reflex was normal; one if the reflex could be elicited with reinforcement; and a score of two if the reflex was absent. Sensory tests included pinprick, light touch with cotton wool, tuning fork and temperature perception with a test tube of cold water. If the patient was unable to sense the stimuli at all levels a score of zero was given; if unable to detect stimuli at the base of the toe a score of 1 was noted. Scores of two, three, four and five were given if the stimuli were not detected at the level of the midfoot, heel, lower leg and knee, respectively. The NDS was calculated by summing the reflex and sensory scores for each modality and a score of five or more was considered abnormal.

While controlling for sex, duration of diabetes, race and palpable pulses, Pham et al (2000) reported that an abnormal NDS was an independent risk factor for foot ulcer (OR = 3.1 [95% CI 1.3, 7.6]). However, the authors did not control for the centre the patient attended which ranged from primary to tertiary care. An abnormal NSS was not found to be an independent risk factor for foot ulcer in this population.

A summary of the evidence for NDS as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 66.

Box 66 Evidence statement matrix for abnormal NDS score as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	C	The study by Pham et al indicates that an abnormal NDS score is a moderate risk factor for the development of foot ulcer.
Generalisability	C	Patients from tertiary care facilities were included in this study which may overestimate the relationship between abnormal NDS score and foot ulcer.
Applicability	B	The study was undertaken in the USA therefore likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is some evidence to show that an abnormal NDS score may be a risk factor for the development of foot ulcer in people with diabetes (Grade C).

Foot pressure

Pham et al (2000) also considered foot pressures as a risk factor for foot ulcer development. Maximal plantar foot pressure was measured using the F-Scan mat system. Patients from both

primary and tertiary care centres walked across a mat to obtain the maximal foot pressure for the entire foot. The mean reading of three mid-gait footsteps was used in the analysis where foot pressures above 6 kg/cm^2 were considered abnormally high. Again, controlling for sex; duration of diabetes; race; and palpable pedal pulses, a high foot pressure reading was determined to be a moderate risk factor for the development of foot ulcer over a 30 month follow-up period (OR = 2.0 [95% CI 1.2, 3.3]). As has been stated previously, this study did not control for the level of care that subjects were receiving.

A summary of the evidence for NDS as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 67.

Box 67 Evidence statement matrix for abnormal foot pressure as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	C	The study by Pham et al indicates that an abnormal high foot pressure is a moderate risk factor for the development of foot ulcer.
Generalisability	C	Patients from tertiary care facilities were included in this study which may overestimate the relationship between high foot pressures and foot ulcer.
Applicability	B	The study was undertaken in the USA therefore likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is some evidence to show that an abnormal high foot pressure (≥ 6 kg/cm^2) may be a moderate risk factor for the development of foot ulcer in people with diabetes (Grade C).

Reflexes

Neuropathy, in terms of absent Achilles and/or patellar tendon reflexes, as a risk factor for poor foot outcomes was assessed in two average quality prospective cohort studies (Table 37). The results of both studies are limited by the analysis only adjusting for age and sex therefore, confounding cannot be ruled out in either study.

In the study by Nelson et al (1988) the relative risk of absent patellar and Achilles tendon reflexes was reported for amputation. In addition to the limitation described above, it is unclear whether the absence of reflexes was either bilateral or unilateral for both predictor variables. With this in mind, the authors indicated that only absent patellar tendon reflexes was a statistically significant risk factor for amputation in an Indigenous American population (RR = 2.0 [95% CI 1.3, 3.1]).

In the Finnish study by Lehto et al (1996), the bilateral absence of the Achilles tendon reflexes was reported to be a strong risk factor for amputation as a result of atherosclerotic vascular disease (RR = 4.3 [95% CI 2.5, 7.3]). As indicated above, it is likely that these results were only adjusted for sex and age and therefore the confounding effects from other risk factors for amputation as a result of atherosclerotic vascular disease cannot be ruled out.

A summary of the evidence for absent reflexes as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 68.

Box 68 Evidence statement matrix for absent reflexes as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	C	Two level II studies with moderate risk of bias.
Consistency	C	Although the measures of association are all in the same direction, the likely effects of confounding in these two studies results in difficulty in assessing the consistency o f the results. Potential confounding ensures that there is considerable uncertainty around these estimates of association.
Clinical impact	C	Although the studies report that the absence of Achilles and patellar tendon reflexes are moderate to strong risk factors for amputation, the uncertainty surrounding these results limits the likely clinical impact.
Generalisability	C	The results are likely to be generalisable to people with diabetes in community settings including indigenous populations. Given the community based setting, it is possible that not all subjects were receiving primary care.
Applicability	B	The studies were undertaken in the USA and Finland therefore likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is insufficient evidence to conclude that absent Achilles and patellar tendon reflexes are risk factors for amputation in people with diabetes (Grade C).

Table 37 Predictive value of absent reflexes as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]	Outcome
(Nelson et al 1988) USA	II Prospective cohort study Average quality	Residents (n = 4,399) with diabetes of Gila River Indian community, Arizona.	Achilles and patellar tendon reflexes *Measurement:* Not reported.	Patellar tendon reflexes: RR 2.0 [1.3, 3.1] Achilles tendon reflexes: RR 1.2 [0.7, 1.9]	Amputation
(Lehto et al 1996) Finland	II Prospective cohort study Average quality	People (n = 1044) with type II diabetes aged between 45 and 64 years receiving reimbursement for diabetic medications.	Achilles tendon reflexes *Measurement:* Not reported.	Bilateral absence RR 4.3 [2.5, 7.3]	Amputation as a result of atherosclerotic vascular disease.

Blood pressure

Systolic and diastolic blood pressure

Systolic blood pressure was analysed in a number of ways when modeling for risk factors of various outcomes. Some studies included systolic blood pressure in the statistical model according to each change of 10mmHg, while others analysed it so the subsequent measure of association was indicative of the change in odds for the outcome for every 1mmHg increase in systolic blood pressure (Table 38).

The study by Resnick et al (2004) reported that systolic blood pressure was a weak risk factor for lower extremity amputation in American Indians however, they did not elaborate on whether the model dichotomised systolic blood pressure, or if it remained as a continuous variable. The authors did indicate that hypertension was diagnosed if systolic blood pressure was equal to or greater than 140mmHg however, hypertension was not a variable in the final model for lower extremity amputation. While the study aimed to identify risk factors for lower extremity amputation in American Indians, the authors did not consider neuropathy or history of foot ulcer in their model.

It is uncertain if much weight should be given to the results of the study by Roy et al (2008). The analysis reported in this study was aimed at identifying the independent risk factors for amputation which was achieved by considering two models. The difference between the models was severity of retinopathy was included in the second model while systolic blood pressure was excluded. It is unclear why two models were produced, or why systolic blood pressure was excluded from the second model when they have concluded that it was an independent risk factor

In the study by Lee et al (1993) which also looked at risk factors for lower extremity amputation in an American Indian community, systolic blood pressure was found to be a risk factor in men (OR = 1.15 [95% CI 1.03, 1.28]) whereas diastolic blood pressure was a risk factor in women (OR = 1.28 [95% CI 1.05, 1.56]).

Interesting results were reported by Moss et al (1996) where, in the younger onset diabetes group, increasing diastolic blood pressure was associated with increased lower extremity amputation (OR = 2.13 [95% CI 1.51, 2.99]) but in the older onset cohort, increasing diastolic blood pressure was determined to be protective against amputation (OR = 0.73 [95% CI 0.54, 0.97] at the 10 year follow-up.

A summary of the evidence for systolic and diastolic blood pressure as risk factors for poor foot outcomes according to NHMRC criteria is provided in Box 69.

Box 69 Evidence statement matrix for systolic and diastolic blood pressure as risk factors for poor foot outcomes

Component	Rating	Description
Evidence base	C	Five level II studies with a moderate risk of bias.
Consistency	B	Most studies consistently showed that systolic and diastolic blood pressure are risk factors for poor foot outcomes in people with and without foot ulcer.
Clinical impact	C	The evidence suggests that blood pressure is a weak to moderate risk factor for poor foot outcomes. Although some studies show a moderate strength of relationship, the confidence intervals around the estimate may suggest a lesser clinical impact.
Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting. Two studies were in American indigenous populations.
Applicability	B	All four studies were conducted in the USA therefore, the evidence is likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is some evidence to indicate that increasing systolic and diastolic blood pressure are risk factors lower extremity amputation particularly in American Indians. Less evidence is available for blood pressure as a risk factor for foot ulcer (Grade C).

Table 38 Value of blood pressure as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]			Outcome
(Resnick et al 2004) USA	II Prospective cohort study Average quality	American Indians (n = 1,974) with diabetes.	Systolic blood pressure *Measurement*: Not reported	OR	1.02	[1.01, 1.03]	Lower extremity amputation
(Roy & Peng 2008) USA	II Prospective cohort study Average quality	African-Americans (n = 483) with type I diabetes	Systolic blood pressure *Measurement*: Measured twice both sitting and standing, and the average measurement was used in the analysis.	OR	1.02	[1.01, 1.04]	Lower extremity arterial disease (toe, foot, or leg amputation; angioplasty for poor circulation in lower limbs; absence of one or more major arterial pulses in lower limbs)
(Lee et al 1993) USA	II Prospective cohort study Average quality	Oklahoma Indians (n = 990) with type II diabetes	Systolic blood pressure (per 10mmHg change) Diastolic blood pressure (per 10mmHg change)	Men: OR Systolic blood pressure Women: OR Diastolic blood pressure	1.15 1.28	[1.03, 1.28] [1.05, 1.56]	Lower extremity amputation
(Moss et al 1992; Moss et al 1996; Moss et al 1999) USA	II Prospective cohort study Average quality	Patients (n = 2,366) with diabetes receiving primary care at 452 practices in southern Wisconsin.	Diastolic blood pressure (per 10mmHg change) *Measurement*: Not reported	At 4 years follow-up: Younger onset [a]: OR At 10 years follow-up: Younger onset [a]: OR Older onset [a]: OR At 14 years follow-up: Younger onset [a]: OR	2.10 2.13 0.73 1.58	[1.3, 3.5] [1.51, 2.99] [0.54, 0.97] [1.20, 2.07]	Lower extremity amputation
				At 4 years follow-up: Older onset [a]: OR	0.8	[0.6, 1.0]	Foot ulcer

[a] Age at onset of diabetes, Younger if onset at < 30 years of age

Hypertension

Two average quality prospective studies provided data for hypertension as a risk factor of poor foot outcomes (Table 39). One study reported data on the association between hypertension and amputation in an Indigenous population (Nelson et al 1988), while the other reported on hypertension and major morbidities which were not necessarily foot related (Hypertension in Diabetes Study 1993). These included myocardial infarction, ischaemic heart disease, stroke, amputation, blindness and renal failure.

The results of the study by Nelson et al (1988) are limited as hypertension was not defined by the authors, and the reported estimates were adjusted for sex and age only therefore providing only marginally more information than a univariate analysis. Despite these limitations, the study did not detect a statistically significant association between hypertension and amputation.

The Hypertension in Diabetes Study (HDS) was a substudy of the United Kingdom Prospective Diabetes Study, and assessed the relationship between hypertension and major morbidities in patients who were newly diagnosed with type 2 diabetes at baseline. This study did report a statistically significant relationship between hypertension, which was well defined; however this was likely due to the composite nature of the outcome. With this in mind, the study reported that hypertension was a moderate risk factor for major morbidity (OR = 1.56 [95% CI 1.27, 1.92]).

A summary of the evidence for hypertension as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 70.

Box 70 Evidence statement matrix for hypertension as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	C	Two level II studies with a moderate risk of bias.
Consistency	C	Both studies reported measures of association in the same direction. It is likely that the HDS reported a statistically significant relationship as a result of the composite nature of the outcome.
Clinical impact	D	Given the uncertainty surrounding the evidence, it is unclear what the clinical impact would be.
Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting. One study was in an American indigenous population.
Applicability	B	The studies were conducted in the USA and UK therefore, the evidence is likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is insufficient evidence regarding the relationship between hypertension and poor foot outcomes (Grade C).

Table 39 Value of hypertension as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]			Outcome
(Nelson et al 1988) USA	II Prospective cohort study Average quality	Residents (n = 4,399) with diabetes of Gila River Indian community, Arizona.	Hypertension *Measurement:* Not reported	RR	1.4	[0.8, 2.2]	Amputation
(Hypertension in Diabetes Study 1993) UK	II Prospective cohort study Average quality	People (n = 3,648) with newly diagnosed type 2 diabetes recruited into the UKPDS.	Hypertension *Measurement:* Defined as mean systolic ≥ 160mmHg and / or diastolic ≥ 90 mmHg, or if patient was already on hypertensive medication.	OR	1.56	[1.27, 1.92]	Major morbidity including myocardial infarction, ischaemic heart disease, stroke, amputation, blindness and renal failure.

UKPDS = United Kingdom Prospective Diabetes Study

Glycosylated haemoglobin

Four prospective cohort studies reported glycosylated haemoglobin as a risk factor for poor foot outcomes in people with and without diabetic foot ulcer (Table 40).

The four studies all reported glycosylated haemoglobin as a moderate risk factor for lower extremity amputation with odds ratios ranging from 1.25 to 3.48 depending on the level of glycosylated haemoglobin detected. This included amputation is a result of atherosclerotic vascular disease as reported by Lehto et al (1996). Additionally, the study by Moss et al (1992) also provided evidence that increasing glycosylated haemoglobin was significantly associated with the development of foot ulcer in populations of both younger and older onset diabetes.

A summary of the evidence for glycosylated haemoglobin as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 71.

Box 71 Evidence statement matrix for glycosylated haemoglobin as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Four level II studies with a low to moderate risk of bias.
Consistency	B	Most studies consistently showed that glycosylated haemoglobin is a risk factor for poor foot outcomes in people with and without foot ulcer. Any inconsistencies are likely explained by the short follow-up period.
Clinical impact	C	The evidence suggests that glycosylated haemoglobin is a moderate risk factor for poor foot outcomes.
Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	B	The studies were conducted in Australia, Finland, UK and the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is reasonable evidence to indicate that increasing levels of glycosylated haemoglobin (> 6.5%) is a risk factor for lower extremity amputation in people with diabetes. Further evidence is required with regard to foot ulcer development (Grade B).

Table 40 Value of HbA_{1c} as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]				Outcome
(Resnick et al 2004) USA	II Prospective cohort study Average quality	American Indians (n = 1,974) with diabetes.	HbA_{1C} *Measurement:* Not reported	6.5% 6.5%–9.5% > 9.5%	OR OR OR	1.0 2.26 3.48	Reference [1.07, 4.77] [1.68, 7.20]	Lower extremity amputation
(Lehto et al 1996) Finland	II Prospective cohort study Average quality	People (n = 1044) with type II diabetes aged between 45 and 64 years receiving reimbursement for diabetic medications.	HbA_{1C} *Measurement:* Affinity chromatography	≤ 10.7% > 10.7%	OR OR	1.0 2.4	Reference [1.4, 4.0]	Amputation as a result of atherosclerotic vascular disease.
(Davis et al 2006) Western Australia	II Prospective cohort study Average quality	People (n = 1294) with type I or type II diabetes residing in the Fremantle Hospital catchment area.	HbA_{1C} *Measurement:* Automated biochemical analysis	Per 1% increase	HR	1.30	[1.10, 1.54]	First lower extremity amputation
(Moss et al 1992; Moss et al 1996; Moss et al 1999) USA	II Prospective cohort study Average quality	Patients (n = 2,366) with diabetes receiving primary care at 452 practices in southern Wisconsin.	HbA_{1C} *Measurement:* Micro-column technique	At 4 years follow-up (per 2% increase): Younger onset [a]: Older onset [a]: At 10 years follow-up (per 1% increase): Younger onset [a]: Older onset [a]: At 14 years follow-up: Younger onset [a]: Older onset [a]:	 OR OR OR OR OR OR	 1.40 1.50 1.39 1.28 1.39 1.25	 [1.0, 2.1] [1.0, 2.2] [1.19, 1.60] [1.11, 1.48] [1.22, 1.59] [1.09, 1.43]	Lower extremity amputation
				At 4 years follow-up: Younger onset [a]: Older onset [a]:	 OR OR	 1.60 1.60	 [1.3, 2.0] [1.3, 2.0]	Foot ulcer

[a] Age at onset of diabetes, Younger if onset at < 30 years of age

Plasma glucose

Three studies reported increasing plasma glucose levels as a risk factor for amputation in general or, as a result of atherosclerotic vascular disease (Table 41).

The average quality study of Nelson et al (1988) reported that increasing levels of both fasting plasma glucose and 2hr post-load glucose were significantly associated with increased risk of amputation (4.2, $p < 0.04$ and 9.3, $p < 0.002$ respectively). Given the likelihood of confounding in this study (as discussed previously), little weight should be given to these results.

Lehto et al (1996) also reported that fasting plasma glucose levels greater than 13.4mmol/l were associated with increased risk of amputation as a result of atherosclerotic vascular disease (RR = 2.5 [95% CI 1.5, 4.3]). However, these results are also considerably weakened by the likelihood for confounding due to the possible lack of adjustment for potential confounders.

The average quality study by Lee et al (1993) reported that a one millimolar increase in the concentration of fasting blood glucose was associated with an eight percent increase in risk of lower extremity amputation in American Indian men with type 2 diabetes (RR = 1.08 [95% CI 1.03, 1.13]).

A summary of the evidence for plasma glucose as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 72.

Box 72 Evidence statement matrix for plasma glucose as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Three level II studies with a moderate risk of bias.
Consistency	C	All studies reported estimates of association in the same direction however given the limitations of two studies, genuine uncertainty still remains.
Clinical impact	C	Given the uncertainty surrounding plasma glucose as a risk factor it is difficult to assess the likely clinical impact.
Generalisability	B	The evidence is likely to be generalisable to the target population, including indigenous populations, although it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	B	The studies were conducted in Finland and the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is limited evidence to indicate that increasing levels of plasma glucose is a risk factor for lower extremity amputation in people with diabetes. (Grade C).

Table 41 Predictive value of plasma glucose as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]	Outcome
(Nelson et al 1988) USA	II Prospective cohort study Average quality	Residents (n = 4,399) with diabetes of Gila River Indian community, Arizona.	Plasma glucose – fasting and 2hr post load *Measurement:* Laboratory examination	Crude incidence (cases per 1000 person-years) Fasting (mg/dl): < 140 3.8 140 – 199 6.5 ≥ 200 16.1 = 4.2, p < 0.04 2hr post-load (mg/dl): < 250 3.2 250 – 349 9.9 350 –499 14.0 ≥ 500 17.2 = 9.3, p < 0.002	Amputation
(Lehto et al 1996) Finland	II Prospective cohort study Average quality	People (n = 1044) with type II diabetes aged between 45 and 64 years receiving reimbursement for diabetic medications.	Fasting plasma glucose *Measurement:* Glucose oxidase	Fasting plasma: > 13.4mmol/l RR 2.5 [1.5, 4.3]	Amputation as a result of atherosclerotic vascular disease.
(Lee et al 1993) USA	II Prospective cohort study Average quality	Oklahoma Indians (n = 990) with type II diabetes	Fasting blood glucose (mM) *Measurement:* Not reported	Men: RR 1.08 [1.03, 1.13]	Lower extremity amputation

Retinopathy

Retinopathy as a risk factor for lower extremity amputation was evaluated by eight prospective cohort studies of average quality. In these studies retinopathy was measured in a number of different ways ranging from self-report to ophthalmic examination and grading of the severity of retinopathy. All studies reported that retinopathy was a moderate to strong risk factor for lower extremity amputation and also lower extremity arterial disease with odds ratios of up to 6.1. Interestingly, the study by Roy et al (2008) reported that in comparison to people with no retinopathy, those with minimal eye disease were less likely to require lower extremity amputation (OR = 0.95 [95% CI 0.23, 3.98]). Given that for the more severe levels of retinopathy, there was a substantial risk of amputation (OR = 2.64 and 4.93), it is possible that there were insufficient numbers of amputation in people with minimal disease to detect a significant association. Also of note in the study by Roy et al (2008) is that patients were recruited from the New Jersey Hospital Discharge Data for patients with diabetes mellitus. The authors did not indicate the time between hospital discharge and recruitment into the study or whether patients were being managed in primary care at the time of enrolment. It is therefore possible that the patients in this study may have been at higher baseline risk of amputation than people who are being managed in a primary care setting.

A summary of the evidence for retinopathy as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 73.

Box 73 Evidence statement matrix for retinopathy as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Nine level II studies with a low to moderate risk of bias.
Consistency	B	Most studies consistently showed that retinopathy is a risk factor for poor foot outcomes in people with and without foot ulcer.
Clinical impact	B	The evidence suggests that retinopathy is a moderate to strong risk factor for poor foot outcomes.
Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	B	The studies were conducted in Australia, Finland, UK and the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is reasonable evidence to indicate that increasing severity of retinopathy (including self-reported retinopathy) is a risk factor for lower extremity amputation in people with diabetes. There is also some evidence to suggest that retinopathy is a risk factor for foot ulcer and ulcer recurrence (Grade B).

Table 42 Value of retinopathy as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]	Outcome
(Davis et al 2006) Western Australia	II Prospective cohort study Average quality	People (n = 1294) with type I or type II diabetes residing in the Fremantle Hospital catchment area.	Retinopathy *Measurement:* Any grade of retinopathy, including maculopathy, detect by opthalmoscopy in one or both eyes and/or on more detailed assessment by an ophthalmologist.	HR 2.99 [1.10, 1.54]	First lower extremity amputation
(Lee et al 1993) USA	II Prospective cohort study Average quality	Oklahoma Indians (n = 990) with type II diabetes	Retinopathy *Measurement:* As defined in (Lee et al 1992)	Men: RR 3.19 [1.86, 5.49] Women: RR 3.33 [1.98, 5.59]	Lower extremity amputation
(Lehto et al 1996) Finland	II Prospective cohort study Average quality	People (n = 1044) with type II diabetes aged between 45 and 64 years receiving reimbursement for diabetic medications.	Retinopathy *Measurement:* Ophthalmoscopic examination performed by a physician after papillary dilation. Retinopathy diagnosed if one or more of microaneurysms; exudates; preretinal haemorrhages; or proliferative retinopathy.	RR 3.6 [2.2, 6.1]	Amputation as a result of atherosclerotic vascular disease.
(Hamalainen et al 1999) Finland	II Prospective cohort study Average quality	People with type I or type II diabetes (n = 733)	History of retinopathy Visual handicap *Measurement:* History – structured interview Visual handicap – ability to read standard newspaper text after correcting refraction.	History of retinopathy OR 6.1 [1.9, 19.6] Visual handicap OR 4.9 [1.4, 17.4]	Lower extremity amputation

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]	Outcome
(Nelson et al 1988) USA	II Prospective cohort study Average quality	Residents (n = 4,399) with diabetes of Gila River Indian community, Arizona.	Retinopathy *Measurement:* Ophthalmoscopic examination performed by a physician after papillary dilation. Retinopathy diagnosed if one or more of microaneurysms; exudates; preretinal or vitreous haemorrhages; or proliferative retinopathy.	RR 2.1 [1.3, 3.4]	Amputation
(Roy & Peng 2008) USA	II Prospective cohort study Average quality	African-Americans (n = 483) with type I diabetes	Severity of retinopathy *Measurement:* Fundus photographs graded with modified Airlie House classification. Levels 10–15 = no retinopathy; levels 20–35 = minimal non-proliferative retinopathy; levels 43–53 = moderate non-proliferative retinopathy; and levels ≥ 61–85 = severe proliferative retinopathy.	No retinopathy OR 1.0 Reference Minimal OR 0.95 [0.23, 3.98] Moderate OR 2.64 [0.62, 11.31] Severe OR 4.93 [1.13, 21.55]	Lower extremity arterial disease (toe, foot, or leg amputation; angioplasty for poor circulation in lower limbs; absence of one or more major arterial pulses in lower limbs)
(Klein et al 2007) USA	II Prospective cohort study Average quality	Diabetic patients (n = 1,370) receiving primary care.	Retinal vessel caliber *Measurement:* Central retinal arteriolar and venular equivalents	Central retinal arteriolar equivalents HR 2.20 [1.14, 4.24] Central retinal venular equivalents HR 1.21 [0.64, 2.30]	Lower extremity amputation (14 year follow-up)
(Moss et al 1992; Moss et al 1996; Moss et al 1999) USA	II Prospective cohort study Average quality	Patients (n = 2,366) with diabetes receiving primary care at 452 practices in southern Wisconsin.	Severity of retinopathy *Measurement:* Fundus photographs graded with modified Airlie House classification.	Per 2 step increase in classification: At 4 years follow-up: Younger onset [a]: OR 1.40 [1.0, 1.9]	Amputation
				Per 2 step increase in classification: At 4 years follow-up: Younger onset [a]: OR 1.3 [1.1, 1.6]	Foot ulcer

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]				Outcome
				Older onset [a]:	OR	1.2	[1.0, 1.4]	
(Winkley et al 2007) UK	II Prospective cohort study Good quality	People (n = 253) with diabetes presenting with first foot ulcer at either hospital foot clinic or community podiatry clinics.	Microvascular complications (retinopathy (background or proliferative); nephropathy (macroalbuminuria or dialysis); or neuropathy (VPT ≥ 25V))		HR	3.34	[1.17, 9.56]	Ulcer recurrence

[a] Age at onset of diabetes, Younger if onset at < 30 years of age

Nephropathy/Proteinuria

Renal disease or nephropathy was determined in a number of different ways including self-reported kidney problems and automated analysis for the presence of proteinuria (Table 43).

For lower extremity amputation, four studies reported nephropathy or proteinuria as a risk factor in six articles. Nephropathy, defined as heavy persistent proteinuria or an albumin:creatinine ratio ≥ 3.0 mg/mmol, was shown to be a slight to moderate risk factor in the Australian study by Davis et al (2006) (HR = 1.34 [95% CI 1.07, 1.66]) and in Gila River Indians (RR = 2.2 [95% CI 1.4, 3.6]) (Nelson et al 1988) respectively. The results of Davis et al (2006) should be interpreted that for every 2.72 fold increase in albumin:creatinine ratio, there is an increase in the hazard rate of 34%. Proteinuria was measured and analysed as a risk factor in a number of ways. The study by Resnick et al (2004) analysed the presence of microalbuminuria or macroalbuminuria as risk factors for lower extremity amputation in a large cohort of American Indians. Interestingly, the authors reported that microalbuminuria was a statistically significant and stronger risk factor compared to macroalbuminuria (OR = 2.67 [95% CI 1.48, 4.84] and 1.72 [95% CI 0.86, 3.41] respectively). The lack of statistical significance for macroalbuminuria may be due to the substantially smaller number of subjects with urinary albumin:creatinine ratio ≥ 300mg/g.

Proteinuria was also reported as a moderate risk factor for incident and recurrent foot ulcer, as well as mobility impairment. Although the effect size for the outcome of recurrent foot ulcer is substantial (HR = 3.34 [95% CI 1.17, 9.56]), it should be noted that the variable considered was microvascular complications which included nephropathy and therefore may not reflect the true strength of the relationship between these two variables.

A summary of the evidence for nephropathy/proteinuria as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 74.

Box 74 Evidence statement matrix for nephropathy/proteinuria as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	C	Seven level II studies (9 articles) with a moderate risk of bias.
Consistency	B	Most studies consistently showed that nephropathy or proteinuria is a moderate risk factor for poor foot outcomes.
Clinical impact	C	The evidence suggests that nephropathy/proteinuria is a moderate risk factor for poor foot outcomes.
Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	B	The studies were conducted in Australia, Finland, UK and the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is evidence to indicate that the presence of nephropathy or proteinuria is a risk factor for lower extremity amputation in people with diabetes. There is also some evidence to suggest that nephropathy or proteinuria is a risk factor for foot ulcer, ulcer recurrence and mobility impairment (Grade C).

Table 43 Predictive value of nephropathy/proteinuria as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]	Outcome
(Davis et al 2006) Western Australia	II Prospective cohort study Average quality	People (n = 1294) with type I or type II diabetes residing in the Fremantle Hospital catchment area.	Nephropathy *Measurement:* Nephropathy was defined as urinary albumin:creatinine ratio ≥ 3.0 mg/mmol on first morning urine sample.	ln(albumin:creatinine ratio)[c] HR 1.34 [1.07, 1.66]	First lower extremity amputation
(Resnick et al 2004) USA	II Prospective cohort study Average quality	American Indians (n = 1,974) with diabetes.	Proteinuria *Measurement:* Microalbuminuria = urinary albumin:creatinine ratio 30–299mg/g Macroabluminuria = urinary albumin:creatinine ratio ≥ 300mg/g	Microalbuminuria OR 2.67 [1.48, 4.84] Macroalbuminuria OR 1.72 [0.86, 3.41]	Lower extremity amputation
(Lehto et al 1996) Finland	II Prospective cohort study Average quality	People (n = 1044) with type II diabetes aged between 45 and 64 years receiving reimbursement for diabetic medications.	Proteinuria *Measurement:* Coomasie brilliant blue method using morning spot urine specimen	Proteinuria RR 1.3 [1.1, 1.6]	Amputation as a result of atherosclerotic vascular disease.
(Nelson et al 1988) USA	II Prospective cohort study Average quality	Residents (n = 4,399) with diabetes of Gila River Indian community, Arizona.	Nephropathy *Measurement:* Overt nephropathy was diagnosed if heavy and persistent proteinuria (≥ 113mg/mM) was present.	Nephropathy RR 2.2 [1.4, 3.6]	Amputation
(Moss et al 1992; Moss et al 1996; Moss et al 1999) USA	II Prospective cohort study Average quality	Patients (n = 2,366) with diabetes receiving primary care at 452 practices in southern Wisconsin.	Proteinuria *Measurement:* Present if reagent strip indicated ≥ 0.30 g/l.	At 4 years follow-up: Older onset [a]: OR 4.3 [1.6, 11.5] At 10years follow-up: Older onset [a]: OR 2.40 [1.02, 5.67] At 14 years follow-up:	Amputation

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]				Outcome
				Older onset [a]:	OR	1.19	[1.04, 1.37]	
				At 4 years follow-up: Older onset [a]:	OR	2.2	[1.1, 4.3]	Foot ulcer
(Winkley et al 2007) UK	II Prospective cohort study Good quality	People (n = 253) with diabetes presenting with first foot ulcer at either hospital foot clinic or community podiatry clinics.	Microvascular complications (retinopathy (background or proliferative); nephropathy (macroalbuminuria or dialysis); or neuropathy (VPT ≥ 25V))		HR	3.34 [b]	[1.17, 9.56]	Ulcer recurrence
(Bruce et al 2005) Western Australia	II Prospective cohort study Average quality	People with type II diabetes (n = 1752) residing in the Fremantle Hospital catchment area.	Proteinuria *Measurement*: Automated biochemical analysis	ln (urinary albumin:creatinine ratio) [c]	HR	1.15	[1.04, 1.26]	Mobility impairment

[a] Age at onset of diabetes, Younger if onset at < 30 years of age; [b] also reported for retinopathy (Table 42); [c] 2.72 fold increase in albumin:creatinine ratio corresponds to an increase of 1 in ln(urinary albumin:creatinine ratio); ln = natural logarithm

Duration of diabetes

A number of studies have shown that duration of diabetes is a weak risk factor for amputation and foot ulcer (Table 44).

When considering each year with diabetes, the increase in risk of poor foot outcomes is only marginally higher (2–8%) (Boyko et al 1996; Lee et al 1993; Resnick et al 2004; Roy & Peng 2008). However, Lehto et al (1996) reported that the risk of poor outcomes due to atherosclerotic disease increased by 120% when the duration of diabetes is greater than 9 years (RR = 2.2 [1.3, 3.6]). For every 10 years with diabetes, the odds of a first foot ulcer increased by 50–80%% (Moss et al 1992; Moss et al 1996; Moss et al 1999).

Interestingly, the one good quality study which reported on diabetes duration, found that it was not a statistically significant risk factor for foot ulcer in a population with a history of full thickness foot lesion (OR = 1.55 [95% CI 0.71, 3.38]) (Ledoux et al 2005).In this study, the investigators reported risk factors for ulcer occurrence in a cohort enrolled in a randomised controlled trial of footwear therefore, it is likely that the study was powered to detect a treatment effect but not necessarily for risk factors.

A summary of the evidence for diabetes duration as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 75.

Box 75 Evidence statement matrix for diabetes duration as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Six level II studies (8 articles) with a low to moderate risk of bias.
Consistency	B	Most studies consistently showed that diabetes duration is a weak risk factor for poor foot outcomes.
Clinical impact	D	The evidence suggests that diabetes duration is a weak risk factor for poor foot outcomes.
Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	B	The studies were conducted in Finland and the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is reasonable evidence to indicate that the diabetes duration is a weak risk factor for lower extremity amputation in people with diabetes (Grade B).

There is also some evidence to suggest that diabetes duration is a weak risk factor for foot ulcer (Grade C).

Table 44 Predictive value of diabetes duration as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]	Outcome
(Resnick et al 2004) USA	II Prospective cohort study Average quality	American Indians (n = 1,974) with diabetes.	Diabetes duration *Measurement:* Not reported	OR 1.03 [1.01, 1.06]	Lower extremity amputation
(Lee et al 1993) USA	II Prospective cohort study Average quality	Oklahoma Indians (n = 990) with type II diabetes	Diabetes duration (years) *Measurement:* Interview	Men: RR 1.05 [1.01, 1.09] Women: RR 1.08 [1.04, 1.13]	Lower extremity amputation
(Lehto et al 1996) Finland	II Prospective cohort study Average quality	People (n = 1044) with type II diabetes aged between 45 and 64 years receiving reimbursement for diabetic medications.	Diabetes duration *Measurement:* Interview	Duration > 9 years: RR 2.2 [1.3, 3.6]	Amputation as a result of atherosclerotic vascular disease.
(Roy & Peng 2008) USA	II Prospective cohort study Average quality	African-Americans (n = 483) with type I diabetes	Diabetes duration (years) *Measurement:* Structured interview	In a model including blood pressure but not retinopathy: OR 1.08 [1.03, 1.13] In a model including retinopathy but not blood pressure: OR 1.07 [1.01, 1.13]	Lower extremity arterial disease (toe, foot, or leg amputation; angioplasty for poor circulation in lower limbs; absence of one or more major arterial pulses in lower limbs)
(Moss et al 1992; Moss et al 1996; Moss et al 1999) USA	II Prospective cohort study Average quality	Patients (n = 2,366) with diabetes receiving primary care at 452 practices in southern Wisconsin.	Diabetes duration (per 10 years) *Measurement:* Not reported	At 4 years follow-up: Older onset [a]: OR 1.8 [1.0, 3.2] At 10years follow-up: Older onset [a]: OR 1.67 [1.10, 2.46]	Amputation
				At 4 years follow-up: Older onset [a]: OR 1.5 [1.0, 2.1]	Foot ulcer
(Ledoux et al 2005) USA	II Prospective cohort study (RCT) Good quality	People (n = 400) with diabetes with a history of full thickness foot lesion.	Diabetes duration *Measurement:* Not reported	> 10 years OR 1.55 [0.71, 3.38]	Foot ulcer

[a] Age at onset of diabetes, Younger if onset at < 30 years of age; RCT = randomised controlled trial

Age

Most studies controlled for age (and sex) in multivariate models of risk factors for poor foot outcomes however, only a few reported the effect size associated with these relationships. These results have been reported in Table 45.

Three studies assessed age as a risk factor for amputation. The study reported by Moss et al (1992, 1996, 1999) considered the risk of amputation in age groups of 10 years. In this analysis, age was considered to be a moderate risk factor for amputation in patients who had a younger onset of diabetes (< 30 years) (Table 45). In contrast, the other two studies which considered mean age (compared with 10 year age groups) reported effect sizes in the opposite direction (Resnick et al 2004; Winkley et al 2007). In the study by Winkley et al (2007) did not find that it was a statistically significant risk factor for amputation (HR = 0.99 [95% CI 0.97, 1.02]). The average quality study by Resnick et al (2004) reported that age was protective against amputation in American Indians with diabetes after a follow- up period of approximately 7 years (OR = 0.96 [95% CI 0.93, 0.99]).

Similarly for the outcome of foot ulcer, two studies reported that age was not a statistically significant risk factor, while one study reported that an increase in age was associated with a statistically significant decrease in the risk of foot ulcer. The average quality study by Moss et al (1992) reported that when measuring age in 10 year groups, there was no significant relationship with incident foot ulcer in a cohort of people with diabetes receiving primary care (OR = 1.1 [95% CI 0.8, 1.4]). The good quality study by Ledoux et al (2005) reported a moderate effect size for mean age in people with a history of diabetic foot ulcer however, this was not a statistically significant relationship (OR = 1.43 [95% CI 0.95, 2.16]). In contrast, in people with peripheral neuropathy, Abbott et al (1998) reported that increasing age was protective against first foot ulcer (HR = 0.95, p = 0.01).

A summary of the evidence for age as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 76.

Box 76 Evidence statement matrix for age as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Six level II studies (7articles) with a low to moderate risk of bias.
Consistency	D	For amputation, there is some genuine inconsistency in the results with one study showing age groups as moderate risk factors for amputation but one study showing that mean age is protective against amputation. For foot ulcer, there is some inconsistency in the direction of the effect sizes although only one study showed a statistically significant (protective) relationship between age and foot ulcer.
Clinical impact	D	The evidence suggests that age has a weak relationship with poor foot outcomes.
Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	B	The studies were conducted in Australia, the UK and USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is insufficient evidence to indicate that age is a (weak) risk factor for lower extremity amputation and foot ulcer in people with diabetes (Grade C).

Table 45 Predictive value of age as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]	Outcome
(Winkley et al 2007) UK	II Prospective cohort study Good quality	People (n = 253) with diabetes presenting with first foot ulcer at either hospital foot clinic or community podiatry clinics.	Age *Measurement:* Mean age (years)	HR 0.99 [0.97, 1.02]	Amputation
				HR 0.99 [0.97, 1.00]	Ulcer recurrence
(Moss et al 1992; Moss et al 1996; Moss et al 1999) USA	II Prospective cohort study Average quality	Patients (n = 2,366) with diabetes receiving primary care at 452 practices in southern Wisconsin.	Age *Measurement:* Per 10 years	At 4 years follow-up: Younger onset [a]: OR 2.0 [1.2, 3.1] At 10 years follow-up: Younger onset [a]: OR 2.04 [1.48, 2.81] At 14 years follow-up: Younger onset [a]: OR 1.71 [1.30, 2.24]	Amputation
				At 4 years follow-up: Younger onset [a]: OR 1.1 [0.8, 1.4]	Foot ulcer
(Resnick et al 2004) USA	II Prospective cohort study Average quality	American Indians (n = 1,974) with diabetes.	Age *Measurement:* Not reported	OR 0.96 [0.93, 0.99]	Lower extremity amputation
(Ledoux et al 2005) USA	II Prospective cohort study (RCT) Good quality	People (n = 400) with diabetes with a history of full thickness foot lesion.	Age *Measurement:* Mean age	OR 1.43 [0.95, 2.16]	First new ulcer
(Abbott et al 1998) UK, USA and Canada	II Prospective cohort study Average quality	People (n = 1,035) with peripheral neuropathy (VPT ≥ 25V on at least one foot, ≤ 50V on both feet and at least one palpable pedal pulse).	Age *Measurement:* Age at study entry	HR 0.95 p = 0.01	First foot ulcer
(Bruce et al 2005) Western Australia	II Prospective cohort study Average quality	People with type II diabetes (n = 1752) residing in the Fremantle Hospital catchment area.	Age *Measurement*: Not reported	HR 1.06 [1.04, 1.08]	Mobility impairment

[a] Age at onset of diabetes, Younger if onset at < 30 years of age

Sex

As for age, sex was often controlled for in multivariate risk models indicating that it is considered an effect modifier. However, few studies actually reported the effect size of the association between sex (male) and poor foot outcomes in people managed in a primary care setting.

Four studies reported the relationship between sex and amputation with another study considering the outcome of lower extremity arterial disease which also included lower extremity amputation (as well as angioplasty and absence of one or more pedal pulses). The average quality study reported by Moss et al (1992, 1996 and 1999) indicated that being male was a strong risk factor in people with younger onset diabetes compared to older onset where male sex was a moderate risk factor (Table 46). Given the strength of the relationship in the cohort with younger onset diabetes, it is interesting to note that male sex was not included in the final risk model for amputation presumably as it was not an independent risk factor. For people with older onset diabetes the strength of the relationship was attenuated considerably with odds ratios between 2.56 and 2.8 for follow-up periods between 4 and 14 years.

Other studies also reported maleness as a moderate risk factor for amputation (Hamalainen et al 1999; Resnick et al 2004; Roy & Peng 2008). The average quality study by Resnick et al (2004) reported that male sex was a moderate risk factor for amputation in American Indians with diabetes (OR = 2.06 [95% CI 1.29, 3.30]) and Hamalainen reported a smaller study that showed males with type I or II diabetes were at moderately higher risk of amputation than females (HR = 3.3 [95% CI 1.0, 10.8]).

There is insufficient evidence to suggest that male sex is a risk factor for first new foot ulcer. The good quality study of Ledoux et al (2005) reported a moderate strength of association in a cohort with a history of foot lesions, but this was not of statistical significance (OR = 2.38 [95% CI 0.71, 7.99]).

A summary of the evidence for male sex as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 77.

Box 77 Evidence statement matrix for male sex as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Six level II studies (8 articles) with a low to moderate risk of bias.
Consistency	B	Most studies consistent and inconsistencies may be explained.
Clinical impact	C	The evidence suggests that age has a moderate relationship with poor foot outcomes.
Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	B	The studies were conducted in Australia, the UK and USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is evidence to indicate that male sex is a moderate risk factor for lower extremity amputation in people with diabetes (Grade B).

There is insufficient evidence to indicate that male sex is a risk factor for new foot ulcer (Grade B).

Table 46 Predictive value of sex as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]	Outcome
(Winkley et al 2007) UK	II Prospective cohort study Good quality	People (n = 253) with diabetes presenting with first foot ulcer at either hospital foot clinic or community podiatry clinics.	Sex (male)	HR 1.12 [0.56, 2.26]	Amputation
				HR 1.42 [0.87, 2.33]	Ulcer recurrence
(Moss et al 1992; Moss et al 1996; Moss et al 1999) USA	II Prospective cohort study Average quality	Patients (n = 2,366) with diabetes receiving primary care at 452 practices in southern Wisconsin.	Sex (male)	At 4 years follow-up: Older onset [a]: OR 2.8 [1.0, 7.5] At 10 years follow-up: Younger onset [a]: OR 5.21 [2.20, 12.33] Older onset [a]: OR 2.56 [1.34, 4.86] At 14 years follow-up: Younger onset [a]: OR 5.21 [2.50, 10.88] Older onset [a]: OR 2.66 [1.49, 4.76]	Amputation
				At 4 years follow-up: Older onset [a]: OR 1.6 [1.0, 2.7]	Foot ulcer
(Resnick et al 2004) USA	II Prospective cohort study Average quality	American Indians (n = 1,974) with diabetes.	Sex (male)	OR 2.06 [1.29, 3.30]	Lower extremity amputation
(Hamalainen et al 1999) Finland	II Prospective cohort study Average quality	People with type I or type II diabetes (n = 733)	Sex (male)	OR 3.3 [1.0, 10.8]	Lower extremity amputation
(Roy & Peng 2008) USA	II Prospective cohort study Average quality	African-Americans (n = 483) with type I diabetes	Sex (male)	In a model including blood pressure but not retinopathy: OR 2.28 [0.94, 5.56] In a model including retinopathy but not blood pressure: OR 2.70 [1.11, 6.53]	Lower extremity arterial disease (toe, foot, or leg amputation; angioplasty for poor circulation in lower limbs; absence of one or more major arterial pulses in lower limbs)
(Ledoux et al 2005) USA	II Prospective cohort study (RCT)	People (n = 400) with diabetes with a history of full thickness foot lesion.	Sex (male)	OR 2.38 [0.71, 7.99]	First new ulcer

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]	Outcome
	Good quality				

[a] Age at onset of diabetes, Younger if onset at < 30 years of age

Peripheral vascular disease

Ankle-brachial index (ABI)

Three studies reported on ABI as a risk factor for lower extremity amputation including the average quality Australian study by Davis et al (2006). The community-based study reported that an ABI on either side of less than or equal to 0.9 was associated with an increased risk of first lower extremity amputation, 2.2 times that of those subjects with an ABI greater than 0.9 (HR = 2.21 [95% CI 1.11, 4.42]).

The study by Resnick et al (2004) also reported that an ABI of less than 0.9 was associated with an increased risk of lower extremity amputation however, this association did not reach statistical significance (OR = 1.50 [95% CI 0.66, 3.40]). The authors believed this to be a result of the low number of amputations in this group of subjects. The study also provided some evidence that an ABI of greater than 1.4 was statistically significantly associated with an increased risk of amputation (OR1.80 [95% CI 1.02, 3.17]).

A summary of the evidence for ABI as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 78.

Box 78 Evidence statement matrix for ABI as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Three level II studies with a low to moderate risk of bias.
Consistency	B	Most studies consistent and inconsistencies may be explained.
Clinical impact	B	The evidence suggests that ABI has a moderately strong relationship with mortality and lower extremity amputation.
Generalisability	B	The evidence is likely to be generalisable to the target population, including indigenous populations, although it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	B	The studies were conducted in Australia, the UK, Finland and USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is evidence to indicate that an ABI less than 0.9 is a moderate risk factor for lower extremity amputation in people with diabetes (Grade B).

There is also evidence that an ABI greater than 1.3 is a moderate risk factor for lower extremity amputation (Grade B).

Table 47 Predictive value of ankle/brachial index as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]				Outcome
(Resnick et al 2004) USA	II Prospective cohort study Average quality	American Indians (n = 1,974) with diabetes.	ABI *Measurement:* Not reported	< 0.9 ≥ 0.9 to ≤ 1.4 > 1.4	OR OR OR	1.50 1.0 (reference) 1.80	[0.66, 3.40] [1.02, 3.17]	Lower extremity amputation
(Hamalainen et al 1999) Finland	II Prospective cohort study Average quality	People with type I or type II diabetes (n = 733)	ABI (Change in group) *Measurement:* Ankle systolic pressure divided by brachial systolic pressure. Subjects were divided into three groups: ABI < 0.9; 0.9 – 1.3; > 1.3.		OR	8.2	[2.8, 24.0]	Lower extremity amputation
(Davis et al 2006) Western Australia	II Prospective cohort study Average quality	People (n = 1294) with type I or type II diabetes residing in the Fremantle Hospital catchment area.	Peripheral arterial disease *Measurement:* Diagnosed if ABI ≤ 0.9 on either side.		HR	2.21	[1.11, 4.42]	First lower extremity amputation

ABI = ankle/brachial index

Claudication

Claudication was reported as a risk factor in only one community-based study (Bruce et al 2005). Conducted in Australia, this average quality study looked at mobility impairment using the General Health Status questionnaire in patients with type II diabetes who had been recruited to the Fremantle Diabetes Study. After substantial loss to follow-up (56%) after approximately 4.5 years, the presence of self-reported claudication was found to be a moderate risk factor for mobility impairment in a cohort who were without problems associated with activities of daily living at baseline (HR = 1.67 [95% CI 1.13, 2.46]).

A summary of the evidence for claudication as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 79.

Box 79 Evidence statement matrix for claudication as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	C	The strength of the relationship between claudication and impaired mobility is moderate.
Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	A	This study was undertaken in Western Australia.

Evidence statement

There is limited evidence to suggest that self-reported claudication may be a risk factor for impaired mobility in a population with type II diabetes (Grade C).

Peripheral pulses

The absence of two or more arterial pulses was reported as a risk factor in one average quality prospective cohort study (Lehto et al 1996). The authors followed a sample of people with type II diabetes in Finland aged between 45 and 64 years. They were identified through the Social Insurance Institution's central register of diabetic subjects who received drug reimbursements. Patients were not included in this study if they had a history of amputation.

The outcome in this study was amputation as a result of atherosclerotic vascular disease which was ascertained by questionnaire and medical records. The analysis, using Cox regression modeling, only controlled for sex and age and was therefore of limited value in identifying independent risk factors. The authors provided scant information regarding the assessment of peripheral arterial pulses but reported that the absence of two or more had a substantial association with amputation as a result of atherosclerotic vascular disease (HR = 3.9 [95%CI 2.3, 6.8]).

A summary of the evidence for peripheral pulses as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 80.

Box 80 Evidence statement matrix for peripheral pulses as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	B	The strength of the relationship between absent pulses and amputation is substantial however, insufficient information regarding the measurement of peripheral arterial pulses was provided.
Generalisability	C	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting. Furthermore, it may only be generalisable to people with peripheral arterial disease.
Applicability	B	This study was undertaken in Finland and is likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is insufficient evidence to indicate that the absence of two or more peripheral arterial pulses may be a risk factor for amputation due to atherosclerotic disease in a population with type II diabetes (Grade C).

Arterial calcification

Everhart et al (1988) reported an average quality study which considered the value of medial arterial calcification (MAC) as a risk factor for diabetic complications and mortality. This was a longitudinal study conducted in a community-based cohort (n = 913) of Pima Indians in Arizona, USA.

Examinations were conducted regularly on participants aged 15 years and over. These examinations included posteroanterior x-ray of the hands and feet and soft tissue x-rays of the lateral left calf and anteroposterior left thigh. Examinations were initially at 2 year intervals which were later adjusted to every 4 years. MAC was indicated by linear calcification, and patchy calcification was indicative of intimal calcification. For the purposes of this analysis, Everhart et al (1988) considered x-rays with both intimal and medial calcification were classified as MAC, while x-rays considered to be indeterminate or having only intimal calcification were classified as not having MAC.

For first lower extremity amputation, and controlling for age; sex; plasma glucose; blood pressure; serum cholesterol; vibration perception threshold; ankle reflexes; proteinuria and body mass index; the presence of MAC within 5 years after diabetes diagnosis was found to be a strong risk factor (HR = 5.5 [95% CI 2.1, 14.4]).

The results from this cohort were also reported by Nelson et al (1988). Although in this analysis, MAC was only controlled by age, sex and diabetes duration. The relative risk of first amputation in this analysis was 4.8 [95% CI 2.9, 8.1].

A summary of the evidence for absent pedal pulses as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 81.

Box 81 Evidence statement matrix for medial arterial calcification as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	C	One level II study (reported in two articles) with moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	B	The strength of the relationship between MAC and first amputation is substantial.
Generalisability	C	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting. Furthermore, it may only be generalisable to American Indians.
Applicability	B	This study was undertaken in the USA and is likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is some evidence to indicate that the presence of medial arterial calcification is a strong risk factor for first lower extremity amputation in a diabetic indigenous population (Grade C).

Cardiovascular disease

One study reported that a history of cerebrovascular disease was a strong risk factor for first lower extremity amputation (Davis et al 2006). As described previously, this community-based study was conducted in Western Australia and followed people with diabetes without indicating if they were receiving primary care for their diabetes or any other related-complications. After a mean follow-up period of 9 years ± 3 years, the authors found that a history of cerebrovascular disease, as determined by self-report and prior hospitalisations, was a strong risk factor for amputation (HR = 5.45 [95% CI 2.51, 11.85]). The authors indicated that coronary heart disease was assessed as a risk factor however; it was no statistically significant at the univariate level.

A further three studies reported CVD as a moderate risk factor for falls and mobility impairment however as these are secondary outcomes, they will not be discussed further here.

A summary of the evidence for CVD as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 82.

Box 82 Evidence statement matrix for cardiovascular disease as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Four level II studies with low to moderate risk of bias.
Consistency	B	Most studies consistent and inconsistency may be explained.
Clinical impact	B	The strength of the relationship between CVD and falls or mobility impairment is moderate. The strength of the relationship between CVD and first lower extremity amputation is strong however only one study reports on this outcome.
Generalisability	C	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	B	These studies were undertaken in Australia, the UK and the USA and are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is evidence to indicate that a history of cerebrovascular disease is a strong risk factor for lower extremity amputation in people with diabetes (Grade C).

Table 48 Predictive value of cardiovascular disease as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]	Outcome
(Davis et al 2006) Western Australia	II Prospective cohort study Average quality	People (n = 1294) with type I or type II diabetes residing in the Fremantle Hospital catchment area.	History of cerebrovascular disease *Measurement:* Self-reported with prior hospitalisations	HR History of cerebrovascular disease 5.45 [2.51, 11.85]	First lower extremity amputation
(Volpato et al 2005) USA	II Prospective cohort study Average quality	Community dwelling women (n = 136) with diabetes aged 65 years or older.	History of stroke *Measurement* Not reported	HR Stroke 2.05 [0.87, 4.86]	Self-reported falls
(Bruce et al 2005) Western Australia	II Prospective cohort study Average quality	People with type II diabetes (n = 1752) residing in the Fremantle Hospital catchment area.	Coronary heart disease (including myocardial infarction, angina, coronary artery bypass grafting, angioplasty) *Measurement*: Self-reported with prior hospitalisations or definite myocardial infarction on Minnesota coding or resting 12-lead ECG	HR Group 1[a]: Present or history 2.23 [1.51, 3.33] Group 2[b]: Present or history 1.92 [1.27, 2.91]	Group 1: Mobility impairment Group 2: Activities of daily living disability
(Wallace et al 2002) USA	II Prospective cohort study Average quality	People (n = 400) with diabetes and without foot deformities which require customised footwear or history of foot ulcer.	Co-morbidities *Measurement:* Patient history of stroke, cardiovascular bypass surgery, chronic respiratory disease, heart failure, cancer or depression	OR (for any fall) ≥ 1 co-morbid condition 2.10 [1.28, 3.44] OR (multiple falls) Foot deformity 2.29 [1.29, 4.08]	Any falls Multiple falls

[a] Free of mobility impairment and independent in Activities of Daily Living at baseline; [b] Free of Adtivities of Daily Living problems at baseline; ECG = electrocardiogram

Lipids

In total, four studies assessed cholesterol measurements as risk factors for amputation and foot ulcers. Of these, three studies reported on the outcome of amputation.

All three studies reporting on amputation had considerable follow-up periods ranging from 7 years to 12 years.

The Finnish study of Lehto et al (1996) reported the risk of high levels of total cholesterol, low high density lipoprotein (HDL) and high triglyceride levels (Table 49). Interestingly, an HDL level less than 0.9mmol/l was not found to be statistically significant risk factor for amputation as a result of atherosclerotic vascular disease (RR = 1.3 [95% CI 0.7, 2.5]). Similarly, triglyceride levels greater than 2.3 mmol/l were not found to be significantly associated with atherosclerotic amputation (RR = 1.4 [95% CI 0.8, 2.4]) after a 7 year follow-up period. However, a total cholesterol level greater than 6.2mmol/l were found to be a statistically significant risk factor for atherosclerotic amputation (RR = 1.8 [95% CI 1.1, 3.2]).

The average quality study by Lee et al (1993) found an 18 per cent increase in risk of lower extremity amputation with every 1mM increase of plasma cholesterol concentration in American Indian women (RR = 1.18 [95% CI 1.08, 1.29]) however, plasma cholesterol levels were not found to be a significant risk factor in the male population studied.

Litzelman et al (1997) reported that decreasing HDL concentrations were significantly associated with development of foot ulcers with a Seattle Wound Classification of greater than or equal to 1.3 that is, non-ulcerated minor lesions (OR = 1.63 [95% CI 1.11, 2.39]). This good quality study was carried out in a population of socioeconomically disadvantaged people and may therefore be limited in its generalisability to a general diabetes population.

A summary of the evidence for lipids as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 83.

Box 83 Evidence statement matrix for lipids as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Four level II studies with low to moderate risk of bias.
Consistency	B C	Most studies consistent and inconsistency may be explained. For foot lesion as the outcome, only one study was available.
Clinical impact	C	The strength of the relationship between total cholesterol and amputation i s likely to be moderate particularly with cholesterol levels > 6.2mmol/l for atherosclerotic amputation. The strength of the relationship between increasing HDL levels and foot ulcer is moderate.
Generalisability	C	The studies covered a broad range of populations including socioeconomically disadvantaged and indigenous populations.
Applicability	B	These studies were undertaken in Finland and the USA and are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is some evidence to indicate that increasing total cholesterol concentration, higher than 6.2mmol/l, may be a moderate risk factor for lower extremity amputation, in particular as a result of atherosclerotic vascular disease, in people with diabetes (Grade B).

There is some evidence to indicate that an increasing HDL concentration is a moderate risk factor for foot lesions with a Seattle Classification ≥ 1.3, in people with diabetes (Grade C).

Table 49 Predictive value of HDL or cholesterol as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]	Outcome
(Nelson et al 1988) USA	II Prospective cohort study Average quality	Residents (n = 4,399) with diabetes of Gila River Indian community, Arizona.	Serum cholesterol *Measurement:* Laboratory examination	Crude incidence (cases per 1000 person-years) < 180mg/dl 7.9 180 – 239mg/dl 12.2 ≥ 240 mg/dl 19.9 = 2.9, p<0.09	Amputation
(Lehto et al 1996) Finland	II Prospective cohort study Average quality	People (n = 1044) with type II diabetes aged between 45 and 64 years receiving reimbursement for diabetic medications.	Total cholesterol *Measurement:* Automated enzymatic methods using fresh serum samples taken after 12hr overnight fast.	Total cholesterol: > 6.2mmol/l RR 1.8 [1.1, 3.2] HDL cholesterol: < 0.9mmol/l RR 1.3 [0.7, 2.5] Triglycerides: > 2.3mmol/l RR 1.4 [0.8, 2.4]	Amputation as a result of atherosclerotic vascular disease.
(Lee et al 1993) USA	II Prospective cohort study Average quality	Oklahoma Indians (n = 990) with type II diabetes	Plasma cholesterol (mM) *Measurement:* Not reported	Women: RR 1.18 [1.08, 1.29]	Lower extremity amputation
(Litzelman et al 1997) USA	II Prospective cohort study (RCT) Good quality	Patients (n = 395) receiving primary care at a university affiliated general medicine practice serving socioeconomically disadvantaged people.	HDL *Measurement:* Measured on venous blood sample from subjects who had fasted.	Seattle Wound Classification ≥ 1.3 HDL (mmol/l): OR 1.63 [1.11, 2.39]	Foot ulcer

HDL = high density lipoprotein

Body mass index (BMI)

Three studies assessed BMI or overweight and its relationship with amputation, first foot ulcer and self-reported falls (Table 50).

Interestingly, the two studies which reported on lower extremity amputation and first new foot ulcer in higher risk populations, indicated that increasing BMI was not a risk factor for either outcome (Ledoux et al 2005; Resnick et al 2004). The study by Ledoux et al (2005) was primarily aimed at assessing the relationship between foot deformity and first new ulcer. Consequently, only ulcers deemed to have been footwear-related and therefore of mechanical etiology were included in the analysis. This is likely to have contributed to the lack of power and may also limit the generalisability of the results.

In contrast, overweight was significantly associated with self-reported falls in a population of community-based women aged 65 years and older (OR = 3.50 [95% CI 1.21, 10.1]) (Volpato et al 2005). The analysis of obesity and falls was underpowered possibly due to smaller numbers of women who reported falls in this group.

A summary of the evidence for BMI as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 84.

Box 84 Evidence statement matrix for BMI as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Three level II studies with low to moderate risk of bias.
Consistency	C	Some inconsistency reflecting genuine uncertainty around the clinical question.
Clinical impact	D	Given the uncertainty around the point estimates it is unclear what the clinical impact would be.
Generalisability	C	The studies covered a broad range of populations including indigenous populations, people with a history of ulcer and elderly women in the community.
Applicability	B	These studies were undertaken in the USA and are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is insufficient evidence to indicate that increasing BMI is a risk factor for poor foot outcomes in people with diabetes (Grade C).

Table 50 Predictive value of BMI as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]				Outcome
(Resnick et al 2004) USA	II Prospective cohort study Average quality	American Indians (n = 1,974) with diabetes.	BMI (kg/m^2) *Measurement* Weight / (height)^2		OR	0.94	[0.90, 0.98]	Lower extremity amputation
(Ledoux et al 2005) USA	II Prospective cohort study (RCT) Good quality	People (n = 400) with diabetes with a history of full thickness foot lesion.	BMI (kg/m^2) *Measurement* Weight / (height)^2		OR	0.78	[0.56, 1.07]	First new ulcer
(Volpato et al 2005) USA	II Prospective cohort study Average quality	Community dwelling women (n = 136) with diabetes aged 65 years or older.	BMI (kg/m^2) *Measurement* Over weight: 25 < BMI < 29.9 Obese: BMI ≥ 30	Overweight Obesity	OR OR	3.50 2.03	[1.21, 10.1] [0.73, 5.65]	Self-reported falls

BMI = body mass index

Smoking

Four studies considered smoking as a risk factor for amputation, foot ulcer recurrence or mobility impairment (Table 51).

No evidence was identified to indicate that smoking was a risk factor for amputation. Both studies which reported this outcome were inadequately powered to detect smoking status as in independent predictor of amputation (Nelson et al 1988; Winkley et al 2007).

For the outcomes of mobility impairment and disability with regard to activities of daily living, there was a moderate association between current smokers and ex-smokers respectively (Table 51).

A summary of the evidence for smoking as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 84.

Box 85 Evidence statement matrix for smoking as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Three level II studies with low to moderate risk of bias.
Consistency	C	Some inconsistency reflecting genuine uncertainty around the clinical question.
Clinical impact	D	Given the lack of power in most of the studies it is difficult to assess the likely clinical impact.
Generalisability	C	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	B	These studies were undertaken in the USA and Australia and are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

Based on the evidence identified, there is insufficient evidence to indicate that smoking is a risk factor for amputation in people with diabetes (Grade C).

For mobility impairment and poor activities of daily living, there is some evidence to suggest that smoking is a moderate risk factor (Grade C).

Table 51 Predictive value of smoking as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]				Outcome
(Winkley et al 2007) UK	II Prospective cohort study Good quality	People (n = 253) with diabetes presenting with first foot ulcer at either hospital foot clinic or community podiatry clinics.	Smoking status *Measurement*: Non-smoker or ex-smoker; smoker	Non-smoker or ex-smoker Smoker	 HR	reference 0.88	 [0.36, 2.14]	Amputation
				Non-smoker or ex-smoker Smoker	 HR	reference 1.16	 [0.64, 2.11]	Foot ulcer recurrence
(Nelson et al 1988) USA	II Prospective cohort study Average quality	Residents (n = 4,399) with diabetes of Gila River Indian community, Arizona.	Smoking status *Measurement*: Non-smoker; current smoker; ex-smoker	Current smoker	HR	1.1	[0.6, 1.8]	Amputation
(Bruce et al 2005) Western Australia	II Prospective cohort study Average quality	People with type II diabetes (n = 1752) residing in the Fremantle Hospital catchment area.	Smoking status *Measurement*: Self-reported	Current smoker: No Yes Ex-smoker: No Yes	 reference HR reference HR	 1.64 1.55	 [1.12, 2.40] [1.13, 2.14]	Mobility impairment Activities of daily living disability

Foot characteristics

Foot ulcer (presence/depth/size/ location)

Three studies reported the relationship between a foot ulcer or wound at baseline and subsequent poor foot outcomes (Table 52).

Two average quality studies reported the presence of a foot or ankle ulcer at baseline as a risk factor for lower extremity amputation or arterial disease (Davis et al 2006; Roy & Peng 2008). The average quality Australian study by Davis et al (2006) recorded the presence of foot ulcer at baseline and reported that this was associated with a 5.5 times increase in risk of first lower extremity amputation (HR = 5.56 [95% CI 1.24, 25.01]). There is considerable uncertainty around this estimate which is likely to be a result of the small number of amputations which occurred.

A summary of the evidence for foot ulcer at baseline of during the study as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 86.

Box 86 Evidence statement matrix for foot ulcer as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Three level II studies with low to moderate risk of bias.
Consistency	B	Most studies consistent and inconsistency may be explained.
Clinical impact	B	The presence or development of a foot ulcer appears to be a moderate or strong risk factor for lower extremity amputation or arterial disease.
Generalisability	C	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	B	These studies were undertaken in the UK, USA and Australia and are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is evidence to indicate that the presence of a foot ulcer is a moderate risk factor for lower extremity amputation or arterial disease (Grade B).

Table 52 Predictive value of ulcer presence / depth / size as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]	Outcome
(Winkley et al 2007) UK	II Prospective cohort study Good quality	People (n = 253) with diabetes presenting with first foot ulcer at either hospital foot clinic or community podiatry clinics.	Foot ulcer size, location and depth *Measurement*: Size was determined by digital imaging. Depth was coded either superficial (extending through dermis or epidermis only) or severe (wounds penetrating tendons, joint capsule, bone, or joint).	Depth: Superficial Reference Severe HR 3.18 [1.53, 6.59] Size: ≤ 1 cm^2 Reference > 1 cm^2 HR 1.40 [0.69, 2.85]	Amputation
				Location: Plantar Reference Dorsal HR 0.68 [0.45, 1.05]	Foot ulcer recurrence
(Davis et al 2006) Western Australia	II Prospective cohort study Average quality	People (n = 1294) with type I or type II diabetes residing in the Fremantle Hospital catchment area.	Foot ulcer present *Measurement*: At baseline.	HR 5.56 [1.24, 25.01]	First diabetes-related lower extremity amputation.
(Roy & Peng 2008) USA	II Prospective cohort study Average quality	African-Americans (n = 483) with type I diabetes	Foot/ankle ulcer *Measurement*: At baseline	In a model including blood pressure but not retinopathy: OR 2.90 [1.02, 8.19] In a model including retinopathy but not blood pressure: OR 2.51 [0.86, 7.29]	Lower extremity arterial disease (toe, foot, or leg amputation; angioplasty for poor circulation in lower limbs; absence of one or more major arterial pulses in lower limbs)
(Litzelman et al 1997) USA	II Prospective cohort study (RCT) Good quality	Patients (n = 395) receiving primary care at a university affiliated general medicine practice serving socioeconomically disadvantaged people.	Baseline wound *Measurement:* Seattle Wound Classification score	Seattle Wound Classification ≥ 1.2 Baseline wound [a]: OR 1.76 [0.80, 3.89] Seattle Wound Classification ≥ 1.3 Baseline wound [b]: OR 13.41 [3.19, 56.26]	Foot ulcer

[a] = Baseline wound defined as a lesion at baseline rated at least 1.2 by the Seattle Wound Classification Score (Superficial or healing minor lesion with no functional interruption of the protective cutaneous barrier); [b] = Baseline wound was defined as a wound rated at least 1.3 by the Seattle Wound Classification Score (Non-ulcerated minor lesions, < 4 weeks duration with clinical evidence of healing progress or a blister.

Foot deformity / shape

Three studies investigated foot deformity or shape as a risk factor for poor foot outcomes in diabetic patients (Cowley et al 2008; Ledoux et al 2005; Wallace et al 2002).

Cowley et al (2008) assessed foot type and deformities to determine their relationship with new foot ulcer in a good quality prospective study (Table 53). The only variables measured which were determined to be significant risk factors were hammer/claw toes and other foot types (HR = 1.40 [95% CI 1.03, 1.90] and HR = 1.76 [95% CI 1.04, 3.04] respectively).

Ledoux et al (2005) also reported a good quality study which investigated foot type and deformity as risk factors for ulcer recurrence. This study reported similar results but suggested that fixed hammer/claw toes were a significant risk factor (OR = 3.91 [95% CI 1.57, 9.71]) compared to supple hammer/claw toes OR = 0.68 [95% CI 0.25, 1.87]). The authors also reported that hallux limitus was a moderately strong risk factor in patients with a history of foot ulcers (OR = 3.02 [95% CI 1.37, 6.66]). The increase in the strength of association between this foot deformity and ulcer recurrence is unlikely to be a result of the increase in baseline risk of patients with a history of foot ulcer compared to those attending a general medicine clinic as the study by Cowley et al (2008) controlled for ulcer history in their analysis. It may be however, related to the differences in sample size between the studies which has resulted in the wider confidence intervals in the study by Ledoux et al (2005).

A summary of the evidence for foot deformity and shape as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 87.

Box 87 Evidence statement matrix for foot deformity and shape as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Three level II studies with low to moderate risk of bias.
Consistency	B	For the risk factors which were statistically significant, most studies were consistent and the inconsistency may be explained.
Clinical impact	C	The presence of a hammer/claw toe or hallux limitus are moderate risk factors first new foot ulcer and ulcer recurrence.
Generalisability	C	The evidence may be generalisable to the target population.
Applicability	B	These studies were undertaken in the USA and are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is evidence to indicate that hallux limitus and hammer/claw toe is a moderate risk factor for new foot ulcer and ulcer recurrence (Grade B).

Table 53 Predictive value of foot shape / deformity as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]	Outcome
(Cowley et al 2008) USA	II Prospective cohort study Good quality	Patients (n = 1520, 3040 feet) attending general internal medicine clinic with diabetes	Foot type *Measurement:* Physical examination by research nurse.	HR[a] Hallux valgus 0.8 [0.60, 1.06] Hallux limitus 1.11 [0.83, 1.49] Hammer/claw toes 1.40 [1.03, 1.90] Graded hammer claw toes: Absent 1.0 Slight 1.22 [0.81, 1.87] Moderate 0.99 [0.67, 1.50] Marked 1.43 [0.95, 2.17] Not graded 1.49 [0.95, 2.43] Prominent metatarsal head 1.19 [0.90, 1.59] Plantar callus 0.99 [0.76, 1.29] Ankle dorsiflexion (10°) 1.02 [0.83, 1.25] MTPJ dorsiflexion (10°) 0.95 [0.84, 1.07] MTPJ plantar flexion (10°) 0.92 [0.82, 1.04] Muscle atrophy 1.08 [0.80, 1.46] Bony prominences 1.29 [0.95, 1.76] Foot type neutrally aligned 1.0 Pes cavus 1.01 [0.72, 1.40] Pes planua rigid 0.72 [0.40, 1.27] Pes planus flexible 1.00 [0.60, 1.66] Other 1.76 [1.04, 3.04]	New foot ulcer
(Ledoux et al 2005) USA	II Prospective cohort study (RCT) Good quality	People (n = 400) with diabetes with a history of full thickness foot lesion.	Foot type and foot deformity *Measurement:* Physical examination	OR [b] Foot type Neutrally aligned 1.0 (reference) Pes planus 1.25 [0.53, 2.98] Pes cavus 0.77 [0.25, 2.37] Hallux valgus 1.97 [0.9, 4.31] Hammer/claw toes None 1.0 (reference) Supple 0.68 [0.25, 1.87]	Ulcer recurrence

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]			Outcome
				Fixed Hallux limitus	3.91 3.02	[1.57, 9.71] [1.37, 6.66]	
(Wallace et al 2002) USA	II Prospective cohort study Average quality	People (n = 400) with diabetes and without foot deformities which require customised footwear or history of foot ulcer.	Foot deformity *Measurement:* Not reported	 Foot deformity Foot deformity	OR (for any fall) 0.81 OR (multiple falls) 0.82	 [0.50, 1.30] [0.49, 1.41]	Any falls Multiple falls

[a] adjusted for neuropathy, age, BMI, insulin medication, ulcer history, amputation history and stratified by gender; [b] adjusted for gender; age BMI; diabetes duration and neuropathy.

Foot ulcer history

One study reported on the association between history of foot or leg ulcer and amputation in people with diabetes (Table 54).

Moss et al (1992 and 1999) reported that history of sores or ulcers was a statistically significant risk factor for amputation in people with diabetics being managed in a primary care setting. This study reported results for this risk factor after 4 and 14 years of follow-up. As would be expected, the longer follow-up period provided greater precision in the estimate of the strength of the risk factor. The association between history of ulcer and amputation was similar at 14 years in people with younger and older onset of diabetes (OR = 3.19 [95% CI 1.71, 5.95] and OR = 3.56 [95% CI 1.84, 6.89] respectively).

A summary of the evidence for foot ulcer history as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 88.

Box 88 Evidence statement matrix for foot ulcer history as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	C	One level II studies with moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	B	History of foot ulcer appears to be a moderate risk factor for amputation after 14 years of follow-up.
Generalisability	A	The evidence is generalisable to the target population.
Applicability	B	These studies were undertaken in the USA and are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is some evidence that history of sores or ulcers is a moderate risk factor for amputation in people with diabetes managed in a primary care setting (Grade C).

Table 54 Predictive value of foot ulcer history as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]	Outcome
(Moss et al 1992; Moss et al 1999)	II Prospective cohort study Average quality	Patients (n = 2,366) with diabetes receiving primary care at 452 practices in southern Wisconsin.	History of sores or ulcers *Measurement:* Not reported	At 4 years follow-up: Younger onset [a]: OR 10.5 [6.7, 29.8] Older onset [a]: OR 4.6 [1.7, 12.2] At 14 years follow-up: Younger onset [a]: OR 3.19 [1.71, 5.95] Older onset [a]: OR 3.56 [1.84, 6.89]	Amputation

Insulin treatment

Insulin therapy or other methods of diabetic control were assessed as risk factors for poor foot outcomes in three studies (Table 55).

The good quality study by Winkely et al (2007) compared the risk of foot ulcer recurrence associated with insulin treatment and tablet medication. Compared to insulin, there was a decrease in risk associated with tablet medication of approximately 31% however this was not statistically significant (HR = 0.69 [95% CI 0.44, 1.06]).

For self-reported falls or mobility impairment, there was a significant risk associated with insulin treatment (Bruce et al 2005; Volpato et al 2005). Volpato et al (2005) reported that insulin use was a significant risk factor for falls as opposed to oral medications. The authors indicated that even with adjustment for other diabetic complications, insulin treatment remained a significant risk factor for falls in elderly women with diabetes (OR = 2.02 [95% CI 1.10, 3.71]).

A summary of the evidence for insulin use as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 89.

Box 89 Evidence statement matrix for insulin use as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Three level II studies with low to moderate risk of bias.
Consistency	C	Given the different outcomes reported it is difficult to determine whether these results are consistent. There appears to be consistency for the secondary outcomes however this is not so for ulcer recurrences.
Clinical impact	C	It would appear that insulin use is a moderate risk factor for falls and mobility impairment. There is insufficient evidence to determine the clinical impact for ulcer recurrence.
Generalisability	A	The evidence is generalisable to the target population.
Applicability	B	These studies were undertaken in Australia, the UK and the USA and are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is some evidence to indicate that insulin use is a moderate risk factor for falls and mobility impairment in people with diabetes (Grade C).

There is insufficient evidence for insulin use as a risk factor for foot ulcer recurrence in people with diabetes (Grade C).

Table 55 Predictive value of insulin treatment as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association [95% CI]	Outcome
(Winkley et al 2007) UK	II Prospective cohort study Good quality	People (n = 253) with diabetes presenting with first foot ulcer at either hospital foot clinic or community podiatry clinics.	Diabetic treatment *Measurement*: Record of either insulin or tablet treatment	HR Diabetes treatment: Insulin 1.0 (reference) Tablet 0.69 [0.44, 1.06]	Foot ulcer recurrence
(Volpato et al 2005) USA	II Prospective cohort study Average quality	Community dwelling women (n = 136) with diabetes aged 65 years or older.	Diabetic treatment *Measurement* Oral hypoglycaemic agent or insulin.	HR[a] Insulin 2.02 [1.01, 3.71]	Self-reported falls
(Bruce et al 2005) Western Australia	II Prospective cohort study Average quality	People with type II diabetes (n = 1752) residing in the Fremantle Hospital catchment area.	Diabetic treatment *Measurement*: Self-reported insulin treatment.	HR Group 1[a]: Insulin treatment 2.17 [1.49, 3.18]	Group 1: Mobility impairment

[a] model is also adjusted for previous fall in the last 12 months, Mini-Mental State Examination symptoms of depression, use of pain medications, use of hypotensive medications, and visual impairment.

Depression

Two studies investigated depression as a risk factor for poor foot outcomes (Bruce et al 2005; Winkley et al 2007).

The good quality study by Winkely et al (2007) assessed depression as a risk factor for amputation and foot ulcer recurrence (Table 56). Depression was assessed during an interview using the WHO's SCAN2.1 which was based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Over a relatively short study period of 1.8 years, the presence of any depressive symptoms was associated with increased risk of poor foot outcomes relative to no depressive symptoms however, this did not reach statistical significance for any of the reported outcomes.

The Australian study by Bruce et al (2005) also reported that self-reported depression was associated with a 41% increase in Activities of Daily Living difficulties (HR = 1.41 [95% CI 1.02, 1.95]). The self-reported depression outcome was partially validated with a convenience sample which was examined by an experienced researcher who assessed for the presence of DSM-IV depression syndromes. From this, it was determined that self-report of mood symptoms using the General Health Questionnaire was an adequate measure of depressive symptoms in this population.

A summary of the evidence for depression as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 90.

Box 90 Evidence statement matrix for depression as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Two level II studies with low to moderate risk of bias.
Consistency	B	Most studies are consistent and the inconsistency may be explained.
Clinical impact	C	It would appear that depressive symptoms are a moderate risk factor for difficulties in Activities of Daily Living
Generalisability	B	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	B	These studies were undertaken in Australia and the UK and are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is some evidence that depressive symptoms are a moderate risk factor for difficulties in Activities of Daily Living in people with diabetes (Grade B).

Table 56 Value of depression as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association + [95% CI]	Outcome
(Winkley et al 2007) UK	II Prospective cohort study Good quality	People (n = 253) with diabetes presenting with first foot ulcer at either hospital foot clinic or community podiatry clinics.	Depression *Measurement*: During interview using WHO's SCAN 2.1 based on the DSM-IV criteria.	HR No depression 1.0 (reference) Any depression 1.38 [0.70, 2.72]	Amputation
				HR No depression 1.0 (reference) Any depression 1.18 [0.77, 1.81]	Foot ulcer recurrence
(Bruce et al 2005) Western Australia	II Prospective cohort study Average quality	People with type II diabetes (n = 1752) residing in the Fremantle Hospital catchment area.	Depression *Measurement*: Based on self-reporting of mood symptoms contained in the General Health Status questionnaire.	HR 1.41 [1.02, 1.95]	Activities of Daily living difficulties

WHO = World Health Organization; DSM –IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition

Type I or type II diabetes

One study assessed the relationship between type I or type II diabetes and poor foot outcomes (Table 57).

Winkely et al (2007) reported on the relationship between type of diabetes and foot ulcer recurrence but was unable to detect a statistically significant association between type of diabetes and foot ulcer recurrence.

A summary of the evidence for diabetes type as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 91.

Box 91 Evidence statement matrix for diabetes type as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	One level II studies with low to moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	D	It is unclear what the clinical impact of this evidence would be given the uncertainty around the association between type of diabetes and poor foot outcomes
Generalisability	B	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	B	These studies were undertaken in the USA and UK and are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is insufficient evidence to suggest that the type of diabetes is a risk factor for foot ulcer recurrence (Grade C).

Table 57 Type I or type II diabetes as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association + [95% CI]	Outcome
(Winkley et al 2007) UK	II Prospective cohort study Good quality	People (n = 253) with diabetes presenting with first foot ulcer at either hospital foot clinic or community podiatry clinics.	Diabetes *Measurement*: Type of diabetes was defined according to WHO criteria	HR Type I diabetes 1.0 (reference) Type II diabetes 0.84 [0.49, 1.45]	Foot ulcer recurrence

WHO = World Health Organization

Physical activity

Two studies assessed the relationship between physical activity and poor foot outcomes in people with diabetes (Bruce et al 2005; LeMaster et al 2003).

A good quality study reported by LeMaster et al (2003) described the relationship between physical activity and foot ulcer recurrence in a population of people aged between 45 and 84 years with diabetes and a history of full thickness foot lesions or a foot infection requiring antibiotic treatment (Table 58). Subjects were excluded if they had foot deformities requiring a custom shoe, lower extremity amputation of more than one digit, a lesion either unhealed or healed for less than 1 month and a history or active Charcot's foot. All patients in this study were participants in a randomised controlled trial of therapeutic foot wear and insoles for the prevention of foot ulcer recurrence.

After a two year follow-up period which involved daily weight bearing activity being recorded at every 17 week follow-up visit, the authors indicated that weight bearing activity was not a risk factor for ulcer recurrence but in fact, increasing long term activity (cumulative number of active hours measured from enrolment through to a given follow-up visit) was protective against recurrence (OR = 0.77 [95% CI 0.81, 0.96]).

The Australian study by Bruce et al (2005) also provided evidence that any self-reported exercise in the previous two weeks reduced the risk of mobility impairment and Activities of Daily Living disability (HR = 0.61 [95% CI 0.45, 0.83] and HR = 0.53 [95% CI 0.38, 0.73]).

A summary of the evidence for physical activity as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 92.

Box 92 Evidence statement matrix for physical activity as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	B	Two level II studies with low to moderate risk of bias.
Consistency	B	Most studies consistent and inconsistency may be explained.
Clinical impact	C	Physical activity is a moderate protective factor against foot ulcer recurrence and mobility impairement.
Generalisability	B	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting.
Applicability	B	These studies were undertaken in the USA and Australia and are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is evidence to suggest that the weight bearing activity is protective against foot ulcer recurrence and mobility impairment (Grade B).

Table 58 Value of physical activity as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association + [95% CI]	Outcome
(LeMaster et al 2003) USA	II Prospective cohort study Good quality	People with diabetes and a history of foot ulcer (n = 400) attending two health maintenance organisations originally enrolled in a RCT of footwear	Physical activity *Measurement:* Interview every 17 weeks using a 24hr activity questionnaire. An active hour was 60 minutes in which subjects participated in any weight-bearing activity.	OR (without imputed data) Current activity[a] 0.82 [0.86, 1.01] Long term activity[b] 0.77 [0.81, 0.96] Short term activity[c] 1.10 [0.99, 1.22] OR (with imputed data) Current activity 0.84 [0.68, 1.02] Long term activity 0.80 [0.64, 1.0] Short term activity 1.07 [0.96, 1.20]	Foot ulcer recurrence
(Bruce et al 2005) Western Australia	II Prospective cohort study Average quality	People with type II diabetes (n = 1752) residing in the Fremantle Hospital catchment area.	Exercise *Measurement*: Self-reported exercise in two weeks prior to assessment.	HR Group 1[a]: Any exercise 0.61 [0.45, 0.83] Group 2[b]: Any exercise 0.53 [0.38, 0.73]	Group 1: Mobility impairment Group 2: Activities of daily living disability

[a] the number of active hours in the previous 24 hour period before a follow-up visit; [b] cumulative number of active hours measured from enrolment through to a given follow-up visit; [c] difference between number of active hours per day between follow-up visit; RCT = randomised controlled trial

Education

Resnick et al (2004) reported data from the Strong Heart Study in American Indians with diabetes but without a history of lower extremity amputation. The average quality study enrolled 1,880 subjects based in American Indian communities in the USA. A number of potential predictor variables were assessed at baseline including hypertension; smoking; at-risk drinking; lipids and microalbuminuria.

After a mean follow-up period of 8 years, outcome data were collected by trained examiners through direct observation of both legs. Data were then analysed to determine the baseline predictors of the first lower extremity amputation in this population. The authors did not indicate how data on education was collected but the measure was presumably self-reported. Multivariate logistic regression indicated that American Indians with high school education or higher were less likely to undergo first lower extremity amputation (OR = 0.46 [95% CI 0.27, 0.76]). This estimate was achieved when controlling for age; sex; community centre; duration of diabetes; level of HbA_{1c}; systolic blood pressure; BMI; proteinuria and ankle-brachial index.

A summary of the evidence for education as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 93.

Box 93 Evidence statement matrix for education as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	C	One level II study with a moderate risk of bias.
Consistency	N/A	Only one study available
Clinical impact	B	The evidence does not suggest that high school education or higher is a risk factor for first lower extremity amputation.
Generalisability	B	The evidence is likely to be generalisable to a community-based indigenous population. Given the community setting, it can't be ruled out that some subjects were not receiving primary care.
Applicability	B	The studies was conducted in the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is evidence to indicate that high school education level or higher is not a risk factor for first lower extremity amputation in indigenous populations with diabetes (Grade C).

Risk score

Rith-Najarian et al (1992) reported the use of a screening exam in primary care to identify those at high risk of lower extremity amputation. The average quality prospective cohort study enrolled 358 diabetic patients. Minimal information is provided regarding the identification and recruitement of subjects however, people on the diabetes registry received the foot examination annually and were coded according to their respective foot risk category. The foot screening exam assessed sensation to 10g monofilament across eight areas of the foot. If subjects had sensation in all eight areas of both feet they were coded as sensate. Deformities identified included hallux varus or valgus, claw and hammer toes, bony prominence, or Charcot's foot. History of a lower extremity event included ulceration and amputation. Based on the rating of these three areas, subjects were assigned to a risk category as indicated in Table 59.

Table 59 Classification of risk category according to Rith-Najarian et al (1992)

Risk category	Sensate to 10g monofilament	Deformity present	History of lower extremity event	Crude odds ratio (95% CI not reported)
0 (reference)	+	+/–	–	1.00
1	–	–	–	15
2	–	+	–	32
3	+/–	+/–	+	78

+ = criteria present; – = criteria absent

Patients were followed for 32 months and the occurrence of foot ulcer or amputation was recorded. The authors reported increasing risk of ulcer or amputation with increase in risk category ($p < 0.0001$ for trend) however; these results are unadjusted for potential confounders including age, sex and duration of diabetes. Given the uncontrolled nature of these results, it is not appropriate to suggest that risk category is itself a risk factor for poor foot outcomes.

A summary of the evidence for risk score as a risk factor for poor foot outcomes according to NHMRC criteria is provided in Box 94.

Box 94 Evidence statement matrix for risk score as a risk factor for poor foot outcomes

Component	Rating	Description
Evidence base	C	One level II study with a moderate risk of bias.
Consistency	N/A	Only one study available
Clinical impact	D	The unadjusted nature of the results prevents an assessment of the clinical impact.
Generalisability	B	The evidence is likely to be generalisable to a community-based indigenous population. Given the community setting, it can't be ruled out that some subjects were not receiving primary care.
Applicability	B	The study was conducted in the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is insufficient evidence to indicate that risk score is a risk factor for amputation or ulceration in an American indigenous population (Grade C).

Other potential risk factors

Other potential risk factors were also reported for the outcomes of mobility impairment, physical disability or falls. These have been reported in Table 60 and will be discussed below. The results were reported from the average quality studies described by Bruce et al (2005) and Volpato et al (2005)

The risk factors reported by Volapto et al (2005) for self-reported falls in an elderly female population included lower extremity pain (OR = 3.61 [95% CI 1.26, 10.4]), particularly in three or more sites (OR = 5.58 [95% CI 1.89, 16.5]). The presence of knee osteoarthritis was not a statistically significant risk factor for falls however, the summary score used to measure physical performance used in this study was a risk factor for scores less than 9 (OR = 7.76 [95% CI 1.03, 58.8]) although there was considerable uncertainty around this estimate.

Bruce et al (2005) considered characteristics which were associated with mobility impairment and physical disability as indicated by Activities of Daily Living disability. It is unclear whether the instrument used to measure these outcomes has been validated in a diabetic population however, the presence of arthritis, non-fluency in English and Indigenous status were all

reported as risk factors for mobility impairment or physical disability. In contrast, being married provided a protective effect against these outcomes in community based people with diabetes.

A summary of the evidence for other potential risk factors for poor foot outcomes according to NHMRC criteria is provided in Box 95.

Box 95 Evidence statement matrix for other potential risk factors for poor foot outcomes

Component	Rating	Description
Evidence base	C	Two level II studies with a moderate risk of bias.
Consistency	N/A	For the one common risk factor assessed by the two studies, the effect sizes were in the same direction although the result of Volpato et al (2005) did not reach statistical significance.
Clinical impact	B-C	Arthritis and fluency in English were both moderate risk factors for poor outcomes, while lower extremity pain, indigenous status and poor physical performance were strong risk factors for poor outcomes.
Generalisability	B	The evidence is likely to be generalisable to a community-based population. Given the community setting, it can't be ruled out that some subjects were not receiving primary care.
Applicability	B	The studies was conducted in Australia and the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is some evidence to indicate that lower extremity pain, indigenous status, poor physical performance, fluency in English and arthritis are risk factors for mobility impairment or physical disability (Grade C).

Table 60 Other potential factors as a risk factor for poor foot outcomes

Author Country	Level and quality of study	Population and care setting	Risk factor	Measure of association + [95% CI]	Outcome
(Volpato et al 2005) USA	II Prospective cohort study Average quality	Community dwelling women (n = 136) with diabetes aged 65 years or older.	Knee osteoarthritis ascertained according to predefined criteria (no other information provided)	OR 1.78 [0.93, 3.39]	Self-reported falls
			Lower extremity pain 1-2 sites 3-4 sites	OR 3.61 [1.26, 10.4] 5.58 [1.89, 16.5]	Self-reported falls
			Summary physical performance – summary of walking speed, chair stands and balance tests. Scored 0 if unable to complete task.	OR Score < 9 7.76 [1.03, 58.8]	Self-reported falls
(Bruce et al 2005) Western Australia	II Prospective cohort study Average quality	People with type II diabetes (n = 1752) residing in the Fremantle Hospital catchment area.	Arthritis	HR 1.82 [1.37, 2.42]	Mobility impairment
			Marriage status	HR Married 0.68 [0.51, 0.92]	Mobility impairment
			English fluency	HR Non-fluent 2.83 [1.96, 4.08]	Activities of daily living disability
			Indigenous Australian	HR 4.33 [1.04, 18.08]	Activities of daily living disability

Research Question 6: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer?

Box 96 Inclusion criteria for the evaluation of interventions to improve foot-related clinical outcomes for people with or without foot ulcer

Parameter	Inclusion criteria
Population	Adults with type 1 or type 2 diabetes Subgroups- a) who have potentially elevated risk of ulceration (eg long duration of disease, injury, smoking, uncontrolled glucose levels for extended periods, age); or b) with the presence of a risk factor eg PVD, peripheral neuropathy or foot deformity; or c) people with a history of foot ulcer; or d) in people with Charcot's neuroarthropathy; or e) in Indigenous populations; and/or f) in people with foot ulcer
Intervention	Management strategies which may include blood pressure control; glucose control; lipid management; anti-platelet therapy; education; footwear; attendance at podiatry/foot care appointments; telemedicine; models of care; patient self-care / self-management; multidisciplinary approach; drug therapy or any combination of these or other strategies.
Comparator	No treatment; sham treatment; usual care; other therapies; or other means of service delivery
Outcomes	*Primary outcomes:* Mortality/survival; ulceration; local or major amputation; recurrence rates; quality of life; independence; mobility restriction; long-term mobility; healing; harms; side effects. *Secondary outcomes:* Percentage healing; general functioning; deformity and pre-ulcer lesions; hospitalisation; average length of stay. *Cost-effectiveness outcomes:* Cost per event avoided; cost per life year gained; cost per quality adjusted life year or disability adjusted life year; incremental cost-effectiveness ratio
Study design	Randomised, pseudo-randomised or non-randomised controlled trials; cohort studies, or systematic reviews of these study designs.
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified.
Publication date	1966 – 11/2009
Limitations	Human

Interventions that aimed to improve clinical outcomes for people with diabetes, with or without a foot ulcer, ranged from educational programs, to the application of antibiotic creams and the use of oxygen hyperbaric therapy. Articles were identified that fulfilled the inclusion criteria as per Box 96. A detailed discussion is provided below.

Systemic therapeutic drug interventions

Nine studies (two good quality level II evidence, six average quality level II evidence, and one average quality level III-1 evidence) investigated the effectiveness of administering 8 different therapeutic agents (7 classes) systemically in addition to standardised care for treating diabetic foot ulcers (see Table 61 to Table 67). Six of these drug classes were administered with the intention of improving the microvascular blood flow in the lower extremities of diabetic patients (with and without ischaemia) in order to improve the ulcer healing rate. The seventh drug class was administered to improve immune function.

Drugs for the improvement of microvascular blood flow

ANGIPARS versus standard wound care

ANGIPARS is a herbal extract that has been reported to have angiogenic properties which may help to re-vascularise a wound area as it heals (Bahrami et al 2008). Two level II studies of average quality, conducted in Iran, investigated the effectiveness of administering ANGIPARS systemically in conjunction with standard wound care at healing chronic diabetic foot ulcers (Table 61).

Bahrami et al (2008) conducted a small single-blind randomised controlled trial of average quality to determine the effectiveness of ANGIPARS in addition to standard care. Two intervention groups who received oral administration of ANGIPARS, with or without additional topical application of a 3% ANGIPARS gel, were compared to standard wound care alone. Investigators enrolled 21 patients with a chronic diabetic foot ulcer who attended Sina University Hospital in Tabriz. Bahrami et al (2008) found no statistically significant difference in the % reduction in ulcer size for patients receiving systemic ANGIPARS with or without additional topical application (87.8% ± 11% and 84.4% ± 3.5%, respectively; p = 0.49). However, when compared to standard treatment alone (25.1% ± 14.5% reduction), both intervention groups showed a statistically significant improvement in the reduction in ulcer size (p = 0.002). This difference was also reflected in the number of patients with ulcers that healed. All twelve patients from the intervention groups had ulcers which healed or improved, whereas only three of the nine ulcers from the patients receiving standardised care alone healed or improved (RR = 3.00 [95% CI 1.55, 3.00]) (Bahrami et al 2008). However, it should be noted that the average size of the ulcers at baseline for the group that received oral ANGIPARS was approximately half the size of those in the other two groups (375.0 ± 118 mm^2 compared to 916.7 ± 228.6 mm^2 and 766.2 ± 320.2 mm^2). The group with the smaller ulcers is more likely to have ulcers that healed completely during the study period, and thus this may have confounded the results.

Larijani et al (2008) conducted a randomised controlled trial, also small and of average quality involving 25 diabetic patients with chronic foot ulcers to determine the effectiveness of intravenous administration of ANGIPARS daily for 28 days in addition to standard care. In parallel with the previous study, the average size of the ulcers in the group receiving ANGIPARS are approximately half the size of ulcers in the control group (479.9 ± 379.8 mm^2 compared to 766.2 ± 960.5 mm^2). The authors reported similar results to Bahrami et al (2008); the percent reduction of ulcer size after 28 days was significantly greater in the group that received ANGIPARS compared to standard care (64% and 25% respectively, p = 0.015) .

The data from these two clinical trials indicate that systemic administration of ANGIPARS (either oral or intravenous) may be a useful adjunct to standardised care for the treatment of diabetic foot ulcers. However, for ease of use and patient comfort, oral administration may be preferred, especially in outpatient settings. No additional benefit was detected for topical application of ANGIPARS in addition to oral administration (RR = 1.20 [95% CI 0.90, 1.20]). The study conducted by Bahrami et al (2008) was probably underpowered for this comparison, given the small sample size.

Box 97 Evidence statement matrix for ANGIPARS therapy in addition to standard wound care

Component	Rating	Description
Evidence base	C	Two level II studies with a moderate risk of bias.
Consistency	C	Comparisons between these two studies are limited due to the potential for some overlap in populations and also differences in ulcer size at baseline.
Clinical impact	A	Clinically and statistically significant benefits were reported for complete ulcer healing in one study, and the percent reduction in ulcer size in both studies.
Generalisability	B	Populations consisted of diabetic patients with chronic foot ulcers.
Applicability	D	One study was conducted in Iran, and the other in Iran and United Arab Emirates, which has different healthcare for diabetes patients compared to the Australian healthcare context.

Evidence statement

There is evidence to suggest that systemic administration of ANGIPARS may decrease ulcer size for people with chronic diabetic foot ulcers (Grade C).

Table 61 Studies which evaluated the effectiveness of ANGIPARS for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Bahrami et al 2008) Iran	Level II RCT Average quality study	N = 21. Diabetic patients with a foot ulcer attending Sina University Hospital, Tabriz, Iran. Intervention group 1: n = 6; age (yrs) 60.7 ± 3.0; male 4/6 (67%); weight (kg) 78.8 ± 3.9; ulcer size (mm^2) 375.0 ± 118.1; Wagner grade 2 6/6 (100%). Intervention group 2: n = 6; age (yrs) 51.0 ± 3.7; male 4/6 (67%); weight (kg) 79.4 ± 12.1; ulcer size (mm^2) 916.7 ± 228.6; Wagner grade 2 6/6 (100%). Comparator group 3: n = 9; age (yrs) 59.0 ± 3.7; male 5/9 (566%); weight (kg) 65.4 ± 3.6; ulcer size (mm^2) 766.2 ± 320.2, Wagner grade 2 9/9 (100%).	Group 1: n = 6 100 mg ANGIPARS capsule twice daily for 6 weeks plus standard wound care. Group 2: n = 6 100 mg ANGIPARS capsule twice daily plus 3% ANGIPARS gel was administered topically, for 6 weeks plus standard wound care.	Group 3: n = 9 Standard wound care only. Standard wound care included debridement, irrigation, dressings, pressure off-loading, and antibiotic therapy.	% reduction in ulcer size (mean ± SD) Group 1 / Group 3 87.8±11 / 25.1±14.5 / p = 0.002 Group 2 84.4±3.5 / p = 0.002 Group 2 / Group 1 84.4±3.5 / 87.8±11 / p = 0.49 Number of patients with ulcers that healed completely (>70% ulcer size reduction) Group 1 / Group 3 5/6 (83.3%) / 2/9 (22.2%) / RR = 3.75 [95% CI 1.23, 7.23] Group 2 6/6 (100%) / RR = 4.5 [95% CI 1.71, 4.50] Group 2 / Group 1 6/6 (100%) / 5/6 (83.3%) / RR = 1.20 [95% CI 0.84, 1.72] Number of patients with ulcers that improved (10-70% ulcer size reduction) Group 1 / Group 3 1/6 (16.7%) / 1/9 (11.1%) / RR = 1.50 [95% CI 0.16, 13.7] Group 2 0/6 (0%) / RR = 0.00 [95% CI 0.00, 5.48] Total number of patients with ulcers that healed or improved Group 1 + 2 / Group 3 12/12 (100%) / 3/9 (33%) / RR = 3.00 [95% CI 1.55, 3.00]		

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Larijani et al 2008) Iran and United Arab Emirates	Level II RCT Average quality study	N = 25. Diabetic patients with a chronic foot ulcer attending medical centres in Tabriz, Tehran or Dubai. Intervention group: n = 16; age (yrs) 50.6 ± 12.7; male 13/16 (81.3%); weight (kg) 73.1 ± 18.2; diabetes type 2 14/16 (87.5%); duration of diabetes (yrs) 10.6 ± 4.8; fasting blood glucose (mg/dl) 182.9 ± 74.4; ulcer surface area (mm^2) 479.9 ± 379.8. Comparator group: n = 9; age (yrs) 59.0 ± 11.0; male 5/9 (55.6%); weight (kg) 65.4 ± 9.4; diabetes type 2 9/9 (100%); duration of diabetes (yrs) 14.8 ± 9.6; fasting blood glucose (mg/dl) 155.0 ± 35.4; ulcer surface area (mm^2) 766.2 ± 960.5.	n = 16 Intravenous infusion (30-60 mins) of 4 cc ANGIPARS (diluted in 50-100 cc normal saline) daily for 28 days and standard wound care.	n = 9 Standard wound care, which included wound debridement, betadine baths, dressings, antibiotic therapy, pressure decompression, foot deformity correction, as required.	% reduction in ulcer area 64	25	p = 0.015

CI = confidence interval; RR = relative risk; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot.

Low-molecular-weight heparins versus placebo

Low-molecular-weight heparins have beneficial effects on microvascular blood circulation including the inhibition of platelet aggregation (thrombin formation), improvement of fibrin gel porosity, and also have some anti-inflammatory properties. Two level II intervention studies of good quality were conducted to determine the clinical benefits of using the low-molecular-weight heparins, bemiparin and dalteparin, to increase the rate of ulcer healing (Table 62).

Rullan et al (2008) conducted a double-blind randomised controlled trial involving 70 diabetic patients with chronic Wagner stage 1 or 2 diabetic foot ulcers to determine the efficacy of bemiparin versus placebo. Patients attended 39 primary care centres in Mallorca, Spain where the intervention group received bemiparin via subcutaneous injections of 3500 IU/day for 10 days followed by 2500 IU/day for 3 months in addition to standard wound care. The control group received standard wound care as well as a subcutaneous placebo injection. There were two adverse bleeding events reported during this study; one minor conjunctival haemorrhage in the bemiparin group and one major post-procedure bleeding episode in the placebo group. For patients with a Wagner grade 2 ulcer, Rullan et al (2008) found that bemiparin had a statistically significant effect on the number of patients with improved ulcers (defined as >50% reduction in ulcer area and/or a decrease in Wagner grade) at 3 months (85.7% compared to 40%; RR = 2.14 [95% CI 1.01. 5.75]). This effect did not reach statistical significance in patients with a grade 1 ulcer however, overall the effect was still statistically significant and clinically important (70.3% versus 45.5%; RR = 1.56 [95% CI 1.03, 2.31]).

Kalani et al (2003) reported a double-blind randomised controlled trial of good quality involving 85 diabetic patients with chronic Wagner stage 1 or 2 foot ulcers and peripheral arterial occlusive disease in a multi-centre study conducted in Sweden. This trial was undertaken to determine the effectiveness of daily subcutaneous injection of dalteparin for 6 months versus placebo in addition to standard wound care in both groups. Adverse effects were reported for one patient receiving dalteparin who developed a retinal haemorrhage after 9 weeks and treatment was stopped. Kalani et al (2003) found that there was a trend towards beneficial outcomes for ulcer healing or improvement when administering dalteparin compared to placebo, but this did not reach statistical significance. However, there was a statistically significant and clinically important reduction in the number of amputations required during the 6 month study period for patients receiving dalteparin compared to the placebo group (4.7% versus 19%; RR = 0.24 [95% CI 0.06, 0.94]).

Interpretation of the data on ulcer healing is complicated by differences in comorbidities of patients in the two studies. Whilst both studies treated diabetic patients with chronic foot ulcers, the patients in the study by Kalani et al (2003) also had peripheral arterial occlusive disease. Thus, a large improvement in the microcirculation would be required to improve healing outcomes for these patients. The reduction in amputation rate observed by Kalani et al (2003) after using dalteparin is consistent with its mode of action on improving microvascular blood circulation. It is known that diabetic patients with ischaemia are more likely to require amputations than diabetic patients with adequate perfusion to their lower limbs (Armstrong et al 1998). Consequently, the use of low-molecular-weight heparins, such as dalteparin and bemiparin, may be beneficial for diabetic patients with ischaemia and for those with Wagner grade 2 ulcers. Any use of blood thinning medication like a low-molecular-weight heparin must, of course, be considered in the context of the associated bleeding risk.

Box 98 Evidence statement matrix for low-molecular weight heparin therapy in addition to standard wound care

Component	Rating	Description
Evidence base	B	Two level II studies with a low risk of bias.
Consistency	B	It is unclear if the results of the studies are directly comparable. The diabetic patients differed in the comorbidities present between the two studies; the patients in one study had peripheral arterial occlusive disease (PAOD) in addition to chronic foot ulcers. However, results were in the same direction for both studies.
Clinical impact	B	A clinically significant benefit for amputation was observed with dalteparin in a population with PAOD. A clinically significant benefit for ulcer improvement was observed with bemiparin in a general diabetic population with Wagner grade 2 ulcers.
Generalisability	C	Dalteparin was used in a comorbid diabetic population with PAOD and foot ulcers. Whereas bemiparin was used in a general diabetic population with foot ulcers.
Applicability	B	The two studies were conducted in Spain and Sweden, which have comparable healthcare for diabetic patients when compared to the Australian healthcare context.

Evidence statement

Systemic low-molecular-weight heparins in addition to standard wound care provided a significant benefit in Wagner grade 2 ulcers only over a 3 month period in patients with diabetes when compared with placebo and standard wound care. The risk of amputation is similarly reduced in diabetic patients with comorbid peripheral arterial occlusive disease (Grade B).

Table 62 Studies which evaluated the efficacy of low-molecular-weight heparins for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Rullan et al 2008) Spain	Level II RCT Good quality study	N = 70. Patients with diabetes for at least 3 years with a foot ulcer persisting for >3 months between June 2001 and April 2003, presenting at one of 39 primary care centres across Spain. Intervention group: n = 37; age (yrs) 61.5 ± 9.3; male 25/37 (67.6%); BMI (kg/m^2) 31.7 ± 5.7; duration of diabetes (yrs) 16 (2-38); type I diabetes 9/37 (24.3%); insulin therapy 18/37 (48.6%); glucose (mmol/l) 11.5 ± 4.8; HbA1c (%) 7.9 ± 1.6; ankle-brachial index 0.88 ± 0.27; smoker 12/37 (32.4%); hypertension 23/37 (62.2%); dyslipidaemia 11/37 (29.7%); chronic venous insufficiency 14/37 (37.8%); ischaemic heart disease 4/37 (10.8%); cerebrovascular disease 3/37 (8.1%); heart failure 3/37 (8.1%); previous peripheral revascularisation 7/37 (18.9%); intermittent claudication 12/37 (32.4%); previous amputation 12/37 (32.4%); sign of infection 1/37 (2.7%); Wagner grade 1 23/37 (62.2%); grade 2 14/37 (37.8%); ulcer area (mm^2) 163 (8-1954). Comparator group: n = 33; age (yrs) 67.8 ± 13.4; male 22/33 (66.7%); BMI (kg/m^2) 29.7 ± 4.1; duration of diabetes (yrs) 10 (3-42); type I diabetes 11/33 (33.3%); insulin therapy 17/33 (51.5%); glucose (mmol/l) 8.6 ± 3.6; HbA1c (%) 7.3 ± 2.7; ankle-brachial index 0.88 ± 0.25; smoker 4/33 (12.1%); hypertension 18/337 (54.5%); dyslipidaemia 9/33 (27.3%); chronic venous insufficiency 5/33 (15.2%); ischaemic heart disease 4/33 (12.1%); cerebrovascular disease 5/33 (15.2%); heart failure 6/33 (18.2%); previous peripheral revascularisation 3/33 (9.1%); intermittent claudication 8/33 (24.2%); previous amputation 13/33 (39.4%); sign of infection 3/33 (9.1%); Wagner grade 1 28/33 (84.8%); grade 2 5/33 (15.2%); ulcer area (mm^2) 157 (7-4837).	n = 37 Bemiparin was administered by subcutaneous injection at a dose of 3500 IU/day for the first 10 days, followed by 2500 IU/day for 3 months in addition to standard outpatient care	n = 33 Injected subcutaneously with an identical placebo-filled syringe in addition to standard outpatient care. Standard outpatient care includes debridement, wet and dry dressings with saline or hydrogel, and oral antibiotics at signs of infection. Patients were visited 9 times in the 3 month study duration	Number of patients with ulcers that healed completely at 3 months Total 13/37 (35.1%) / 11/33 (33.3%) / RR = 1.05 [95% CI 0.56, 2.03] Wagner grade 1 6/23 (26.1%) / 11/28 (39.3%) / RR = 0.66 [95% CI 0.29, 1.46] Wagner grade 2 7/14 (50%) / 0/5 (0%) / RR = 5.00 [95% CI 0.78, 49.90) Number of patients with ulcers that improved (> 50% decrease in size or in Wagner grade) at 3 months Total 26/37 (70.3%) / 15/33 (45.5%) / RR = 1.56 [95% CI 1.03, 2.31] Wagner grade 1 14/23 (60.9%) / 13/28 (46.4%) / RR = 1.31 [95% CI 0.78, 2.12] Wagner grade 2 12/14 (85.7%) / 2/5 (40%) / RR = 2.14 [95% CI 1.01. 5.75] Number of patients with ulcers that decreased in size by > 50% at 3 months 21/37 (56.8%) / 14/33 (42.4%) / RR = 1.34 [95% CI 0.84, 2.17] Number of patients with ulcers that decreased a Wagner grade at 3 months 17/37 (46%) / 13/33 (39.4%) / RR = 1.17 [95% CI 0.68, 2.03]		

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
					Number of patients with ulcers that healed completely at 9 months follow-up (71.4% 50/70 patients) 19/37 (51.4%)	12/33 (36.4%)	RR = 1.41 [95% CI 0.83, 2.45]
(Kalani et al 2003) Sweden	Level II RCT Good quality study	N = 85. Diabetic patients with chronic Wagner stage 1 or 2 foot ulcers of at least 2 months duration and with peripheral arterial occlusive disease, attending 1 of 4 clinics from June 1997 to February 2001. Intervention group: n= 43; age (yrs) 73 ± 8; male 29/43 (67.4%); BMI (kg/m2) 27 ± 5; diabetes type 1 5/43 (11.6%); diabetes duration (yrs) 20 ± 13; smokers 5/43 (11.6%); ex-smokers 10/43 (23.3%); insulin therapy 33/43 (76.7%); previous amputation 10/43 (23.3%); previous myocardial infarction and/or stroke 20/43 (46.5%); previous vascular reconstruction and/or angioplasty 8/43 (18.6%); peripheral neuropathy 43/43 (100%); treatment with aspirin 43/43 (100%); toe blood pressure (mmHg) 53 ± 23; toe/arm blood pressure index 0.33 ± 0.14; ulcer surface area (length x width; mm^2) 413 ± 820. Comparator group: n = 42; age (yrs) 72 ± 11; male 31/42 (73.8%); BMI (kg/m2) 26 ± 4; diabetes type 1 7/42 (16.7%); diabetes duration (yrs) 21 ± 14; smokers 6/42 (14.3%); ex-smokers 17/42 (40.5%); insulin therapy 33/42 (78.6%); previous amputation 11/42 (26.2%); previous myocardial infarction and/or stroke 20/42 (47.6%); previous vascular reconstruction and/or angioplasty 11/42 (26.2%); peripheral neuropathy 42/42 (100%); treatment with aspirin 42/42 (100%); toe blood pressure (mmHg) 53 ± 20; toe/arm blood pressure index 0.35 ± 0.12; ulcer surface area (length x width; mm^2) 535 ± 1086.	n = 43 Subcutaneous injection of 0.2 ml dalteparin (25,000 units/ml) daily for a maximum of 6 months. Treatment stopped if: ulcer healed: increased > 50% in area; or amputation required. Patients also received standard treatment by a foot care team All patients from both groups were treated with a daily dose of 75 mg aspirin for at least 4 weeks before randomisation and this was continued during the study period.	n = 42 Daily subcutaneous injections of 0.2 ml normal saline in addition to standard treatment by a foot care team. Standard treatment included: debridement, dressings, off-loading, antibiotic therapy as needed.	Number of patients with ulcers that healed completely in 6 months 14/43 (33%)	9/42 (21%)	RR = 1.52 [95% CI 0.75, 3.14]
					Number of patients with ulcers that improved (decreased in size by > 50%) 15/43 (35%)	11/42 (26%)	RR = 1.33 [95% CI 0.70, 2.56]
					Total number of patients that improved and healed 29/43 (67.4%)	20/42 (47.6%)	RR = 1.42 [95% CI 0.98. 2.03]
					Number of patients that required amputations Total 2/43 (4.7%)	8/42 (19%)	RR = 0.24 [95% CI 0.06, 0.94]

CI = confidence interval; RR = relative risk; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot.

Iloprost versus standard wound care

Iloprost is a synthetic analogue of prostacyclin and has potent vasodilation properties and inhibits platelet aggregation. Sert et al (2008) conducted a randomised controlled trial (level II evidence) of average quality involving 60 comorbid diabetic patients with severe ischaemic foot ulcer who were unsuited for a revascularisation procedure (Table 63). The purpose of the trial was to determine the effectiveness of administering an iloprost infusion in addition to standard wound care for 10 days, compared to standard wound care alone, for the treatment of ischaemic foot ulcers. Adverse events were reported for three patients who received iloprost, including macula-papular skin lesions, itching, dyspnoea, tachycardia, headache, and hypertension. Treatment was discontinued in two of these patients. The authors found no statistical difference in the rate of amputation or healed ulcers between patients who received iloprost and those that did not (RR = 5.00 [95% CI 0.84, 32.0], RR = 1.00 [95% CI 0.54, 1.85] and 0.77 [95% CI 0.46, 1.27] for healed ulcers, minor and major amputations, respectively). However, both the ulcer healing and major amputation outcomes appear to be underpowered in this small trial, so there is some residual uncertainty as to whether iloprost offers any clinical or statistical advantages for treating ischaemic foot ulcers over standard care.

Box 99 Evidence statement matrix for iloprost therapy in addition to standard wound care

Component	Rating	Description
Evidence base	C	One level III study with a moderate risk of bias
Consistency	N/A	There is only one study
Clinical impact	D	There was no statistically significant difference in the number of ulcers that healed or needed amputations after administering iloprost in addition to standard wound care relative to standard wound care alone.
Generalisability	B	The population consisted of diabetic patients with a severe peripheral ischemic foot ulcer unsuitable for revascularisation, and thus, the study results would apply to diabetic patients at the severe end of the disease spectrum.
Applicability	C	The study was conducted in Turkey, which have different healthcare for diabetic patients when compared to the Australian healthcare context.

Evidence statement

It is unclear whether iloprost therapy is likely to provide any clinical benefit in addition to standard wound care when treating patients for diabetic foot ulcers. Further large trials are required to determine the impact on wound healing and major amputation rates (Grade D).

Table 63 Evaluation of the effectiveness of Iloprost for the treatment of ischaemic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Sert et al 2008) Turkey	II RCT Average quality study	N = 60. Patients with type 2 diabetes mellitus and a severe peripheral ischaemic foot ulcer unsuited for a revascularisation procedure, hospitalised at the University Endocrinology and Metabolism Clinic in Adana, between June 2004 and October 2006. Intervention group : n = 30; age (yrs) 60.5 ± 9.1; male 18/30 (60%); duration of diabetes (yrs) 14.53 ± 8.12; oral hyperglycaemics 11/30 (37%); insulin 10/30 (33%); fasting blood glucose (mg/dL) 236.7 ± 105.5; % HbA_{1c} 10.4 ± 2.1; retinopathy 29/30 (97%); nephropathy 28/30 (93%); neuropathy 30/30 (100%); coronary artery disease 7/30 (23%); smoking history (pack years) 22.53 ± 28.52; duration of ulcer (days) 69.83 ± 69.16; osteomyelitis 16/30 (53%); Wagner grade 3.4 ± 0.89. Comparator group: n = 30, age (yrs) 63.1 ± 9.2; male 18/30 (60%); duration of diabetes (yrs) 14.10 ± 7.26; oral hyperglycaemics 16/30 (53%); insulin 13/30 (43%); fasting blood glucose (mg/dL) 232.8 ± 103.4; % HbA_{1c} 10.8 ± 2.3; retinopathy 30/30 (100%), nephropathy 30/30 (100%); neuropathy 30/30 (100%); coronary artery disease 13/30 (43%); smoking history (pack years) 19.83 ± 19.23; duration of ulcer (days) 68.67 ± 35.46; osteomyelitis 16/30 (53%); Wagner grade 3.4 ± 0.89.	n = 30 Administration of an iloprost infusion at a dose of 0.5-2 ng/kg/ min over 6 h for 10 days, in addition to routine standard wound care treatment strategies	n = 30 Routine standard wound care treatment strategies only.	Number of patients with ulcers that healed without amputation		
					5/30 (16.7%)	1/30 (3.3%)	RR = 5.00 [95% CI 0.84, 32.0]
					Number of patients that required minor amputations		
					12/30 (40%)	12/30 (40%)	RR = 1.00 [95% CI 0.54, 1.85]
					Number of patients that required major amputations		
					13/30 (43.3%)	17/30 (56.7%)	RR = 0.77 [95% CI 0.46, 1.27]

CI = confidence interval; RR = relative risk; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot.

Ketanserin versus placebo

Ketanserin is a serotonin antagonist that may improve wound healing in patients with severe peripheral vascular disease by improving blood flow and inhibiting platelet aggregation. Apelqvist et al (1990) conducted a double-blind placebo-controlled trial of good quality involving 40 diabetic patients with foot ulcers and severe peripheral vascular disease. This study evaluated the effectiveness of ketanserin for healing ischaemic foot ulcers in addition to standard wound care relative to placebo plus standard wound care. The details of the dosing regimen and type of standard wound care are outlined in Table 64. The authors reported no statistically significant difference between patients who received ketanserin and those that did not, with regard to ulcer healing or amputation rate. This would suggest that ketanserin may not offer any clinical advantages for treating ischaemic foot ulcers over standard wound care, although the size of the trial and the wide confidence intervals would suggest there was a lack of statistical power to detect a difference that was not attributable to chance.

Box 100 Evidence statement matrix for ketanserin in addition to standard wound care

Component	Rating	Description
Evidence base	B	One level II study with a low risk of bias
Consistency	N/A	There is only one study
Clinical impact	D	There was no statistically significant difference in the number of ulcers that healed or patients requiring amputation after administration of ketanserin in addition to standard wound care. The trial was small and likely underpowered for these outcomes.
Generalisability	C	These results are generalisable to diabetic patients with a foot ulcer and severe peripheral vascular disease
Applicability	B	The study was conducted in Sweden, where the care of diabetic foot ulcers is likely to be similar to Australia.

Evidence statement

It is unclear whether ketanserin therapy is likely to provide any clinical benefit in addition to standard wound care when treating patients for diabetic foot ulcers, relative to standard wound care alone (Grade D).

Table 64 Evaluation of the effectiveness of ketanserin for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Apelqvist et al 1990a) Sweden	Level II RCT Good quality study	N = 40. Diabetic patients referred to the Dept. of Internal Medicine for a foot ulcer with an area of 1 cm^2 or more and severe peripheral vascular disease (systolic toe pressure below 45 mmHg). Intervention group: n = 20; age (yrs) 71 ± 10; male 13/20 (65%); duration of diabetes (yrs) 20 ± 12; insulin treatment 15/20 (75%); smokers 1/20 (5%); ex-smokers 10/20 (50%); % HbA_{1c} 7.8 ± 1.9; retinopathy 7/20 (35%); systolic arm pressure (mmHg) 17 ± 32; systolic ankle pressure (mmHg) 89 ± 36; oedema 8/20 (40%); pain at rest 2/20 (10%); superficial ulcer 8/20 (40%); deep ulcer 12/20 (60%); positive bacterial culture 12/20 (60%); wound size (cm^2) 2.0 (0.8-24). Comparator group: n = 20; age (yrs) 67 ± 10; male 12/20 (60%); duration of diabetes (yrs) 18 ± 12; insulin treatment 16/20 (80%); smokers 5/20 (25%); ex-smokers 6/20 (30%); % HbA_{1c} 7.7 ± 1.8; retinopathy 6/20 (30%); systolic arm pressure (mmHg) 157 ± 23; systolic ankle pressure (mmHg) 103 ± 40; oedema 5/20 (25%); pain at rest 5/20 (25%); superficial ulcer 7/20 (35%); deep ulcer 13/20 (65%); positive bacterial culture 11/20 (55%); wound size (cm^2) 1.5 (1.0-160).	n = 20 20 mg ketanserin tablets 3 times daily for 1 month, then 40 mg tablets 3 times daily for another 2 months, in addition to standard wound care. All patients had a 2 week run-in period on placebo tablets.	n = 20 Placebo tablets plus standard wound care, which consisted of: dressings, debridement and off-loading, as well as antibiotic therapy to treat infections and diuretics to treat oedema.	Number of patients with ulcers that healed completely		
					7/20 (35%)	5/20 (25%)	RR = 1.40 [95% CI 0.55, 3.68]
					Number of patients with ulcers that improved		
					4/20 (20%)	2/20 (10%)	RR = 2.00 [95% CI 0.47, 8.96]
					Number of patients that required amputations		
					2/20 (10%)	4/20 (20%)	RR = 0.50 [95% CI 0.11, 2.13]

CI = confidence interval; RR = relative risk;

Pentoxifylline versus standard wound care

Pentoxifylline is a xanthine derivative that reduces blood viscosity and inhibits platelet aggregation and thrombus formation. Ramani et al (1993) conducted a, pseudo-randomised trial (level III-1 evidence) of average quality involving 40 diabetic patients with an ischaemic foot ulcer admitted to Kasturba Medical College Hospital, Manipal, India. To determine the efficacy of pentoxifylline in healing ischaemic foot ulcers, pentoxifylline was administered orally as 400 mg tablets thrice daily for 8 weeks in conjunction with standard wound care and compared to standard wound care alone. Adverse events were reported for one patient who had nausea and vomiting while taking pentoxifylline, but continued treatment (Ramani et al 1993). There was no statistical difference between the two groups with respect to amputation rate and duration of hospital stay even though there was a trend towards a shorter hospital stay for patients that received pentoxifylline. However, the number of patients that "responded" to pentoxifylline treatment and standard wound care after 8 weeks was significantly different compared to the number that "responded" to standard wound care alone (80% compared to 50%; p = 0.047). The authors failed to clearly define what constituted a "response" so the clinical importance of this is difference cannot be determined (Ramani et al 1993). Taken together, these results suggest that pentoxifylline may only offer a marginal clinical benefit for the treatment of ischaemic foot ulcers over standard wound care. This study appears to have an imbalance in the mean ulcer duration, and potentially the use of vasodilators, between trial arms which may have impacted to an unknown extent on the results.

Box 101 Evidence statement matrix for pentoxifylline therapy in addition to standard wound care

Component	Rating	Description
Evidence base	D	One level III-1 study with a moderate risk of bias
Consistency	N/A	There was only one study
Clinical impact	C	The clinical importance of the statistically significant difference in the number of ulcers that 'responded' to treatment is unknown, given the lack of definition of response. No differences in amputation rate or the length of hospital stay was observed after administering pentoxifyllinein addition to standard wound care compared with standard wound care alone.
Generalisability	C	Population consists of diabetic patients with ischemic foot ulcers of Wagner grade 2 or more
Applicability	D	This study was conducted in India, where health care is likely to be provided differently to patients with diabetic foot ulcers than in Australia.

Evidence statement

Pentoxifylline therapy is unlikely to provide further benefit in addition to standard wound care when treating diabetic patients with ischaemic foot ulcers of Wagner grade 2 or more (Grade D).

Table 65 Studies included which evaluated the efficacy of pentoxifylline for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Ramani et al 1993) India	III-1 pseudo-RCT Average quality study	N = 40. Diabetic patients with ischaemic foot ulcers of Wagner grade 2 or more admitted to Kasturba Medical College Hospital, Manipal. Intervention group: n = 20; age (yrs) 59.10; duration of diabetes (yrs) 11.5; duration of ulcer (days) 59.2; smoking 14/20 (70%); peripheral neuropathy 20/20 (100%); ischaemic heart disease 10/20 (50%); Wagner grade 2 2/20 (10%); grade 3 6/20 (30%); grade 4 12/20 (60%); grade 5 0/20 (0%). Comparator group: n = 20; age (yrs) 61.95; duration of diabetes (yrs) 12.5; duration of ulcer (days) 39.2; smoking 15/20 (75%); peripheral neuropathy 20/20 (100%); ischaemic heart disease 10/20 (50%); Wagner grade 2 2/20 (10%); grade 3 6/20 (30%); grade 4 10/20 (50%); grade 5 2/20 (10%).	n = 20 Administered 400 mg pentoxifylline orally thrice daily, in addition to vasodilators and standard care.	n = 20 Standard care only Unclear if this group also received vasodilators. All patients were instructed not to alter their smoking or exercise habits for the duration of the study.	Number of patients with ulcers that responded to treatment after 8 weeks		
					16/20 (80%)	10/20 (50%)	RR = 1.60 [95% CI 1.01, 2.32] p = 0.047
					Duration of hospital stay (days)		
					67 ± 30.7	95 ± 66.2	p = 0.09
					Number of patients that required amputation		
					Toes		
					10/20 (50%)	8/20 (40%)	RR = 1.25 [95% CI 0.63, 2.48]
					Below knee		
					0/20 (0%)	3/20 (15%)	RR = 0.00 [95% CI 0.00, 1.19]
					Above knee		
					0/20 (0%)	1/20 (5%)	RR = 0.00 [95% CI 0.00, 3.78]
					Total		
					10/20 (50%)	12/20 (60%)	RR = 0.83 [95% CI 0.48, 1.45]

CI = confidence interval; RR = relative risk; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot.

Pycnogenol versus standard wound care

Pycnogenol is a French maritime pine bark extract that has both anti-diabetic effects (improves glucose and HbA_{1c} levels) and benefits for microangiopathy. It has been shown to improve microcirculation, reduce oedema, increase permeability of blood vessel walls, decrease blood viscidity, and prevent platelet aggregation (Belcaro et al 2006). Belcaro et al (2006) conducted a randomised controlled trial (level II evidence) of average quality involving 30 diabetic patients with severe microangiopathy causing chronic foot ulceration that attended a clinic in Italy, in order to determine the efficacy of pycnogenol in treating ischaemic foot ulcer. The patients were randomised into four groups to receive in conjunction with standard wound care either: a 50 mg pycnogenol capsule orally three times daily; 100 mg pf pycongenol powder (from inside capsule) spread over ulcerated area after cleaning; both oral and topical applications of pycnogenol; or standard wound care alone. After 6 weeks, and despite the very small sample sizes, all three groups receiving pycongenol had a significantly greater % reduction in ulcer size than the group receiving standard wound care only (33.3%, 41.3%, and 74.4% compared to 22.7%; $p < 0.05$). Additionally, the group that received both oral and topical pycnogenol had a significantly greater % reduction in ulcer size than the groups receiving either oral or topical pycnogenol ($p < 0.05$). All three groups that received pycnogenol had a similar % of ulcers completely healed (89%, 85% and 84%), which was significantly greater than the % healed in the standard wound care only group (61%, $p < 0.05$). The difference would appear to be clinically important. Thus, topical and/or oral application of pycnogenol appears to offer clinical advantages for healing ischaemic foot ulcer when compared to standard wound care alone in this study. However, given the very small sample sizes in the trial arms of this study, it is uncertain as to the extent that these results would be replicated when applied more widely.

Box 102 Evidence statement matrix for pycnogenol therapy in addition to standard wound care

Component	Rating	Description
Evidence base	C	One level II study with a moderate risk of bias
Consistency	N/A	There was only one study
Clinical impact	B	There was a statistically significant difference in the % reduction of ulcer area after topical or oral application of pycnogenol compared to standard wound care alone. The application of both topical and oral pycnogenol together offers an additional benefit.
Generalisability	C	Population consisted of diabetic patients being treated with insulin, with severe microangiopathy causing chronic foot ulceration. Given the small sample size caution would be needed in generalising these results to a larger diabetic foot ulcer population group
Applicability	B	This study was conducted in Italy, which is likely to provide similar health care to diabetic foot patients as in Australia.

Evidence statement

Pycnogenol therapy may reduce ulcer size when used in addition to standard wound care compared to standard wound care alone, in diabetic patients with ischaemic foot ulcers (Grade C).

Table 66 Studies included which evaluated the efficacy of pycnogenol for the treatment of diabetic foot ulcer

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Belcaro et al 2006) Italy	II RCT Average quality study	N = 30. Diabetic patients, being treated with insulin, with severe microangiopathy causing chronic foot ulceration, who had tibial arteries with flow that could be documented by Doppler and a peripheral tibial pressure exceeding 60 mmHg Intervention group 1: n = 8; age (yrs) 54.3 ± 4.4; male 3/8 (37.5%); duration of diabetes 11.3 ± 2.6; skin perfusion pressure (mmHg) > 68 ± 5; ulcer area (mm^2) 43 ± 4. Intervention group 2: n = 6; age (yrs) 55.0 ± 3.0; male 4/6 (66.7%); duration of diabetes 11.2 ± 4.0; skin perfusion pressure (mmHg) > 65 ± 6; ulcer area (mm^2) 45 ± 4. Intervention group 3: n = 8; age (yrs) 55.0 ± 5.0; male 3/8 (37.5%); duration of diabetes 11.0 ± 2.4; skin perfusion pressure (mmHg) >66 ± 5; ulcer area (mm^2) 46 ± 6. Comparator group: n = 8; age (yrs) 52.4 ± 6.1; male 4/8 (50%); duration of diabetes 12.0 ± 3.0; skin perfusion pressure (mmHg) >65 ± 7; ulcer area (mm^2) 44 ± 5.2.	Group 1 n = 8 50 mg pycnogenol capsule 3 times a day orally plus 100 mg powder from capsules was distributed as a fine layer over ulcerated area after daily cleaning in addition to standard ulcer care. Group 2 n = 6 50 mg pycnogenol capsule 3 times a day orally in addition to standard ulcer care. Group 3 n = 8 100 mg pycnogenol powder from capsules was distributed as a fine layer over ulcerated area after daily cleaning in addition to standard ulcer care.	n = 8 Standard ulcer care, which included careful washing and cleaning of ulcers daily with warm water and a mild local disinfectant. Ulcers were dried with paper tissue and covered with a soft paper, non- allergic dressing and a layer of tensoplast elastic adhesive bandage. An exercise plan was presented to all subjects, friction-free socks were used to protect the foot and keep dressings in place during the study period.	% reduction in ulcer area (administration route) Group 1 (oral + local) 74.4% Group 2 (oral) 33.3% Group 3 (local) 41.3% Comparison of intervention groups (administration route) Group 1 (oral + local) 74.4% Group 1 (oral + local) 74.4% Group 2 (oral) 33.3%	22.7% 22.7% 22.7% Group 3 (local) 41.3% Group 2 (oral) 33.3% Group 3 (local) 41.3%	p < 0.01 p < 0.05 p < 0.01 p < 0.05 p < 0.05 p > 0.05

RCT= randomized controlled trial

Drugs that improve immune function

Tinospora cordifolia versus standard wound care

The aqueous extract of the creeper *Tinospora cordifolia* induces leukocytosis and improves macrophage phagocytic and intracellular killing activity by the enhancement of GM-CSF activity (Purandare et al 2007). Purandare and Supe (2007) conducted a level II, average quality study involving 45 patients, with diabetic foot ulcer of Wagner grade 1 or 2 and not less than 4 cm in diameter, that were admitted to surgical wards of KEM Hospital, Mumbai, India (Table 67). The aim of this study was to determine the efficacy of administering a purified and bio-standardised aqueous extract of *Tinospora cordifolia* to treat diabetic foot ulcer compared to a placebo. The method of administering the herbal extract and the dose of the herbal extract were not disclosed. This randomised controlled trial found no statistically significant difference in the ulcer healing rate between diabetic patients that received the herbal extract and those that did not, even though the data showed a trend suggesting that the herbal extract may have some positive effect on ulcer healing. Nevertheless, in addition to standard wound care, treatment of diabetic foot ulcers with the aqueous extract of *Tinospora cordifolia* did not offer any statistically significant clinical benefit over the placebo.

Box 103 Evidence statement matrix for *Tinospora cordifolia* therapy in addition to standard wound care

Component	Rating	Description
Evidence base	C	One level II study with a moderate risk of bias
Consistency	NA	There was only one study
Clinical impact	D	There were no statistically significant clinical benefits after the additional administration of *Tinospora cordifolia* to standard wound care.
Generalisability	C	Population consisted of diabetic patients admitted to hospital with Wagner grade 1 or 2 diabetic foot ulcers of not less than 4 cm in diameter or non-healing ulcers on foot with digital, ray or forefoot amputation.
Applicability	D	This study was conducted in India, where health care is likely to be provided differently to patients with diabetic foot ulcers than in Australia.

Evidence statement

Tinospora cordifolia therapy is unlikely to provide additional clinical benefit to standard wound care when treating patients for diabetic foot ulcer (Grade D).

Table 67 Studies included which evaluated the efficacy of an extract of *Tinospora cordifolia* for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Purandare & Supe 2007) India	II RCT Average quality study	N = 45. Diabetic patients, aged over 18, admitted to surgical wards of KEM Hospital, with diabetic foot ulcer, Wagner grade 1 or 2, not less than 4 cm in diameter or non-healing ulcers on foot with digital, ray or forefoot amputation. Intervention group: n = 23; age (yrs) 56.26 (32.4-80.6); male 17/23 (73.9%); duration of diabetes (yrs) 5.95 (0-18); duration of ulcer (days) 21.08 (12-35). Comparator group: n = 22; age (yrs) 56.32 (32.4-80.6); male 19/22 (86.4%); duration of diabetes (yrs) 8.27 (0-22); duration of ulcer (days) 30.36 (21-44).	n = 23 The purified and bio-standardised aqueous extract of *Tinospora cordifolia* was administered for 1 month. Method and dose of administration was not disclosed. All patients were assessed weekly, until healing was complete.	n = 22 Placebo All patients received conventional therapy for diabetes and standard wound care for ulcer, which included: sharp debridement as needed, gentle cleansing with half-strength 1.5% hydrogen peroxide solution and ample amounts of saline, antibiotics as required, gauze dressings, minimal ambulation and protective foot wear advised.	Number of patients with ulcers that improved 17/23 (73.9%)	13/22 (59.1%)	RR = 1.25 [95% CI 0.83, 1.82] p = 0.292
					Rate of change of ulcer area (cm^2/day) 0.15 ± 1.00	-0.07 ± 0.89	*p* = 0.145
					Rate of change of ulcer perimeter (mm/day) 0.09 ±0.04	-0.07 ± 0.06	p = 0.089
					Mean difference in ulcer depth over 1 month study period (cm) 2.17 ± 1.33	1.36 ±1.31	*p* = 0.096
					Change in wound severity score. 14.39 ± 8.39	10.59 ± 8.88	*p* = 0.149

CI = confidence interval; RR = relative risk; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot.

Other drugs

Fenofibrate versus placebo

The good quality randomised controlled trial by Rajamani et al (2009) evaluated the use of fenofibrate to reduce the risk of amputation, relative to placebo.

Although the source population was not defined in the article, the sample recruited were subjects aged between 50 years and 75 years with type II diabetes and who did not require lipid modifying therapy (Table 68). Patients were randomised to either fenofibrate or a matching placebo and followed up every four to six months for a median of 5 years. The primary outcome of the study was the risk of cardiovascular outcomes however; risk of amputation was a pre-specified tertiary outcome and was the focus of this article.

It was not apparent in the published report if subjects were blinded to their allocation however, other publicly available information suggests that both subjects and investigators were masked to allocation (NHMRC Clinical Trials Centre). Outcome ascertainment was verified by two clinicians independently and any discrepancies were resolved by mutual agreement. All subjects who underwent amputation had either before or during the study period undergone lower-limb angiogram and duplex ultrasound to determine the presence of atherosclerotic disease in the large peripheral arteries.

Cox proportional analysis was used to determine the effect of fenofibrate on the risk of amputation. Of a total of 115 amputations during the study, 45 occurred in subjects in the fenofibrate group (HR = 0.64 [95% CI 0.44, 0.94], p = 0.02, NNT = 196 [95% CI 106, 1,226]). Of those with a minor amputation, defined as below the ankle, 24occurred in the fenofibrate group (HR = 0.54 [95% CI 0.34, 0.85], p = 0.007], NNT = 204 [95% CI 116, 755]). The number of major amputations did not differ between the two groups (HR = 0.93 [95% CI 0.53, 1.62], p = 0.79).

The risk of minor amputation in subjects without large vessel disease in the fenofibrate group was statistically significantly different relative to placebo (HR = 0.53 [95% CI 0.30, 0.94], p = 0.027, NNT = 307 [95% CI 158, 2,761]) however, no difference was detected in subjects with large vessel disease who underwent minor or major amputation.

Any serious adverse events reported as a result of treatment with fenofibrate were reported elsewhere.

These results suggest that fenofibrate may be effective at reducing the overall amputation rate in people with type II diabetes who do not require lipid therapy. Fenofibrate is likely to be most effective in people without peripheral vascular disease.

This evidence is summarised in Box 104 according to NHMRC criteria.

Box 104 Evidence statement matrix for fenofibrate versus placebo

Component	Rating	Description
Evidence base	B	One level II study with a low risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	C	There was no effect on major amputations although a major effect on minor amputations without large vessel disease.
Generalisability	A	Populations consisted of people with type II diabetes who did not require lipid modifying therapy.
Applicability	A	This study was conducted in Australia, New Zealand and Finland which would make it directly applicable to the Australian healthcare context.

Evidence statement

There is evidence to suggest that treatment with fenofibrate may reduce the risk of amputation, and in particular minor amputation, in people with type II diabetes (Grade C).

Table 68 Included study of fenofibrate versus placebo

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data Intervention Comparator Effect size [95% CI] p-value
(Rajamani et al 2009) Australia	II RCT SIGN: Good quality	N = 9,795 Patients aged between 50 and 75 years with type II diabetes not receiving lipid modification therapy.	n = 4,895 200mg micronised fenofibrate once daily.	n = 4,900 Matching placebo	First (any) amputation: 45/4,895 (0.92%) 70/4,900 (1.42%) HR = 0.64 [95% CI 0.44, 0.94] p = 0.02 Minor amputation: 28/4,895 (0.6%) 52/4,900 (1.1%) HR = 0.54 [95% CI 0.34, 0.85] p = 0.007 Major amputation: 24/4,895 (0.5%) 26/4,900 (0.5%) HR = 0.93 [95% CI 0.53, 1.62] p = 0.79 Minor amputation without large vessel disease 18/4,895 (0.4%) 34/4,900 (0.7%) HR = 0.53 [95% CI 0.30, 0.94] p = 0.027 Major or minor amputation with large vessel disease 34/4,895 (0.7%) 42/4,900 (0.9%) HR = 0.81 [95% CI 0.52, 1.28] p = 0.37

HR = hazard ratio; CI = confidence interval

Surgical interventions

Comparison of Surgical Achilles tendon lengthening and total contact cast plus standard wound care

One average quality randomised controlled trial and a poor quality sub-study from the same trial considered Achilles tendon lengthening (ATL) surgery for the treatment of diabetic foot ulcer and reported findings in relation to healing time of existing foot ulcers, ulcer recurrence and quality of life (Table 69).

Mueller et al (2003) compared immobilisation with a total contact cast versus surgical Achilles tendon lengthening (ATL) plus immobilisation with a total contact cast in a cohort of 30 subjects who had recurrent or non healing ulcers. The authors found a slight trend in ulcer healing over a mean 17 ± 29 days with 100% of those who received ATL surgery considered healed compared to 88% in the control group (RR = 1.1 [95% CI 1.0, 1.3]). However, the difference appears to have limited clinical importance. Participants who received ATL surgery achieved quicker healing times although the difference was not statistically significant (41 ± 28 days for the ATL group versus 58 ± 47 days for the total contact cast group). The authors did find evidence of a lower recurrence of foot ulcers in those who received ATL surgery compared to the control group over a 6 month and 2 year follow up (RR = 0.25 [95% CI 0.09, 0.58]; RR = 0.47 [95% CI 0.32, 0.76], respectively). In both groups, superficial skin abrasions due to the cast were reported in; whilst one patient developed deep infection requiring debridement in the surgical group and one patient died due to a myocardial infarction in the control group.

Mueller et al (2004) also reported results on quality of life measured with the SF-36 questionnaire in a sub study concerning 28 of the original 64 patients. A score of zero was associated with poor perceived health and a score of 100 as good health. The authors reported that those subjects who received ATL surgery had a significantly poorer perceived physical well being compared to the control group 8 months after treatment (31 ± 6.2 in ATL group versus 39 ± 11 in the control group, $p < 0.04$). It should be noted that an average 8 point difference on a 100 point quality of life scale is unlikely to indicate that this difference in physical wellbeing was clinically important. There was no statistically significant difference in the mental quality of life between the two groups.

ATL surgery in addition to total contact cast treatment does not significantly improve either foot ulcer healing or time to healing compared to total contact cast treatment, though ATL does appear to have a clinically significant benefit at preventing recurrence of foot ulcer in diabetic patients. Box 105 provides an overview of the body of evidence for surgical Achilles tendon lengthening according to the NHMRC criteria.

Box 105 Evidence matrix for comparison of surgical Achilles tendon lengthening for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	C	One level III study with moderate risk of bias.
Consistency	N/A	Only one study available
Clinical impact	D- ulcer healing C- recurrence	The study indicated a low clinical impact for ulcer healing although a moderate to substantial preventative clinical impact for ulcer recurrence (RR of 0.25 and RR of 0.47 over 6 months and 2 years respectively). In contrast, ATL surgery had a slight negative clinical impact on the physical well being of the diabetes subjects, although not to a clinically important degree. No effect was found on the mental wellbeing.
Generalisability	B	The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population. The sample did have an overrepresentation of males.
Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.

Evidence statement

The results suggest that in addition to immobilisation with a total contact cast and standard wound care, surgical Achilles tendon lengthening is effective at preventing foot ulcer recurrence in diabetic patients, although it does not appear to improve ulcer healing (Grade C).

Table 69 Studies included which compare Achilles tendon lengthening to total contact cast for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
(Mueller et al 2003) USA	II RCT average quality study	Diabetic patients attending Diabetic Foot clinic at teaching hospital. Intervention group: n=31, mean age 56.6±9.2 years, 84% male (n=26), DM type II 83% (n=25), mean duration DM (yrs) 17±11, BMI 33±7.8, HbA1c (%) 8.8±1.9, number of previous ulcer 3.7±4.4, ulcer length (mm) 14.3±9.2, ulcer width (mm) 11.3±8.0, hammer or claw toe (n) 71% (n=22), past myocardial infarction 32% (n=10), coronary artery bypass graft 19% (n=6), congestive heart failure 16% (n=5), hypertension 58% (n=18), lower extremity revascularisation 3% (n=1), renal failure 19% (n=6), transmetatarsal amputation 10% (n=3), toe and/or ray section 29% (n=9), hallux valgus 19% (n=6) Comparator group: n=33, mean age 56.2±10 years, 69% male (n=23), DM type II 67% (n=22), mean duration DM (yrs) 20±13, BMI 31±6.8, HbA1c (%) 8.8±1.7, number of previous ulcer 3.3±4.0, ulcer length (mm) 15±12, ulcer width (mm) 13±12, hammer or claw toe (n) 73% (n=24), past myocardial infarction 27% (n=9), coronary artery bypass graft 15% (n=5), congestive heart failure 18% (n=6), hypertension 55% (n=18), lower extremity revascularisation 9% (n=3), renal failure 12% (n=4), transmetatarsal amputation 6% (n=2), toe and/or ray section 18% (n=6), hallux valgus 21% (n=7)	N=31, Percutaneous Achilles tendon lengthening followed by immobilisation in a total-contact cast	N=33, immobilisation in a total-contact cast	% ulcers healed post-treatment (17±29 days) Intervention 100% n=31 / Control 88% n=29 / Effect size [95% CI] RR 1.1 [1.0, 1.3] Time to healing mean ± SD (days) Intervention 41±28 / Control 58±47 / p= ns % ulcer recurrence in first 6 months Intervention 15% (n=4) / Control 59% (n=16) / Effect size [95% CI] RR 0.25 [0.09, 0.58] % ulcer recurrence in first 2 years Intervention 39% (n=10) / Control 81% (n=21) / Effect size [95% CI] RR 0.47 [0.32, 0.76]
(Mueller et al 2004) USA	II RCT poor quality study	Diabetic patients attending Diabetic Foot clinic at teaching hospital. Intervention group: n=14, Male 78.6% (n=11), mean age (yrs) 54.8±9.5, BMI (kg/m²) 33.6±6.0, DM type II 78.6% (n=11), duration DM (yrs) 19.9±10.2, HbA1c (%) 8.7±1.8 Comparator group: n=14, Male 71.4% (n=10), mean age (yrs) 54.3±9.9, BMI (kg/m²) 31.8±6.8, DM type II 64.3% (n=9), duration DM (yrs) 17.9±13.9, HbA1c (%) 8.9±2.0	N=14, surgical Achilles tendon-lengthening (ATL) and total contact casting (TCC) + standard wound care	N=14, treated with total contact casting (TCC) + standard wound care	SF-36 Physical summary score mean ±SD at 8 months post treatment Intervention 31±6.2 / Control 39±11 / p<0.04 SF-36 Mental summary score mean ±SD at 8 months post treatment Intervention 52±13 / Control 52±12 / P=0.56

BMI= Body Mass Index; CI= confidence interval; DM= Diabetes Mellitus; RCT= Randomised Controlled Trial; RR= relative risk;

Resection arthroplasty versus standard wound care and offloading for the treatment of diabetic foot ulcers

One good and one average quality observational study considered surgical resection arthroplasty for the treatment of diabetic foot ulcer and reported outcomes on time to heal, ulcer recurrence, amputation and infection (Table 70).

Both studies investigated the clinical impact of resection arthroplasty in addition to offloading and standard wound care, but concentrating on surgery on different aspects of the plantar foot. Armstrong et al (2003) assessed surgical intervention on the first metatarsophalangeal joint, while Armstrong et al (2005) assessed surgical intervention on the fifth metatarsal head. Both types of surgical intervention were compared to standard wound care and offloading.

Both studies reported clinically important differences in time to healing between the two groups. Armstrong et al (2003) reported a mean time to healing of 24±9.9 days for surgery versus a mean of 67±17 days for standard care, ($p<0.001$). Armstrong et al (2005) reported a mean of 5.8±2.9 weeks until healing after surgery versus 8.7±4.3 weeks with standard care ($p=0.02$). Additionally, the recurrence of foot ulcer was found by the early and later studies of Armstrong et al to be reduced by surgical arthroplasty compared to nonsurgical care over a 6 month follow up period (RR=0.14 [95%CI 0.02, 0.73] and RR=0.16 [95%CI 0.02, 0.93], respectively). Both studies did not find a clinically important difference between the two groups with respect to amputation. Armstrong et al (2003) also provided results on infection as an outcome, but again did not find a clinically important difference between the two groups.

The evidence indicates that surgical arthroplasty results in a significantly quicker time to healing and reduction in recurrent foot ulceration. Though the results for recurrence reflect uncertainty in the magnitude of the point estimate as the confidence interval are wide, which might be explained by the small study sample in each group. Box 106 summarises the body of evidence according to the NHMRC grading criteria.

Box 106 Evidence matrix for comparison of surgical arthroplasty for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	C	One level III study with low risk of bias and on level III study with moderate risk of bias.
Consistency	A	Studies are consistent.
Clinical impact	B	The studies suggest substantial clinical impact with respect to the healing time of foot ulcer and a large preventative clinical impact for ulcer recurrence (RR of 0.14 and RR of 0.16).
Generalisability	B	The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population. The sample did have an over representation of males.
Applicability	C	The studies took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.

Evidence statement

The results suggest that in addition to standard off loading and wound care, surgical arthroplasty is effective at preventing foot ulcer recurrence in diabetes subjects and reduces the healing time of foot ulcer (Grade C).

Table 70 Studies included which compare surgical resection arthroplasty to standard wound care and offloading for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
(Armstrong et al 2003) USA	III-2 retrospective cohort study Good quality study	Diabetic patients attending large-based diabetes foot clinic in teaching hospital. Intervention group: n=21, mean age 70.5±7.6 years, male 90.5% (n=19), GHb (%) 7.9±1.4, mean duration of DM (yrs) 14.1±3.4, mean duration of wound (wks) 15.6±6.4 Comparator group: n=20, mean age 69.8±10.3 years, male 100% (n=20), GHb (%) 8.4±1.2, mean duration of DM (yrs) 13.7±3.1, mean duration of wound (wks) 15.5±5.9	N=21, Keller procedure; first metatarsophalangeal joint arthroplasty with inear incision dorsal over the digit and metatarsophalangeal joint followed by standard off-loading (Active Offloading Walker, (DH Walker; Royce Medical, California)) and wound care.	N=20, Control subjects received standard nonsurgical care, received standard off-loading and wound care	Time to healing mean ± SD (days) Intervention 24±9.9 / Control 67±17 / P<0.001 % ulcer recurrence Intervention 4.8% (n=1) / Control 35% (n=7) / Effect size [95% CI] RR 0.14 [0.02, 0.73] % of infection Intervention 40% (n=8) / Control 38% (n=8) / P=0.90 % Amputation Intervention 5% (n=1) / Control 9.5% (n=2) / Effect size [95% CI] RR 0.53 [0.07, 3.9]
(Armstrong et al 2005c) USA	III-2 retrospective cohort study average quality study	Diabetic patients attending department of surgery, Veterans Affairs medical centre. Intervention group: n=22, mean age 65±9.0 years, male 81.8% (n=18), mean wound size (cm²) 2.3±1.4, GHb (%) 8.3±1.6, mean duration of DM (yrs) 13.7±4.9 Comparator group: n=18, mean age 64±7.7 years, male 83.3% (n=15), mean wound size (cm²) 2.6±1.6, GHb (%) 8.4±1.6, mean duration of DM (yrs) 12.4±5.5	N=22, surgical resection of fifth metatarsal head, approached through a dors- lateral incision from the distal one-third of the fifth metatarsal to the proximal one-third of the base of the	N=18, standard wound care that consisted of wound dressing changes, aggressive offloading, and weekly debridement	Mean time to heal (weeks) ±SD Intervention 5.8±4.3 / Control 8.7±4.3 / P=0.02 % Re- ulceration at 6 months Intervention 4.5% (n=1) / Control 28% (n=5) / Effect size [95% CI] RR 0.16 [0.02, 0.93]

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
			proximal phalanx. Post-operative care with standardised removable cast walker offloading (DH Walker; Royce Medical, California)		% amputation at 6 months		
					Intervention 4.5% (n=1)	Control 12% (n=2)	Effect size [95% CI] RR 0.4 [0.05, 2.9]

DM= Diabetes Mellitus; GHb= Glycaemic Haemoglobulin; RR= relative risk

Conservative orthopaedic surgery versus medical care for the treatment of diabetic foot osteomyelitis

The average quality level III-2 study by Ha Van et al (1996) considered conservative orthopaedic surgery, involving resection of infected bone, for the treatment of diabetes foot osteomyelitis and reported outcomes on the proportion of healed ulcers, as well as time to heal (Table 71).

The authors found that conservative surgery in addition to standard medical treatment accelerated the time to healing of the infected foot ulcer compared to standard medical treatment (antibiotics, offloading and wound care) alone (181 ± 30 days versus 462 ± 98 days, respectively). However, there was no statistically significant difference in the proportion of healed foot ulcers between the two treatments, perhaps due to the small sample size as the difference between the two treatments was quite large and favoured the surgical option. No adverse events were reported.

The results suggest that conservative orthopaedic surgery for foot osteomyelitis might have some benefits in terms of time to ulcer healing, but uncertain clinical impact on the proportion of healed foot lesions. Box 107 summarises the body of evidence according to the NHMRC grading criteria.

Box 107 Evidence matrix for comparison of conservative orthopaedic surgery and medical care for treating diabetic foot osteomyelitis

Component	Rating	Description
Evidence base	C	One level III-2 study with moderate risk of bias.
Consistency	N/A	Only one study available
Clinical impact	C	The study indicated a substantial clinical impact of the intervention on time for foot ulcer healing compared to standard medical care. No significant clinical impact was found in terms of the proportion of healed foot lesions, by treatment group.
Generalisability	C	The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population. The sample did have an overrepresentation of males.
Applicability	C	The study took place in France, which has similar health care for diabetes patients compared to the Australia health care context.

Evidence statement

The results suggest that in addition to standard medical care involving antibiotics, off loading and wound care, conventional orthopaedic surgery accelerates time to foot ulcer healing in diabetes patients with foot osteomyelitis (Grade C).

Table 71 Studies included which compare conservative orthopaedic surgery medical treatment for diabetic foot osteomyelitis

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
(Ha Van et al 1996) USA	III-2 retrospective cohort study average quality study	Diabetic patients attending outpatient clinic of department of Diabetology and Metabolism. Intervention group: n=32, mean age 59.4±10.4 years, male 91% (n=29), NIDDM 72% (n=23), diabetes duration (yrs) 18.3±11.6, HbA1c (%) 8.1±1.6, retinopathy 81% (n=26), renal insufficiency 28% (n=9), plasma creatinine (µmol/l) 172±249, ischaemic heart disease 25% (n=8), history of previous foot lesion 72% (n=23), plantar wound 31% (n=10), toe wound 69% (n=22), neuropathy 91% (n=29), peripheral vascular disease 47% (n=15) Comparator group: n=35, mean age 60.3±10 years, male 71% (n=25), NIDDM 74% (n=26), diabetes duration (yrs) 15.6±11.3, HbA1c (%) 7.6±1.9, retinopathy 69% (n=24), renal insufficiency 37% (n=13), plasma creatinine (µmol/l) 131±151, ischaemic heart disease 17% (n=6), history of previous foot lesion 63% (n=22), plantar wound 40% (n=14), toe wound 60% (n=21), neuropathy 89% (n=31), peripheral vascular disease 54% (n=19)	N=32, treated with conservative orthopaedic surgery, resection of infected part of the phalanx or metatarsal bone under the wound plus antibiotic treatment, offloading, and wound care for diabetic foot ulcers	N=35, treated with antibiotic treatment, offloading and wound care for diabetic foot ulcers.	Time to ulcer healing mean ± SD (days)		
					Intervention 181±30	Control 462±98	P<0.01
					% healed ulcer		
					Intervention 78% (n=25)	Control 57% (n=20)	Effect size [95% CI] RR 1.37 [0.97, 1.81]

NIDDM= Non insulin dependent diabetes mellitus; RR= relative risk

Human growth factors

Human growth factor in various forms has been the focus of 23 articles from 22 level II RCTs evaluated in this section. The various forms of human growth factor that have been considered include recombinant human epidermal growth factor (rhEGF), recombinant human platelet-derived growth factor (rhPDGF), granulocyte-colony stimulating factor (G-CSF), recombinant human vascular endothelial growth factor (rh VEGF), platelet rich plasma gel/releasate, recombinant human transforming growth factor β2 (rhTGF) and basic fibroblast growth factor (bFGF). These growth factors are considered individually, below.

Recombinant human epidermal growth factor

Amongst the various types of human growth factor to be discussed, the first to be considered is recombinant human epidermal growth factor (rhEGF). Two good and one average quality level II RCTs considered the use of rhEGF, which was applied either topically or by intralesion injection during daily wound dressing changes, to treat diabetic foot ulcers.

Topical application

In a good quality study, Tsang et al (2003) observed participants for up to 24 weeks after daily topical treatment of either 0.4%, or 0.2% rhEGF or standard wound care, for 12 weeks (Table 72). They observed that statistically significant benefits were gained by the use of 0.4% rhEGF although when the dose was reduced to 0.2% rhEGF the difference between groups was not significant (number of patients healed within 12 weeks 95% (20/21) in 0.4% group, 57% (12/21) in 0.2% group and only 42% (8/19) in the control group).

Afshari et al (2005) reported that there were benefits to using rhEGF in terms of the numbers of ulcers healed and time to healing when compared to standard wound care and placebo, however the study comprised a small sample size and participants were only observed for four weeks. The authors commented that 23.3 percent (7/30) of participants in the intervention group versus 10 percent (2/20) in the control group had ulcers that were completely healed within the four week time period (p=0.3). Due to the short follow-up and lack of statistical power, this finding was not significant, however participants receiving rhEGF were three times more likely to have >70 percent of the ulcer healed by the end of the study (50% (15/30) versus 15% (3/20) p=0.05). Length of hospital stay was not significantly shorter for the intervention group due to difficulties coordinating aspects of the study which required participants to stay in hospital longer than medically required.

All of the studies reported greater improvements in time to healing of ulcers for participants receiving rhEGF than those receiving standard wound care plus or minus placebo, however for some outcomes the benefits did not reach statistical significance. When the data for healing with the topical application of rhEGF were pooled, the estimate of relative risk was 1.87 [95%CI 1.11, 3.14] in favour of rhEGF which was statistically significant (p=0.018). The results of the meta-analysis can be seen in Figure 1.

Box 108 Evidence statement matrix for topical recombinant human epidermal growth factor (rhEGF)

Component	Rating	Description
Evidence base	B	Two level II RCTs with low and moderate risk of bias
Consistency	B	Most studies were consistent and any inconsistencies can be explained
Clinical impact	C	Topical application of rhEGF is likely to have a moderate clinical impact in regard to ulcer healing.
Generalisability	B	Participants were diabetic patients with existing Wagner Grade I or II foot ulcers and are therefore generalisable to target population
Applicability	C	Although the studies were carried out in Iran and Hong Kong which have different health care systems to Australia, the evidence is probably applicable to the Australian healthcare context with some caveats.

Evidence statement

There is evidence to suggest that topical application of recombinant human epidermal growth factor may have some effect at increasing the number of foot ulcers healed or partially healed, relative to standard wound care plus or minus placebo, in patients with Wagner grade I or II diabetic foot ulcers with adequate perfusion (Grade B).

Intralesion injection

Fernandez-Montquin et al (2007) followed up participants for 12 months and noted that a substantial proportion of ulcers healed after five weeks of treatment, a time point not reached by Afshari et al (2005). Fernandez-Montequin et al (2007) used an intralesion injection of rhEGF as opposed to a topical application of cream as used by Afshari et al (2005) and Tsang et al (2003). The findings are particularly important as the cohort in the Fernandez-Montquin et al (2007) study included patients with more severe ulcers (Wagner Grade III or IV, at high risk of requiring an amputation), which were excluded in the Afshari et al (2005) and Tsang et al (2003) studies. The findings of the Fernandez-Montequin et al (2007) study did not reach statistical significance for several of the outcomes measured, however this may be because both the intervention and control groups received the rhEGF and the only point of difference was the dose given to participants (75µg versus 25µg rhEGF). It should also be noted that all participants in the control group had Grade III ulcers whereas 22 percent (5/23) of the intervention group had a Grade IV ulcer. Ethical requirements at the institution where the study was undertaken prevented a placebo being acceptable therefore both intervention and control groups showed benefit from the rhEGF.

A summary of the evidence is provided in Box 109 according the NHMRC grading criteria.

Box 109 Evidence statement matrix for intralesion injection of recombinant human epidermal growth factor (rhEGF)

Component	Rating	Description
Evidence base	B	One level II RCT with low risk of bias
Consistency	N/A	Only one study available.
Clinical impact	D	Due to the lack of statistical power no statistically significant benefit was seen following the intralesion application of rhEGF.
Generalisability	B	Participants were diabetic patients with existing Wagner Grade III or IV foot ulcers at risk of amputation.
Applicability	C	Although the study was carried out in Cuba the evidence is probably applicable to the Australian healthcare context with some caveats.

Evidence statement

There is insufficient evidence to suggest that higher dose intralesion application of recombinant human epidermal growth factor has any beneficial effect at increasing the number of foot ulcers healed or partially healed, relative to low dose intralesion application of recombinant human epidermal growth factor and standard wound care, in patients with Wagner grade III or IV diabetic foot ulcers at high risk of amputation (Grade C).

Table 72 Recombinant Human Epidermal Growth Factor (rhEGF)

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
(Tsang et al 2003) Hong Kong	Level II RCT. Good quality study	N=61 diabetic patients attending a diabetic ambulatory care centre Intervention group 0.04% rhEGF: n = 21, mean age 62.24 ± 13.68 years, male 29% (n=6), BMI 23.83 ± 3.17 kg/m^2, duration of diabetes (yrs) 9.05 ± 6.19, insulin use 42% (n=9), HbA_{1c} 8.5 ± 1.34%, serum creatinine > 2 mg 14% (n=3), ankle brachial index 1.05 ± 0.19, vibration threshold > 25 62% (n=13), abnormal 10 g monofilament test 48% (n=10), nephropathy 57% (n=12), retinopathy 76% (n=16), other comorbidities 90% (n=19), ulcer duration 11.48 ± 14.68 weeks, ulcer area 3.4 ± 1.1 cm^2, ulcer location: toes 48% (n=10), sole 29% (n=6), ankle 19% (n=4), other 4% (n=1) Intervention group 0.02% rhEGF: n = 21, mean age 68.76 ± 10.45 years, male 62% (n=13), BMI 23.33 ± 3.11 kg/m^2, duration of diabetes (yrs) 9.85 ± 7.79, insulin use 33% (n=7), HbA_{1c} 8.7 ± 1.99%, serum creatinine > 2 mg 9% (n=2), ankle brachial index 1.03 ± 0.22, vibration threshold > 25 66% (n=14), abnormal 10 g monofilament test 48% (n=10), nephropathy 76% (n=16), retinopathy 57% (n=12), other comorbidities 76% (n=16), ulcer duration 8.24 ± 5.55 weeks, ulcer area 2.78 ± 0.82 cm2, ulcer location: toes 52% (n=11), sole 14% (n=3), ankle 24% (n=5), other 9% (n=2) Comparator group – N = 19, mean age 64.37 ± 11.67 years, male 53% (n=10), BMI 25.69 ± 5.21 kg/m^2, duration of diabetes (yrs) 10.11 ±8.29, insulin use 47% (n=9), HbA_{1c} 7.97 ± 1.81%, serum creatinine > 2 mg 16% (n=3), ankle	n=21 Intervention group 1: received standard treatment including debridement, daily saline dressings after cleansing, assessment of ulcer such as size, exudates, signs of infection, granulation tissue and presence of necrotic tissue. Topical application of actovegin 5% cream which also contained 0.04% human epidermal human growth factor (hEGF), wound was covered with sterile gauze N=21 Intervention group 2: same as group 1 except that 0.02% hEGF was added to the actovegin cream	n=19 Comparison group received standard treatment including debridement, daily saline dressings after cleansing, assessment of ulcer such as size, exudates, signs of infection, granulation tissue and presence of necrotic tissue. Topical application of actovegin 5% cream, then wound covered with sterile gauze	Number of patients healed within 12 weeks		
					Intervention 1 95% (20/21) Intervention 2 57% (12/21)	Control 42% (8/19) Control 42% (8/19)	Effect size [95% CI] RR=2.26 [1.47, 2.62] Effect size [95% CI] RR=1.36 [0.73, 2.57]

		brachial index 0.99 ± 0.16, vibration threshold > 25 68% (n=13), abnormal 10 g monofilament test 32% (n=6), nephropathy 63% (n=12), retinopathy 47% (n=9), other comorbidities 89% (n=17), ulcer duration 12.00 ± 15.47 weeks, ulcer area 3.48 ± 0.82 cm^2, ulcer location: toes 58% (n=11), sole 10% n=(2), ankle 10% (n=2), other 21% (n=4)			
(Afshari et al 2005) Iran	Level II RCT. Average quality study	N=50 diabetic patients with foot ulcers. Intervention group: n = 30, mean age 56 ± 12.7 years, male 53% (n=16), duration of diabetes (yrs) 12.6 ± 7.5, smokers 40% (n=12), BMI 24.0 ± 3.4 kg/m^2 , ankle-brachial index < 1 46.4% (n=11), fasting blood glucose 137.9 ± 53.9 mg/dL, HbA1c 10.5 ± 2.6%, erythrocyte sedimentation rate 47.9 ± 25 mm/h, leukocyte count 9405 ± 3736 (10^9/ml), creatinine 1.2 ± 0.83 mg/dL, triglyceride 184 ± 100 mg/dL, total cholesterol 186 ± 58 mg/dL, retinopathy 83% (n=25), vasculopathy 43% (n=13) nephropathy 77% (n=23), neuropathy 93% (n=28), ulcer: duration 42.9 ± 38.4 days, size 87.5 ± 103.2 mm^2, signs of infection 70% (n=21) Comparator group: n = 20, mean age 59.7 ± 12.3 years, male 55% (n=11), duration of diabetes (yrs) 14.9 ± 7.1, smokers 45% (n=9), BMI 22.8 ± 3.8 kg/m^2, ankle-brachial index < 1 50% (n=10), fasting blood glucose 157.6 ± 53.2 mg/dL, HbA1c 10.9 ± 1.65%, erythrocyte sedimentation rate 47.9 ± 22 mm/h, leukocyte count 8730 ± 3093 (10^9/ml), creatinine 0.99 ± 0.33 mg/dL , triglyceride 148 ± 64 mg/dL, total cholesterol 169 ± 48 mg/dL, retinopathy 100% (n=20), vasculopathy 40% (n=8), nephropathy 80% (n=16), neuropathy 100% (n=20), ulcer: duration 59.7 ± 55.5 days, size 103.4 ± 147.8 mm^2, signs of infection 60% (n=12)	n=30 After wound debridement and infection control, wounds were washed with normal saline and dressed with sterile gauze and adhesive tape every day. 1 mg Epidermal Growth Factor (EGF) /1000 mg of 1% silver sulphadiazine in a hydrophilic base was applied once a day at time of wound dressing for 28 days. Ulcers were evaluated once per week for severity and size.	n=20 After wound debridement and infection control, wounds were washed with normal saline and dressed with sterile gauze and adhesive tape every day. Placebo of 1% silver sulphadiazine in the same hydrophilic base as the treatment group was applied once a day at time of wound dressing for 28 days. Ulcers were evaluated once per week for severity and size.	Numbers of ulcers completely healed at 4 weeks Intervention 23% (7/30) | Control 10% (2/20) | Effect size [95% CI] RR=2.33 [0.63, 9.57] p=0.3 Number of ulcers partially healed Intervention 77% (23/30) | Control 90% (18/20) | Effect size [95% CI] RR=0.85 [0.74, 1.11] p=0.3 Number of ulcers healed >70% Intervention 50% (15/30) | Control 15% (3/20) | Effect size [95% CI] RR=3.33 [1.27, 10.8] p=0.05 Number of ulcers healed <70% Intervention 50% (15/30) | Control 85% (17/20) | Effect size [95% CI] RR=0.59 [0.46, 0.88] p=0.05 Average hospital stay (days) Intervention 29.6±20.95 | Control 28.9±15.1 | p=0.9
(Fernández Montequín et al 2007) Cuba	Level II RCT. Good quality study	N=41 diabetic patients with an advanced foot ulcer at risk of amputation. Intervention group: n = 23, mean age 63.0 ± 12.0, male 52% (n=12), caucasian 65% (n=15), duration of diabetes (yrs) 20.1 ± 8.5, type 1 diabetes 9% (n=2), history of heart	n=23 Standard wound care including debridement, dressing with saline moistened gauze, off-	n=18 Standard wound care including debridement, dressing with saline moistened gauze, off-	Number of ulcers completely healed Intervention 57% (13/23) | Control 50% (9/18) | Effect size [95% CI] RR=1.13 [0.65, 2.05] 75 – 100% healing after 5 weeks

		disease 26% (n=6), ankle brachial index > 0.8 30.4% (n=7), median ulcer duration 1.0 ±1.5 months, ulcer area 22.5 ± 35.0 cm^2, ulcer: neuropathic 26% (n=6), ischaemic 75% (n=17), Wagner grade III 78% (n=18), grade IV 22% (n=5), ulcer location: toes 65% (n=15), internal edge 4% (n=1), external edge 13% (n=3), dorsum 17% (n=4), sole 22% (n=5), transmetatarsal 13% (n=3), ankle 13% (n=3) Comparator group: n = 18, mean age 67.5 ± 19.5 years, male 55.6% (n=10), caucasian 72% (n=13), duration of diabetes (yrs) 17.5 ± 10.1, type 1 diabetes 11% (n=2), history of heart disease 17% (n=3), ankle brachial index > 0.8 22% (n=4), median ulcer duration 1.0 ±1.5 months , ulcer area 25.0 ± 10.9 cm^2, ulcer: neuropathic 44% (n=8), ischaemic 56% (n=10), Wagner grade III 100%, grade IV 0%, ulcer location: toes 67% (n=12), internal edge 0%, external edge 22% (n=4), dorsum 11% (n=2), sole 22% (n=4), transmetatarsal 11% (n=2), ankle 11% (n=2)	loading and antibiotics as well as strict metabolic control of glycaemia plus intralesion injections of 75µg rhEGF (recombinant human epidermal growth factor) in 5ml saline 3x per week on alternate days until complete response or for 5-8 weeks. If partial response observed treatment continued for an additional 3 weeks	loading and antibiotics as well as strict metabolic control of glycaemia plus intralesion injections of 25µg rhEGF (recombinant human epidermal growth factor) in 5ml saline 3x per week on alternate days until complete response or for 5-8 weeks. If partial response observed treatment continued for an additional 3 weeks	Intervention 74% (17/23)	Control 50% (9/18)	Effect size [95% CI] RR=1.48 [0.92, 2.38]
					Time to healing (weeks)		
					Intervention 20.6 weeks [17.0, 24.2] Control 19.5 weeks [16.3, 22.7]		
					Amputation rate		
					Intervention 35% (8/23)	Control 33% 6/18)	Effect size [95% CI] RR=1.04 [0.46, 2.5]
					Above knee amputations		
					Intervention 38% (3/8)	Control 17% (1/6)	Effect size [95% CI] RR=2.25 [0.41, 14.9]
					Below knee amputations		
					Intervention 25% (2/8)	Control 66% (4/6)	Effect size [95% CI] RR=0.38 [0.12, 1.28]
					Transmetatarsian amputations		
					Intervention 25% (2/8)	Control 17% (1/6)	Effect size [95% CI] RR=1.5 [0.23, 10.9]
					Toe amputations		
					Intervention 13% (1/8)	Control 0% (0/6)	Effect size [95% CI] RR=1.5 [0.12, 19.9]
					Time to amputation (months)		
					Intervention 15.6 months [11.9, 19.3] Control 13.9 months [9.3, 18.5]		

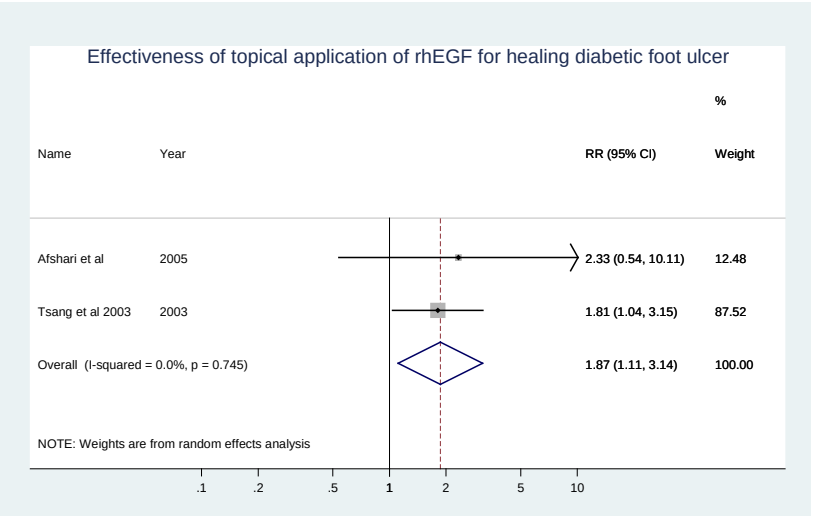
rhEGF=recombinant human epidermal growth factor; Wagner Classification of ulcers, Grade I = superficial ulcer, Grade II = deep ulcer to tendon, capsule or bone, Grade III = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade IV = localised gangrene of forefoot or heel, Grade V = gangrene of entire foot; RR = relative risk

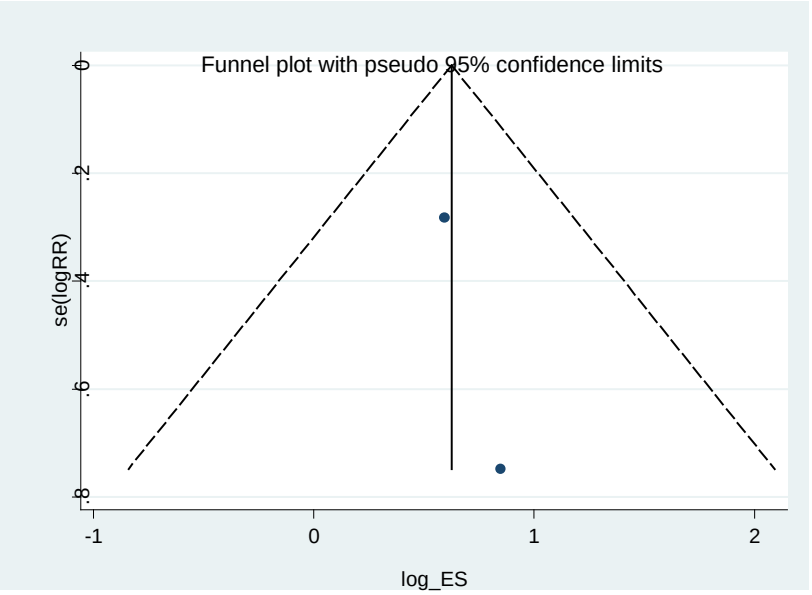
Figure 1 Meta-analysis of the effectiveness of the topical application of rhEGF for healing diabetic foot ulcers

Study	RR	[95% Conf.	Interval]	% Weight
Afshari et al	2.333	0.539	10.109	12.48
Tsang et al 2003	1.810	1.040	3.148	87.52
D+L pooled RR	1.868	1.113	3.135	100.00

Heterogeneity chi-squared = 0.11 (d.f. = 1) p = 0.745
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000

Test of RR=1 : z= 2.36 p = 0.018





Recombinant human platelet-derived growth factor (rhPDGF) versus placebo

Five good quality level II RCT's reported in six articles considered the use of recombinant human platelet-derived growth factor for the treatment of diabetic foot ulcers (Table 73). In addition to good wound care, d'Hemecourt et al (1998) compared becaplermin (rhPDGF-BB) gel 100µg/g or sodium carboxymethylcellulose (NaCMC) gel and determined that both interventions were superior to good wound care alone in treating chronic diabetic foot ulcers. Results of the study showed 36% of those receiving placebo NaCMC versus 44 percent of those receiving rhPDGF had ulcers completely healed. Participants in the rhPDGF-BB intervention group also achieved faster healing times although these were not statistically significant (85 days with rhPDGF-BB versus 98 days for NaCMC). d'Hemecourt et al (1998) also reported that the rhPDGF-BB group had the greatest reduction in median relative ulcer area and better wound evaluation scores which were summarised for all patients at endpoint and reflected changes from baseline. (Wound assessment was performed by independent assessors blinded to treatment or control status, assessment criteria detailed below table 3). Adverse events were reported by all groups (21% rhPDGF-BB, 27% NaCMC) but were mostly considered to be due to the disease process rather than the study medication.

Hardikar et al (2005) also compared rhPDGF-BB 100µg/g with a placebo gel formulated with NaCMC and concluded that using rhPDGF-BB significantly increased the incidence of complete healing at 10 weeks (71% vs 31%, RR=2.29, 95% CI [1.55, 3.44], p<0.001). Further, by 20 weeks 85 percent of the intervention group compared to 53 percent of the control group had achieved complete healing (RR=1.60, 95% CI [1.25, 1.94], p<0.05). Average time taken to heal was significantly shorter in the intervention group: 46 days versus 61 days (p<0.001) at 10 weeks and 57 days versus 96 days (p<0.001) at 20 weeks. Hardikar et al (2005) also identified that there was a significantly greater percent reduction in ulcer size in the rhPDGF-BB intervention group at 10 weeks (58% versus 26% p<0.001). Overall the conclusions made by Hardikar et al (2005) were that rhPDGF-BB caused a greater reduction in the size of the ulcers, resulted in a greater number of ulcers being healed and that it occurred in less time. Taking into consideration all the variables assessed at baseline such as site and size of ulcer, arterial blood flow, HbA1c, and ankle brachial pressure index, the ultimate conclusion made by Hardikar et al (2005) was that rhPDGF-BB based gel was twice as effective in healing ulcers as the placebo particularly at the 10 week assessment. Adverse events were not specified by Hardikar et al (2005) other than that they were not significantly different between groups (13% in the intervention group and 17% in the control group) and considered not to be related to treatment. Compared to the other reports, the subjects in this study had a noticeably shorter duration of ulcer which may have contributed in part to the higher rate of healing.

Steed et al (1995; 2006) reported findings in two articles for the same study which compared rhPDGF-BB 30µg/g gel with a matching placebo gel to determine number of ulcers healed, reduction of ulcer area, time to healing and recurrence rates of completely healed ulcers. A dose of 2.2 µg/cm2 rhPDGF-BB was applied daily. This was a multi-centre study where it was noted that different centres performed debridement (as part of standard wound care) more frequently than other centres. Results indicated that a greater proportion of the intervention group achieved complete healing of their ulcer than participants in the placebo group (48% versus 25%, p=0.01). Ulcers also healed more quickly in the intervention group (p=0.01) and there was a greater reduction in wound area of the ulcer, although the results were not significant for this latter outcome (p=0.09). Recurrence rates of healed ulcers were also not statistically significant although a benefit against recurrence was identified in the intervention group (26% had recurrence in the intervention group versus 46% in the control group). There was no significant difference in reported adverse events between the two groups.

When considering the results of the intervention and placebo groups by centre, it is apparent that patients who were more frequently debrided had better rates of healing regardless of whether they received the intervention or the placebo. Therefore, the effect size reported by Steed et al (1995, 2006) should not be attributed to rhPDGF alone. Consequently, the results of this study will also be discussed in the debridement section of this review.

Wieman et al (1998) compared becaplermin gel (rhPDGF-BB) 100µg/g with rhPDGF-BB 30µg/g as well as a placebo. Outcomes were measured in terms of numbers of ulcers healed and time to complete healing of ulcer. The use of rhPDGF-BB 100µg/g significantly increased the incidence of ulcer healing compared to placebo (50% versus 35%, p=0.01, RR=1.43, 95% CI [1.07, 1.93]), whereas contrary to the results found by Steed et al (1995; 2006) 30µg/g rhPDGF-BB provided no real benefit compared to placebo (36% in the intervention group versus 35% in the control group RR=1.05, 95% CI [0.76, 1.46]). Becaplermin 100µg/g also significantly reduced the time to achieve complete healing by 32 percent (86 days for the intervention group versus 127 days for the placebo group, p=0.01) (Wieman et al 1998). It is possible that the discrepant results for rhPDGF-BB 30µg/g when compared to Steed et al (1995; 2006) may have been due to the use of off-loading devices in Wieman's study for both trial arms.

Smiell et al (1999) also used becaplermin gel (rhPDGF-BB) 100µg per gram to treat patients with chronic diabetic foot ulcers and compared its' efficacy against sodium carboxymethylcellulose (NaCMC) aqueous based gel containing parabens, m-cresol and L-lysine. The only outcome reported by Smiell was the number of ulcers completely healed, and the results indicated statistically there was no significant difference (36% versus 32%). Smiell et al's (1989) trial was the largest of the five trials, with the exception of Wieman et al (1998), and would appear to be adequately powered. The inconsistent results may be related to the distribution of patient's between trial arms as well as the refractory nature of the ulcers. Patients in the control arm had an average ulcer duration that was 23 weeks longer than the intervention arm and in both arms ulcers had remained unhealed for over a year.

Most of the studies in this section reported statistically and clinically significant benefits from using recombinant human platelet-derived growth factor in the treatment of chronic full-thickness stage III or IV ulcers. There were some inconsistencies which, for the most part could be explained. Becaplermin in varying doses reduced the time to complete ulcer healing and rate of healing. Pooled analysis of the effect sizes indicates that there is a statistically significant benefit for using rhPDGF in addition to standard wound care in terms of foot ulcer healing (RR = 1.56, 95% CI [1.22, 2.03], $p < 0.001$) (Figure 2). Of the three studies which assessed adverse events, no significant differences in adverse events were reported (d'Hemecourt 1998; Hardikar 2005; Steed 1995, 2006).

Box 110 Evidence statement matrix for recombinant human platelet-derived growth factor (rhPDGF) versus placebo

Component	Rating	Description
Evidence base	A	Four level II studies with low risk of bias. One level II study with moderate risk of bias.
Consistency	B	Most studies were consistent and any inconsistencies can be explained
Clinical impact	B	Substantial clinical impact in relation to number of ulcers healed, reduced healing time and decreased ulcer area for non-healed ulcers
Generalisability	B	Evidence directly generalisable to the target population of diabetic patients with existing chronic foot ulcers with adequate perfusion.
Applicability	C	Studies were from the USA and India which although not similar to the Australian healthcare system, is probably applicable with few caveats

Evidence statement

In patients with full thickness chronic foot ulcers and adequate perfusion, recombinant human platelet-derived growth factor 100µg/g gel is effective in substantially increasing the number of completely healed ulcers, reducing healing time and reducing the surface area of ulcers not completely healed compared to placebo (Grade B).

Table 73 Recombinant human platelet-derived growth factor (rhPDGF) versus placebo

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
(d'Hemecourt et al 1998) USA	Level II RCT. Good quality study	N=172 diabetic patients with at least one full-thickness chronic lower extremity grade III or IV (assessment classification not stated) ulcers of at least 8 weeks duration. Patients were randomly assigned in a 2:2:1 ratio to either good wound care alone, good wound care plus NaCMC gel, or good wound care plus becaplermin gel 100μg/g Intervention group: n=34, male 71% (n=24), mean age 58.5 ± 11.9 years, white 82% (n=28), weight 99.8 ± 20.94 kg, ulcer area 2.4 ± 2.02cm^2, ulcer depth 0.3 ± 0.15cm, ulcer duration 20.0 ± 14.39 weeks, ulcer location: leg 12% (n=4), foot 88% (n=30), Wagner stage III 94% (n=32), Wagner stage IV 6% (n=2), $TcPO_2$ mmHg 49.4 ± 11.9 Control 2: n=70, 70% male (n=49), mean age 56.9±13.02 years, 90% white (n=63), weight 93.0±21.03 kg, ulcer area 3.2±2.75cm^2, ulcer depth 0.4±0.20cm, ulcer duration 52.8±60.92 weeks, location, leg 4.3% (n=3), foot 95.7% (n=67), stage III 100% (n=70), $TcpO_2$mmHg 57.4±27.5	Intervention: n=34 Standard wound care including debridement, off-loading and systematic control of infection plus becaplermin (rhPDGF-BB) gel 100μg/g dressings daily	Control 2: n= 70 Standard wound care including debridement, off-loading and systematic control of infection plus sodium carboxy-methylcellulose (NaCMC) gel dressings daily	Complete healing of ulcers Intervention 44% (15/34) | Control 2 36% (25/70) | Effect size [95% CI] RR=1.24 [0.74, 1.96] Time to heal (days) Intervention 85 days | Control 2 98 days | No statistics given only a statement that there were no significant differences between groups Change in wound evaluation ulcer scores relative to baseline (see below for scoring values) Intervention -1.26 | Control 2 -1.04 Ulcer related adverse effects Intervention 21% (7/34) | Control 2 27% (19/70) | Effect size [95% CI] RR=0.76 [0.35, 1.56] Relative ulcer area (cm^2 median) Intervention 0.13 | Control 2 0.31
(Hardikar et al 2005) India	Level II RCT. Good quality study	N=103 diabetic patients attending outpatient departments of 8 public hospitals in India with at least 1 but less than 3 full thickness chronic neuropathic ulcers of at least 4 weeks duration and stage III or IV ulcers according to the Wound Ostomy and Continence Society wound evaluation score	n=55 Standard wound care including sharp surgical debridement, daily ulcer cleaning and dressing, off-loading (wheelchair, crutches or bed rest),	n=58 Standard wound care including sharp debridement, daily ulcer cleaning and dressing, off-loading (wheelchair, crutches or bed rest),	Number of ulcers completely healed at 10 weeks Intervention 71% (39/55) | Control 31% (18/58) | Effect size [95% CI] RR=2.29 [1.55, 3.44] p<0.001 Number of ulcers completely healed at 20 weeks

<table>
<tr><th>Author
Country</th><th>Level and quality of study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th colspan="3">Outcome data</th></tr>
<tr><td></td><td></td><td>Intervention group: n=55, mean age 54.7 ± 9.0 years, male 73% (n=40), duration of diabetes (yrs) 11.5 ± 6.7, mean HbA_{1c} 7.8 ± 1.7, fasting plasma glucose 154 ± 65.0 mg/dL, 2 hour post-prandial plasma glucose 215.8 ± 91.5 mg/dL, total serum protein 7.1 ± 0.6 g/dL, serum creatinine 0.90 ± 0.29 mg/dL, ankle brachial index 1.07 ± 0.16, ulcer surface area 11.9 ± 9.9cm^2, wound evaluation score 0.11 ± 0.20, duration of ulcer 25.5 ± 31.9 weeks
Control group: n=58, mean age 54.5 ± 9.9 years, male 69% (n=40), duration of diabetes (yrs) 11.5 ± 6.5, mean HbA_{1c} 7.2 ± 1.3, fasting plasma glucose 143.4 ± 59.3 mg/dL, 2-hour post-prandial glucose 191.7 ± 83.9 mg/dL, total serum protein 7.0 ± 0.6 g/dL, serum creatinine 0.95 ± 0.30 mg/dL, ankle brachial index 1.05 ± 0.14, ulcer surface area 13.7 ± 11.2cm^2, wound evaluation score 0.12 ± 0.22, duration of ulcer 19.8 ± 39.8 weeks</td><td>examined once per week for the first 8 weeks then fortnightly till the end of the study. Regular use of diabetic medication and antibiotics as required plus recombinant human derived growth factor homodimer-BB (rhPDGF-BB) as a 0.01% gel containing 100µg of rhPDGF-BB/g applied as a 1.5mm layer covered with moist saline gauze as a dressing, for a period of up to 20 weeks</td><td>examined once per week for the first 8 weeks then fortnightly till the end of the study. Regular use of diabetic medication and antibiotics as required. Placebo was the same low bioburden topical gel formulated with sodium carboxymethylcellulose and other ingredients but no rhPDGF-BB</td><td>Intervention
85% (47/55)</td><td>Control
53% (31/58)</td><td>Effect size [95% CI]
RR=1.60
[1.25, 1.94] p<0.05</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td colspan="3">Average time to healing (days)</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Intervention
46 days</td><td>Control
61 days</td><td>p<0.001</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td colspan="3">Average % reduction in ulcer size</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Intervention
58%</td><td>Control
26%</td><td>p<0.001</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td colspan="3">Adverse events</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td colspan="2">Intervention
13% (7/55) not specified</td><td>Control
17% (10) not specified</td></tr>
<tr><td>(Smiell et al 1999)
USA</td><td>Level II RCT.
Good quality study</td><td>N=252 diabetic patients with full thickness diabetic chronic ulcers
Intervention group: n=128, mean age 59 ± 10.8 years, male 71% (n=91), white 81% (n=104), mean weight 221 ± 57.5 pounds, foot dorsum $TcPO_2$ 59.7 ± 24.49mmHg, ulcer duration 59 ±</td><td>n=128
All patients visited the clinic weekly in the first 6 weeks and then fortnightly for up to 20 weeks. Initial sharp debridement of</td><td>n=124
All patients visited the clinic weekly in the first 6 weeks and then fortnightly for up to 20 weeks. Debridement</td><td colspan="3">Number of ulcers completely healed</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Intervention
36% (46/128)</td><td>Control
32% (40/124)</td><td>Effect size [95% CI]
RR=1.11
[0.79, 1.57]</td></tr>
</table>

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
		72.4 weeks, mean ulcer area 3.2 ± 4.73cm^2 Control group: n=124, mean age 60 ± 11.9 years, male 71% (n=87), white 80% (n=97), mean weight 213 ± 44.3 pounds, foot dorsum $TcPO_2$ 55.9 ± 18.13mmHg ulcer duration 82 ± 156.6 weeks, mean ulcer area 2.5 ± 3.82 cm^2	target ulcer, moist saline dressings changed twice daily and patients instructed to apply a continuous thin layer of gel containing becaplermin (rhPDGF-BB 100µg/g) to entire ulcer area once daily, preferably in the evening, amount of gel based on ulcer area and determined at each visit	was carried out if needed at each visit. Good wound care consisted of the dressing changes, debridement, off-loading and adequate control if infection if present. Placebo consisted of vehicle gel (sodium carboxymethylcellulose aqueous based gel containing parabens, m-cresol and L-lysine).	
(Steed 1995); (Steed 2006) USA	Level II RCT. Good quality study	N=118 diabetic patients Intervention group: n=61, mean age 63.2 years, male 70.5% (n=43), mean $TcPO_2$ at wound edge 45.7 mmHg and at dorsum 58.6 mmHg, duration of ulcer 81.8 weeks (range 6.6-536.0), surface area median 3.1 cm^2, mean 5.5 cm^2 (range 0.2-57.4), mean depth 0.64cm. Size ranges <2.4 cm^2 37.7% (n=23), 2.4-5.7 cm^2 33% (n=20), >5.7 cm^2 30% (n=18). Control group: n=57, mean age 58.3 years, male 81% (n=46), mean $TcPO_2$ at wound edge 58.9 mmHg and at foot dorsum 59.7 mmHg, duration of ulcer 74.5 weeks (6.7-349.6), surface area: median 4.9 cm^2 and mean 9.0 cm^2 (range 0.6-111.2), mean depth 0.65 cm size ranges <2.4 cm^2 26% (n=15), 2.4-5.7 cm^2 32% (n=18), >5.7 cm^2 42% (n=24).	n=61 Before randomisation patients underwent aggressive surgical debridement of ulcer and further debridement occurred during the trial as required. Patients were assessed weekly for 1 month then fortnightly until completion. 30µg rhPDGF-BB/g gel applied to target ulcer at dose of 2.2µg rhPDGF-BB/cm^2, spread evenly over ulcer area, daily for 20 weeks or until completely healed. A non-adherent saline soaked gauze dressing was placed over the ulcer and the foot wrapped in gauze. After 12	n=57 Same treatment as intervention group with placebo matching gel	Number of completely healed ulcers Intervention: 48% (29/61) | Control: 25% (14/57) | Effect size [95% CI]: RR=1.94 [1.17, 3.28], p=0.01 Median % reduction in ulcer area Intervention: 99% | Control: 82% | p=0.09 Time to complete healing (days) Intervention group decreased by 30-40 days compared to control p=0.01 Recurrence rate of demonstrated completely healed ulcers Intervention group 26% (mean time to recur 8.6 weeks) Control group: 46% (mean time to recur 8.5 weeks) Adverse events Intervention: 51% (31/61) not related to study medication | Control: 60% (34/57) not related to study medication

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
			hours the gel was removed by irrigation with saline then dressed as above without gel. At the next dressing change, the gel was reapplied		16% (10/61) possibly related to study medication 11.4% (7/61) wound related infections		18% (10/57) possible related to study medication 26.3% (15/57) wound related infections
(Wieman et al 1998) USA	Level II RCT. Good quality study	N=382 diabetic outpatients Intervention group 1: n=123, mean age 57 ± 11.5 years, male 67% (n=82), white 81% (n=101), foot dorsum $TcPO_2$ mmHg 55.0 ± 22.60, ulcer duration 46 ± 54.7 weeks, mean ulcer area 2.6 ± 3.41 cm^2, ulcer depth 0.4 ± 0.46 cm. Intervention group 2: n=132 mean age 58±11.3 years, male 62% (n=82), white 82% (n=108), foot dorsum $TcPO_2$ mmHg 54.1 ± 20.94, ulcer duration 56 ± 80.3 weeks, mean ulcer area 2.6 ± 2.69 cm^2, ulcer depth 0.5 ± 0.48cm. Control group: mean age 58±11.8 years, male 72% (n=91), white 79% (n=100), foot dorsum $TcPO_2$ mmHg 55.5±19.61, ulcer duration 46 ± 52.1 weeks, mean ulcer area 2.8 ± 4.14 cm^2, ulcer depth 0.5 ± 0.54 cm.	Intervention group 1: n=123 All patients visited the clinic weekly for the first 6 weeks and then fortnightly for up to 20 weeks. Debridement as needed at each visit. Good wound care consisted of dressing changes, debridement, off-loading and adequate control of infection if present. Moist saline dressings were changed twice daily with a continuous thin layer of becaplermin (rhPDGF-BB) gel 100µg/g to entire ulcer area once daily, preferably at night. Amount of gel based on ulcer size and determined at each visit. Intervention group 2: as for intervention group 1 but 30µg/g of rhPDGF-BB gel used	n=127 As for the intervention groups but placebo of sodium carboxymethylcellulose (NaCMC) aqueous based gel containing parabens, m-cresol and L-lysine used instead of intervention medication	Number of ulcers completely healed		
					Intervention 1 50% (61/123)	Control 35% (44/127)	Effect size [95%CI] RR=1.43 [1.07, 1.93] p=0.007
					Intervention 2 36% (48/132)	Control 35% (44/127)	Effect size [95% CI] RR=1.05 [0.76, 1.46]
					Median time to complete healing (days)		
					Intervention 86 days (combined)	Control group 127 days	p=0.01 (32% reduction)

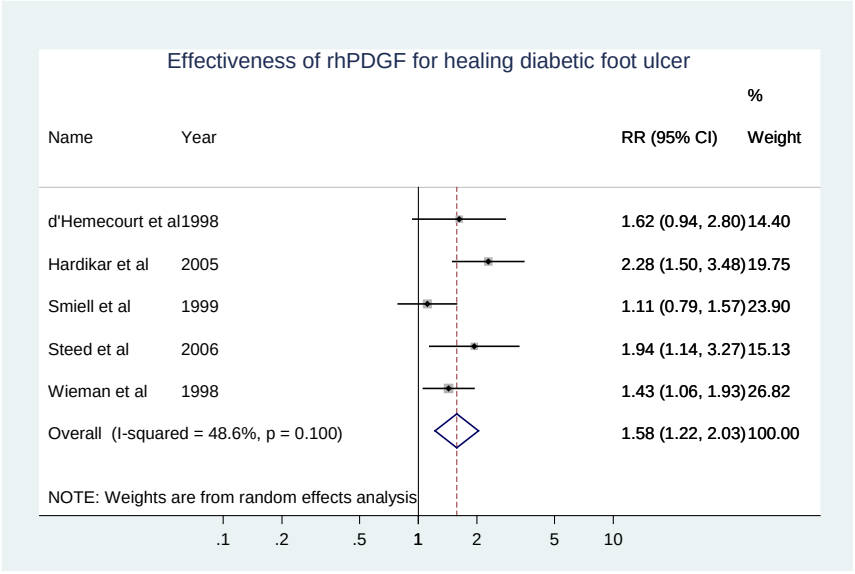
D'Hemecourt et al (1998) Wound Evaluation Score= six parameters (erythema, oedema, purulence, necrotic tissue, fibrin and drainage), scored as absent(0), mild (1), moderate (2) or marked (3) added together as total score; rhPDGF= recombinant human platelet derived growth factor; rhPDGF-BB= recombinant human platelet-derived growth factor- β receptor homodimer; Wound, Ostomy and Continence Society, Stages of a wound/ulcer: I= intact skin with non-blanchable redness of a localised area usually over a bony prominence; stage II= partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed without slough, may present as an abrasion or as an intact or open/ruptured serum-filled blister; stage III= full thickness tissue loss, subcutaneous fat may be visible but bone, tendon or muscle are not exposed, presents as a deep crater; stage IV= full thickness with extensive destruction, tissue necrosis and loss with exposed bone, tendon or muscle, slough or eschar may be present on some parts of the wound bed; University of Texas Diabetic Foot Classification System= 01. A0 Pre – or post ulcerative lesion completely epithelialised, 02. A1 superficial wound not involving tendon, capsule or bone, 03. A2 Wound penetrating to tendon or capsule, 04. A3 wound penetrating to bone or joint, 05. B0 pre or post ulcerative lesion completely epithelialised with infection, 06. B1 superficial wound, not involving tendon, capsule or bone with infection, 07. B2 wound penetrating to tendon or capsule with infection, 08. B3 wound penetrating to bone or joint with infection, 09. C0 pre or post ulcerative lesion completely epithelialised with ischaemia, 10. C1 superficial wound not involving tendon, capsule or bone with ischaemia, 11. C2 wound penetrating to tendon or capsule with ischaemia, 12. C3 wound penetrating to bone or joint with ischaemia, 13. D0 pre or post ulcerative lesion completely epithelialised with infection and ischaemia, 14. D1 superficial wound not involving tendon, capsule or bone with infection and ischaemia, 15. D2 wound penetrating to tendon or capsule with infection and ischaemia, 16. D3 wound penetrating to bone or joint with infection and ischaemia,

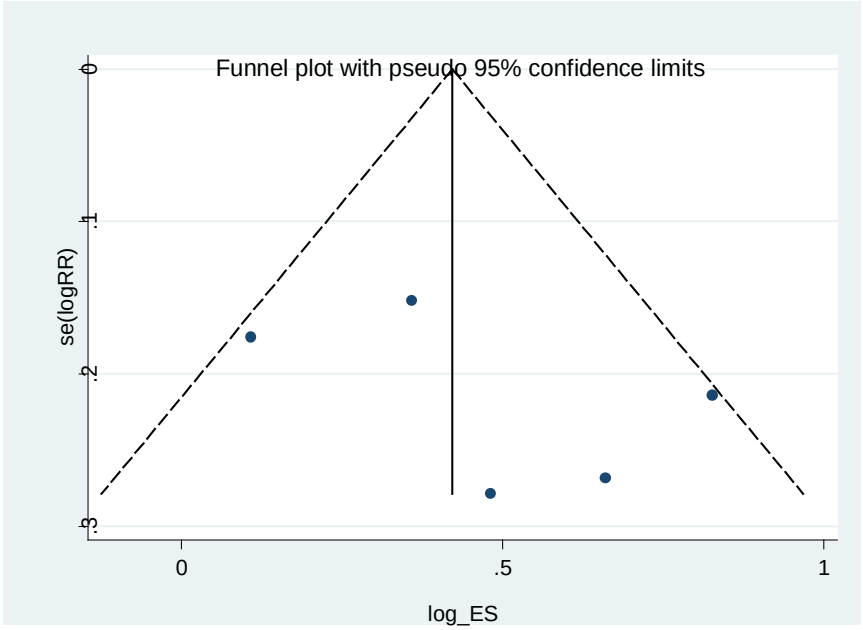
Figure 2 Meta-analysis of the effectiveness of rhPDGF in addition to standard wound care for healing diabetic foot ulcers

Study	RR	[95% Conf.	Interval]	% Weight
d'Hemecourt et al	1.619	0.938	2.796	14.40
Hardikar et al	2.285	1.502	3.475	19.75
Smiell et al	1.114	0.790	1.572	23.90
Steed et al	1.936	1.144	3.275	15.13
Wieman et al	1.431	1.063	1.928	26.82
D+L pooled RR	1.575	1.220	2.034	100.00

Heterogeneity chi-squared = 7.77 (d.f. = 4) p = 0.100
I-squared (variation in RR attributable to heterogeneity) = 48.6%
Estimate of between-study variance Tau-squared = 0.0401

Test of RR=1 : z= 3.49 p = 0.000





Recombinant human platelet-derived growth factor (rhPDGF) versus standard wound care with saline dressings

One good quality level II RCT compared becaplermin (rhPDGF-BB) gel 100 µg/g and standard wound care with saline dressings for the treatment of chronic diabetic foot ulcers (Table 74). Results of the study showed 22% (15/68) of those receiving standard wound care with saline dressings and 44 percent (15/34) of those receiving rhPDGF had ulcers completely healed by the end of the 20 week study period (RR=2.0 [1.1, 3.5]). Participants in the rhPDGF-BB intervention group also achieved quicker healing times although these were not statistically significant (85 days versus 141 days for the NaCMC group). d'Hemecourt et al (1998) also reported that the rhPDGF-BB group had the greatest reduction in median relative ulcer area and better wound evaluation scores which were summarised for all patients at endpoint and reflected changes from baseline. Adverse events were reported by all groups (21% rhPDGF-BB, 37% standard wound care alone) but were generally considered to be due to the disease process rather than the study medication.

Two systematic reviews identified five studies that investigated the cost-effectiveness of becaplermin (recombinant human platelet-derived growth factor) plus standard wound care compared to standard wound care alone (Chow et al 2008; Langer & Rogowski 2009). However, due to differences in the evaluations only a narrative analysis of the studies was reported. Langer et al (2009) also noted that most of the studies were either funded by pharmaceutical companies or co-authored by their employees. These studies studies also reported results in favour of the sponsors' product.

Ghatnekar et al (2000) modeled the cost of becaplermin versus standard wound care for the number of ulcer days averted and found it to be cost saving in the UK. These results were not sensitive to changes in standard wound care healing rates, time horizon, and duration of one becaplermin tube. Another study by Ghatnekar et al (2001) used a 12 month Markov simulation with effectiveness data from a trial of patients with grade II–IV neuropathic foot ulcers and found the cost of becaplermin versus standard wound care for the number of ulcer-free months gained was cost saving in the UK, Sweden and Switzerland, but at a higher cost in France. The incremental cost of becaplermin versus standard wound care per ulcer-free month gained was US$19 in France. Sensitivity analysis found that the cost of treating less persistent ulcers was cost-saving in all four countries but for more persistent ulcers, cost-savings occurred in all countries except France (ICER = US$142). Kantor and Margolis (2001) found that the incremental cost of becaplermin in addition to standard wound care per additional 1% of ulcers healed was US$37 in the USA. Sensitivity analysis showed that changes in medication costs and the number of office visits did not significantly affect the cost-effectiveness of the treatment. Persson et al (2000) found that the cost of becaplermin in addition to standard wound care for the number of ulcer months avoided was cost saving in Sweden when improvements in monthly healing rates were greater than 34% and this was relatively insensitive to most parameters. The fifth study by Sibbald et al (2003) reported that the incremental cost of becaplermin in addition to standard wound care per number of ulcer days averted was Can$6 (US$5) in Canada. Sensitivity analysis found that the results were sensitive to becaplermin efficacy, cost of home care, and rates of healing with standard wound care.

Box 111 Evidence statement matrix for recombinant human platelet-derived growth factor (rhPDGF) versus standard wound care with saline dressings

Component	Rating	Description
Evidence base	B	One good quality level II RCT
Consistency	N/A	Only one study
Clinical impact	B	Substantial clinical impact regarding number of ulcers completely healed, reduction in ulcer area and time to healing of diabetic foot ulcers
Generalisability	B	Generalisable to population of diabetic patients with chronic foot ulcers
Applicability	C	Probably applicable to the Australian healthcare context with some caveats

Evidence statement

In patients with full thickness chronic ulcers with adequate perfusion, recombinant human platelet-derived growth factor 100µg/g gel is effective in substantially increasing the number of completely healed ulcers, reducing healing time and reducing the surface area of ulcers not completely healed compared to standard wound care with saline dressings (Grade C).

Table 74 Recombinant human platelet-derived growth factor (rhPDGF) versus standard wound care (saline dressings)

<table>
<tr><th>Author
Country</th><th>Level and quality of study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th colspan="3">Outcome data</th></tr>
<tr><td rowspan="11">(d'Hemecourt et al 1998)
USA</td><td rowspan="11">Level II RCT.
Good quality study</td><td rowspan="11">N=172 diabetic patients with at least one full-thickness chronic lower extremity grade III or IV (assessment classification not stated) ulcer of at least 8 weeks duration
Intervention group: n=34, male 71% (n=24), mean age 58.5±11.9 years, white 82% (n=28), weight 99.8±20.94 kg, ulcer area 2.4±2.02 cm^2, ulcer depth 0.3±0.15 cm, ulcer duration 20.0±14.39 weeks, ulcer location, leg 12% (n=4), foot 88% (n=30), Wagner stage III 94% (n=32), Wagner stage IV 6% (n=2), $TcPO_2$ mmHg 49.4 ± 11.9
Control group : n=68, male 79% (n=54), mean age 59.6 ± 11.29 years, white 90% (n=55), weight 97.8 ±2 5.84 kg, ulcer area 3.5 ± 3.53 cm^2, ulcer depth 0.4 ± 0.52 cm, ulcer duration 42.0 ± 42.0 weeks, ulcer location: leg 7% (n=5), foot 93% (n=63), Wagner stage III 96% (n=65) Wagner stage IV 4% (n=3), $TcPO_2$ mmHg 56.5 ± 24.5</td><td rowspan="11">Intervention: n=34
Standard wound care including debridement, off-loading and systematic control of infection plus becaplermin (rhPDGF-BB) gel 100ug/g dressings daily</td><td rowspan="11">Control: n=68
Standard wound care including debridement, off-loading and systematic control of infection plus saline dressings every 12 hours</td><td colspan="3">Complete healing of ulcers</td></tr>
<tr><td>Intervention 2
44% (15/34)</td><td>Intervention 1
22% (15/68)</td><td>Effect size [95% CI]
Intervention vs control 2
RR=2.0 [1.1, 3.5]</td></tr>
<tr><td colspan="3">Time to heal (days)</td></tr>
<tr><td>Intervention 2
85 days</td><td>Intervention 1
141 days</td><td>No statistics given only a statement that there were no significant differences between groups</td></tr>
<tr><td colspan="3">Change in wound evaluation ulcer scores relative to baseline (see below for scoring values)</td></tr>
<tr><td colspan="2">Intervention
-1.26</td><td>Control 2
-0.49</td></tr>
<tr><td colspan="3">Ulcer related adverse effects</td></tr>
<tr><td>Intervention
21% (7/34)</td><td>Control 2
37% (25/68)</td><td>Effect size [95% CI]
Intervention vs control 2
RR=0.5 [0.2, 1.1]</td></tr>
<tr><td colspan="3">Relative ulcer area (median)</td></tr>
<tr><td>Intervention
0.13</td><td>Control
0.28</td><td></td></tr>
</table>

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
(Chow et al 2008; Langer & Rogowski 2009) United Kingdom	Level I systematic review Good quality study	N = 5 studies investigating the cost-effectiveness of Becaplermin in addition to standard wound care for the treatment of diabetic foot ulcer. (Ghatnekar et al 2000) Markov model for treating diabetic lower extremity ulcers over 12 months	Becaplermin plus SWC	SWC	No ICER reported The cost of becaplermin vs SWC for the number of ulcer days averted was found to be cost saving in the UK Average cost for SWC = £10,880 Average cost for becaplermin plus SWC = £10,403 Number of ulcers healed: SWC = 56% SWC plus becaplermin = 65% Average months spent in healed state: SWC = 3.41 SWC plus becaplermin = 4.22 Average number of amputations: SWC = 6.50% SWC plus becaplermin = 5.91% These results were not sensitive to changes in SWC healing rates, time horizon, and duration of one becaplermin tube. Becaplermin plus SWC costs were slightly higher than SWC alone when efficacy was only 24%
France, Sweden, Switzerland, UK		(Ghatnekar et al 2001) Price year = 1999 Markov model for treatment of diabetic lower extremity ulcers over 12 months.	Becaplermin plus SWC	SWC	The cost of becaplermin vs SWC for the number of ulcer-free months gained was found to be cost saving in the UK, Sweden and Switzerland. ICER = US$19 per ulcer-free month gained in France. For less persistent ulcers: considered to be cost-effective in all 4 countries. Average cost to treat ulcer with becaplermin plus SWC vs SWC :

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
					US$11,977 vs US$11,993 in France US$12,168 vs US$11,783 in Sweden US$14,112 vs US$13,832 in Switzerland US$17,601 vs US$17,133 in the UK Sensitivity analysis: total cost of treatment was lower for less persistent ulcers but higher for more persistent ulcers for both intervention and comparator. For less persistent ulcers: considered to be cost-effective in all 4 countries. For more persistent ulcers: cost savings occurred in all countries except France (ICER = US$142 per ulcer free month gained)
USA		(Kantor & Margolis 2001)Price year = 1999 efficacy data from phase III trial by Weiman et al (1998)	Becaplermin plus SWC	SWC	ICER = US$37 per additional 1% of ulcers healed The incremental cost of becaplermin vs specialised multidisciplinary wound care per additional 1% of ulcers healed = US$71 Sensitivity analysis: changes in medication costs and number of office visits did not significantly affect the relative cost-effectiveness of the treatments
Sweden		(Persson et al 2000) Price year = 1999 Markov model for diabetic lower extremity ulcers	Becaplermin plus SWC	SWC	ICER not reported The cost of becaplermin vs SWC for the number of ulcer months avoided was found to be cost saving, in Sweden. Based on amputation rates and costs associated with treatment, becaplermin plus SWC was the dominant therapy. Sensitivity analysis: relatively insensitive to changes in most parameters Becaplermin was not cost saving when improvements in monthly healing rates was only 24% Becaplermin was not cost neutral when improvements in monthly healing rates was 34%

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
Canada		(Sibbald et al 2003) Price year = 1998 Updated to 2002 efficacy data from phase III trial by Weiman et al (1998)	Becaplermin plus SWC	SWC	Becaplermin was only cost-effective when improvements in monthly healing rates > 34% ICER = Can$6 (US$5) per number of ulcer days averted The average cost per patient treated was slightly lower with SWC than with becaplermin plus SWC Sensitivity analysis: the results were sensitive to becaplermin efficacy, cost of home care and rates of healing with SWC.

D'Hemecourt et al (1998) Wound Evaluation Score= six parameters (erythema, oedema, purulence, necrotic tissue, fibrin and drainage), scored as absent (0), mild (1), moderate (2) or marked (3) added together as total score; rhPDGF= recombinant human platelet derived growth factor; rhPDGF-BB= recombinant human platelet derived growth factor- β receptor homodimer; SWC = standard wound care; ICER = incremental cost-effectiveness ratio.

Autologous/homologous platelet-rich plasma gel or releasate

Six RCTs (four good quality, one average and one poor quality), reported the comparison of autologous or homologous platelet-rich plasma gel or releasate versus placebo for the treatment of diabetic foot ulcers (Table 75). Driver et al (2006) compared autologous platelet-rich plasma against placebo in relation to time to healing, complete healing and recurrence of ulcers in a good quality trial. The exclusion criteria for the study was extensive, the loss to follow-up was moderate (8/72, 11%) and there were protocol violations by 33% of the patients (24/72). Intention to treat analysis suggests that the use of platelet-rich plasma for the treatment of chronic diabetic foot ulcers was not significantly better than placebo (median time to healing = 45 days for intervention group versus 85 days in control group, p=0.13). The authors state that due to the reduced power of the study (due to the attrition of participants), statistically significant differences between groups could realistically have been expected if there had been a larger sample size.

Steed et al (1992) examined CT-102 activated platelet supernatant against a placebo of plain saline to ascertain if there were any advantages for wound healing. The sample size was very small, however Steed et al (1992) reported that 71% (5/7) of participants in the intervention group had their ulcer healed by week 15 whereas it was week 20 before one (17%) participant in the control group achieved complete healing of their ulcer. By week 20, participants in the intervention group had achieved 94% area reduction of their ulcers compared to 73% ulcer area reduction in the placebo group ($p<0.02$). Reduction in wound volume was assessed at each visit along with the reduction in ulcer size. The intervention group's ulcers achieved significantly better healing than the placebo group with the mean average reduction in ulcer volume of 73.8 ± 112.2 mm^3 versus 21.8 ± 19.9 mm^3, respectively ($p<0.05$), and at a faster rate with the mean daily rate of reduction in ulcer size 6.2 ± 4.8 mm^2 versus 1.8 ± 1.1 mm^2, respectively ($p<0.03$) (Steed et al 1992).

These results were further supported by Holloway et al (1993) who also found CT-102 provided significant benefit over placebo for number of ulcers healed, reduction in ulcer volume and ulcer area. This good quality study compared three different doses of CT-102 with a placebo, as well as comparing the average of ulcers healed across all three intervention groups versus placebo and found that the higher dose of CT-102 versus placebo was superior (80% (12/15), 62% (8/13) and 52% (11/21), respectively for the intervention groups versus 29% (6/21) for the placebo group, p=0.01) for number of ulcers healed. There was no statistically significant difference between the intervention groups but there appeared to be a trend towards a dose-response relationship for healing across the three groups (Holloway et al 1993). Reduced surface area (mm^2) and volume of ulcers (mm^3) also occurred in the intervention groups (average across groups versus placebo (93.0 ± 14.4 mm^2 versus 77.1 ± 25.7 mm^2, p=0.002 and 94.9 ± 12.0 mm^3 versus 82.7 ± 21.5 mm^3, p=0.01, respectively).

Saldalamacchia et al (2004), in an average quality level II RCT investigated the use of autologous platelet gel and determined that it provided advantages over standard wound care in terms of number of ulcers healed and greater wound surface area healed within the five week study period (71.4% (5/7) versus 28.6% (2/7) healed p=0.3).

Unlike the other studies in this section, Krupski et al in their earlier 1991 study did not recommend the use of platelet derived healing factor over standard wound care for the treatment of diabetic foot ulcers. This good quality level II RCT compared platelet-derived wound healing factor (PDWHF) with physiological saline identical in appearance to PDWHF and reported that there was no benefit in the treatment and that in fact some ulcers in the intervention group actually increased in size during the trial. This particular study did not include diabetic patients exclusively with 78 percent (14/18) of participants having diabetic

mellitus. Wound aetiology for the intervention group was diabetes 80% (8/10), peripheral vascular disease 80% (8/10) and venous disease 30% (3/10), with some patients having one or more of these aetiologies. For the placebo group, diabetes was associated with ulcer aetiology in 75 percent (6/8), peripheral vascular disease in 63 percent (5/8) and venous disease in 25 percent (2/8). Generalisability of the study findings was further compromised by the fact that all participants in the study were men. The study compared healing rates of ulcers and results were reported based on both ulcer and patient number. Krupski et al (1991) reported no significant differences between randomised groups however 10 patients in the intervention group had 17 ulcers whereas 8 patients in the control group had 9 ulcers. The sample size of the study was very small and underpowered to find any differences. Although no statistically significant differences were detected, the analysis of healing in patients showed a greater proportion of healing in the intervention group (30%, 3/10) relative to the control group (25%, (2/8), RR=1.20, 95% CI [0.29, 5.4]). In contrast the analysis of the number of ulcers healed (as opposed to patients) show the control group had a greater proportion of healing (33% (3/9) versus 24% (4/17), RR=0.57, 95% CI [0.18, 2.06]), perhaps because there were fewer ulcers and of shorter duration than in the intervention group.

Steed et al (1996) investigated the recurrence rate of ulcers treated with homologous platelet growth factor for 20 weeks. Only two participants in the control group had ulcers that healed compared to 14 in the intervention group. Further details were not provided regarding numbers in each arm of the trial, randomisation and other aspects of data collection and analysis necessary for accurate assessment. The sample size was small (n=36) which may bias the findings. Recurrent ulcers were reported in 71.4 percent (10/14) of the intervention group compared to 50 percent (1/2) of the control group (RR=1.4, 95% CI [0.7, 7.7]).

When pooling all studies, the poor quality study by Steed et al (1996), which did not provide information regarding the denominator, was excluded. A non-significant effect was calculated with the addition of platelet-rich plasma gels for the healing of foot ulcers (RR = 1.63, 95%CI [1.00, 2.65], $p < 0.051$). No significant heterogeneity of effects was detected between the studies even when considering the different intervention groups in the study by Holloway et al (1993) (Figure 3).

Box 112 Evidence statement matrix for autologous/homologous platelet-rich plasma gel or releasate

Component	Rating	Description
Evidence base	B	Four good quality level II RCTs with low risk of bias, one average and one poor quality level II RCTs with moderate risk of bias
Consistency	B	Most studies consistent and any inconsistencies can be explained
Clinical impact	C	Moderate clinical impact
Generalisability	B	Evidence directly generalisable to target population
Applicability	C	Studies were from Italy and the USA which although not the same as the Australian healthcare system are probably applicable to the Australian healthcare context with some caveats

Evidence statement

Autologous/homologous platelet-rich plasma gel or releasate is moderately effective in reducing healing time, ulcer volume and surface area of chronic diabetic foot ulcers when compared to standard wound care/placebo (Grade B).

Table 75 Autologous/homologous platelet-rich plasma gel or releasate

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
(Driver et al 2006) USA	Level II RCT. Good quality study	N=72 diabetic patients attending 14 outpatient clinics Intervention group: n=40, mean age 56.4 ± 10.2 years, male 80% (n=32), HbA_{1c} 8.1 ± 1.8%, white 65% (n=26), ulcer location: toes 33% (n=13), heel 45% (n=8), ulcer area 4.0 ± 5.3 cm^2, ulcer volume 1.7 ± 4.1 cm^3 Control group: n=32, mean age 57.5 ± 9.1 years, male 84% (n=27), HbA_{1c} 8.0 ± 1.8%, white 56% (n=18), ulcer location: toes 44% (n=14), heel 31% (n=10), ulcer area 3.2 ± 3.5 cm^2, ulcer volume 0.9 ± 1.2 cm^3	n=40 Initially 7-day screening period for all patients, including surgical debridement, baseline measurements and evaluation, treated with control saline gauze and used fixed ankle-foot orthoses with crutches or walker. Plus up to 20ml blood (depending on size of ulcer) was drawn from patient and spun in centrifuge to separate the platelet-rich plasma (PRP) from the whole blood. The autologous PRP was extracted and reagents to activate the platelets were added as well as agents to achieve proper gel consistency. Gel was immediately applied to the wound and covered with a contact dressing. This was then covered with the absorbent side of a foam dressing and secured. Barrier cream was placed on the skin surrounding the wound	n=32 Initially 7-day screening period for all patients, including surgical debridement, baseline measurements and evaluation, treated with control saline gauze and used fixed ankle-foot orthoses with crutches or walker. Normal saline was applied to the wound and then covered as for intervention patients. Treatment was continued twice weekly until ulcer healed or the end of the 12 week study period Blood was drawn from control patients to maintain blinding	Complete healing at 12 weeks (intention to treat) Intervention 33% (13/40) | Control 28% (9/32) | Effect size [95% CI] RR=1.16 [0.58, 2.38] p=0.79 Excluded participants due to non-compliance, non-completion or protocol violation Intervention 53% (21/40) | Control 34% (11/32) Per protocol dataset for complete healing at 12 weeks Intervention 68% (13/19) | Control 43% (9/21) | Effect size [95% CI] RR=1.60 [0.91, 2.68] p=0.13 Per protocol median time to healing (days) Intervention 45 days | Control 84 days | p=0.13 Per protocol recurrent ulcers Intervention 0.8% (1/13) | Control 0% (0/9) | Effect size [95% CI] RR=1.39 [0.11, 18.5] p=0.57 Per protocol dataset standardised for ulcer size complete healing at 12 weeks Intervention 81% (13/16) | Control 42% (8/19) | Effect size [95% CI] RR=1.93 [1.12, 2.85] p=0.04

<table>
<tr><th>Author
Country</th><th>Level and quality of study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th colspan="4">Outcome data</th></tr>
<tr><td rowspan="11">(Holloway et al 1993)
USA</td><td rowspan="11">Level II RCT.
Good quality study</td><td rowspan="11">N=80 diabetic patients with at least 1 non-healing ulcer of at least 8 weeks duration with no sign of infection (grading system described in table notes below)
Intervention group 1: n=15 mean age 60.7 ± 13.5 years, male 73% (n=11), white 60% (n=9), HbA_{1c} 6.6 ± 1.3%, $TcPO_2$ 51 ± 8 mmHg, wound grade (see table notes): grade 2: 73% (n=11); grade 3: 27% (n=4); grade 4: 0%; grade 5: 0%; median ulcer duration 15.7 (range 2-60) months, mean wound severity score 37.7 ± 8.7, ulcer volume 5460 ± 5454 mm^3, ulcer area 765 ± 633 mm^2
Intervention group 2: n=13 mean age 59.4 ± 13.8 years, male 77% (n=10), white 92% (n=12), HbA_{1c} 7.0 ± 1.2%, $TcPO_2$ 50 ± 8 mmHg, wound grade (see table notes): grade 2; 69% (n=9); grade 3: 23% (n=3); grade 4: 8% (n=1); grade 5: 0%, median ulcer duration 17.6 (range 2-60) months, mean wound severity score 32.2 ± 7.3, ulcer volume 4500 ± 4800 mm^3, ulcer area 600 ± 441 mm^2
Intervention group 3: n=21 mean age 62.6 ± 8.6 years, male 81% (n=17), white 76% (n=16), HbA_{1c} 6.5 ± 1.3%, $TcPO_2$ 47 ± 17 mmHg, wound grade (see table notes): grade 2: 71% (n=15); grade 3: 19% (n=4); grade 4: 5% (n=1); grade 5: 5% (n=1); median ulcer duration 11.7 (range 2-108) months, mean wound severity score 29.2 ± 6.0, ulcer volume 5788 ± 1163 mm^3, ulcer area 603 ± 742 mm^2
Control group: n=21 mean age 60.4 ± 9.6</td><td rowspan="11">All patients received standard wound care including debridement, wound assessment and instruction re use of medication. Assessments were weekly for the first 2 weeks, then bi-weekly until 20 weeks or wound healed. Plus
Intervention group 1: n=15
Activated platelet supernatant CT-102 prepared from single apheresis donors and standardised to a β-thromboglobulin level of 24 mg/ml to a dilution of 0.01 CT-102
Intervention group 2: n=13 as for intervention group 1 but a dilution of 0.33 CT-102
Intervention group 3: n=21 as for intervention groups 1 & 2 but with a dilution of 0.1 CT-102</td><td rowspan="11">n=21
All patients received standard wound care including debridement, wound assessment and instruction re use of medication. Assessments were weekly for the first 2 weeks then bi-weekly until 20 weeks or wound healed. Plus placebo of isotonic platelet buffer containing N-2-hydroxyethyl piperazine-N-2-ethanesulphonic acid (HEPES), glucose, sodium chloride and potassium chloride (pH=6.6)</td><td colspan="4">Number of ulcers healed (%)</td></tr>
<tr><td>Intervention 1.
80 (12/15)</td><td>Control
29 (6/21)</td><td colspan="2">Effect size [95% CI]
1 vs placebo p=0.01
RR=2.8 [1.45, 4.59]</td></tr>
<tr><td>Intervention 2.
62 (8/13)</td><td></td><td colspan="2">2 vs placebo p=0.08
RR= 2.15
[0.98, 4.37]</td></tr>
<tr><td>Intervention 3.
52 (11/21)</td><td></td><td colspan="2">3 vs placebo p=0.21
RR= 1.83
[0.87, 4.02]</td></tr>
<tr><td>Average 3 interventions
63 (31/49)</td><td></td><td colspan="2">Average vs placebo
RR=2.21 [1.20, 4.62]</td></tr>
<tr><td colspan="4">Mean % decrease in ulcer area (mm^2)</td></tr>
<tr><td>Intervention
1. 95.7
2. 87.8
3. 94.3
Average
93.0 ± 14.4</td><td>Control
77.1 ± 25.7</td><td colspan="2">p>0.01
p=ns
p>0.01
p=0.002</td></tr>
<tr><td colspan="4">Mean % decrease in ulcer volume (mm^3)</td></tr>
<tr><td>Intervention
1. 96.9
2. 90.7
3. 96.0
Average
94.9±12.0</td><td>Control
82.7 ± 21.5</td><td colspan="2">p>0.01
p=ns
p>0.01
p=0.01</td></tr>
</table>

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
		years, male 67% (n=14), white 81% (n=17), HbA_{1c} 6.7 ± 1.3%, $TcPO_2$ 48 ± 9, wound grade (see table notes): grade 2: 86% (n=18); grade 3: 9% (n=2); grade 4: 5% (n=1); grade 5: 0%, median ulcer duration 25.3 (range 2-120) months, mean wound severity score 35.9 ± 7.7, ulcer volume 3236 ± 2592 mm^3, ulcer area 507 ± 609 mm^2,			
(Krupski et al 1991) USA	Level II RCT. Good quality study	N=18 patients with 26 lower extremity ulcers (78% of participants were diabetic) Intervention group: n=10 (n=17 wounds), mean age 66.0 ± 5.0 years, male 100%, smokers 30% (n=3), ankle-brachial index 1.04 ± 0.56, $TcPO_2$ 37.1 ± 9.1 mmHg, previous arterial revascularisation 20% (n=2), platelets 354 ± 215 $x10^8/mm^3$, Hb 13.3 ± 1.9 gm/dL, leukocytes 9.5 ± 3.2 $x10^8/mm^3$, sodium 137 ± 5.4 meq/L, potassium 4.5 ± 0.5 meq/L, glucose 189 ± 97 mg/dL, blood urea nitrogen 23.0 ± 11.9 mg/dL, creatinine 1.2 ± 0.4 mg/dL, albumin 4.0 ± 3.1 gm/L, wound aetiology: diabetes 80% (n=8), peripheral vascular disease 80% (n=8), venous disease 30% (n=3), ulcer duration 6.2 ± 4.4 months, wound score 2.29 ± 0.85, ulcer area 13.0 ± 14.4 cm^2, ulcer volume 1.4 ± 3.6 cm^3 Control group: n=8 (n=9 wounds), mean age 67.0 ± 4.5 years, male 100%, smokers 25% (n=2), ankle-brachial index 0.93 ± 0.54, $TcPO_2$ 37.8 ± 11.9 mmHg, previous arterial revascularisation 50% (n=4), platelets 327 ± 189 $x10^8/mm^3$, Hb 12.0 ± 1.7 gm/dL, leukocytes 8.5 ± 3.3 $x10^8/mm^3$, sodium 138 ± 4.7 meq/L, potassium 4.7 ± 0.5 meq/L,	n=10 Standard wound care including rinsing of wound with saline, standard 4x4 gauze placed over wound followed by a layer of petroleum-impregnated gauze and gauze-wrap dressings plus autologous platelet-derived wound healing factor (PDWHF), prepared from patient's own blood and supplied frozen in 10ml aliquots. Each aliquot was thawed as needed and used for 1 dressing change.	n=8 Standard wound care including rinsing of wound with saline, standard 4x4 gauze placed over wound followed by a layer of petroleum-impregnated gauze and gauze-wrap dressings plus physiological saline identical to PDWHF in appearance	Initial ulcer area (mm^2) Intervention 13.0 ± 14.4 — Control 28.9 ± 45.2 Final ulcer area (mm^2) Intervention 43.5 ± 87.4 — Control 8.7 ± 12.9 Rate of wound healing area (cm^2/week) Intervention -4.3 ± 12.2 — Control 1.9 ± 2.7 — p>0.05 Initial ulcer volume (cm^3) Intervention 1.4 ± 3.6 — Control 2.0 ± 3.4 Final ulcer volume (cm^3) Intervention 2.6 ± 4.6 — Control 0.4 ± 0.5 Rate of wound healing volume (cm^3/week) Intervention -0.1 ± 0.7 — Control 0.1 ± 0.2

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
		glucose 245 ± 127 mg/dL, blood urea nitrogen 23.9 ± 20 mg/dL, creatinine 1.7 ± 0.7 mg/dL, albumin 3.9 ± 0.4 gm/L, wound aetiology: diabetes 75% (n=6), peripheral vascular disease 63% (n=5), venous disease 25% (n=2), ulcer duration 4.3 ± 4.1 months, wound score 2.11 ± 0.33, ulcer area 28.9 ± 45.2 cm^2, ulcer volume 2.0 ± 3.4 cm^3			Number of patients healed Intervention 30% (3/10) | Control 25% (2/8) | Effect size [95% CI] RR=1.20 [0.29, 5.4] Number of ulcers healed Intervention 24% (4/17) | Control 33% (3/9) | Effect size [95% CI] RR=0.57 [0.18, 2.06]
(Steed et al 1992) USA	Level II RCT. Good quality study	N=13 diabetic patients in outpatient setting Intervention group: n=7 mean age 58.7 ± 12.4 years, male 72% (n=5), duration of diabetes (yrs) 26 ± 6.6, mean HbA_{1c} 7.1 ± 1.4%, $TcPO_2$ 51 ± 8.4 mmHg, transferrin 254.3 ± 32.8 mg/dL, duration of ulcer 17.1 ± 15.9 months, wound volume 7,385 ± 7,184.1 mm^3, wound surface area 864.3 ± 457.6 mm^2 Control group: n=6 mean age 54.2 ± 12.9 years, male 67% (n=4), duration of diabetes (yrs) 10.3 ± 5.9, mean HbA_{1c} 7.5 ± 1.4%, $TcPO_2$ 45 ± 7.4 mmHg, transferrin 274.3 ± 67.2 mg/dL, duration of ulcer 13.0 ± 14.4 months, wound volume 4,391.2 ± 3,553.8 mm^3, wound surface area 412.2 ± 259.5 mm^2	n=7 Aggressive debridement was carried out before entry into trial. Patients were evaluated each week for the first 3 weeks and then fortnightly until the wound healed or patient completed 20 weeks of therapy. Ulcers were dressed every 12 hours and CT-102 was applied to a cotton gauze sponge and placed on the wound in the evening. This was covered with petroleum-impregnated gauze to keep area moist. The following morning the dressing was removed and a normal saline cotton gauze was applied to the wound for the next 12 hours.	n=6 Aggressive debridement was carried out before entry into trial. Patients were evaluated each week for the first 3 weeks and then fortnightly until the wound healed or patient completed 20 weeks of therapy. Ulcers were dressed every 12 hours and plain saline was applied to a cotton gauze sponge and placed on the wound in the evening. This was covered with petroleum-impregnated gauze to keep area moist. The following morning the dressing was removed and a normal saline cotton gauze was applied to the wound for the next 12 hours	Number of ulcers healed Intervention 71.4% (5/7) achieved by week 15 | Control 16.7% (1/6) at end of study week 20 | Effect size [95% CI] RR=4.29 [1.01, 24.31] Average % of wound healed by 20 weeks Intervention 94% | Control 73% | p<0.02 Average mean daily reduction in ulcer volume (mm^3) Intervention 73.8 ± 112.2 | Control 21.8 ± 19.9 | p<0.05 Average mean daily reduction in ulcer area (mm^2) Intervention 6.2 ± 4.8 | Control 1.8 ± 1.1 p<0.03
(Saldalamacchia	Level II RCT.	N= 14 diabetic patients with Wagner Grade II	n=7	n=7	Percentage reduction in wound area at 5 weeks

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
et al 2004) Italy	Average quality study	or III ulcers Intervention group: n=7 mean age 61.1 ± 9.4 years, male 57% (n=4), duration of diabetes (yrs) 16.3 ± 7.9, HbA_{1c} 9.5 ± 1.7%, ankle brachial index 0.95 ± 0.18, wound surface area 273 ± 156 mm^2 Control group: n=7 mean age 58.1 ± 7.8 years, male 29% (n=2), duration of diabetes (yrs) 19.7 ± 9.9, HbA_{1c} 8.8 ± 1.7%, ankle brachial index 1.02 ± 0.10, wound surface area 170 ± 89 mm^2	Standard wound care plus weekly topical applications of autologous platelet gel for 5 weeks	Standard wound care	Intervention 71.9 ± 22.5	Control 9.2 ± 67.8	p=0.039
					50-100% healed		
					Intervention 71.4% (5/7)	Control 28.6% (2/7)	Effect size [95% CI] RR=2.5 [0.83, 7.53] p=0.286
(Steed et al 1996) USA	Level II RCT. Poor quality study	N=36 diabetic patients with a foot ulcer on the plantar surface of the foot, before treatment the ulcers had been present for 15.5 months (range 2-60months) No details were supplied other than both groups were comparable in ulcer duration and area	n=not stated Topical application of homologous platelet growth factor preparation each evening then 12 hours later saline was applied to all wounds. Off-loading and use of half shoe for duration of treatment with crutches or wheel chair. Treatment for 20 weeks including assessments at each visit	n=not stated Application of buffered saline dressings identical in appearance to intervention dressing	Number of ulcers healed during 20 weeks		
					Intervention 14 Control 2 Total 44% 16/36		
					Recurrence of ulcer (total recurred 68.8% 11/16)		
					Intervention 71.4% (10/14)	Control 50% (1/2)	Effect size [95% CI] RR=1.4 [0.7, 7.7]
					Ulcers that remained healed		
					Intervention 29% 4/14	Control 50% (1/2)	

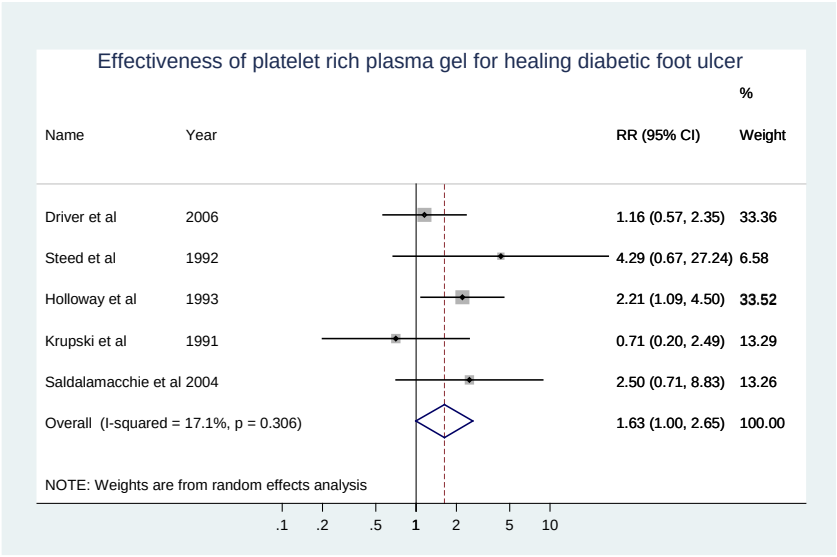
Holloway Wounds Grading= Grade 1: partial thickness ulcer involving only dermis and epidermis; Grade 2: full thickness ulcer involving subcutaneous tissue only; Grade 3: full thickness ulcer involving tendon, bone, ligament, and/or joint and includes an abscess and/or osteomyelitis; Grade 5: full thickness ulcer involving tendon, bone, ligament, and/or joint and has necrotic tissue/gangrene in the wound; Grade 6: full thickness ulcer involving tendon, bone, ligament, and/or joint and has gangrene in the wound and surrounding tissue; Functional Healing Assessment = Rating 1: less than 100% epithelised, has drainage, needs a dressing; Rating 2: 100% epithelised, has drainage, needs a dressing; Rating 3: 100% epithelised, maturing skin with a small amount of drainage, requires protective dressing only; Rating 4: 100% epithelised, 100% mature functional skin, no dressing required; Wagner Classification of ulcers = Grade I = superficial ulcer, Grade II = deep ulcer to tendon, capsule or bone, Grade III = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade IV = localised gangrene of forefoot or heel, Grade V = gangrene of entire foot;

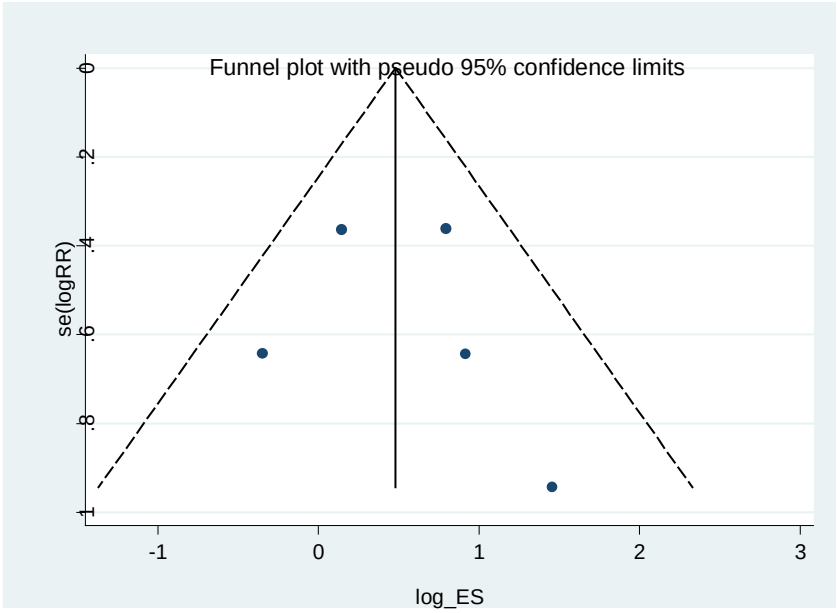
Figure 3 Meta-analysis of the effectiveness of platelet rich plasma gel for diabetic foot ulcers

Study	RR	[95% Conf.	Interval]	% Weight
Driver et al	1.156	0.567	2.354	33.36
Steed et al	4.286	0.674	27.243	6.58
Holloway et al	2.214	1.090	4.500	33.52
Krupski et al	0.706	0.200	2.489	13.29
Saldalamacchie et al	2.500	0.708	8.827	13.26
D+L pooled RR	1.625	0.997	2.650	100.00

Heterogeneity chi-squared = 4.83 (d.f. = 4) p = 0.306
I-squared (variation in RR attributable to heterogeneity) = 17.1%
Estimate of between-study variance Tau-squared = 0.0547

Test of RR=1 : z= 1.95 p = 0.051





Recombinant human granulocyte-colony stimulating factor (rhG-CSF)

Five level II RCTs (three good quality and two average quality) investigated the use of recombinant human granulocyte-colony stimulating factor (rhG-CSF) versus standard wound care/placebo for the treatment of diabetic foot ulcers (Table 76). Subcutaneous injections of rhG-CSF was used in four studies (de Lalla et al 2001; Gough et al 1997; Kästenbauer et al 2003; and Yomen et al 2001) and one study used G-CSF to mobilise peripheral blood mononuclear cells (PBMNCs) which were then autologously injected back into the patient (Huang et al 2005). Conflicting findings were evident in the trials, although several outcomes indicated both clinically and statistically significant beneficial effects from treatment with rhG-CSF.

Subcutaneous injections of G-CSF were compared to saline by Gough et al (1997) in patients with diabetic foot ulcers and extensive cellulitis. The intervention was found to reduce the risk of surgery (amputations and debridement 0% (0/20) versus 20% (4/20), respectively, p=0.1), reduce healing time (20% (4/20) healed versus 0% (0/20), p=0.9), shorten hospital stays (10 days versus 12 days, p=0.02), antibiotic use (p=0.02) and accelerate the resolution of cellulitis (p=0.03), although some outcomes did not reach statistical significance. Very few participants had limb-threatening ulcers although they still required hospitalisation and most ulcers were of short duration (median 21 days, (range 2 to 1278 days) in the G-CSF group and 39.5 days (range 2 to 1825 days) in the control group). Outcomes such as healing within 7 days did not reach statistical significance yet it is worth noting that 4/20 participants receiving G-CSF healed within 7 days while none of the control group achieved this clinically significant target (Gough et al 1997).

In a study by Huang et al (2005), rhG-CSF mobilised by daily injections of harvested peripheral blood mononuclear cells (PBMNCs) were administered to diabetic patients with critical limb ischaemia and foot ulcers. Findings suggest that the use of rhG-CSF in this way can reduce pain at rest (3.86±0.36 points at baseline down to 1.07±0.92 points at 3 months p=0.001, see table notes for scoring scale), increase pain-free walking distance (from 0.0±0.0 at baseline to 306.4±289.1m, p=0.001), and increase the number of ulcers healed by the end of the 12 week study period, 77.8 percent (14/18) in the intervention group versus 38.9 percent (7/18) in the control group (RR=2.0, 95% CI [1.12, 3.29], p=0.02). No lower limb amputations were required in the intervention group (0%, 0/23), however five control patients (21%, 5/24) required amputations (p=0.01). Further benefits of rhG-CSF identified by Huang et al (2005) included an increased ankle-brachial index (>0.1) with 65.2 percent (15/23) limbs in the intervention group versus 16.7 percent (4/24) limbs in the control group (p=0.001) improving by week 12 of the study. Blood flow perfusion to the toes and mean ankle-brachial index were significantly better in the intervention group and reached statistical significance (p=0.001) for both outcomes. No adverse effects were reported and the anticipated complication of embolism due to increased circulating blood cells was pre-empted by the use of a heparin infusion for five days during rhG-CSF treatment. Huang et al (2005) identified many benefits of using rhG-CSF in the treatment of diabetic foot ulcers however the treatment consists of many injections into an already painful area which may detract patients from choosing this management option.

Kästenbauer et al (2003) reported that only one of outcomes measured in their study reached statistical significance when comparing the use of G-CSF to standard wound care. This may in part be due to the level of 'standard' care given to the control group. Both intervention and control group participants were subjected to total bed rest for 10 days in hospital during the trial and aggressive debridement and intravenous antibiotic treatment was given to all participants. Kästenbauer et al (2003) concluded that the bed rest and antibiotic treatment was of significant benefit to diabetic patients with foot ulcers and that the use of G-CSF provided no additional benefit. The only outcome to reach statistical significance was ulcer volume which was reduced

by 59 percent in the intervention group and 35 percent in the control group (p=0.0005). In other measured outcomes such as resolution of cellulitis, presence of erythema, rates of lymphangitis, and infection summary scores, there were no statistically significant difference between the groups. In this study the hospital stay was a mandatory 10 days for all participants and complete bed rest was a requirement of participation. Other studies in this section have identified shorter hospital stays and reduced healing times as significant benefits of using G-CSF.

De Lalla et al (2001) in an average quality level II RCT compared rhG-CSF against standard wound care and found that no significant improvement in either the intervention or control group had occurred during the first three weeks of treatment and that by nine weeks the results remained similar for both groups (number of ulcers healed at nine weeks - 35 percent (7/20) in both groups RR=1.00, 95% CI [0.43, 2.31]). After three weeks of treatment one participant in the intervention group (5%, 1/20) and five in the control group (25%, 5/20) required an amputation, although this was not a statistically significant difference (p=0.08). By week nine of the study, three amputations (15%) were required in the intervention group and nine (45%) in the control group (p=0.04), and while only two of these amputations were major both occurred in the control group. Overall there were eight toes amputated, two from the intervention group and six from the control group. Follow-up at six months revealed that 65 percent (13/20) of the intervention group and 75 percent (15/20) of the control group were healed or stable (p>0.05). Participants in this study had limb-threatening infections which was an exclusion criterion for other studies assessing rhG-CSF and indicates the severity of the wounds. While there appeared to be no benefit from the intervention in terms of improvement of the ulcer, the reduction in the number of amputations at nine weeks of follow-up was statistically significant (p=0.04) and clinically important.

The other average quality study in this section was conducted by Yonem et al (2001) and again the authors found that treatment with rhG-CSF did not give a significant benefit over standard wound care in the management of diabetic foot ulcers. Measured outcomes, including length of hospital stay, time to resolution of cellulitis and number of amputations, were all statistically non-significant. Yonem et al (2001) found rhG-CSF to have a statistically significant effect on the number of neutrophils circulating which caused a significant improvement in phagocytosis, although this did not result in a shortening of hospitalisation or duration of antibiotic therapy. No adverse events were observed throughout the study.

When considering the diversity of findings of the five studies in this section it is important to take into account the participants studied. The populations ranged from patients with limb-threatening diabetic foot ulcers (de Lalla et al 2001), to patients with ulcers classified as Wagner Grade 1 or less (Yonem et al 2001). Most, however, had infection and were at the severe end of the wound spectrum. Measured outcomes varied from size of ulcer, to length of hospitalisation and fasting blood glucose levels. Gough et al (1997) found treatment resulted in shortened hospital stays (p=0.02), decreased antibiotic use (p=0.02) and accelerated resolution of cellulitis (p=0.03), while Huang et al (2005) found increased ulcer healing, reduced pain at rest (p=0.001), increased pain-free walking distance (p=0.001), improved blood perfusion (p=0.001) and reduced number of amputations (p=0.01). Yonem et al (2001) found the only benefit to be increased neutrophils and phagocytosis and Kastenbauer et al (2003) reported the only benefit was reduced ulcer volume. However, the wide range of outcomes measured makes it difficult to draw conclusions regarding the effectiveness of rhGCSF. The benefits identified may not ne of sufficient clinical significance to warrant the cost and discomfort of using rhG-CSF injections for the treatment of diabetic foot ulcer.

Pooling the data from the studies which reported amputation as an outcome suggests that rhG-CSF is able to reduce the risk of amputation when used in addition to standard wound care (Figure 4). The relative risk of amputation in patients receiving rhG-CSF was 0.39 ([95%CI 0.17, 0.92], p = 0.03) compared to those who received only standard wound care. Analysis showed that there was no statistically significant heterogeneity of effects however the confidence interval was reasonably wide for the pooled estimate.

For the outcome of ulcer healing, there was a lack of statistical power to detect any effect when pooling the results of the studies (Figure 5). Cochrane's test for heterogeneity showed that there was no significant heterogeneity of effects and the I^2 statistic indicates that there was only a low to moderate proportion of real variability between studies.

Careful consideration should therefore be given to the results of the studies as the benefits identified may not be of sufficient clinical significance to warrant the cost and discomfort of using rhG-CSF for the treatment of diabetic foot ulcers.

Box 113 Evidence statement matrix for recombinant human granulocyte-colony stimulating factor (rhG-CSF)

Component	Rating	Description
Evidence base	B	Five level II studies: three good quality with low risk of bias and two average quality with a moderate risk of bias
Consistency	C	Some inconsistency reflecting genuine uncertainty aroung the clinical question.
Clinical impact	B-D	Clinical impact varied from slight/restricted to substantial depending on the outcome measured and the quality of the study.
Generalisability	B	Evidence directly generalisable to the target population of diabetics with foot ulcers
Applicability	B	Studies were conducted in Italy, China, Austria, England and Turkey, with the majority being different from the Australian healthcare system however probably applicable to the Australian healthcare context with some caveats

Evidence statement

Recombinant human granulocyte-colony stimulating factor (rhG-CSF) may reduce the number of amputations and improve ulcer healing in people with severe limb-threatening diabetic foot ulcers and infection when compared to standard wound care/placebo (Grade C).

Table 76 Recombinant human granulocyte-colony stimulating factor (rHuG-CSF)

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
(Gough et al 1997) England	Level II RCT. Good quality study	N=40 diabetic patients with extensive cellulitis (spreading infection) Intervention group: n=20 mean age 65 (range 30-86) years, male 70% (n=14), caucasian 90% (n=18), BMI mean 28.4 (range 21.0-40.8) kg/m^2, current smokers 15% (n=3), duration of diabetes (yrs) 18.5 (range 0.1-50), type I diabetes 30% (n=6), insulin use 65% (n=13), HbA_{1c} 9.25% (range 5.5-13.7), ankle brachial index 1.00 (range 0.53-1.28), vibration threshold 35.7 (range 18.3-50.0), nephropathy 25% (n=5), retinopathy 60% (n=12), history of coronary/cerebrovascular disease 35% (n=7), previous minor amputation or debridement 45% (n=9) Control group: n=20 mean age 66 (range 58-81) years, male 75% (n=15), caucasian 75% (n=15), BMI mean 24.9 kg/m^2 (range 21.1-40.7), current smokers 15% (n=3), duration of diabetes (yrs) 19 (range 1-44), type I diabetes 20% (n=4), insulin use 75% (n=15), HbA_{1c} 8.7% (range 5.5-12.9), ankle brachial index 0.99 (range 0.65-1.50), vibration threshold 37.4 (range 8.3-50.0), nephropathy 25% (n=5), retinopathy 65% (n=13), history of coronary/cerebrovascular disease 50% (n=10), previous minor amputation or debridement 65% (n=13)	n=20 Standard wound care including antibiotic therapy, glycaemic control with insulin and use of standard foam dressings. Plus subcutaneous injection of G-CSF daily for 7 days. Initial dose of 5 µg/kg after 2 doses lowered to 2.5 µg/kg if absolute neutrophil count higher that 25x10 g/L, if count remained high only given on alternate days	n=20 Standard wound care including antibiotic therapy, glycaemic control with insulin and use of standard foam dressings. Plus saline injections given in same manner as for intervention group	Median days (range) to hospital discharge Intervention 10 (7-31) / Control 12 (5-93) / p=0.02 Number requiring surgery Intervention 0% (0/20) / Control 20% (4/20) / Effect size [95% CI] p=0.11 Number of ulcers healed at day 7 Intervention 20% (4/20) / Control 0% (0/20) / Effect size [95% CI] RR=8.0 [0.84, 83.98]
(Huang et al 2005) China	Level II RCT. Good quality study	N=28 diabetic patients with Critical Limb Ischaemia (CLI), Intervention Group: n=14, mean age 71.1±5.9 years, male 64% (n=9), duration of diabetes (yrs) 12.9±8.9, type I diabetes 29%	n=14 Standard wound care consisting of debridement as necessary, wound dressing, pressure relief and broad	n=14 Standard wound care consisting of debridement as necessary, wound dressing, pressure relief,	Number of ulcers healed Intervention 78% (14/18) / Control 39% (7/18) / Effect size [95% CI] RR=2.0 [1.12, 3.29] Number of amputations

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
		(n=4), ankle-brachial index (ABI) 0.50 ± 0.21, lower limbs with ABI<0.9 82.1% (n=23 legs), lower limbs with ulcers 64% (n=18 legs). Patients with ischaemic ulcers 43% (n=6), neuroischaemic ulcers 57% (n=8), ulcer on forefoot 71% (n=10), midfoot 21% (n=3), hindfoot 7% (n=1), University of Texas Grade 1: Stage C 29% (n=4), Stage D 36% (n=5), Grade 2: Stage C 14% (n=2), Stage D 28% (n=2), Grade 3: Stage C 0% (n=0), Stage D 7% (n=1), ulcer size 2.71 ± 1.32 cm2 Control group: n=14 mean age 70.9 ± 6.0 years, male 64% (n=9), duration of diabetes (yrs) 11.6 ± 8.0, type I diabetes 29% (n=4), ankle-brachial index (ABI) 0.49 ± 0.25, lower limbs with ABI<0.9 86% (n=24 legs), lower limbs with ulcers 64% (n=18 legs). Patients with: ischaemic ulcers 36% (n=5), neuroischaemic ulcers 64% (n=9), ulcer on forefoot 64% (n=9), midfoot 29% (n=4), hindfoot 7% (n=1), University of Texas Grade 1: Stage C 36% (n=5), Stage D 29% n=4), Grade 2: Stage C 14% (n=2), Stage D 28% (n=2), Grade 3: Stage C 0% (n=0), Stage D 7% (n=1), ulcer size 2.39 ± 1.15 cm2	spectrum antibiotics as required, plus, transplantation of recombinant human granulocyte colony stimulating factor (rhG-CSF) mobilised peripheral blood mononuclear cells (PBMNCs). Treatment consisted of subcutaneous injections of 600µg/day recombinant human G-CSF for 5 days and a perfusion of 10,000 units/day of heparin (to reduce risk of embolism). The 300ml of blood containing increased numbers of blood circulating PBMNCs was collected through a blood-cell separator and concentrated to $1x10^8$MNCs/ml and excess cells were frozen in liquid nitrogen, 3 hours later each diseased limb was intramuscularly injected (40 sites 3x3 distance, 1-1.5 cm deep, $7.5x10^8$ PBMNCs/site) into thigh and leg with a total of $3x10^9$ PBMNCs. 40 days later severely diseased lower limb was given an additional transplantation with the same number of frozen PBMNCs.	broad spectrum antibiotics as required plus intravenous injection of 90-200 µg/day prostaglandin E1	Intervention: 0% (0/23 legs) | Control: 21% (5/24 legs) Number of participants able to walk pain free at baseline (see table notes re scoring) Intervention: 0% (0/14) | Control: 0% (0/14) Pain free walking distance (metres) at 3 months Intervention: 306.4 ± 289.1 | Control: 78.6 ± 142.3 | Effect size [95% CI] from baseline: Intervention p=0.001, Control p=0.06 Number recovered normal sleep Intervention: 79% (11/14) | Control: 43% (6/14) | Effect size [95% CI]: RR=1.83 [0.99, 3.02] Ankle-brachial index >0.1 at week 12 Intervention: 65.2% (15/23 limbs) | Control: 16.7% (4/24 limbs) | Effect size [95% CI]: p<0.001 Blood perfusion at week 12 compared to baseline Intervention: From 0.44±0.11 to 0.57±0.14 p<0.001 | Control: From 0.49±0.25 to 0.51±0.28 p=0.223
(Kästenbauer et	Level II RCT.	N=37 diabetic patients with moderate sized	n=20	n=17	Number of amputations

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
al 2003) Austria	Good quality study	infected neuropathic Wagner Grade II or III ulcer, with cellulitis and adequate foot pulse. Intervention group: n=20, mean age 60.8 ± 11.1 years, ,male 75% (n=15), duration of diabetes (yrs) 14.7 ± 8.5, type I diabetes 95% (n=19), HbA_{1c} 8.9±1.7%, leukocyte count 8.1 ± 2.6 x10 g/L, baseline C-Reactive Protein (CRP) 1.73 ± 2.2 mg/dL, Wagner Grade II 75% (n=15), Grade III 25% (n=5), ulcer volume 203 ± 203 µl Control group: n=17, mean age 58.2±8.1 years, male 77% (13/17), duration of diabetes (yrs) 14.7±8.5, type I diabetes 94% (n=16), HbA_{1c} 9.2±2.6%, leukocyte count 7.7±1.9 x10g/L, baseline CRP 1.71±2.31 mg/dL, Wagner Grade II 82% (n=14), Grade III 18% (n=3), ulcer volume 358±395 µl	Standard wound care including debridement of wound, total bed rest in hospital for 10 days, and intravenous antibiotics until inflammation visibly improved then oral antibiotics plus Granulocyte-Colony Stimulating Factor (G-CSF) 5µg/kg body weight injected subcutaneously daily. Neutrophil and leukocyte counts were measured daily. Treatment was stopped if neutrophil count was >50,000/L and leukocyte count was >75,000/L and restarted if counts dropped below 30,000 and 50,000, respectively. Cellulitis, infection summary score (ISS), ulcer volume and Wagner Grade were evaluated daily	Standard wound care including debridement of wound, total bed rest in hospital for 10 days, intravenous antibiotics until inflammation visibly improved then oral antibiotics plus placebo of 0.9% sterile saline injected subcutaneously daily. Cellulitis, infection summary score (ISS), ulcer volume and Wagner Grade were evaluated daily	Intervention: 5% (1/21) | Control: 5.9% (1/17) | Effect size [95% CI]: RR=0.85 [0.09, 8.01] Number of ulcers improve by 1 Grade Intervention: 40% (8/20) | Control: 24% (4/17) | Effect size [95% CI]: RR=1.70 [0.66, 4.73] % improvement in Infection Summary Score (as scored by an independent blinded assessor) Intervention: 77.3 | Control: 65.8 Infection Summary Score Day 1 Intervention: 29.5 ± 18.4 | Control: 26.0 ± 14.2 | p=0.83 Infection Summary Score Day 10 Intervention: 6.7 ± 6.3 | Control: 26.0 ± 14.2 | p=0.33 Ulcer volume (µl) Intervention Day 1: 203 ± 203 | Control Day 1: 358 ± 395 | p=0.20 Day 10: 83 ± 140 | Day 10: 233 ± 235 | p=0.07 % Ulcer volume reduction Intervention: 59 | Control: 35 | p=0.0005 Resolution of cellulitis Intervention: 7 days | Control: 12 days

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
					Length of hospital stay Intervention 10 days Control 17.5 days
(de Lalla et al 2001) Italy	Level II RCT. Average quality study	N=40 diabetic patients with osteomyelitic limb-threatening foot ulcer infection Intervention group: n=20, mean age 56.6 ± 8.6 years, male 80% (n=16), duration of diabetes (yrs) 15.6 ± 8.6, ankle brachial index 0.96 ± 0.34, vibrator perception threshold 35.8 ± 14.6 volts, mean neutrophil count 7,800 ± 3,500 cells/mm^3, white blood count (WBC) count >10,000/mm^3 5% (n=1), erythrocyte sedimentation rate (ESR) >70mm/h 55% (n=11), positive blood cultures 0%, life-threatening infection 0%, osteomyelitis 100% (n=20), ulcer type: neuropathic 65% (n=13), ischaemic 10% (n=2), mixed 25% (n=5), Wagner Grade III 65% (n=13), Grade IV 35% (n=7), number of patients with >1 ulcer 30% (n=6), mean number of ulcers/patient 1.4 ± 0.6, mean number of isolates/patient 2.05 ± 1.2, polymicrobial infection 70% (n=14), cellulitis >2cm diameter 50% (n=10), probing to bone 100% (n=20), abscess 5% (n=1), ulcer > 2cm diameter 65% (n=13) Control group: n=20, mean age 59.8 ± 9.6years, male 70% (n=14), duration of diabetes (yrs) 18.5 ± 8.6, ankle-brachial index 1.29 ± 0.5, vibrator perception threshold 43.2 ± 0.47 volts, mean neutrophil count 8,300 ± 3,500 cells/mm^3, WBC count >10,000/mm^3 25% (n=5), erythrocyte sedimentation rate >70 mm/h 65% (n=13), positive blood cultures 10% (n=2), life-threatening infection	n=20 Local treatment consisting of careful debridement at enrolment, daily inspections, cleaning with sterile water, disinfection with povidone iodine, further debridement as needed, occlusive dressing of foot lesions. Antibiotic treatment with ciprofloxacin and clindamycin, according to consensus standard. Intravenous therapy used for more serious infections. Plus glycosylated recombinant human granulocyte colony stimulating factor (rhG-CSF) (lenograstin) administered subcutaneously at a doage of 263µg daily for 21 days. If neutrophil count exceeded 35,000 cells/mm^3, the dose was temporarily dropped to 175µg and it was discontinued if count was over 50,000 cells/mm^3	n=20 Local treatment consisting of careful debridement at enrolment, daily inspections, cleaning with sterile water, disinfection with povidone iodine, further debridement as needed, occlusive dressing of foot lesions. Antibiotic treatment with ciprofloxacin and clindamycin, according to consensus standard. Intravenous therapy used for more serious infections.	Number of ulcers completely healed Intervention 3 weeks 0% (0/20) 9 weeks 35% (7/20) Control 3 weeks 0% (0/20) 9 weeks 35% (7/20) Effect size [95% CI] RR=1 RR=1 [0.43, 2.33] Number of ulcers improved Intervention 3 weeks 60% (12/20) 9 weeks 40% (8/20) Control 3 weeks 45% (9/20) 9 weeks 20% (4/20) Effect size [95% CI] RR=1.33 [0.74, 2.38] RR=2.00 [0.76, 5.61 Number of amputations Intervention 3 weeks 5% (1/20) 9 weeks 15% (3/20) Control 3 weeks 25% (5/20) 9 weeks 45% (9/20) Effect size [95% CI] RR=0.20 [0.03, 1.15] RR=0.33 [0.11, 1.05] p=0.04 Condition at 6 months (healed or stable)

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
		10% (n=2), osteomyelitis 100% (n=20), ulcer type: neuropathic 70% (n=14), ischaemic 0%, mixed 30% (n=6), Wagner Grade III 70% (n=14), Grade IV 30% (n=6), number of patients with >1 ulcer 25% (n=5), mean number of ulcers/patient 1.4 ± 1.0, mean number of isolates/patient 2.30 ± 1.6, polymicrobial infection 50% (n=10), cellulitis >2cm diameter 75% (n=15), probing to bone 100% (n=20), abscess 15% (n=3), ulcer >2cm diameter 55% (n=11)			Intervention 65% (13/20)	Control 75% (15/20)	Effect size [95% CI] RR=0.87 [0.61, 1.29]
					Condition at 6 months (worsened)		
					Intervention 15% (3/20)	Control 25% (5/20)	Effect size [95% CI] RR=0.60 [0.17, 2.03]
(Yonem et al 2001) Turkey	Level II RCT. Average quality study	N=30 diabetic patients with Wagner Grade II or less, foot ulcers or pedal cellulitis. Intervention group: n=15, mean age 60.3 ± 1.3 years, male 47% (n=87), duration of diabetes (yrs) 13.5 ± 1.2, mean fasting plasma glucose 12.7 ± 1.0 mmol/L, total cholesterol 6.1 ± 0.2 mmol/L, LDL 3.8 ± 0.2 mmol/L, HDL 1.0±0.0 mmol/L, triglycerides 2.8±0.3 mmol/L, total WBC 10300 ± 700n/mm^2, neutrophil count 5200 ± 500n/mm^2, lymphocyte count 4300 ± 500n/mm^2, basal phagocytosis test 70.4±2.0%, basal respiratory burst	n=15 Standard wound care and antibiotic therapy plus subcutaneous injection of recombinant human granulocyte-colony stimulating factor rhG-CSF (filgrastin) daily for 7 days. Initial dose of 5µg/kg, after 3 doses lowered to 2.5µg/kg given on alternate days if neutrophil count higher than 30x10g/L, if count above	n=15 Standard wound care including antibiotic therapy.	Length of hospital stay (days)		
					Intervention 26.9 ± 2.0	Control 28.3 ± 2.2	p>0.05
					Time to resolution of cellulitis (days)		
					Intervention 23.6 ± 1.8	Control 22.3 ± 1.7	p>0.05
					Number of amputations		
					Intervention 13.3% (2/15)	Control 20% (3/15)	Effect size [95% CI] RR=0.67 [0.14, 3.04]

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
		1.6±0.3mV Control group: n=15 mean age 61.0±1.4 years, male 40% (n=6), duration of diabetes (yrs) 12.7±0.9, mean fasting plasma glucose 12.8±0.9mmol/L, total cholesterol 5.9±0.3mmol/L, LDL 3.7±0.3mmol/L, HDL 1.0±0.0mmol/L, triglycerides 2.8±0.4mmol/L, total WBC 9800±700n/mm^2, neutrophil count 5700±600n/mm^2, lymphocyte count 3800±400n/mm^2, basal phagocytosis test 68.1±2.2%, basal respiratory burst 2.0±0.4mV	45x10g/L rhG-CSF treatment was stopped		

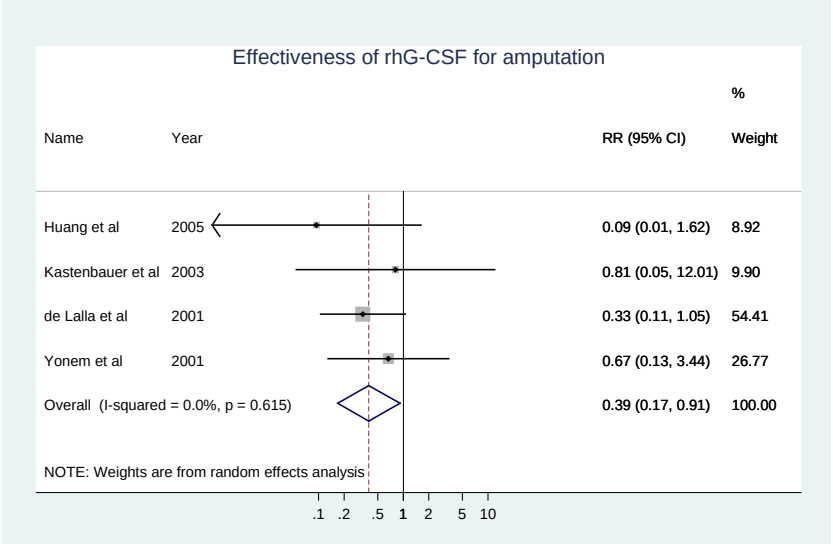
BMI=Body Mass Index; CLI=Critical Limb Ischaemia; CRP=C-Reactive Protein; G-CSF= granulocyte colony stimulating factor; Huang et al 2005 Rest pain scoring = 0 points for the best complete relief of pain with no use of analgesics, to 4 points for the worst result; ISS=Infection Summary Score included CRP (absolute values), erythrocyte sedimentation rate (1-h value/10), the presence of erythema (local, dorsal and lower leg. 10 points each), and lymphangitis (20 points) and the difference in circumference (in cms) between study compared with control foot at the forefoot, ankle and lower leg level; PBMNCs= peripheral blood mononuclear cells; PDWHF= platelet-derived wound healing factor; University of Texas Diabetic Foot Classification System= 01. A0 Pre – or post ulcerative lesion completely epithelialised, 02. A1 superficial wound not involving tendon, capsule or bone, 03. A2 Wound penetrating to tendon or capsule, 04. A3 wound penetrating to bone or joint, 05. B0 pre or post ulcerative lesion completely epithelialised with infection, 06. B1 superficial wound, not involving tendon, capsule or bone with infection, 07. B2 wound penetrating to tendon or capsule with infection, 08. B3 wound penetrating to bone or joint with infection, 09. C0 pre or post ulcerative lesion completely epithelialised with ischaemia, 10. C1 superficial wound not involving tendon, capsule or bone with ischaemia, 11. C2 wound penetrating to tendon or capsule with ischaemia, 12. C3 wound penetrating to bone or joint with ischaemia, 13. D0 pre or post ulcerative lesion completely epithelialised with infection and ischaemia, 14. D1 superficial wound not involving tendon, capsule or bone with infection and ischaemia, 15. D2 wound penetrating to tendon or capsule with infection and ischaemia, 16. D3 wound penetrating to bone or joint with infection and ischaemia; Wagner Classification of ulcers, Grade I = superficial ulcer, Grade II = deep ulcer to tendon, capsule or bone, Grade III = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade IV = localised gangrene of forefoot or heel, Grade V = gangrene of entire foot.

Figure 4 Meta-analysis of rhG-CSF for amputation

Study	RR	[95% Conf.	Interval]	% Weight
Huang et al	0.095	0.006	1.621	8.92
Kastenbauer et al	0.810	0.055	12.010	9.90
de Lalla et al	0.333	0.106	1.053	54.41
Yonem et al	0.667	0.129	3.436	26.77
D+L pooled RR	0.392	0.168	0.915	100.00

Heterogeneity chi-squared = 1.80 (d.f. = 3) p = 0.615
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000

Test of RR=1 : z= 2.17 p = 0.030



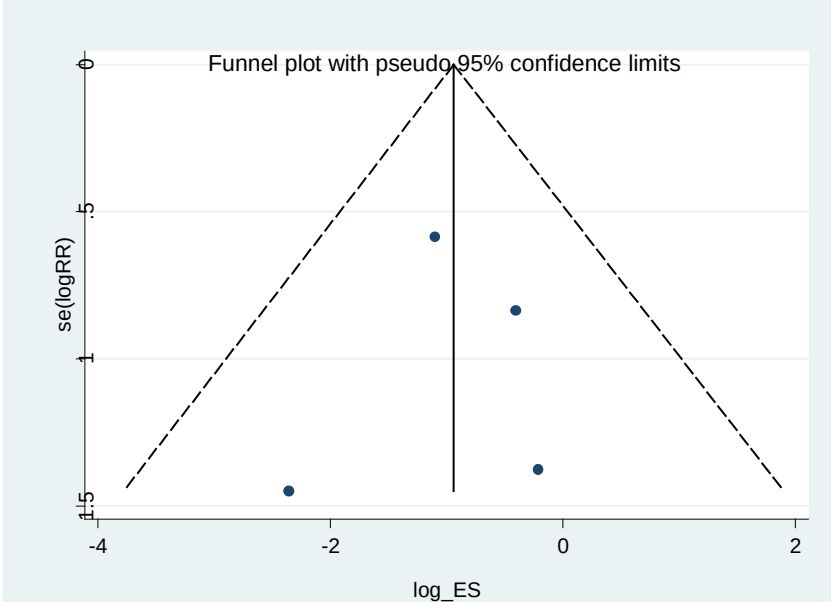
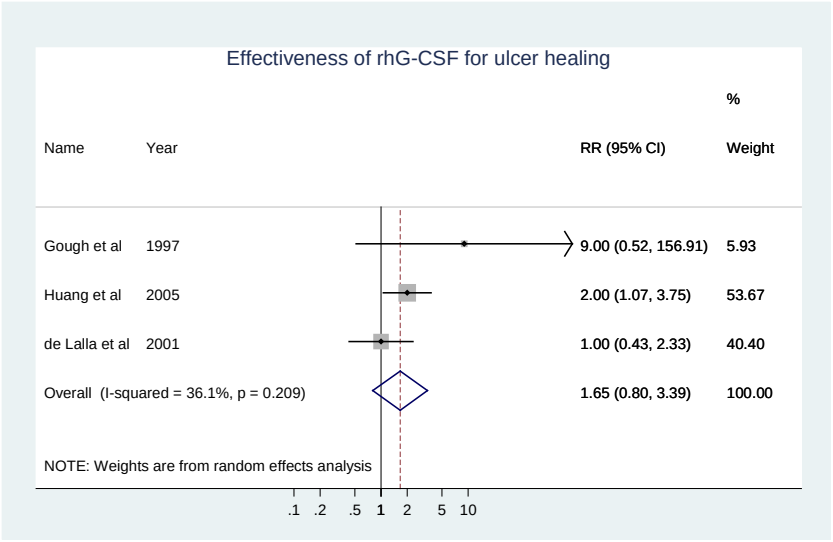


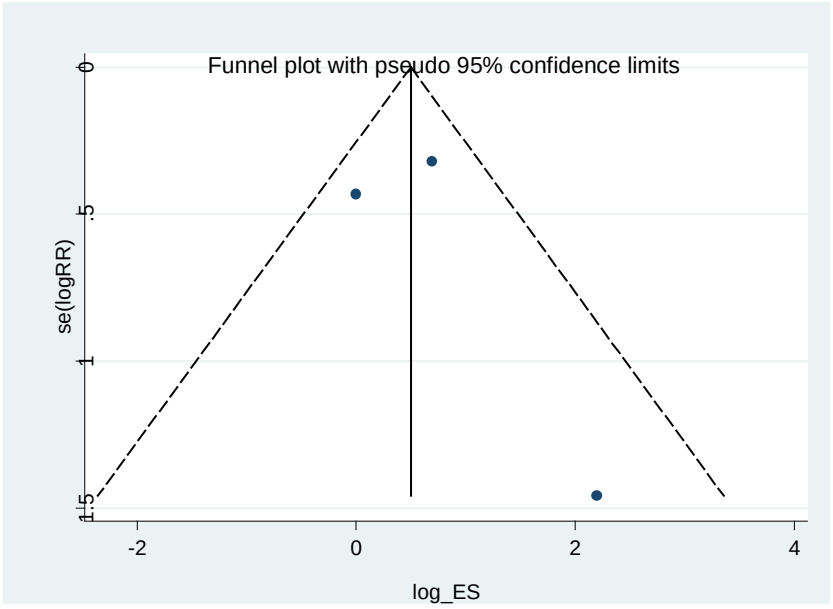
Figure 5 Meta-analysis of rhG-CSF for ulcer healing

Study	RR	[95% Conf.	Interval]	% Weight
Gough et al	9.000	0.516	156.910	5.93
Huang et al	2.000	1.066	3.754	53.67
de Lalla et al	1.000	0.430	2.327	40.40
D+L pooled RR	1.652	0.804	3.394	100.00

Heterogeneity chi-squared = 3.13 (d.f. = 2) p = 0.209
I-squared (variation in RR attributable to heterogeneity) = 36.1%
Estimate of between-study variance Tau-squared = 0.1481

Test of RR=1 : z= 1.37 p = 0.171





Transforming growth factor β2

One RCT evaluated the use of transforming growth factor β2 (TGF-β2) in the treatment of diabetic foot ulcers (Table 77). Robson et al (2002) in a good quality randomised, double-blind, placebo-controlled multi-centre trial compared various doses of TGF-β2 in addition to standard wound care with respect to time to wound closure, wound area reduction and closure of wound by week 21. Findings suggest that as the dose of TGF-β2 increased, the percent of complete wound closure by the endpoint also increased (placebo 32% (7/22), 0.05 μg/cm^2 TGF-β2 58% (25/43), 0.5 μg/cm^2 TGF-β2 57% (25/44), 5.0 μg/cm^2 TGF-β2 61% (27/44)). However, the standard wound care group had a closure rate of 71 percent (17/24) which was significantly better than the placebo (p=0.01). As all participants received standard wound care with or without the intervention or placebo, and randomisation ensured there were no significant baseline differences between groups, the authors could not explain why such unexpected results were achieved by standard wound care alone. Results for wound area reduction showed the 5.0μg/cm^2 TGF-β2 group achieved an 85 ± 28 percent reduction while placebo achieved 74 ± 36 percent (when compared, p=0.04). The standard wound care group achieved a 79 ± 38 percent reduction in wound area compared to placebo 74 percent (p=0.05). For the ulcers that did not heal by the 21 week endpoint, participants in the 0.5μg/cm^2 TGF-β2 group showed a 72 ± 30 percent reduction in wound area while the standard wound care group showed only a 25 ± 35 percent reduction in wound area.

A considerable number of adverse events were reported by participants in this study however these were similar across all treatment groups and all but four events were not considered to be related to study participation (Robson et al 2002). The four adverse events included three cases of cellulitis and one of osteomyelitis with all patients recovering without incident. The results for the standard wound care alone group are difficult to explain however TGF-β2 in addition to standard wound care was shown to be effective at reducing wound area and time to closure of wound, particularly for the larger doses.

Box 114 **Evidence statement matrix for Transforming Growth Factor β2**

Component	Rating	Description
Evidence base	B	One good quality level II study
Consistency	N/A	Not applicable, only one study
Clinical impact	C vs placebo D vs standard wound care	Moderate clinical impact in relation to numbers of ulcers healed and reducing ulcer area for wounds not completely healed in intervention group versus placebo. However the standard wound care alone group performed similarly. The level of standard wound care was particularly intense.
Generalisability	B	Evidence directly generalisable to the target population
Applicability	B	Evidence applicable to that Australian healthcare context with few caveats

Evidence statement

The evidence is inconclusive regarding whether transforming growth factor β2 is superior to standard wound care. In addition to standard wound care, increasing doses of TGF-β2 provided increased the clinical benefit compared to placebo with regard to number of ulcers healed and reducing ulcer area. However, these findings were not statistically significantly better than standard wound care alone (Grade C).

Table 77 **Transforming growth factor β2**

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data	
(Robson et al 2002) USA	Level II RCT. Good quality study	N=177 diabetic patients with full thickness ulcers present for at least 8 weeks Intervention group 3: n=43, mean age 56±11 years, male 77% (n=33), height 177 ± 10 cm, weight 99 ± 26 kg, caucasian 67% (n=29), current smoker 23% (n=10), duration of ulcer 51.0 ± 64 weeks, ulcer area 2.1 ± 3.1 cm^2. Intervention group 4: n=44, mean age 56 ± 12years, male 77% (n=34), height 176 ± 10 cm, weight 100 ± 26kg, caucasian 77% (n=34), current smoker 7% (n=3), duration of ulcer 59.0 ± 74 weeks, ulcer area 2.7 ± 3.6 cm^2. Intervention group 5: n=44, mean age 56 ± 8 years, male 77% (n=34), height 178 ± 12 cm, weight 102 ± 32kg, caucasian 73% (n=32), current smoker 23% (n=10), duration of ulcer 54.0 ± 72 weeks, ulcer area 2.7 ± 3.5cm^2. Control group 2: n=22, mean age 60 ± 10 years, male 82% (n=18), height 180 ± 6 cm, weight 96 ± 15 kg, caucasian 82% (n=18), current smoker 9% (n=2), duration of ulcer 41.0 ± 47 weeks, ulcer area 2.7 ± 3.0 cm^2. Control group 1: n=24, mean age 55 ± 9 years, male 92% (n=22), height 182 ± 6 cm, weight 104 ± 21kg, caucasian 88% (n=19), current smoker 17% (n=37), duration of ulcer 59.0 ± 103 weeks, ulcer area 2.1 ± 1.9cm^2.	*Intervention group 3* *0.05 µg/cm^2 TGF-β2* n=43 Standard wound care (SWC) including sharp debridement, coverage with non-adherent dressing and weight off-loading plus topical collagen sponges containing recombinant human transforming growth factor (rhTGR-β2) 0.05µg/cm^2 *Intervention group 4* *0.5 µg/cm^2 TGF-β2* n=44 SWC including sharp debridement, coverage with non-adherent dressing and weight off-loading plus topical collagen sponges containing rhTGR-β2 0.5µg/cm^2 *Intervention group 5* *5 µg/cm^2 TGF-β2* n=44 SWC including sharp debridement, coverage with non-adherent dressing and weight off-loading plus topical collagen sponges containing rhTGR-β2 5µg/cm^2	*Control group 1* *Standard wound care (SWC)* n=24 Standard wound care including sharp debridement, coverage with non-adherent dressing and weight off-loading. *Control group 2* *Placebo* n=22 Standard wound care including sharp debridement, coverage with non-adherent dressing and weight off-loading plus topical placebo collagen sponge	Complete wound closure by week 21	
					Intervention group 3 *0.05 µg/cm^2 TGF-β2* 58% (25/43)	Effect size [95% CI] rhTGFvs placebo RR1.83 [1.01, 3.64] p=0.05
					Intervention group 4 *0.5 µg/cm^2 TGF-β2* 57% (25/44)	RR=1.79 [0.99, 3.57] p=0.06
					Intervention group 5 *5 µg/cm^2 TGF-β2* 61% (27/44)	RR=1.93 [1.08, 3.8] p=0.02
					Control group 2 *Placebo* 32% (7/22)	
					Control group 1 *SWC* 71% (17/24)	p=0.01
					% mean wound are reduction by week 21	
					Intervention group 3 *0.05 µg/cm^2 TGF-β2* 83±32	rhTGF-β2 versus placebo Int gp 3 vs placebo p=0.07
					Intervention group 4 *0.5 µg/cm^2 TGF-β2* 80±36	Int gp 4 vs placebo p=0.12

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data	
					Intervention group 5 *5 µg/cm² TGF-β2* 85±28 Control group 2 Placebo 74±36 Control group 1 79±38	Int gp 5 vs placebo p=0.04 Control gp 1 vs placebo p=0.05
					Median time to wound closure	
					Intervention group 3 *0.05 µg/cm² TGF-β2* 16 weeks Intervention group 4 *0.5 µg/cm² TGF-β2* 12 weeks Intervention group 5 *5 µg/cm² TGF-β2* 2 weeks Control group 2 N/A Control group 1 9 weeks	rhTGF-β2 versus placebo p=0.13 p=0.09 p=0.03 p=0.01

rHTGR-β2= recombinant human transforming growth factor β2

Vascular endothelial growth factor

Two good quality level II RCTs compared the use of vascular endothelial growth factor, (one using recombinant human VEGF (rhVEGF) and the other using plasmid DNA containing the human VEGF gene (phVEGF)) versus standard wound care/placebo for the treatment of diabetic foot ulcers (Table 78). Hanft et al (2008) measured outcomes such as percentage reduction of ulcer size, number of ulcers healed, number of ulcers recurring, and the incidence of ulcers increasing in size (Hanft et al 2008). The use of rhVEGF appeared to be well tolerated by participants and any reported adverse events were deemed to be unrelated to the treatment. While there were trends towards more positive outcomes in the treatment group, the benefits did not reach statistical significance in any of the measured outcomes.

Kusumanto et al (2006) administered phVEGF (vascular endothelial growth factor gene-carrying plasmid) compared to placebo with the primary measured outcome of amputation rate. There were no significant differences in amputations between groups with 11 percent (3/27) in the placebo group versus 22 percent (6/27) in the intervention group. However, time to amputation was significantly earlier (p=0.01) in the placebo group (25.5 days) compared to the intervention group (78 days). Several clinically important benefits were identified such as haemodynamic improvement in the placebo group (0.4%, 1/27) compared to the intervention group (26%, 7/27) (p=0.05) and in the number of ulcers improved (0/17 in the placebo group versus 33% (7/21) in the intervention group, p=0.01). In this study only 17/27 participants in the placebo group and 21/27 participants in the intervention group had existing ulcers. The overall response rate of participants in each arm of the study was 11 percent (3/27) in the placebo group and 52 percent (14/27) in the intervention group (p=0.003). Kusumanto et al (2006) also reported significant improvements in physical and social functioning and health change for those participants with improved clinical and haemodynamic outcomes (p=0.002; p=0.05 and p=0.05 respectively). No adverse events were identified and the intervention appeared to be well tolerated. Kusumanto et al (2006) concludes that phVEGF was superior to placebo for wound healing and reducing haemdynamic insufficiency. In the prevention of amputations, although phVEGFhalved the risk of amputation, a statistically significant benefit was not found probably as a consequence of the small sample size.

Box 115 Evidence statement matrix for vascular endothelial growth factor

Component	Rating	Description
Evidence base	B	Two level II good quality studies
Consistency	B	Most studies consistent and inconsistencies can be explained
Clinical impact	D	Slight clinical benefit however the benefits that achieved statistical significance were not the focus of this study. Study was underpowered for amputation outcome where point estimate indicated a clear clinical benefit.
Generalisability	B	Evidence directly generalisable to the target population
Applicability	C	Studies were from the Netherlands and USA which are different to the Australian healthcare context however probably applicable with some caveats

Evidence statement

Vascular endothelial growth factor versus standard wound care/placebo is superior in reducing time to amputation and facilitating clinical improvements in ulcers. However, positive trends for other clinical outcomes did not reach statistical significance in these small studies (Grade B).

Table 78 Vascular endothelial growth factor

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
(Hanft et al 2008) USA	Level II RCT. Good quality study	n=55 diabetic patients with a University of Texas wound classification Grade 1A of at least 4 weeks duration **Intervention group**: n=29, mean age 59.5 years (range 42-74), male 66% (n=19), caucasian 62% (n=18), mean weight 101.8 kg (range 59-208), mean glucose at screening 179.1 mg/dl (range 29-593), HbA_{1c} 8.3% (range 5.6-13.6), ulcer location: plantar 79% (n=23), dorsal 7% (n=2), lateral 7% (n=2), medial 7% (n=2), ulcer debridement at screening: yes 93% (n=27), ulcer area: length x width 1.92 cm^2 (range 0.96-4.08), planimetry at day 1 1.35 cm^2 (range 0.59-3.51) **Control group**: n=26, mean age 59.3 years (range 38-81), male 69% (n=18), caucasian 65% (n=17), mean weight 105.9 kg (range 59-177), mean glucose at screening 225.8 mg/dl (range 77-463), HbA_{1c} 8.4% (range 5.5-13.6), ulcer location: plantar 81% (n=21), dorsal 8% (n=2), lateral 8% (n=2), medial 4% (n=1), ulcer debridement at screening: yes 81% (n=21), ulcer area: length x width 1.85 cm^2 (range 1.08-2.90), planimetry at day 1 1.05 cm^2 (range 0.62-2.34)	n=29 All patients received standard wound care including periodic sharp debridement and off-loading. Weekly photographs were taken and the surface area measured using planimetry tracings of the ulcer perimeter. Clinicians administered 72mg/cm^2 topical telbermin gel evenly over the ulcer surface 3 times/week for up to 6 weeks. The ulcer was then covered with a sterile semi-permeable barrier and wrapped in cotton gauze.	n=26 All patients received standard wound care including periodic sharp debridement and off-loading. Weekly photographs were taken and the surface area measured using planimetry tracings of the ulcer perimeter. Placebo of methylcellulose gel was applied according to protocol. The ulcer was then covered with a sterile semi-permeable barrier and wrapped in cotton gauze.	% reduction in ulcer surface area (cm^2)		
					Intervention Day 29 Median 87.0 Mean 59.4±53.7	Control Day 29 Median 79.3 Mean 67.9±35.9	p=0.80
					Day 43 Median 94.5 Mean 65.0±52.0	Day 43 Median 85.3 Mean 67.4±47.0	p=0.67
					Day 84 Median 100 Mean 64.7±55.5	Day 84 Median 92.1 Mean 66.9±54.0	p=0.49
					Number of ulcers healed		
					Intervention Day 29 24.1% (7/29)	Control Day 29 11.5% (3/26)	Effect size [95% CI] RR=2.09 [0.66, 7.08] p=0.30
					Day 43 41.4% (12/29)	Day 43 26.9% (7/26)	RR=1.54 [0.74, 3.34] p=0.39
					Day 84 51.7% (15/29)	Day 84 34.6% (9/26)	RR=1.49 [0.81, 2.83] p=0.28

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Number of healed ulcers that recurred		
					Intervention 27% (4/15)	Control 33% (3/9)	Effect size [95% CI] RR=0.80 [0.25, 2.82] p=0.57
					Number of ulcers increased in size by >15%		
					Intervention 20.7% (6/29)	Control 7.7% (2/26)	Effect size [95% CI] RR=2.69 [0.68, 11.32]
					Number of ulcers progressing to a worse stage		
					Intervention 6.9% (2/29)	Control 3.9% (1/26)	Effect size [95% CI] RR=1.79 [0.24, 13.54]
(Kusumanto et al 2006) Netherlands	Level II RCT. Good quality study	n=54 diabetic patients with critical limb ischaemia, rest pain and/or ulcers that had not healed for a minimum of 2 weeks Intervention group: n=27, mean age 68.7 (range 45-85) years, male 59% (n=16), diabetes type 1 19% (n=5), duration of diabetes (yrs) 17.0 (range 0.08-14), insulin dependent 30% (n=8), mean HbA_{1c} 8.1% (range 6.4-12.2), pain 89% (n=24), ulcer 78% (n=1), duration of ulcer 3.0 (range 1-12) months, hypertension 56% (n=15), hypercholesterolaemia 33% (n=9), coronary artery disease 44% (n=12), duration of leg ischaemia 8.6 (range 1-30) months, prior vascular reconstruction/percutaneous	n=27 Standard wound care plus 2000µg plasmid DNA containing the Vascular Endothelial Growth Factor gene (phVEGF) injected intramuscularly into the thigh and calf muscle on day 0 and day 28. Follow-up evaluations carried out on days 7, 14, 35, 42, 72, and 100.	n=27 Standard wound care plus normal saline placebo injections as per intervention protocol.	Number of ulcers improved		
					Intervention 33% (7/21)	Control 0% (0/17)	Effect size [95% CI] RR=11.3 [1.3, 114.2]
					Number of amputations		
					Intervention 11% (3/27)	Control 22% (6/27)	Effect size [95% CI] RR=0.50 [0.14, 1.66]
					Mean time to amputation (days)		
					Intervention 78	Control 25.5	p=0.11

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
		angioplasty 37% (n=10), prior amputation 11% (n=3) Control group: n=27, mean age 68.4 (range 40-84) years, male 56% (1n=5), diabetes type 1 15% (n=4), duration of diabetes (yrs) 14.2 (range 0.67-55), insulin dependent 37% (n=10), mean HbA1c 8.0% (range 5.8-9.8), pain 85% (n=23), ulcer 63% (n=17), duration of ulcer 5.0 (range 1-12) months, hypertension 67% (n=18), hypercholesterolaemia 30% (n=8), coronary artery disease 33% (n=9), duration of leg ischaemia 9.5 (range 1-48) months, prior vascular reconstruction/percutaneous angioplasty 37% (n=10), prior amputation 11% (n=3)			

rhVEGF=recombinant human vascular endothelial growth factor; University of Texas Diabetic Foot Classification System= 01. A0 Pre – or post ulcerative lesion completely epithelialised, 02. A1 superficial wound not involving tendon, capsule or bone, 03. A2 Wound penetrating to tendon or capsule, 04. A3 wound penetrating to bone or joint, 05. B0 pre or post ulcerative lesion completely epithelialised with infection, 06. B1 superficial wound, not involving tendon, capsule or bone with infection, 07. B2 wound penetrating to tendon or capsule with infection, 08. B3 wound penetrating to bone or joint with infection, 09. C0 pre or post ulcerative lesion completely epithelialised with ischaemia, 10. C1 superficial wound not involving tendon, capsule or bone with ischaemia, 11. C2 wound penetrating to tendon or capsule with ischaemia, 12. C3 wound penetrating to bone or joint with ischaemia, 13. D0 pre or post ulcerative lesion completely epithelialised with infection and ischaemia, 14. D1 superficial wound not involving tendon, capsule or bone with infection and ischaemia, 15. D2 wound penetrating to tendon or capsule with infection and ischaemia, 16. D3 wound penetrating to bone or joint with infection and ischaemia;

Topical basic fibroblast growth factor

One good quality RCT compared topical recombinant human basic fibroblast growth factor (bFGF) versus standard wound care/placebo for the treatment of diabetic foot ulcers (Table 79). Richard et al (1995) used bFGF reconstituted in saline as a spray which was applied to diabetic foot ulcers daily for six weeks then twice weekly for 12 weeks. Measured outcomes included number of ulcers healed, percentage reduction in ulcer size, time to healing and number of ulcers improved. Results indicated that for all measured outcomes the placebo was superior to the intervention (bFGF), however these findings did not reach statistical significance. The sample size was quite small and all participants were resting in bed for the initial 6 week phase of the study which has been shown to improve outcomes for diabetic ulcer patients. The bFGF was only applied twice weekly during the second phase of the study and the low dose of basic fibroblast growth factor was suggested by the authors as a reason why the treatment appeared to give such a poor result compared to placebo. In other studies where growth factors showed benefit over placebo the intervention was applied daily for as many as 20 weeks (Steed et al 1992; Holloway et al 1993). The authors also consider that the bFGF may have degraded and/or been absorbed into the dressing and that results may have improved if it was incorporated into a gel or cream as opposed to a spray Richard et al 1995). The treatment with bFGF was well tolerated and no adverse events were observed.

Box 116 Evidence statement matrix for topical basic fibroblast growth factor

Component	Rating	Description
Evidence base	B	One level II study of good quality
Consistency	N/A	Only one study
Clinical impact	D	No statistically or clinically significant benefits of the intervention were observed
Generalisability	B	Evidence is directly generalisable to the target population
Applicability	C	The study was conducted in France which is not similar to the Australian healthcare context however it is probably applicable with some caveats

Evidence statement

There is evidence to suggest that topical basic fibroblast growth factor used as a spray and used daily for six weeks and twice weekly for 12 weeks does not provide any clinical benefits in the treatment of diabetic foot ulcers over standard wound care/placebo (Grade C).

Table 79 Topical basic fibroblast growth factor

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
(Richard et al 1995) France	Level II RCT. Average quality study	n=17 diabetic patients with chronic non-healing, neuropathic, Wagner Grade I-III ulcer of at least 0.5cm length on the plantar surface of the foot Intervention group: n=9, mean age 61.9 ± 10.0 years, male 100% (n=9), BMI (kg/m^2) 26.4 ± 4.6, duration of diabetes (yrs) 20.9 ± 12.3, fructosamine 295.1 ± 75.0mM, HbA_{1c} 7.9 ± 1.7%, vibration perception threshold 46.3 ± 6.4 volts, ulcer duration 22.4 ± 27.9 months, ulcer size: largest diameter 18.0 ± 12.0mm, Wagner Grade I 22% (n=2), Grade II 44% (n=4), Grade III 33% (n=3) Control group: n=8, mean age 63.6±7.9 years, male 88% (n=7), BMI (kg/m^2) 29.3±2.6, duration of diabetes (yrs) 18.8±9.5, fructosamine 284.4±42.2mM, HbA_{1c} 7.1±1.7% vibration perception threshold 37.3±14.9 volts, ulcer: duration 27.9±42.2 months, largest diameter 18.1±6.2mm, Wagner Grade I 13% (n=1), Grade II 50% (n=4), Grade III 38% (n=3)	n=9 Patients received initial intensive insulin treatment to tightly control diabetes before randomisation. Intervention consisted of 50µg basic fibroblast growth factor (bFGF) reconstituted at 5µg/ml in saline and sprayed on the ulcer. A volume of 50µl (containing 500ng bFGF) was sprayed over 4.15cm^2 area. One or two sprays per ulcer, depending on size were applied daily for the first 6 weeks or until healed and then twice weekly for another 12 weeks as needed. After spraying, ulcers were covered with sterile petroleum-impregnated gauze or dry compresses and evaluated weekly	n=8 Patients received initial intensive insulin treatment to tightly control diabetes before randomisation. Placebo of lyophilate reconstituted in normal saline was sprayed on ulcer as per intervention protocol. After spraying, ulcers were covered with sterile petroleum-impregnated gauze or dry compresses and evaluated weekly	Number of ulcers healed Intervention: 33.3% (3/9) | Control: 62.5% (5/8) | Effect size [95% CI]: RR=0.53 [0.20, 1.47] Number of ulcers improved (as per Wagner classification) Intervention: 55.5% (5/9) | Control: 75.0% | Effect size [95% CI]: RR=0.74 [0.44, 1.47] % reduction of ulcer perimeter Intervention: 35.8 ± 49.6 | Control: 47.2 ± 36.4 | p=0.6 Time to healing (weeks) Intervention: 87.7±38.0 | Control: 64.8±29.5 | p=0.19 Time to 50% healing (weeks) Intervention: 9.3 ± 2.1 | Control: 5.8 ± 0.4 | p=0.0003 % reduction of ulcer area (cm^2) Intervention: 59.3 ± 44.5 | Control: 75.0 ± 39.1 | p=0.45

Wagner Classification of ulcers, Grade I = superficial ulcer, Grade II = deep ulcer to tendon, capsule or bone, Grade III = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade IV = localised gangrene of forefoot or heel, Grade V = gangrene of entire foot;

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) is the administration of oxygen at pressures greater than 1 atmosphere absolute (ATA). This requires the patient to be confined within an airtight vessel and given 100 percent oxygen for respiration. Sessions usually take between 45 and 120 minutes, once or twice daily, however this varies between settings (Roeckl-Wiedmann et al 2005).

Seven studies considered the use of hyperbaric oxygen therapy for the treatment of diabetic foot ulcers (Table 80). These studies consisted of one good quality systematic review, one good quality and five average quality level II RCTs. Findings of the systematic review by Roeckl-Wiedmann et al (2005) identified significant advantages of using hyperbaric oxygen therapy (HBOT) for the intervention group. In particular, ulcers healed faster with 29 percent of the intervention group compared to five percent of the control group healing within 2 weeks. In addition, there was a reduced risk of both major and minor amputations with 10 percent of the intervention group versus 33 percent of the control group requiring major amputations. Abidia et al (2003) reported the findings of a good quality RCT which found a significant improvement in the number of ulcers healed (63%, 5/8) in the intervention group compared to the control group (0%, 0/8) at one-year. A greater reduction in ulcer size was also reported in the HBOT intervention group. Abidia et al (2003) also considered changes in levels of anxiety and depression using the Hospital Anxiety and Depression (HAD) Scale, which incorporates 14 questions with a scale of 0-3 to ascertain levels of anxiety and depression with a higher score indicating higher levels of depression. The HAD scale was applied pre- and post-intervention and identified a significant reduction in levels of depression amongst all participants, however only those in the control group showed an improvement in anxiety levels. The SF-36 was also used to measure physical and mental well-being amongst participants. The SF-36 covers 8 domains in 36 questions (physical and social functioning, physical and emotional role, general and mental health, bodily pain and vitality), to a maximum score of 100, with a higher score indicating higher levels of health and vitality. Participants in the intervention group showed improvement in general health and vitality however statistically significant improvements in other domains were not evident for either HBOT or standard wound care.

In an average quality level II RCT by Duzgun et al (2008), significantly better results were reported for all measured outcomes when HBOT was used in addition to standard wound care. All ulcers in the intervention group healed without surgery whereas none of the control group's ulcers healed without surgery. Numbers of amputations were significantly less in the intervention group, with only eight percent (4/50) of participants in the HBOT group requiring a proximal amputation as opposed to 82 percent (41/50) in the control group (Duzgun et al 2008). Doctor et al (1992) also reported a reduction in major amputations for the group receiving HBOT, however, differences between the length of hospital stay and minor amputations were not statistically significant between HBOT and standard wound care. Furthermore, it is likely that some patients had already undergone amputation and the wound being evaluated was an amputation wound. In addition, Faglia et al (1996) reported a reduction in major and minor amputations, shorter time to healing and decreased hospital length of stay for patients treated with HBOT.

Time to complete healing of foot ulcer and a reduction in surface area (cm^2) were the measured outcomes of an average quality level II RCT trial by Kessler et al (2003). It was determined that significant benefit could be derived by HBOT in the short term, with reported findings suggesting that a reduction in surface area is achieved at a much quicker rate initially in participants receiving HBOT. However this benefit reduces over time such that by four weeks post-treatment there were no statistically significant differences between the intervention and

control groups. These findings are relevant in terms of length of hospital stay and the consequential reduced cost of treatment overall. The consistent finding of HBOT being superior to conventional wound treatment in relation to a reduced number of amputations is further supported by Kessler et al (2003) with a reduced number of amputations being reported for the group receiving HBOT (12%) compared to the control group (33%) experiencing standard wound care.

Topical hyperbaric oxygen therapy (THOT) is administered using a topical hyperbaric leg chamber which provides humidified 100 percent oxygen at pressures cycling between zero and 30 mmHg (up to 1.04 atmospheres) every 20 seconds. Treatment varied across settings, for example 2 x 90 minute sessions daily (Leslie et al 1988).

When topical hyperbaric oxygen therapy was used over a two week period, no significant difference between the intervention group receiving standard wound care plus HBOT twice daily and the control group receiving standard wound care was reported. Measured outcomes were ulcer size and depth (Leslie et al 1988). Heng et al (2000) also used THOT but for twice the duration of treatment than in the study by Leslie et al (1988) i.e. four weeks. The population in this study was not exclusively diabetic patients however there was enough information regarding the diabetic participants to allow comparisons to be made. Measured outcomes included number of ulcers healed and reduction in ulcer size. Number of (all) ulcers healed within four weeks was 64 percent for the THOT intervention group versus 6 percent in the control group (RR=10.71, 95% CI [4.02, 31.70]) and the number of diabetic ulcers healed within four weeks 76% versus 19% (RR=4.06, 95% CI [(1.71, 10.92]). Reduction in ulcer area was significantly greater after treatment with THOT, whilst ulcers in the control group actually increased in size with standard care. Stage II, III and IV diabetic ulcers were reduced by 100, 73.5 and 45.4 percent, respectively in the THOT group but increased in size in the control group with a reduction of 46.2, 58.7 and 44 percent, respectively ($p<0.05$ for all). Participants were followed for 12 months post- treatment and when considering only the diabetic ulcers, 25 percent of stage III ulcers in the THOT group healed compared to none in the control group. No stage IV diabetic ulcers healed in either group (Heng et al 2000).

Meta-analysis of the studies for the outcomes of ulcer healing and major amputation suggest that HBOT does provide additional benefit in the treatment of diabetic foot ulcers, however, it would appear that there is insufficient evidence of a benefit in terms of minor amputations (Figure 6; Figure 8).

For ulcer healing, the I^2 statistic suggests there was moderate heterogeneity which would explain a substantial proportion of the uncertainty in the pooled relative risk (RR = 6.98, 95% CI [1.83, 26.7], p = 0.005). However, there was no statistically significant difference in effects between the studies (= 5.48, df=, p=1.40). It should be noted that this meta-analysis includes the study by Heng et al (2000) which assessed topical HBOT, however, removing this study reduced the uncertainty around the point estimate although there still remained a statistically significant benefit for HBOT in healing foot ulcers.

For minor amputation there was significant heterogeneity in effects between the studies which is likely a result of the lack of statistical power in the majority of the studies which were pooled (Figure 7). Hence, no significant difference was seen in the incidence of minor amputation with the addition of HBOT to standard care.

Pooling of data for the outcome of major amputation showed that there was a statistically significant benefit with HBOT in addition to standard wound care (RR = 0.25, 95%CI [0.09, 0.70], p = 0.009). Of the four studies included in the meta-analysis, two reported the treatment effect in populations with adequate perfusion. With regard to heterogeneity, little of the

observed variation in effect sizes was in fact attributable to variation in true effect sizes (I^2 = 29.6%).

In the physically measured outcomes including major (not minor) amputation rate, time to healing, hospital length of stay, ulcer surface area and ulcer healing rate, HBOT demonstrated considerable advantage over conventional therapy (NNT=2.0 i.e. for every 2 ulcers treated with HBOT, one more ulcer would be healed within 4 weeks than if they were treated with standard wound care). Outcomes such as well-being, vitality and depression were less conclusive. The use of HBOT does, however, require specialised equipment and trained staff to apply it, plus considerable time commitment by the patient. While the benefit of HBOT has been demonstrated, these and other financial considerations may restrict use of HBOT for the general population of diabetic patients with foot ulcers.

Chow et al (2008) conducted a good quality systematic review of health economic evaluations for the management of diabetic foot ulcers. This review identified one study which assessed the cost-effectiveness of HBOT in the management of diabetic foot ulcers. The USA-based cost-utility analysis study conducted by Guo et al (2003) used a decision tree model and found that the incremental cost of hyperbaric oxygen therapy versus standard wound care per additional quality-adjusted life year gained was US$27,310 at year 1, US$5,166 at year 5, and US$2,255 at year 12. Sensitivity analysis found that efficacy probabilities, number of hyperbaric oxygen treatments per case, costs of hyperbaric oxygen treatment and costs of major or minor lower extremity amputations had a significant impact. However, hyperbaric oxygen therapy plus standard wound care in the treatment of diabetic foot ulcers was considered to be cost effective in the long-term.

Box 117 Evidence statement matrix for Hyperbaric Oxygen Therapy (HBOT)

Component	Rating	Description
Evidence base	B	One good quality systematic review, one good quality level II RCT and five average quality level II RCTs with low risk of bias
Consistency	B	Most studies were consistent and inconsistencies can be explained
Clinical impact	B	Clinically significant benefits were identified for reduction in major amputations, reduction in surface area of ulcers, reduction in number of ulcers and time to heal
Generalisability	B	All but one study exclusively included patients with diabetic foot ulcers and the other study had a cohort of participants with diabetic foot ulcers which are directly generalisable to the target population. Patients had severe chronic foot lesions often requiring admission to hospital.
Applicability	C	Studies were conducted in the USA, UK, Italy, France, Germany, Turkey and India which while not all similar to the Australian healthcare system, are probably applicable to the Australian healthcare context with some caveats

Evidence statement:

Hyperbaric oxygen therapy is superior to standard wound care/placebo in reducing the number of amputations, reducing the surface area of ulcers, reducing healing time and increasing the number of ulcers healed in patients with severe diabetic foot ulcers (Grade B).

Table 80 Hyperbaric oxygen therapy

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
(Roeckl-Wiedmann et al 2005) Germany	Level I Systematic review. Good quality study	Total of 175 patients with diabetic ulcers, 92 receiving standard treatment plus hyperbaric oxygen therapy (HBOT) intervention and 83 controls receiving standard treatment, Inclusion criteria: varied by trial but included any diabetic patient with a chronic foot lesion; patients with ulcers with Wagner grade 0-II and II-IV; diabetic foot ulcer size 1-10mm and present for at least 6 weeks; Studies included in systematic review relevant to inclusion criteria: 1. Doctor et al 1992 2. Faglia et al 1996 3. Kessler et al 2003 4. Abidia et al 2003 These studies are reported separately below. Outcomes included for Roeckl-Wiedmann et al 2005 are for meta analysis not reported elsewhere	K= 4 studies relevant to inclusion criteria n=92 Standard wound care plus HBOT between 4 and 30 times for 45-90 mins per time	n=83 Standard wound care with one study introducing a sham treatment of air	Proportion healed within 2 weeks of treatment n=46 (studies 3 and 4) Intervention 29% (7/24) / Control 5% (1/22) / Effect size [95% CI] RRp=4.78 [0.94, 24.24] Major amputation (studies 1,2 and 4) Intervention 10% (6/60) / Control 33% (19/58) / Effect size [95% CI] RRp=0.31 [0.13, 0.71] Minor amputation n=48 (studies 1 and 4) Intervention 21% (5/24) / Control 8% (2/24) / Effect size [95% CI] RRp=2.20 [0.56, 8.72]
(Chow et al 2008) USA	Level I systematic review Good quality study	Hyperthetical cohort of 1000 diabetic patients with severe foot ulcers (Wagner grade 3 or more) (Guo et al 2003)	Hyperbaric oxygen therapy plus standard wound care	Standard wound care	ICER per QALY = US$27,310 at year 1, US$5,166 at year 5, and $2,255 at year 12. Sensitivity analysis: efficacy probabilities, number of HBO_2 treatments per case, costs of HBO_2 treatment and costs of major and minor lower-extremity amputations had a significant impact on cost-effectiveness ratios.
(Abidia et al 2003) UK	Level II RCT. Good quality study	N=18 diabetic patients presenting to a hospital clinic with ischaemic lower extremity ulcer Intervention group: n = 8, mean age (yrs) 72 ± 12.6, gender 66% male (n=6), (1 patient withdrew, gender not stated), duration of diabetes (yrs) 13 ± 9.9, insulin therapy 50% (n=4), smokers 13% (n=1), BMI 26 ± 7 kg/m^2, biothesiometer reading 47 ± 16.2, great toe-brachial index 0.47 ± 0.24 mV, foot $TcPO_2$ 46 ± 15 mmHg Hb (g/dL) 12.7 ± 1.2, serum albumin 37 ± 2.8 g/L, retinopathy:	n=8 Standard treatment of off-loading, aggressive debridement, moist dressings and antibiotics if any signs of infection present. Plus Hyperbaric Oxygen Therapy (HBOT) with 100% oxygen in a	n=8 Standard treatment of off-loading, aggressive debridement, moist dressings and antibiotics if any signs of	Ulcers healed Intervention 6 weeks 63% (5/8) / Control 6 weeks 13% (1/8) / Effect size [95% CI] RR=5.0 [1.03, 30.55] p=0.046 6 months 63% (5/8) / 6 months 25% (2/8) / RR=2.5 [0.75, 9.52] 1 year 63% (5/8) / 1 year 0% (0/8) / RR=10 [1.29, 101.8] p=0.021

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
		background 88% (n=7) and proliferative 13% (n=1), COPD 13% (n=1), cardiac failure 25% (n=2), previous angioplasty 0/8, previous by-pass surgery 25% (n=2), previous amputation: minor 13% (n=1), major 0/8, previous ulcer 38% (n=3), Society of Vascular Surgeons (SVS) Classification grade V 100% (n=8), ulcer duration 6 (2-18) months, ulcer size 106 (12-823) mm^2 , depth 2.3 (0.5-4) mm , Wagner grade I 0/8, grade II 100% (n=8), signs of infection 38% (n=3) Comparator group: n= 8, mean age 70 ± 6.6 years, male 33% (n=3), (1 patient withdrew, gender not stated), duration of diabetes (yrs) 10 ± 6.3, insulin therapy 63% (n=5), smokers 25% (n=2), BMI 29 ± 4 kg/m^2, biothesiometer reading 55 ± 13.7 mV, great toe-brachial index 0.44 ± 0.3, foot $TcPO_2$ 43 ± 19 mmHg, Hb 12.5 ± 1.7 g/dL, serum albumin (g/L) 38 ± 2.6,. retinopathy: background 100% (n=8) and proliferative 0/8, COPD 25% (n=2), cardiac failure 25% (n=2), previous angioplasty 13% (n=1), previous by-pass surgery 38% (n=3), previous amputation: minor 25% (n=2), major 0/8, previous ulcer 50% (n=4), SVS classification grade V 100% (n=8), ulcer duration 9 (3-60) months, size 78 (18-866) mm^2 , depth 1.6 (0.5-4) mm, Wagner grade I 13% (n=1), grade II 88% (n=7), signs of infection 25% (n=2)	multi-place chamber at a pressure of 2.4 atmospheres absolutes (ATA) for 90 mins per day over 5 days a week to a total of 30 sessions with 20 min decompression time. Multi-disciplinary care from a physician, vascular surgeon, chiropodist and specialist nurse for 6 weeks before treatment, throughout treatment and during the follow up period	infection present. Plus placebo of Hyperbaric Air Therapy in a multi-place chamber at a pressure of 2.4 atmospheres absolutes (ATA) for 90 mins per day over 5 days a week to a total of 30 sessions with 20 min decompression time. Multi-disciplinary care from a physician, vascular surgeon, chiropodist and specialist nurse for 6 weeks before treatment, throughout treatment and follow up period included.	Reduction in ulcer size (mm^2) Intervention 6 weeks 100% / Control 6 weeks 52% / p=0.027 6 months 100% / 6 months 95% / ns Major amputation rate Intervention 13% (1/8) / Control 13% (1/8) / Effect size [95% CI] RR=1 Minor amputation rate Intervention 13% (1/8) / Control 0% (0/8) / Effect size [95% CI] RR=2 [0.15, 26.6] p=0.670 Improvement in Hospital Anxiety and Depression Scale (HAD) score Intervention: Improvement in depression from baseline p=0.011; No improvement in anxiety Control: Improvement in depression from baseline p=0.023; Improvement in anxiety p=0.042 Improvement in SF-36 Intervention: Improvement in general health p=0.012; Improvement in vitality p=0.018 Control: No improvement in general health; No improvement in vitality No improvement in other domains
(Doctor et al	Level II RCT.	N=30 diabetic inpatients with chronic foot lesions	n=15	n=15	Length of hospital stay in days

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
1992) India	Average quality study	Intervention group: n=15, mean age 56.2 (range 45-70) years, gender (M:F) 3:1 (numbers not stated), mean duration of diabetes 9.8 (yrs), insulin dependent 15%, neuropathy 17% , distal pulses absent 13%; lesion evaluated: skin graft (n = 6); amputation stump (n = 5); persistent infection (n = 1). Comparator group – N=15 mean age 59.8 (range 48-70) years, gender (M:F) 2:1, (numbers not stated), mean duration of diabetes 10.9 (yrs), insulin dependent 20%, neuropathy 21%, distal pulses absent 21%; lesion evaluated: skin graft (n = 2); amputation stump (n = 6); persistent infection (n = 3).	Standard treatment of surgical debridement, dressing with eusof (1.25% w/v boric acid and 1.25% of bleaching powder) and antibiotics as necessary plus adjunct HBOT for 45 mins in 4 sittings over 2 weeks	Standard treatment including surgical debridement, dressing with eusof and antibiotics as necessary	Intervention: 40.6 days (range 23-65) / Control: 47 days (range 20-68) / p=NS Amputation rate Intervention: Minor 27% (4/15) / Control: Minor 13% (2/15) / Effect size [95% CI]: RR=0.5 [0.11, 2.06] p=0.36 Major 13% (2/15) / Major 47% (7/15) / RR=0.29 [0.07, 0.98] p<0.05 Total 40% (6/15) / Total 60% (9/15) / RR=0.67 [0.33,1.36] p=0.27
(Duzgun et al 2008) Turkey	Level II RCT. Average quality study	N=100 diabetic patients >18 years with a foot ulcer for at least 4 weeks despite local and systemic treatment. Intervention group: n = 50, mean age 58.1 ± 11.0 years, male 74%, (n=37), duration of diabetes (yrs) 16.9 ± 6.2, insulin dependent 82% (41/50) , hypertension 64% (n=32), BMI > 30 kg/m^2 80% (n=40), current smoker 72% (n=36), high lipid-lipoprotein level 62% (n=31), HbA_{1c} 8.0 ± 1.9 mg/dL, Wagner grade: II 12% (n=6), grade III 38% (n=19), grade IV 50% (n=25) Comparator group: n = 50, mean age 63.3 ± 9.2 years, male 54%, (n=27), duration of diabetes (yrs) 15.9 ± 5.6, insulin dependent 90% (n=45), hypertension 56% (n=28), BMI > 30 kg/m^2 46% (n=23), current smoker 40% (n=20), high lipid-lipoprotein level 54% (n=27), HbA_{1c} 8.7 ± 2.9 mg/dL, Wagner grade: II 24% (n=12), grade III 36% (n=18), grade IV 40% (n=20)	n=50 Standard wound care including debridement, dressing changes and infection control plus hyperbaric oxygen therapy administered for 90 mins 2 times per day followed by 1 session the next day, alternating for between 20 - 30 days	n=50 Standard wound care including debridement, dressing changes and infection control	Number of ulcers healed without surgery Intervention: Wagner Grade II, 100% (6/6) / Control: Wagner Grade II, 0% (0/12) / Effect size [95% CI]: RR=24 [4.03, 24.0] Grade III, 68% (13/19) / Grade III, 0% (0/18) / RR=24.6 [3.3, 240.9] Grade IV, 56% (14/25) / Grade IV, 0% (0/20) / RR=22.4 [2.9, 219.4] Total 66% (33/50) / Total 0% (0/50) / RR=66 [8.1, 638] Number requiring distal amputation according to Wagner classification of ulcer Intervention: Grade II, 0% (0/6) / Control: Grade II, 33% (4/12) / Effect size [95%CI]: RR=0.0 [0.0, 1.45]

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Grade III, 5% (1/19)	Grade III, 94% (17/18)	RR=0.06 [0.02, 0.21]
					Grade IV, 12% (3/25)	Grade IV, 15% (3/20)	RR=0.8 [0.20, 3.27]
					Total 8% (4/50)	Total 48% (24/50)	RR=0.17 [0.06, 0.41]
					Number requiring proximal amputation according to Wagner classification of ulcer		
					Intervention Grade II, 0% (0/6)	Control Grade II, 0% (0/12)	Effect size [95% CI]
					Grade III, 0% (0/19)	Grade III, 0% (0/18)	
					Grade IV, 0% (0/25)	Grade IV, 85% (17/20)	RR=0.0 [0.00, 0.12]
					Total 0% (0/50)	Total 34% (17/50)	RR=0.0 [0.00, 0.20]
					All amputations 8% (4/50)	All amputations 82% (41/50)	RR=0.01 [0.04, 0.20]
(Faglia et al 1996) Italy	Level II RCT. Average quality study	N=70 diabetic patients hospitalised for foot ulcer between 1993-1995. Intervention group: n = 35, mean age 61.7 ± 10.4 years; male 77% (n=27), duration of diabetes (yrs) 16 ± 10; insulin therapy 60% (n=22); smokers 31% (n=12); obesity 26% (n=9); HbA_{1c} 9.3 ± 2.5%; ankle-brachial index 0.65 ± 0.28, $TcPO_2$ 23.25 ± 10.6 mmHg; microalbuminuria 34% (n=12); proteinuria 23% (n=8); impaired vibration sense 88% (n=31); neuropathy: sensorimotor 100%, autonomic 74% (n=26); retinopathy: background 34% (n=12) and proliferative 37% (n=13); renal impairment 11% (n=4);	n=36 Standard wound care including aggressive debridement; wound cleaning with antiseptic and wadding with occlusive dressing twice per day when necrosis or exudates present and daily when clean, then every 2 days during	n=34 Standard wound care including aggressive debridement; wound cleaning with antiseptic and wadding with occlusive dressing twice per day when necrosis or	Total Major amputations		
					Intervention 9% (3/35)	Control 33% (11/33)	Effect size [95% CI] RR=0.26 [0.08, 0.77]
					Major amputations according to Wagner grade classification of ulcer		
					Intervention Grade II 0% (0/4)	Control Grade II 0% (0/5)	Effect size [95% CI] N/A

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
		hypertension 54% (n=20); hyperlipidaemia 31% (n=11); coronary artery disease 40% (n=14); prior stroke 9% (n=3); infection 91% (n=31); peripheral angiography 89% (n=32); bone lysis 31% (n=11); osteopenia 43% (n=15); Monckeberg sclerosis 60% (n=21); ulcer Wagner grade II 12% (n=4), grade III 26% (n=9), grade IV 63% (n=23); previous amputation: minor 17% (n=6), major 0%; previous ulcer 26% (n=9). Comparator group: n = 33, mean age 65.6 ± 9.1 years; male 64% (n=21), duration of diabetes (yrs) 19 ± 9; insulin therapy 67% (n=22) ; smokers 36% (n=12); obesity 27% (n=9); HbA_{1c} 8.5 ± 2.3%; ankle-brachial index 0.64 ± 0.25, $TcPO_2$ 21.29 ± 10.7l mmHg; microalbuminuria 27% (n=9); proteinuria 21% (n=7); impaired vibration sense 85% (n=28); neuropathy: sensorimotor 94% (n=31), autonomic 71% (n=24); retinopathy: background 39% (n=13) and proliferative 27% (n=9); renal impairment 27% (n=9); hypertension 52% (n=17); hyperlipidaemia 24% (n=8); coronary artery disease 45% (n=15); prior stroke 12% (n=4); infection 85% (n=28); peripheral angiography 79% (n=26); bone lysis 27% (n=9); osteopenia 64% (n=21); Monckeberg sclerosis 61% (n=20); ulcer Wagner grade II 15% (n=5), grade III 24% (n=8), grade IV 60% (n=20); previous amputation: minor 30% (n=9), major 0%; previous ulcer 36% (n=12).	granulation period; antibiotics until culture negative; metabolic control of blood sugar; plus hyperbaric oxygen therapy (HBOT) in a multi-place chamber - during first phase pressurised to 2.5 atmospheres absolute (ATA) for 90 mins each session for 30 sessions, then 2.4-2.2 ATA for 90 mins 5 days per week in second phase	exudates present and daily when clean, then every 2 days during granulation period; antibiotics until culture negative; metabolic control of blood sugar	Grade III 25% (1/4) / Grade III 0% (0/8) / RR=4.0 [0.32, 52.6] Grade IV 9% (2/22) / Grade IV 55% (11/20) / RR=0.17 [0.04, 0.54] Total Minor amputations Intervention 60% (21/35) / Control 36% (12/33) / Effect size [95% CI] RR=1.65 [0.99, 2.79] Minor amputations according to site Intervention Forefoot 14% (5/35) / Control Forefoot 12% (4/33) / Effect size [95% CI] RR=1.18 [0.37, 3.86] Toe 46% (16/35) / Toe 24% (8/33) / RR=1.89 [0.97, 3.83] Time to major amputation (days) Intervention 57.6 ± 24 (range 31-78 days) / Control 72.8 ± 59 (range 26-176 days) Length of hospital stay (days) Intervention 43.2 ± 31 / Control 50.8 ± 32 / p=0.37
(Heng et al 2000) USA	Level II RCT. Average quality study	N=40 non-ambulatory diabetic patients (38% diabetic n=15), with a necrotic/gangrenous ulcer. Intervention group: n=13, mean age 73.8±6.4 years, male 100% (n=13), Sub group of Intervention group: n=7, (diabetic participants) 54% (n=7), diabetic ulcers 75% (n=21),	n=13 (7/13 with diabetic ulcers) Standard wound care including initial sharp debridement, antibiotics	n=27 (8/27 diabetic ulcers) Standard wound care including sharp	% reduction in diabetic ulcer area (n=21+16=37 ulcers) Intervention Stage II 100 Stage III 73.5 Stage IV 45.4 / Control Stage II 46.2 Stage III 58.7 Stage IV 44 / p<0.05 p<0.05 p<0.05

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
		diabetic foot ulcers 35% (n=10), Stage II ulcers 71% (n=15), lower limb 60% (n=9), ulcer area 7.4±6.3cm^2, (ulcer staging detailed at end of table) Stage III 19% (n=4), lower limb 50% (n=2), ulcer area 10.2±7.6cm^2 Stage IV 10% (n=2), lower limb 100% (n=2), ulcer area 23.8±4.4cm^2, Control group n=27 mean age 75.5±8.0 years, male 96% (n=26) Sub group of control group n=8 diabetes mellitus patients 30% (n=8), diabetic ulcers 32% (n=16), diabetic foot ulcers 63% (n=10), (ulcer staging detailed at end of table) Stage II ulcers 50% (n=8), lower limb 50% (n=4), ulcer area 10.6±12.9cm^2, Stage III 25% (n=4), lower limb 50% (n=2), ulcer area 10.4±9.7cm^2, Stage IV ulcers 25% (n=4), lower limb 100% (n=4), ulcer area 14.5±14.5cm^2,	as required, wet to dry dressings and pressure relief plus Topical Hyperbaric Oxygen Therapy (THOT). THOT was administered via an 84 inch by 48 inch pleated polyethylene bag. The open end is taped around the chest (allowing multiple ulcers to be treated), using pressures validated by instruments designed to measure low pressures, intra-bag pressures were maintained within a narrow range (1.004-1.013 atmospheres) at all times, ensuring a 15l/min flow rate. Wounds were treated for 4 hours/day, 4 days/week and assessed weekly	debridement, antibiotics as required, wet to dry dressings and pressure relief	Number of diabetic ulcers healed within 4 weeks Intervention: 76% (16/21) | Control: 19% (3/16) | Effect size [95% CI]: RR=4.06 [1.71, 10.92]; NNT=2.0 [1.30, 3.84] Number of (all) ulcers healed during study period Intervention: Stage II 100% 16/16) | Control: Stage II 26% (8/31) | Effect size [95% CI]: RR=3.88 [2.50, 3.88]; NNT=1.0 [1.35, 1.98] Stage III 100% (6/6) | Stage III 38% (3/8) | RR=2.67 [1.22, 2.67]; NNT=2.0 [1.60, 7.65] Stage IV 67% (4/6) | Stage IV 0% (0/11) | RR=14.67 [1.85, 149.85]; NNT=2.0 [1.59, 9.09] Number of diabetic ulcers healed with 4 weeks Intervention: Stage II 100% (15/15) | Control: Stage II 38% (3/8) | Effect size [95% CI]: RR=2.67 [1.45, 2.67] NNT=2.0 [1.60, 3.65] Stage III 25% (1/4) | Stage III 0% (0/4) | RR=2.00 [0.16, 26.13] Stage IV 0% (0/2) | Stage IV 0% (0/4) | p=ns
(Kessler et al 2003) France	Level II RCT. Average quality study	N=27 diabetic patients admitted to a hospital ward for chronic foot ulcers Intervention group – N = 14, mean age 60.2 ± 9.7 years, male 71% (n=10), BMI 29.9 ± 3.1 kg/m^2 , diabetes (type	n=14 hospitalisation for 2 weeks for conventional treatment then 2x90 min	n=13 hospitalisation for 2 weeks for conventional treatment followed	% Reduction in ulcer size (surface area cm^2) Intervention: After 2 weeks | Control: After 2 weeks

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
		1:2) (n=2:12), duration of diabetes (yrs) 18.2 ± 13.2, insulin therapy 93% (n=13), mean HbA_{1c} 9.4 ± 2.4%, $TcPO_2$ foot dorsum 45.6 ± 18.1 mmHg, sensorimotor neuropathy 100% (n=14), stabilised retinopathy 71% (n=10), renal impairment 36% (n=5), coronary artery disease 14% (n=2), carotid arteriopathy 7% (n=1), antibiotic therapy 57% (n=8), bone lysis 50% (n=4), ulcer characteristics: surface area 2.31 ± 2.18 cm^2 Comparator group – N = 13, mean age 67.6 ± 10.5 years, male 69% (n=9), BMI 29.1 ± 5.9 kg/m^2 , diabetes (type 1:2) (n=2:11), duration of diabetes (yrs) 22.1 ± 13.1, insulin therapy 93% (n=12), mean HbA_{1c} 8.1 ± 1.4%, $TcPO_2$ foot dorsum 45.2 ± 24.2 mmHg, sensorimotor neuropathy 100% (n=13), stabilised retinopathy 85% (n=11), renal impairment 46% (n=6), coronary artery disease 31% (n=4), carotid arteriopathy 8% (n=1), antibiotic therapy 69% (n=9), bone lysis 46% (n=6), ulcer surface area 2.82 ± 2.43 cm^2	daily sessions of 100% oxygen in a multi-place hyperbaric chamber pressurised at 2.5 atmospheres absolute (ATA) for 5 days for 2 weeks, followed by outpatient standard wound care and all patients provided with an orthopaedic device	by 2 weeks of treatment as an outpatient and all patients provided with an orthopaedic device	41.8±25.5 | 21.7±16.9 | p=0.037 After 4 weeks 61.9±23.3 | After 4 weeks 55.1±21.5 Complete healing 14.3 (2/14) | Complete healing 0 (0/13) | RR=3.71 [0.34, 42.5]
(Leslie et al 1988) USA	Level II RCT. Average quality study	N=28 diabetic patients admitted to a medical centre for the treatment of a foot ulcer. Patients had a well-demarcated foot ulcer but no visible bone. Intervention group: n=12 mean age 52.8±8.6 years, male 50% (n=6), diabetes type II 100%, duration of diabetes (yrs) 11.4±7.6, ankle/brachial index <0.5 or >1.5 10% (n=1), abnormal x-ray or bone scan 50% (n=6), white blood cell count >12,000/mm^3 0%, erythrocyte sedimentation rate (Westergren method) 72±31mm/hr, previous amputations 58% (n=7), ulcer characteristics: duration 6.4±6.2 weeks, surface area 551.8±546.7mm^2, ulcer depth 8.1±4.5mm Control group: n=16 mean age 46.2±8.5 years, male 62.5% (n=10), diabetes type II 75% (n=12), duration of diabetes (yrs) 13.2±8.0, ankle/brachial index <0.5 or >1.5	n =12 Standard wound care including initial debridement, 2 weeks of intravenous antibiotics, wet to dry local dressings and bed rest plus topical hyperbaric oxygen therapy (THOT). THOT was administered in two daily 90 minute sessions with the topical hyperbaric leg chamber which provided humidified 100% oxygen	n =16 Standard wound care including initial debridement, 2 weeks of intravenous antibiotics, wet to dry local dressings and bed rest.	% reduction in ulcer area at day 7 Intervention 32.9±18.3 | Control 30.4±34.5 | Intervention vs control p=0.8 % reduction in ulcer area at day 14 Intervention 54.4±23.4 | Control 64.4±23 | Intervention vs control p=0.27 Pre vs 7 day post intervention % reduction in ulcer area at day 7 p=0.02 Pre vs 7 day post control % reduction in ulcer area at day 7 p=0.003 % reduction in ulcer depth at day 7

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
		14.3% (n=2), abnormal x-ray or bone scan 31% (n=5), white blood cell count >12,000/mm^3 13% (n=2), erythrocyte sedimentation rate (Westergren method) 66±40 mm/hr, previous amputations 31% (n=5), ulcer characteristics: duration 6.2±7.8 weeks, surface area 319.6±255.7mm^2, ulcer depth 4.8±3.3mm	at pressures that cycled between 0 and 30mmHg every 20 seconds. Wounds were assessed at day 7 and 14		Intervention 4.1±9.1	Control 10.5±29.2	p=0.47
					% reduction in ulcer depth at day 14		
					Intervention 24.2±23.4	Control 32.7±23.5	p=0.35
					Pre vs 14 day post intervention % reduction in ulcer depth p=0.011		
					Pre vs 14 day post control % reduction in ulcer depth p=0.024		

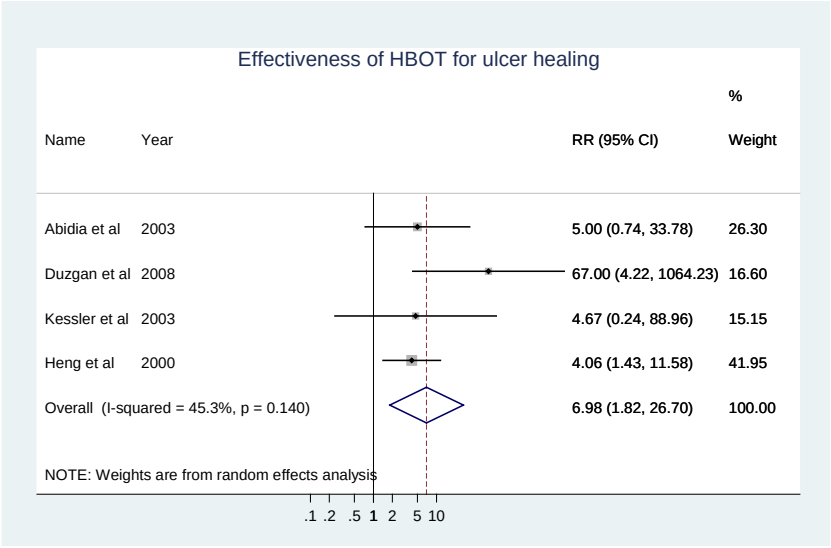
HAD = Hospital Anxiety and Depression Scale (14 questions rating 0-3 with higher score indicating greater depression and anxiety); Heng et al (2000) Ulcer Severity Scale: determined by wound team consensus, modified version of severity staging of pressure ulcers and diabetic ulcers. Stage II = ulcers with necrotic tissue, which after debridement revealed a depth of up to 3mm; Stage III = ulcers infected and/or undermined with necrotic tissue involving the subcutaneous tissue to deep fascia, Stage IV = deep ulcers infected and undermined with necrotic tissue involving muscle, tendons and/or bone; NS = Not significant; RR = Relative Risk; SF-36 = Self report questionnaire (36 questions relating to 8 domains measuring general health and vitality, social and physical functioning, physical and emotional role, bodily pain and mental health. Higher scores indicate better health and vitality); THOT = Topical Hyperbaric Oxygen Therapy; Wagner Classification Grade I = superficial ulcer, Grade II = deep ulcer to tendon, capsule or bone, Grade III = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade IV = localised gangrene of forefoot or heel, Grade V = gangrene of entire foot; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year

Figure 6 Meta-analysis of HBOT for ulcer healing

Study	RR	[95% Conf.	Interval]	% Weight
Abidia et al	5.000	0.740	33.777	26.30
Duzgan et al	67.000	4.218	1064.226	16.60
Kessler et al	4.667	0.245	88.957	15.15
Heng et al	4.063	1.425	11.585	41.95
D+L pooled RR	6.979	1.825	26.695	100.00

Heterogeneity chi-squared = 5.48 (d.f. = 3) p = 0.140
I-squared (variation in RR attributable to heterogeneity) = 45.3%
Estimate of between-study variance Tau-squared = 0.8313

Test of RR=1 : z= 2.84 p = 0.005



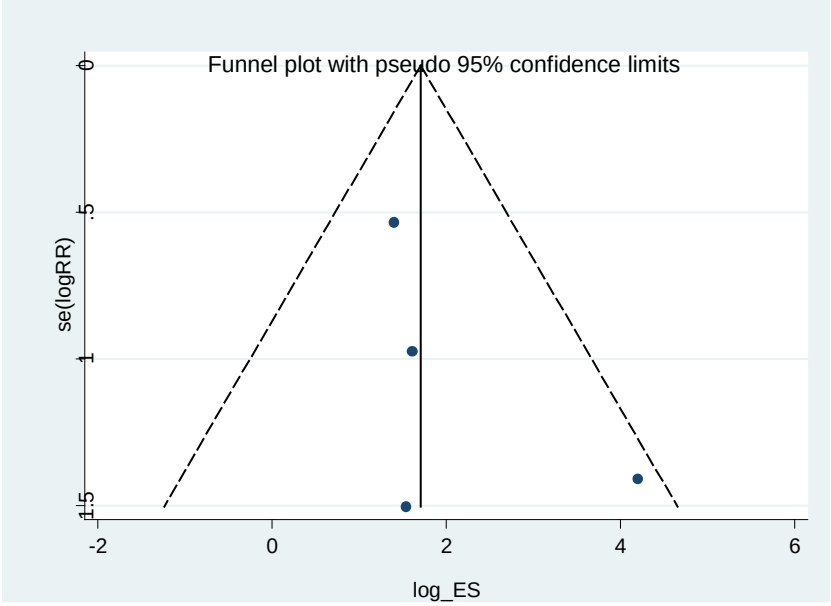
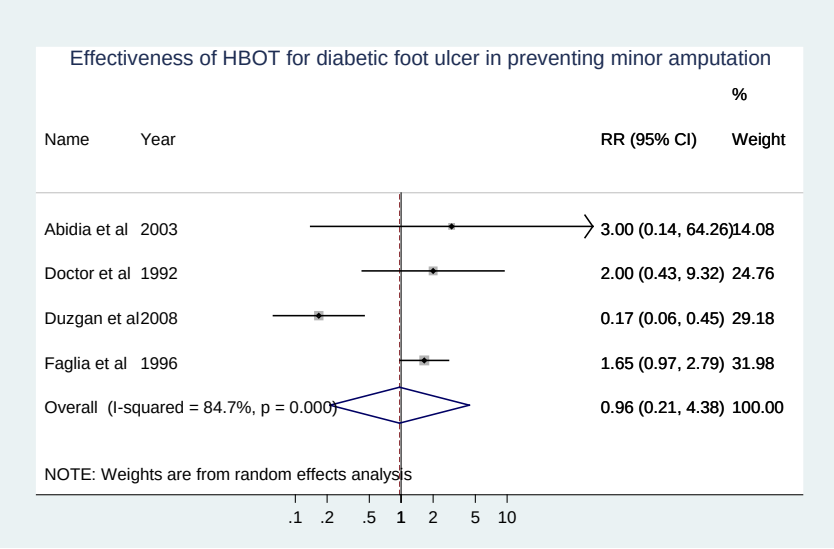


Figure 7 Meta-analysis of the effectiveness of HBOT for diabetic foot ulcers in preventing minor amputation

Study	RR	[95% Conf.	Interval]	% Weight
Abidia et al	3.000	0.140	64.262	14.08
Doctor et al	2.000	0.429	9.321	24.76
Duzgan et al	0.167	0.062	0.446	29.18
Faglia et al	1.650	0.975	2.793	31.98
D+L pooled RR	0.964	0.212	4.384	100.00

Heterogeneity chi-squared = 19.61 (d.f. = 3) p = 0.000
I-squared (variation in RR attributable to heterogeneity) = 84.7%
Estimate of between-study variance Tau-squared = 1.7942

Test of RR=1 : z= 0.05 p = 0.963



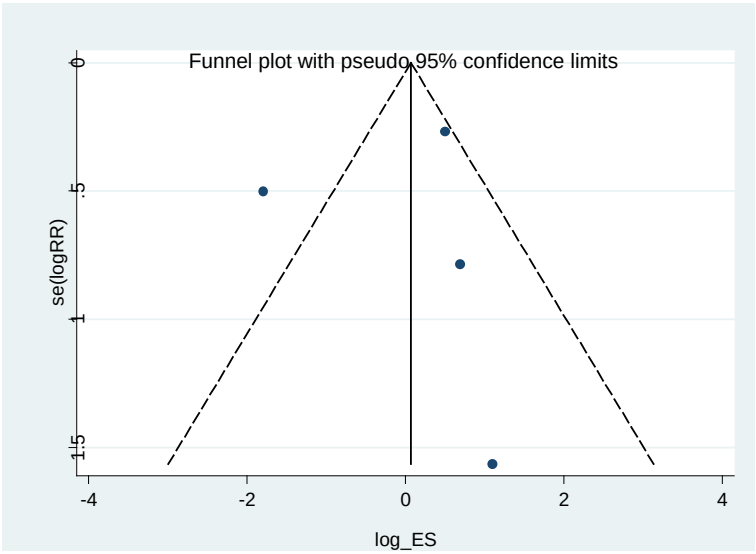
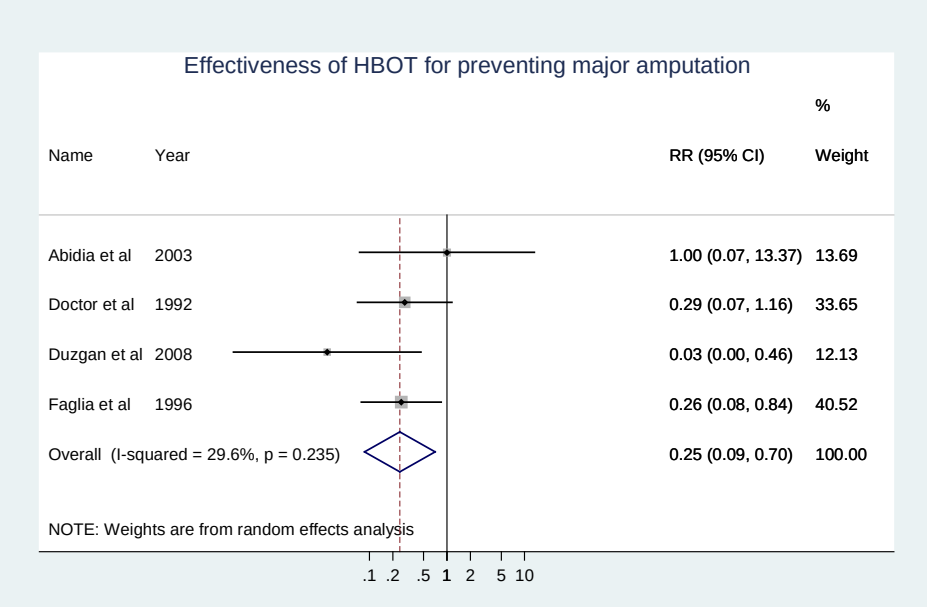


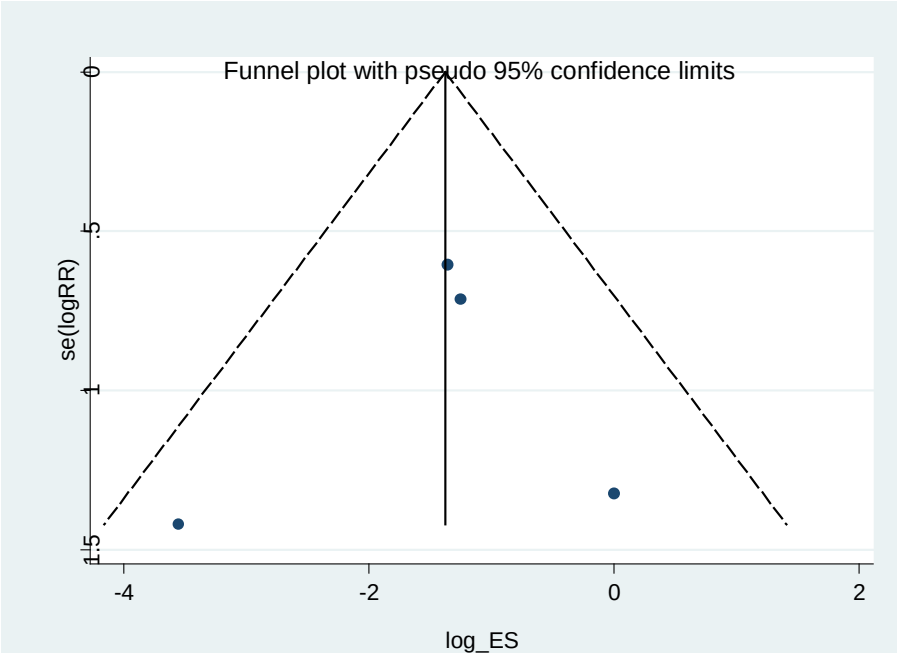
Figure 8 Meta-analysis of the effectiveness of HBOT for diabetic foot ulcers in preventing major amputation

Study	RR	[95% Conf.	Interval]	% Weight
Abidia et al	1.000	0.075	13.367	13.69
Doctor et al	0.286	0.071	1.158	33.65
Duzgan et al	0.029	0.002	0.462	12.13
Faglia et al	0.257	0.079	0.841	40.52
D+L pooled RR	0.246	0.086	0.701	100.00

Heterogeneity chi-squared = 4.26 (d.f. = 3) p = 0.235
I-squared (variation in RR attributable to heterogeneity) = 29.6%
Estimate of between-study variance Tau-squared = 0.3411

Test of RR=1 : z= 2.62 p = 0.009





Negative pressure wound Therapy

For treating diabetic foot ulcers

Negative pressure therapy is non-invasive and creates a localised controlled sub-atmospheric pressure environment to promote faster wound healing (Blume et al 2008). Healing is facilitated through increased local blood flow, the formation of granulation tissue and decreased bacterial colonisation (Etoz et al 2004). Several different companies manufacture equipment suitable to use for negative pressure therapy.

Six level II studies (2 of good quality, and 4 of average quality) investigated the effectiveness of negative pressure therapy in treating diabetic foot ulcers (Table 81). However, five of these studies were small and likely to have been underpowered. The devices and pressures used by these studies include: the Vacuum Assisted Closure (VAC) device (KCI Inc, USA) set at -125 mmHg, the Vasotrain-447 (Enraf-Noniua, the Netherlands) which cycled between -75 and +38.5 mmHg, a standard medical aspirator system (Bicakcilar Inc, Turkey) set at -125 mmHg, and a locally constructed topical negative pressure device (India) set at -125 mmHg. Only one device differed substantially from the others; the Vasotrain-447 which delivers both negative and positive pressure. This mechanism of action relies on the concept that cycles of vacuum (negative pressure) and compression (positive pressure) are reported to increase capillary filling (Akbari et al 2007).

Blume et al (2008) conducted a multi-centre, randomised controlled trial of good quality involving 1 Canadian and 28 US sites and 335 diabetic patients aged 18 years and over. The patients had a Wagner stage 2 or 3 calaneal, dorsal, or plantar foot ulcer, of at least 2 cm^2 in area after debridement and received either negative pressure therapy or advanced moist wound therapy. Negative pressure therapy was carried out using the VAC system programmed according to the manufacturer's guidelines to deliver controlled negative pressure until wound closure. Advanced moist wound therapy consisted of standard wound care using hydrogel, alginate, saline, collagen, hydrocolloid or some other moist wound dressings as the primary dressing. There were significant differences in the outcomes for negative pressure therapy compared to advanced moist wound therapy. Whereas 43.2% of patients undergoing negative pressure therapy healed by secondary intention (100% re-epithelisation), only 28.9% of those receiving advanced moist wound therapy had similar outcomes (RR = 1.49 [95% CI 1.12, 2.01]). Thus, seven patients would need to be treated with negative pressure therapy instead of advanced moist wound therapy for one patient to receive additional clinical benefit (NNT = 7 [95% CI 4, 25]). The patients receiving negative pressure therapy also healed faster than those receiving advanced moist wound therapy (mean ulcer area reduction of 32% compared to 23%; p = 0.021). Additionally the number of patients that required a subsequent minor amputation reduced after negative pressure therapy compared to advanced moist wound therapy (1.2% versus 7.8%; RR = 0.15 [95% CI 0.04, 0.58]), whereas the risk of requiring a major amputation was similar for both groups (RR = 1.23 [95% CI 0.36, 4.18]). Sixteen patients would need to be treated with negative pressure therapy instead of advanced moist wound therapy in order to save one additional patient from requiring an amputation (NNT = 16 [95% CI 10, 173]). The authors have indicated that negative pressure therapy should be carried out in conjunction with debridement, and in this study all patients were initially debrided although it is not clear to what level ie sharp, surgical. It is also not clear from the study if patients were debrided regularly throughout the study period, as required or only at the beginning of the study.

Mody et al (2008) conducted a randomised controlled trial of good quality involving 48 patients admitted to the general surgery, physical medicine and rehabilitation wards of the Christian Medical College, India, for an acute or chronic extremity, sacral or abdominal wound that could

not heal without primary intention (surgical closure). Thus, the wounds in this study were quite severe. This trial included 15 diabetic patients with neuropathic foot ulcers; 6 received negative pressure wound therapy and 9 received standard wound care. As a consequence, the study is likely to have been underpowered for the different outcomes in patients with diabetic foot ulcer. All wounds were surgically debrided as required to remove necrotic tissue. Negative pressure was produced via a locally made system consisting of a wall suction canister set which delivered -125 mmHg and a timer which cycled the suction for 2 minutes on followed by 5 minutes off). There were no statistically significant differences in the number of ulcers that healed, either by delayed primary (surgical closure of healthy granulated wound) or secondary intention (100% re-epithelialisation of ulcer), or for the time to satisfactory healing for either the diabetic foot ulcers or for all the ulcers in this study.

Etoz et al (2004, 2007) conducted a small randomised controlled trial of average quality involving 24 diabetic patients with non-healing wounds of the lower extremity that attended a medical centre in Turkey. The effectiveness of negative pressure therapy was evaluated compared to standard wound care. Negative pressure therapy was carried out using a standard medical aspirator pump set at 125 mmHg continuous negative pressure. Some patients receiving negative pressure therapy experienced bleeding during dressing changes, due to granulation tissue growth into the sponge covering the ulcer. The authors reported that the outcomes for % reduction in ulcer area and for the length of therapy needed to heal sufficiently for primary intention (surgical closure) were significantly better in the group that received negative pressure therapy compared to those that received standard wound care ($p < 0.05$).

Akbari et al (2007) also conducted a small randomised controlled trial of average quality involving 18 diabetic patients with a grade 2 (University of Texas Diabetic wound classification) foot ulcer that penetrated to tendon or capsule, but not involving bone or joint, attending the Razmejo-Moghadam Outpatient Clinic in Iran. In this study, vacuum compression therapy using the Vasotrain-447 set for vascular disease in addition to standard wound care was compared to standard care alone (Akbari et al 2007). The authors reported that debridement was performed as part of standard wound care however; they did not provide information regarding frequency or the level of debridement. There was a significantly larger reduction in the size of the ulcer after vacuum compression therapy (11.79 ± 9.54) when compared to standard wound care (3.73 ± 3.14; $p = 0.03$). Additionally, 55.6% of the ulcers in the vacuum compression therapy group healed compared to 11.1% in the standard wound care group (RR = 5.0 [95% CI 1.03, 30.55]). Only two patients would need to be treated with negative pressure therapy instead of standard wound care for one additional patient to experience an improvement in a foot ulcer (NNT = 2 [2, 112].

Another very small randomised controlled trial (McCallon et al 2000) of average quality involving 10 diabetic patients with a non-healing foot ulcer assessed the effectiveness of negative pressure therapy compared with standard wound care. Negative pressure therapy was carried out at the Diabetic Foot Clinic at Louisiana State University Health Science Centre using the VAC system at -125 mmHg continuous negative pressure for the first 48 h, then intermittent suction at 125 mmHg. As in the previous study, some patients receiving negative pressure therapy experienced bleeding during dressing changes due to granulation tissue growth into the sponge. There were no statistically significant differences between the negative pressure therapy and standard wound care groups for numbers of ulcer healed by either primary or secondary intention, the time to satisfactory healing, or the % reduction of ulcer surface area. It is likely that the study was underpowered to find a difference in these outcomes between the two groups.

Eginton et al (2003) conducted a cross-over randomised controlled trial of average quality involving 6 diabetic patients (with 7 ulcers) attending Froedtert Memorial Hospital or the Clement J Zablocki Veterans Affairs Medical Centre in Milwaukee, Wisconsin. The patients had significant soft tissue damage of the foot that was not expected to heal in 1 month and had adequate perfusion. Negative pressure therapy was compared to standard wound care with a hydrocolloid wound gel and was carried out using the VAC system at -125 mmHg continuous negative pressure, as per manufacturer's instructions. The patients were randomised to receive one of the two treatments for two weeks and then were crossed over to receive the other treatment for another two weeks. This study was extremely small and any potential carry-over effect from the previous treatment was not allowed for at cross-over. Nevertheless, there was a difference in the % reduction of wound area and volume for each 2 week period of treatment between the two groups. There was also a trend towards faster healing in the negative pressure group compared to standard wound care but although the difference in % reduction in the depth and volume of the ulcer were statistically significant ($p < 0.05$ and $p < 0.005$, respectively), the difference in % reduction of ulcer area was not.

Overall, there does seem to be a clinical benefit in using negative pressure therapy after debridement, to treat diabetic foot ulcers compared to using standard wound care. All four studies that looked at the % reduction in ulcer size, showed a statistically significant greater reduction in ulcer size in patients receiving negative pressure therapy compared to those receiving standard wound care (Akbari et al 2007; Blume et al 2008; Eginton et al 2003; Etoz et al 2003:2004). However, of the three studies that investigated the number of ulcers that healed by primary and secondary intention, only one large multicentre study reported a statistically significant increase in the number of ulcers that healed by secondary intention in patients treated with negative pressure therapy compared to those treated with standard wound care (Blume et al 2008). The other two studies were much smaller and showed no statistically significant benefits for using negative pressure therapy compared to standard wound care (McCallon et al 2000; Mody et al 2008). Only one study investigated the effect on amputation rate, showing that there was a statistically significant reduction in the number of minor amputations required by patients receiving negative wound therapy compared to those receiving standard wound care (Blume et al 2008).

Box 118 Evidence statement matrix for negative pressure therapy in addition to standard wound care

Component	Rating	Description
Evidence base	B	Six level II studies (2 with a low risk of bias, and 4 with a moderate risk of bias)
Consistency	B	All 4 studies reporting % reduction in ulcer size were consistent. The 3 studies reporting number of ulcers healed showed some inconsistent trends, but this was probably due to the small size of two of the studies.
Clinical impact	C	Moderate clinical impact. Four studies showed statistically significant % reductions in wound size, the large multicentre study showed a statistically significant difference in the number of ulcers that healed by secondary intention and the number of amputations.
Generalisability	B	The population consisted of diabetic patients who had undergone debridement (generally surgical) for non-healing foot ulcers (plus a few leg ulcers), with and without infections, with varied degrees of severity.
Applicability	C	Three studies were conducted in USA, which has similar healthcare for diabetes patients when compared to the Australian healthcare context. The other three studies took place in Turkey, Iran, and India, which have different healthcare for diabetes patients when compared to the Australian healthcare context.

Evidence statement

Negative pressure therapy after surgical debridement may improve wound healing and reduce the need for minor amputations when compared to standard wound care for the treatment of non-healing diabetic foot ulcers (Grade B).

Table 81 Studies included which investigate the effectiveness of negative-pressure wound therapy in the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Blume et al 2008) USA/Canada	Level II RCT Good quality study	N = 335. Diabetic patients aged 18 years and over, with a Wagner stage 2 or 3 calaneal, dorsal, or plantar foot ulcer, of at least 2 cm^2 in area after debridement. Intervention group: n = 169; age (yrs) 58 ± 12; male 141/169 (83.4%); diabetes type 1 15/169 (8.9%); African American 28/169 (16.6%); Caucasian 95/169 (56.2%); Hispanic 41/169 (24.3%); Native American 3/169 (2.2%); other 2/169 (1.2%); weight (kg) 99.2 ± 25.1; height (cm) 175.0 ± 9.6; current smoker 34/169 (20.1%); drink alcohol 37/169 (21.9%); prealbumin (g/l) 21.1 ± 7.6; albumin (g/l) 3.4 ± 0.6; % HbA_{1c} 8.3 ± 2.0; ankle-brachial index 1.0 ± 0.2; $TcPO_2$ (mmHg) 43.2 ± 10.4; loss of protective sensation 150/166 (90.4%); ulcer duration (days) 198.3 ± 323.5; ulcer area (cm^2) 13.5 ± 18.2; prior treatment for ulcer infection 50/169 (29.6%). Comparator group: n = 166; age (yrs) 59 ± 12; male 122/166 (73.5%); diabetes type 1 14/166 (8.4%); African American 22/166 (13.3%); Caucasian 100/166 (60.2%); Hispanic 40/166 (24.1%); Native American 3/166 (1.8%); other 1/166 (0.6%); weight (kg) 93.8 ± 25.6; height (cm) 175.0 ± 12.4; current smoker 32/166 (19.4%); drink alcohol 45/166 (27.1%); prealbumin (g/l) 19.9 ± 7.9; albumin (g/l) 3.4 ± 0.8; % HbA_{1c} 8.1 ± 1.9; ankle-brachial index 1.0 ± 0.2; $TcPO_2$ (mmHg) 43.3 ± 12.5; loss of protective sensation 143/161 (88.8%); ulcer duration (days) 206.0 ± 365.9; ulcer area (cm^2) 11.0 ± 12.7; prior treatment for ulcer infection 45/166 (27.1%).	n = 169. Debridement[a] of diabetic ulcer plus Negative Pressure vacuum-assisted Wound Therapy (NPWT) plus conventional wound care plus offloading therapy as deemed necessary NPWT was via the Vacuum Assisted Closure device, which was programmed according to the manufacturer's guidelines to deliver controlled negative pressure until wound closure.	n = 166. Debridement of diabetic ulcer plus Advanced Moist Wound Therapy (AMWT): Hydrogels n = 78 Alginate n = 31 Saline n = 17 Collagen n= 11 Hydrocolloid n = 1 Other n = 28 Plus conventional wound care plus offloading therapy as deemed necessary	Number of ulcers that healed by secondary intention with complete closure (100% re-epithelialisation) 73/169 (43.2%) Number of patients with ulcers that healed with primary intention (required surgical closure) 16/169 (9.5%) Number of ulcers that healed in total 89/169 (52.7%) Number of patients with 75% ulcer closure 105/169 (62%) Ulcer area reduction -4.32 cm^2 (32%) Number of patients requiring a secondary amputation Minor: 2/169 (1.2%) Major: 5/169	48/166 (28.9%) 14/166 (8.4%) 62/166 (37.3%) 85/166 (51%) -2.53 cm^2 (23%) 13/166 (7.8%) 4/166	RR = 1.49 [95% CI 1.12, 2.01] NNT = 7 [95% CI 4, 25] RR = 1.12 [95% CI 0.57, 2.21] RR = 1.41 [95% CI 1.11, 1.80] NNT = 7 [95% CI 4, 21] RR = 1.21 [95% CI 1.01, 1.46] NNT = 9 [95% CI 5, 319] p = 0.021 RR = 0.15 [95% CI 0.04, 0.58] NNT = 15 [95% CI 12, 42] RR = 1.23

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
					(3.0%)	(2.4%)	[95% CI 0.36, 4.18]
					Total: 7/169 (4.1%)	17/166 (10.2%)	RR = 0.40 [95% CI 0.18, 0.92] NNT = 16 [95% CI 10, 173]
					No. patients that developed infections or oedema (harms)		
					16/169 (9.5%)	11/166 (6.6%)	RR = 1.43 [95% CI 0.70, 2.96]
(Mody et al 2008) India	Level II RCT Good quality study	N = 48. Patients admitted to the general surgery, physical medicine, and rehabilitation wards of Christian Medical College and referred by the surgical consultants for care of an acute or chronic extremity, sacral, or abdominal wound that could not be treated with primary closure Intervention group: n = 15; diabetic foot ulcer 6/15 (40%); pressure ulcer 2/15 (13%); pressure ulcer area (cm^2) 157.8 ± 72.2; cellulitis/fasciitis wound 3/15 (20%); cellulitis/fasciitis wound area (cm^2) 151.4 ± 163.3; other 4/15 (27%); other ulcer area (cm^2) 20.9 ± 10.7. Diabetic foot ulcers: N = 6; age (yrs) 53.2 ± 15.1; male 4/6 (67%); ulcer duration (days) 8.5 ± 8.3; mean ulcer area (cm^2) 25.7 ± 9.7. Comparator group: n = 33; diabetic foot ulcer 9/33 (27%); pressure ulcer 9/33 (27%); pressure ulcer area (cm^2) 59.6 ± 57.5; cellulitis/fasciitis wound 8/33 (24%); cellulitis/fasciitis wound area (cm^2) 286.6 ± 456.3;	n = 15, n = 6 diabetic patients After initial surgical debridement patients were treated with topical negative pressure (TNP) via a wall suction canister set (locally made) at 125 mmHg and a TNP timer set to intermittently cycle wall suction to 2 mins on followed by 5 mins off. In sensitive wounds suction pressure was reduced to a tolerable level, usually 50-100 mmHg and increased as	n = 33, n = 9 diabetic patients. Diabetics with neuropathic foot ulcers were treated with saline-soaked gauze and dry gauze dressings following surgical debridement of the wound.	Number of days to satisfactory healing: All ulcers 35.9 ± 44.5	28.4 ± 18.9	p = 0.66
					Diabetic foot ulcers 107 (n = 1)	25.6 ± 21.9	p = NS
					Number of ulcers that closed by secondary intention (100% re-epithelialisation): All ulcers 2/15 (13.3%)	2/33 (6.1%)	RR = 2.20 [95% CI 0.40, 11.96]
					Diabetic foot ulcers 1/6 (16.7%)	1/9 (11.1%)	RR = 1.50 [95% CI 0.16, 13.68]
					Number of ulcers that closed by delayed primary intention (surgical closure): All ulcers		

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
		other 7/33 (21%); other ulcer area (cm^2) 103.1 ± 82.0. Diabetic foot ulcers: N = 9; age (yrs) 59.6 ± 8.5, male 6/9 (67%); ulcer duration (days) 5.2 ± 2.3; ulcer area (cm^2) 48.1 ± 53.4.	comfort allowed.		5/15 (33.3%) Diabetic foot ulcers 0/6 (0%)	14/33 (42.4%) 1/9 (11.1%)	RR = 0.79 [95% CI 0.33, 1.63] RR = 0.00 [95% CI 0.00, 5.48]
					Number of ulcers that achieved satisfactory healing: All ulcers 7/15 (47.7%) Diabetic foot ulcers 1/6 (16.7%)		 16/33 (48.4%) 2/9 (22.2%)	 RR = 0.93 [95% CI 0.48, 1.69] RR = 0.75 [95% CI 0.10, 4.96]
(Etoz et al 2004; Etoz & Kahveci 2007) Turkey	Level II RCT Average quality study	N = 24. Diabetic patients with non-healing wounds of the lower extremity. Type 1 diabetes 17/24 ((71%); type 2 diabetes 7/24 (29%); peripheral neuropathy 15/24 (62.5%). Intervention group: n = 12; age (yrs) 66.2 ± 6.8; male 10/12 (83.3%); vascular dysfunction requiring revascularisation 3/12 (25%); chronic renal failure 1/12 (8.3%); ulcer area (cm^2) 109 ± 68.6. Comparator group: n = 12; age (yrs) 64.7 ± 5.2; male 11/12 (91.7%); vascular dysfunction requiring revascularisation 2/12 (16.7%); chronic renal failure 0/12 (0%); ulcer area (cm^2) 94.8 ± 20.9.	n = 12 Initial surgical debridement of wound followed by Negative Pressure Wound Therapy using a standard medical aspirator pump set at 125 mmHg continuous pressure.	n = 12 Initial surgical debridement of wound followed by saline-moisturised gauze dressings changed twice daily.	Number of ulcers closed by primary intention (surgical closure) 10/12 (83.3%) Reduction in ulcer area (cm^2) 19.5 ± 11.7 (17.9%) Length of therapy until wound sufficiently healed for primary intention (surgical closure) 11.25 ± 5.5	 9/12 (75%) 9.5 ± 4.11 (10%) 15.75 ± 2.5	 RR = 1.11 [95% CI 0.77, 1.49] p = 0.03 p = 0.05
(Akbari et al 2007) Iran	Level II RCT Average quality study	N = 18. Diabetic patients with a grade 2 (University of Texas Diabetic wound classification) foot ulcer that penetrates to tendon or capsule, but not involving bone or joint, with no history of deep venous thrombosis attending the Razmejo-Moghadam Outpatient Clinic. BMI (kg/m^2) 23.44 ± 3.7; ulcer duration (days) 45 ±	n = 9. Vacuum compression therapy using the Vasotrain-447 set for vascular disease, and delivering 75 mmHg negative pressure for 60	n = 9. Conventional wound therapy (debridement[a], blood glucose control, systematic antibiotics, wound cleaning with saline, offloading and	Number of patients with ulcers that improved 5/9 (55.6%) Reduction in ulcer size (mm^2)	 1/9 (11.1%)	 RR = 5.00 [95% CI 1.03, 30.55] NNT = 2 [95% CI 2, 112]

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
		6.7. Haemoglobin, albumin, and wound location were similar in both groups. Intervention group: n = 9; age 58.2 ± 8.07; male 2/9 (22.2%); ulcer area (mm^2) 46.88 ± 9.28. Comparator group: n = 9; age 57.6 ± 8.02; male 1/9 (11.1%); ulcer area (mm^2) 46.62 ± 10.03.	s, then 38.5 mmHg positive pressure for 30 s for 1 h/day, 4 times/week, for a total of 12 sessions plus same conventional wound therapy as control group	daily wound dressings)	11.79 ± 9.54 (25.1%)	3.73 ± 3.14 (8%)	p = 0.03
(McCallon et al 2000) USA	Level II RCT Average quality study	N = 10. Diabetic patients aged 18 to 75 years, with a non-healing foot ulcer that had been present longer than one month, attending the Diabetic Foot Clinic at Louisiana State University Health Science Centre. Intervention group: n = 5; age (yrs) 55.4 ± 12.8; blood glucose (mg/dl) 141 ± 37.5. Comparator group: n = 5; age (yrs) 50.2 ± 8.7; blood glucose (mg/dl) 151 ± 51.2. Haemoglobin, albumin, of wound location and the ulcer surface area were similar in both groups.	n = 5. Surgical debridement of foot ulcer plus treatment with Vacuum-assisted Closure device. Treatment was in accordance with the manufacturer's protocol for chronic wounds. The pressure was set at continuous suction at 125 mmHg for the first 48 h, then intermittent suction at 125 mmHg.	n = 5. Surgical debridement of foot ulcer plus standard treatment with saline-moistened gauze changed twice a day	Time to satisfactory healing (days) 22.8 ± 17.4 Number of ulcers healed by secondary intention (epithelialisation) 1/5 (20%) Number of ulcers healed by delayed primary intention (surgical closure) 4/5 (80%) % reduction in surface area 28.4 ± 24.3	42.8 ± 32.5 3/5 (60%) 2/5 (40%) 9.5 ± 16.9	p = 0.26 RR = 0.33 [95% CI 0.06, 1.64] RR = 2.00 [95% CI 0.72, 3.97] p = 0.19
(Eginton et al 2003) USA	Level II cross-over RCT Average quality study	N = 6 patients; n = 7 wounds. Diabetic patients attending Froedtert Memorial Hospital or the Clement J Zablocki Veterans Affairs Medical Centre in Milwaukee, WI, who had significant soft tissue damage of the foot with adequate perfusion and that was not expected to heal in 1 month. male 5/6 (83.3%); ulcer length (cm) 7.7 ± 1.6; ulcer width (cm) 3.5 ± 0.6; ulcer depth (cm) 3.1 ± 0.9.	n = 7 ulcers. Cross-over design, After sharp debridement, randomly assigned to receive treatment for the first 2 weeks using: the Vacuum Assisted Closure device at -125 mmHg continuous negative pressure, as per manufacturer's	n = 7 ulcers or conventional moist dressings changed daily with hydrocolloid wound gel Then crossing-over to receive other treatment	% reduction in wound area, volume and depth in 2 weeks Area 16.4 ± 6.2 Volume 59 ± 9.7 Depth 49 ± 11.1	 -5.9 ± 17.4 0.1 ±14.7 7.7 ± 5.2	 p = NS p < 0.005 p < 0.05

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
			instructions	for 2 weeks.			

[a] level of debridement not reported; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot; University of Texas Diabetic Foot Classification System: 01. A0 Pre – or post ulcerative lesion completely epithelialized, 02. A1 superficial wound not involving tendon, capsule or bone, 03. A2 Wound penetrating to tendon or capsule, 04. A3 wound penetrating to bone or joint, 05. B0 pre or post ulcerative lesion completely epithelialized with infection, 06. B1 superficial wound, not involving tendon, capsule or bone with infection, 07. B2 wound penetrating to tendon or capsule with infection, 08. B3 wound penetrating to bone or joint with infection, 09. C0 pre or post ulcerative lesion completely epithelialized with ischaemia, 10. C1 superficial wound not involving tendon, capsule or bone with ischaemia, 11. C2 wound penetrating to tendon or capsule with ischaemia, 12. C3 wound penetrating to bone or joint with ischaemia, 13. D0 pre or post ulcerative lesion completely epithelialized with infection and ischaemia, 14. D1 superficial wound not involving tendon, capsule or bone with infection and ischaemia, 15. D2 wound penetrating to tendon or capsule with infection and ischaemia, 16. D3 wound penetrating to bone or joint with infection and ischaemia

For treating diabetic foot amputation wounds

One average quality study provided data from a multi-centred study regarding the use of negative pressure wound therapy (NPWT) in diabetic patients who had undergone amputation of the lower limb (Armstrong & Lavery 2005).

Armstrong et al (2005) randomised patients to either NPWT or standard wound care which included moist wound therapy with alginates, hydrocolloids, foams or hydrogels. Dressings in the standard wound care group were changed daily unless otherwise recommended by the clinician. Patients in this group were also provided with off-loading when indicated.

Patients, who were allocated to receive NPWT, did so every 48 hours according to standardised treatment guidelines. No further details regarding the application of this therapy were provided however, as for the control group, all patients received off-loading therapy when indicated.

The primary outcome of the study was complete wound closure of amputation wounds with secondary outcomes of wound healing rate, foot salvage and adverse events. The authors defined complete wound closure as 100 per cent epithelialisation without drainage and outcome ascertainment was performed by clinical wound investigation, photographs and planimetric assessment. As it was not possible for either patient or treating physician to be masked to treatment allocation, the assessment of planimetric measurements was performed blinded to allocation.

After the 112 day study period 43/77 (56%) patients who received NPWT had completely healed compared with 33/85 (39%) who received standard wound care had healed (RR = 1.4 [95% CI 1.03, 2.00], p = 0.04) (

Table 82). In regard to healing by secondary intention, 31/77 (40%) in the NPWT group healed compared to 25/85 (30%) receiving standard wound care (RR = 1.34 [95% CI 0.89, 2.09]). For healing by primary intention, 12/77 (16%) healed in the NPWT group compared to 8/85 (9%) in the standard wound care group (RR = 1.65 [95% CI 0.72, 3.83], p = 0.23).

The difference in median time to complete healing was statistically significantly reduced in those who received NPWT compared to standard wound care (median = 42 days (interquartile range = 26–92 days) and 77 days (interquartile range = 40–112 days) respectively, p = 0.005). However, in considering these results it should be noted that less than 50% of patients in the standard wound care group achieved complete wound healing. Patients in the NPWT group were less likely to require further amputation than those receiving standard wound care however this was not a statistically significant difference (2/77 (3%) and 9/85 (11%) respectively, OR = 0.23 [95% CI 0.05, 1.1], p = 0.06).

This evidence is summarised in Box 121 according to NHMRC criteria.

Box 119 Evidence statement matrix for NWPT versus standard wound care

Component	Rating	Description
Evidence base	C	One level II study with a moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	C	There would be a moderate clinical impact for healing of amputation wounds overall and a significant reduction in time to healing.
Generalisability	B	Populations consisted of people with type II diabetes with an amputation wound and with evidence of adequate perfusion.
Applicability	B	This study was conducted in a number of centres in the USA and would therefore be applicable to the Australian healthcare context with few caveats.

Evidence statement

There is some evidence to suggest that treatment with NPWT may increase the number of patients who achieve complete healing of amputation wounds in people with diabetes and evidence of adequate perfusion. There is also evidence that the time taken to achieve complete healing is reduced in patients receiving NPWT compared to standard wound care (Grade C).

Table 82 Included study of NPWT versus standard wound care

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data Intervention Effect size [95% CI] Comparator p-value
(Armstrong & Lavery 2005) USA	II RCT SIGN: Average quality	N = 162 Patients age ≥ 18 years with a wound from a diabetic foot amputation to the transmetatarsal level and evidence of adequate perfusion.	n = 77 Negative pressure wound therapy applied every 48 hours plus off-loading therapy as indicated.	n = 85 Standard wound care using moist wound therapy with alginates, hydrocolloids, foams or hydrogels. Dressings were changed daily and off-loading therapy provided when indicated.	All healed wounds: 43/77 (56%) 33/85 (39%) RR = 1.4 [95% CI 1.03, 2.00] p = 0.04 Healed by secondary intention: 31/77 (40%) 25/85 (30%) RR = 1.34[a] [95% CI 0.89, 2.09] p = 0.15[a] Healed by primary intention: 12/77 (16%) 8/85 (9%) RR = 1.65[a] [95% CI 0.72, 3.83] p = 0.23[a] Time to healing (Median (IQR)): 56 days (26–92) 77 days (40–112) p = 0.005 Time to achieved 76–100% granulation (with 0–10% granulation at baseline): 42 days (40–56) (n = 19) 84 days (57–112) (n = 15) p = 0.002 Time to achieved 76–100% granulation (with 0–25% granulation at baseline): 42 days (14–56) (n = NR) 82 days (28–112) (n = NR) p = 0.01 Second amputation: 2/77 (3%) 9/85 (11%) OR = 0.23 [95% CI 0.05, 1.1] p = 0.06 One or more adverse events: 40/77 (52%) 46/85 (54%) p = 0.875 Infections or infestations: 25/77 (32%) 27/85 (32%)

					p = 1.0 Treatment related adverse event: 9/77 (12%) 2/85 (2%)

[a] calculated by evaluators after data extraction; IQR = interquartile range; NR = not reported; N/A = not applicable

Nutritional supplements

Two good quality level II RCTs investigated the use of nutritional supplements as treatment for diabetic foot ulcers (Table 83). Eneroth et al (2004) compared 400mL of a 400 kcal nutritional supplement versus 400mL of placebo given daily for six months to patients with diabetic foot ulcers. No significant benefit in wound healing was observed between participants in the intervention and placebo groups. The number of wounds healed at six months was 46 percent (12/26) for the intervention group and 37 percent (10/27) for the control group (RR=1.25, 95% CI [0.56, 2.36]).

Leung et al (2008) compared twice daily intake of a herbal nutritional supplement against the twice daily intake of a starch placebo. The primary outcome of the study was limb salvage and findings showed that three participants in the intervention group and nine in the placebo group required an amputation (RR=0.33, 95% CI [0.10, 1.04], p=0.06). This trend in protective effect for the herbal nutritional supplement could not be explained by the distribution of baseline characteristics in the two groups. Time to healing was also not statistically significant for the intervention group (5.9±1.4 weeks) versus the placebo group (9.2±1.9 weeks, p=0.147), although was reduced in the intervention group.

The benefit of using nutritional supplements for the treatment of diabetic foot ulcers has not been conclusively established. Different supplements were used in each of the studies and the trend towards a positive outcome for the intervention did not reach statistical significance on any of the measures relevant to this investigation.

Box 120 Evidence statement matrix for nutritional supplements

Component	Rating	Description
Evidence base	B	Two good quality level II RCTs with a low risk of bias
Consistency	C	Some inconsistency reflecting genuine uncertainty around question
Clinical impact	D	Slight and uncertain clinical impact regarding number of amputations and time to healing
Generalisability	B	Generalisable to target population of diabetic patients with chronic foot ulcers
Applicability	B	Evidence applicable to the Australian healthcare context with few caveats

Evidence statement

The evidence suggests that nutritional supplements show a positive trend towards improving outcomes for people with diabetic foot ulcers however the differences did not reach statistical significance. Further research is required to confirm any such effect, as well as determine which type of nutritional supplement is associated with the potential benefit (Grade B).

Table 83 Nutritional supplements

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
(Eneroth et al 2004) Sweden	Level II RCT. Good quality study	N=53 diabetic patients referred for diabetic foot care for a Wagner Grade I or II foot ulcers of at least 4 weeks duration. Intervention group: n=26, mean age 74 (range 59-88) years, male 73% (n=19), duration of diabetes (yrs) 16 (range 1-51), insulin use 69% (n=18), smoking history 52% (n=12), neuropathy 100% (n=23), retinopathy 57% (n=13), nephropathy 29% (n=7), hypertension 77% (n=20), ischaemic heart disease 46% (n=12), cardiac failure 23% (n=6), cerebrovascular lesion 15% (n=4), palpable pulses (foot) 12% (n=3), ulcer duration 25 (range 4-100) weeks, ulcer area 3.3±5.8 cm^2, group wound size: <1 cm^2 38% (n=10), 1-3 cm^2 31% (n=8), >3 cm^2 31% (n=8), ulcer site: toes 58% (n=15), mid/hind foot 15% (n=4), plantar metatarsal 27% (n=7), ulcer characteristics: oedema 48% (n=12), rest pain 37% (n=8), increased temperature 30% (n=7), secretion 36% (n=9), necrosis 40% (n=10), granulation 56% (n=14), hyperkeratosis 16% (n=4) Control group: n=27, mean age 75 (range 61-85) years, male 78% (n=21), duration of diabetes (yrs) 15 (range 1-41), insulin use 81% (n=22), smoking history 37% (n=10), neuropathy 92% (n=24), retinopathy 62% (n=16), nephropathy 42% (n=11), hypertension 63% (n=17), ischaemic heart disease 41% (n=11), cardiac failure 19% (n=5), cerebrovascular disease 26% (n=7), palpable pulses (foot) 37% (n=10), ulcer duration 22 (range 4-105) weeks, ulcer area	n=26 Standard wound care plus 400ml Fortinel between meals every day for 6 months	n=27 Standard wound care plus 400 ml placebo, similar in taste and appearance to intervention, every day for 6 months	Number of wound healed at 6 months		
					Intervention 46% (12/26)	Control 37% (10/27)	Effect size [95% CI] RR=1.25 [0.66, 2.36]

<table>
<tr><th>Author
Country</th><th>Level and quality of study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Outcome data</th></tr>
<tr><td></td><td></td><td>4.7 ± 6.7 cm^2, group wound size: <1 cm^2 22% (n=6), 1-3 cm^2 37% (n=10), >3 cm^2 41% (n=11), ulcer site: toes 33% (n=9), mid/hind foot 41% (n=11), plantar metatarsal 26% (n=7), ulcer characteristics: oedema 56% (n=15), rest pain 32% (n=7), increased temperature 19% (n=5), secretion 52% (n=14), necrosis 19% (n=5), granulation 59% (n=16), hyperkeratosis 35% (n=7).</td><td></td><td></td><td></td></tr>
<tr><td>(Leung et al 2008)
Hong Kong</td><td>Level II RCT.
Good quality study</td><td>N=80 diabetic patients with chronic foot ulcers of 7-25 weeks duration.
Intervention group: n=40, mean age 66.3 ± 12.6 years, male 63% (n=25), diabetes type II 88% (n=35), duration of diabetes (yrs) 8.4 ± 7.6, insulin therapy 18% (n=7), oral hypoglycaemic 70% (n=28), diet controlled 13% (n=5), diabetic control: good (steady) 51% (n=19), fair (occasionally fluctuating) 38% (n=14), poor (fluctuating) 8% (n=4), smoker 33% (n=13), body weight 59.1 ± 12.3 kg, serum albumin level 31.7 ± 4.5 g/L, ulcer characteristics: duration 7.8 ± 8.2 weeks, surface area 28.7 ± 31.3 cm^2, ulcer bed: infected with slough 80% (n=30), oedematous with patchy necrosis 17% (n=6), relatively clean 3% (n=1), gangrenous tissue: dry 32% (n=12), wet 50% (n=19), none 18% (n=7).
Control group: n=40, mean age 68.5 ± 11.1 years, male 55% (n=22), diabetes type II 77% (n=30), duration of diabetes (yrs) 12.4 ± 8.8, insulin therapy 20% (n=8), oral hypoglycaemic 65% (n=26), diet controlled 15% (n=6), diabetes control: good (steady)</td><td>n=40
Standard wound care consisting of antibiotic treatment as required, daily cleaning with antiseptics including debridement and dressing of ulcer, plus twice daily consumption of herbal drink containing: radix astragali, rhizoma atractylodis marcocephalae, radix stepheniae tetrandrae, radix polygoni multiflora, radix rehmanniae, radix smilax china, fructus corni, rhizoma dioscoreae, cortex moutan, rhizome alismatis, rhiozoma smilacis glabrae, and fructus schisandrae.</td><td>n=40
Standard wound care consisting of antibiotic treatment as required, daily cleaning with antiseptics including debridement and dressing of ulcer plus twice daily starch placebo drink.</td><td>
<table>
<tr><td colspan="3">Time to ulcer healing (weeks)</td></tr>
<tr><td>Intervention
5.9±1.4</td><td>Control
9.2±1.9</td><td>p=0.15</td></tr>
<tr><td colspan="3">Number of ulcers improved</td></tr>
<tr><td>Intervention
77.5%
(31/40)</td><td>Control
62.5%
(25/40)</td><td>Effect size [95% CI]
RR=1.24 [0.93, 1.61]</td></tr>
<tr><td colspan="3">Number of amputations in first 4 weeks</td></tr>
<tr><td>Intervention
7.5% (3/40)</td><td>Control
7.5% (3/40)</td><td>Effect size [95% CI]
RR=1</td></tr>
<tr><td colspan="3">Total number of amputations</td></tr>
<tr><td>Intervention
7.5% (3/40)</td><td>Control
22.5% (9/40)</td><td>Effect size [95% CI]
RR=0.33
[0.10, 1.04] p=0.06</td></tr>
</table>
</td></tr>
</table>

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
		49% (n=17), fair (occasionally fluctuating) 49% (n=17), poor (fluctuating) 3% (n=1), smoker 40% (n=16), body weight 61.2 ± 12.3 kg, serum albumin level 32.2 ± 4.2g/L, ulcer characteristics: duration 12.9±24.6 weeks, surface area 26.7±27.3cm^2, ulcer bed: infected with slough 83% (n=30), oedematous with patchy necrosis 11% (n=4), relatively clean 6% (n=2), gangrenous tissue: dry 26% (n=8), wet 39% (n=12), none 35% (n=11)			

Wagner Classification of ulcers = Grade I = superficial ulcer, Grade II = deep ulcer to tendon, capsule or bone, Grade III = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade IV = localised gangrene of forefoot or heel, Grade V = gangrene of entire foot.

Debridement interventions for treating diabetic foot ulcers

Twenty studies (1 level I evidence of good quality, 16 level II evidence of varying quality, and 3 level III-2 evidence of average quality) investigated the effectiveness of three different debridement methods for treating diabetic foot ulcers. One of these studies investigated the effectiveness of surgical debridement compared to amputation or standard wound care alone (Table 88). Three studies investigated the effectiveness of using larval therapy for wound debridement in addition to standard wound care compared to standard care with or without surgical debridement (Table 89). Four assessed the use of hydrogels for wound debridement in addition to standard wound care compared to standard wound care alone (Table 84). Six investigated the effectiveness of advanced moist wound dressings as the primary dressing for standard wound care, compared to using dry, greasy or saline-moistened gauze (Table 85). Three studies compared the effectiveness of two different advanced moist wound therapies to treat diabetic foot ulcers (Table 86). Three studies investigated the effectiveness of using Promogran, a moist wound dressing that also inhibits metalloproteinases, as the primary dressing compared to dressings which do not inhibit metalloproteinases, in conjunction with standard wound care (Table 87).

It should be noted that a good quality study by Steed et al (1995) evaluated the effectiveness of recombinant human platelet-derived growth factor in addition to surgical debridement and standard wound care compared to surgical debridement and standard wound care alone. As surgical debridement was in both arms of the study, it does not meet the criteria for inclusion in this section of the review. The study has been discussed in the relevant growth factor section of this chapter however to summarise, the multi-centered study showed that better rates of ulcer healing for both the intervention and control arm, were seen in some centres with increased rates of debridement.

Wound debridement using advanced moist wound therapy

Advanced moist wound therapy provides a moist environment, conducive to preserving healthy tissue and promoting autolysis (the body's natural debridement process), and thus enables a rapid rate of healing (Edwards & Stapley 2010). Hydrogels and dressings that combine with wound exudate to maintain a moist wound environment, are manufactured from various hydrophilic materials such as cellulose, alginate, polyurethane, and polysaccharide, and have been used to treat diabetic foot ulcers.

Wound debridement using hydrogels versus standard wound care

A good quality systematic review (level I evidence) by Edwards and Stapley (2010) identified three randomised controlled trials that investigated the effectiveness of using hydrogels in addition to standard wound care compared to standard wound care alone (d'Hemecourt et al 1998; Jensen et al 1998; Vandeputte & Gryson 1997). The gels used in these studies were: sodium carboxymethyl cellulose, a common food thickener; Elasto-gel, which consists of glycerine and polyacrylamide (Southwest Technologies, Inc); and Carrasyn Hydrogel Wound Dressing, made of polymeric acetylated mannans from Aloe vera (Carrington Laboratories, Inc). The authors conducted a meta-analysis of these studies on two outcomes and found 52% of ulcers healed in the group using hydrogels compared to 28% of those using standard wound care alone (RR_p = 1.84 [95% CI 1.30, 2.61]). They also found that fewer adverse events occurred in the hydrogel-treated patients compared to standard care patients (22% compared to 36%; RR_p = 0.60 [95% CI 0.38, 0.95]). Additional outcomes from these three level II studies are reported below and in Table 84.

d'Hemecourt et al (1998) conducted a randomised controlled trial of good quality involving 138 diabetic patients with at least one full thickness chronic diabetic lower extremity ulcer and adequate perfusion to investigate the efficacy of using sodium carboxymethyl cellulose aqueous-based gel in addition to standard wound care to treat diabetic foot ulcers (see Table 84). The authors found that the time required to ulcer healing shortened from 141 days with standard care only, to 98 days after treatment with sodium carboxymethyl cellulose gel. However, no statistical analysis was performed on these data (d'Hemecourt et al 1998).

Vandeputte and Gryson (1997) conducted an average quality randomised controlled trial that included 29 diabetic patients with foot ulcers, that were either neuropathic or not. The effectiveness of using Elasto-gel in addition to standard wound care was compared to standard wound care alone in treating the foot ulcers. The authors reported the number of patients that required amputations reduced after hydrogel treatment (6.7% compared to 35.7% for standard care alone) but the trend did not quite reach statistical significance (RR = 0.19 [95% CI 0.03, 1.02]).

Jensen et al (1998) conducted a randomised trial of poor quality to evaluate the effectiveness of Carrasyn hydrogel wound dressing in addition to standard wound care compared to standard wound care alone in treating diabetic foot ulcers. The study involved 31 diabetic patients with Wagner grade 2 foot ulcers measuring at least 1 cm diameter, and with no evidence of infection. The authors reported on the time to healing and the number of patients that required an amputation. Neither of these outcomes showed a statistically significant difference between the two groups (Table 84).

All of these studies indicated that the use of hydrogels as an adjunct to standard wound care provided clinical benefits over using standard wound care alone by significantly increasing the number of patients with ulcers that healed, showing a trend towards shorter times taken to heal, significantly reducing the likelihood of an adverse event and potentially reducing the likelihood of requiring an amputation.

Box 121 Evidence statement matrix for hydrogel debridement therapy in addition to standard wound care

Component	Rating	Description
Evidence base	B	One study of level I evidence with a moderate risk of bias, 3 level II evidence studies (one each with a low, moderate and high risk of bias).
Consistency	A	All studies consistently showed either trends or statistically significant benefits for the number of ulcers healed, time to healing and/or reduction of ulcer size for hydrogels compared to standard wound care.
Clinical impact	B	Substantial clinical impact. There was a clinically significant increase in the number of ulcers that healed in the hydrogel treatment groups compared to those that received standard care only. The number of amputations and harms such as infections that occurred were less frequent in the hydrogel groups compared to standard care.
Generalisability	A	Population consisted of diabetic patients with foot ulcers, mostly with full-thickness ulcers with or without infection.
Applicability	B	Two studies, including the level I evidence study, were conducted in Europe (UK and Belgium), which has comparable healthcare for diabetic patients when compared to the Australian healthcare context. Two studies were conducted in USA, which has similar healthcare for diabetic patients when compared to the Australian healthcare context.

Evidence statement

Treatment of diabetic foot ulcers with hydrogels produces a substantial increase in the number of ulcers healed and reduced harms over treatment with standard care alone. (Grade B)

Table 84 Studies included which investigate the effectiveness of using Hydrogels as a debridement therapy in the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Edwards & Stapley 2010) UK	Level I systematic review Good quality study	N = 198, K = 3 Study 2: d'Hemecourt et al (1998) Diabetic patients with a full-thickness chronic diabetic foot ulcer (stage 3 or 4), > 8 weeks duration. Study 3: Jensen et al (1998) Diabetic patients with Wagner grade 2 (full-thickness not involving bones or tendons) foot ulcer of at least 1 cm diameter and adequate perfusion. Study 4: Vandeputte et al (1997) Any diabetic patient with a foot ulcer.	N = 99, K = 3 N = 70 Sodium carboxymethyl cellulose (NaCMC) aqueous-based gel plus standard wound care N = 14 Carrasyn (Acemannan) Hydrogel plus standard wound care N = 15 Hydrogel (Elasto-gel) with 65% glycerine plus standard wound care	N = 99, K = 3 N = 68 Saline dressings plus standard wound care N = 17 Saline gauze plus standard wound care N = 14 Dry gauze plus standard wound care	No. of ulcers completely healed Study 2: 25/70 (36%) Study 3: 12/14 (86%) Study 4: 14/15 (93%) Pooled: 51/99 (52%) No. of adverse events (harms) reported Study 2: 19/70 (36%) Study 3: 2/14 (86%) Study 4: 1/15 (93%) Pooled: 22/99 (22%)	 15/68 (22%) 6/17 (35%) 7/14 (50%) 28/99 (28%) 25/68 (37%) 4/17 (24%) 7/14 (50%) 36/99 (36%)	 RR = 1.62 [95% CI 0.94, 2.80] RR = 2.43 [95% CI 1.23, 4.79] RR = 1.87 [95% CI 1.09, 3.21] RR_p = 1.84 [95% CI 1.30, 2.61] RR = 0.74 [95% CI 0.45, 1.21] RR = 0.61 [95% CI 0.13, 2.84] RR = 0.13 [95% CI 0.02, 0.95] RR_p = 0.60 [95% CI 0.38, 0.95]
(d'Hemecourt et al 1998) USA	Level II RCT Good quality study	N = 138. Diabetic patients with at least one full thickness chronic diabetic lower extremity ulcer and adequate perfusion, measuring 1-10 cm^2 in size and of at least 8 weeks duration.	N = 70 Sodium carboxymeth-yl cellulose (NaCMC) acqueous-based gel	N = 68 Standard wound care which included sharp debridement, wet-to-	Time to healing (days) 98	141	

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
		Intervention group: N = 70; age (yrs) 56.9 ± 13.0; male 49/70 (70%); race: white 63/70 (90%); black 5/70 (7%); other 2/70 (3%); height (cm) 177.6 ± 10.5; weight (kg) 93.0 ± 21.0; $TcPO_2$ (mmHg) 57.4 ± 27.5; ulcer area (cm^2) 3.2 ± 2.8; ulcer depth (cm) 0.4 ± 0.2; ulcer duration (weeks) 52.8 ± 60.9; location of ulcer: leg 3/70 (4.3%); foot 67/70 (95.7%); stage III 70/70 (100%); stage IV 0/70 (0%). Comparator group: N = 68; age (yrs) 59.6 ± 11.3; male 54/68 (79.4%); race: white 55/68 (80.9%); black 7/68 (10.3%); other 6/68 (8.8%); height (cm) 176.8 ± 11.1; weight (kg) 97.8 ± 25.8; $TcPO_2$ (mmHg) 56.5 ± 24.5; ulcer area (cm^2) 3.5 ± 3.5; ulcer depth (cm) 0.4 ± 0.5; ulcer duration (weeks) 42.0 ± 42.0; location of ulcer: leg 5/68 (7.3%); foot 63/68 (92.7%); stage III 65/68 (96%); stage IV 3/68 (4%).	therapy which consisted of standard wound care as for comparator plus application of a thin layer of gel once daily at morning dressing change	moist saline-soaked dressings changed every 12 hours, off loading, and control of infection if present.			
(Vandeputte & Gryson 1997) Belgium	Level II RCT Average quality study	N = 29. Diabetic patients with foot ulcer(s) (neuropathic or not). Patients with necrotic or infected wounds, or those with already amputated toe were not excluded Intervention group: N = 15; n = 15 legs; age (yrs) 62.6 ± 14.7; male 7/15 (46.7%); completely mobile patients 12/15 (80%); neuropathic ulcers 9/15 (60%); infection at baseline 1/15 (6.7%). Comparator group: N = 14; n = 15 legs; age (yrs) 65.3 ± 14.3; male 6/14 (42.8%); completely mobile patients 11/14 (78.6%); neuropathic ulcers 9/14 (64.3%); infection at baseline 1/14 (7.1%).	N = 15, n = 15 legs. Ulcers were treated with hydrogel dressing and the wounds were cleaned with a dermal wound cleanser.	N = 14, n = 15 legs. Ulcers were treated with dry gauze twice a day and irrigated with chlorhexidine 0.05%	No. of patients that required amputation 1/15 (6.7%)	5/14 (35.7%)	RR = 0.19 [95% CI 0.03, 1.02]
(Jensen et al 1998) USA	Level II RCT Poor quality study	N = 31. Diabetic patients with Wagner grade 2 foot ulcers measuring at least 1 cm in diameter, with no evidence of infection and adequate perfusion (palpable foot pulses) Intervention group: N – 14; ulcer duration (months) 8.9. Comparator group: N = 17; ulcer duration (months 3.0. No other baseline data were provided.	N = 14. Carrasyn hydrogel wound dressing (CHWD). After initial debridement, ulcer cleansed with UltraKlenz wound cleanser, covered	N = 17. Standard wet-to-moist saline dressings. After initial debridement, ulcer cleansed with UltraKlenz wound cleanser, dressed	Time to healing (weeks) 10.30 No. of patients that required an amputation 0/14 (0%)	11.69 1/17 (5.8%)	RR = 0.00 [95% CI 0.00, 4.56]

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
			with 1/8 to 1/4-inch layer of CHWD, covered with gauze pad, wrapped in Kling bandage and secured with tape and given custom-made healing sandals for off-loading with instructions for use. Dressings were changed daily.	with gauze pad soaked in sterile saline, wrapped in Kling bandage and secured with tape and given custom-made healing sandals for off-loading with instructions for use. Dressings were changed daily			

RR = relative risk; RR_p = pooled relative risk; CI = confidence interval; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot.

Wound debridement using advanced moist wound dressings versus standard wound care

Six level II evidence studies (three of good quality and three of average quality) investigated the effectiveness of advanced moist wound dressings as the primary dressing for standard wound care, compared to using conventional dry, greasy or saline-moistened gauze (Table 85). The dressings used in these studies were: Aquacel, a hydrofibre dressing made from carboxymethyl cellulose (ConvaTec Ltd, UK); Fibracol, a collagen-alginate dressing (Johnson & Johnson, USA); PolyMem, a polyurethane membrane matrix containing a starch co-polymer (Ferris, USA); and Algosteril and Sorbsan, which are calcium alginate dressings (Laboratories Brothier, France; Dow B Hickam, USA).

Piaggesi et al (2001) conducted a randomised controlled trial of good quality to investigate the effectiveness of using Aquacel hydrofibre dressing compared to saline-moistened gauze as the primary wound dressing to treat diabetic foot ulcers. Twenty diabetic patients with a foot ulcer deeper than 1 cm, of more than 3 weeks duration, and with good peripheral blood supply were randomised to receive standard wound care with either Aquacel or saline-moistened gauze. The authors found that, although there was no statistically significant difference in the number of ulcers that healed, the group using Aquacel took a significantly shorter time to heal than those using saline-moistened gauze (127±46 days compared to 234±61 days; $p < 0.001$). However, more patients using Aquacel required an amputation than those using saline-moistened gauze, even though the difference was not statistically significant (60% versus 30%; RR = 2.00 [95% CI 0.74, 5.66]). There was also no difference in the number of infections between the two groups (Table 85).

Donaghue et al (1998) conducted a randomised controlled trial of average quality at the Harvard Medical School, Boston, USA, involving 75 diabetic patients with a foot ulcer. The effectiveness of using either Fibracol dressing or a saline-moistened gauze as the primary dressing in standard wound care was investigated. There was no statistically significant difference in the number or severity of adverse events recorded for the two groups. The authors found that there was a shorter time to healing with Fibracol when compared to saline-moistened gauze (6.2 ± 0.45 versus 8 ± 0.4 weeks; $p = 0.001$). Blackman et al (1994) conducted a small randomised controlled trial of average quality to investigate the effectiveness of standard wound care using either PolyMem or saline-soaked gauze dressings as the primary dressings to treat 18 diabetic patients with a partial or full thickness foot ulcer. The authors found that there was a statistically significant reduction in ulcer size after 8 weeks of treatment with PolyMem compared to saline-soaked gauze (65 ± 16% reduction compared to a 5 ± 26% increase; $p < 0.001$).

Only three of these six studies, only one of which was of good quality, indicated that the use of advanced moist wound dressings as the primary dressing in standard wound care provided a statistically significant benefit over using conventional gauze dressings. Two studies one of good and one of average quality, showed a statistically significant reduction in time to healing in favour of the advanced moist wound dressings (Donaghue et al 1998; Piaggesi et al 2001). The remaining two good quality studies found no statistically significant differences between the two groups for any outcome measured (Ahroni 1997; Jeffcoate et al 2009). Five of these six studies reported on the number of ulcers healed after standard wound care using advanced moist wound dressings compared to using conventional gauze dressings as the primary dressing (Ahroni 1997; Blackman et al 1994; Donaghue et al 1998; Jeffcoate et al 2009; Piaggesi et al 2001). Pooled analysis on these five studies of the effect sizes indicates that advanced moist wound dressings as the primary dressing in standard wound care provided a small benefit in foot ulcer healing compared to standard wound care using gauze conventional

dressings but the result could be attributable to chance (RR_p = 1.11 [95% CI 0.90, 1.37]; p = 0.66; Figure 9).Thus, there is only weak evidence to suggest that the use of advanced moist wound dressings offer better clinical outcomes for treating diabetic foot ulcers compared to conventional wet, dry or greasy gauze when used as primary dressings with standard wound care.

Box 122 Evidence statement matrix for advanced moist wound therapy dressings in addition to standard wound care

Component	Rating	Description
Evidence base	A	Six level II evidence studies (3 with a low risk of bias, 3 with a moderate risk of bias)
Consistency	B	The three highest quality studies did not find statistically significant differences, with the exception of time to ulcer healing in one study.
Clinical impact	D	Slight/restricted clinical impact. Only one of the three highest quality studies found a statistically significant difference (time to healing) favouring advanced moist wound dressings.
Generalisability	A	Population consisted of diabetic patients with foot ulcers, mostly with full-thickness ulcers not penetrating to the bone or tendons.
Applicability	B	Four studies were conducted in Europe (one in the UK, one in Italy, and two in France), which has comparable healthcare for diabetic patients when compared to the Australian healthcare context. The other two studies were conducted in the USA, which has similar healthcare for diabetic patients when compared to the Australian healthcare context.

Evidence statement

There is little evidence to suggest that the use of advanced moist wound therapy dressings offer better clinical outcomes for treating diabetic foot ulcers compared to wet, dry or greasy gauze as a primary dressing for standard wound care. (Grade B)

Table 85 Studies included which investigated the effectiveness of using advanced moist wound therapy dressings as a debridement therapy in the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Jeffcoate et al 2009) UK	Level II RCT Good quality study	N = 209 diabetic patients, over 18 years, with chronic (at least 6 weeks duration) full-thickness foot ulcer on or below the malleoli, not penetrating to tendon or bone, and with an area of 25-2500 mm^2. Intervention group: N = 103; age (yrs) 59.5 ± 11.5; male 81/103 (77%); duration of diabetes (yrs) 16.0 ± 11.4; type 1 diabetes 22/103 (21%); insulin treatment 43/103 (42%); smokers 15/103 (15%); cerebro-vascular disease 8/103 (8%); cardiovascular disease 37/103 (36%); retinopathy 62/103 (60%); nephropathy 22/103 (21%); first ulcer 35/103 (34%); previous ulcer at same site 27/103 (26%); previous amputation 27/103 (26%); peripheral arterial disease: dorsalis pedis felt 89/103 (86%), posterior tibial felt 84/103 (82%); loss of sensation: under 1st metatarsal head 85/103 (83%), under 5th metatarsal head 68/103 (66%), plantar hallux 71/103 (69%), plantar heel 57/103 (55%); location of ulcer: toe 38/103 (37%), forefoot 44/103 (43%), hindfoot 18/103 (17%), malleolus 3/103 (3%); ulcer area: 25-100 mm^2 53/103 (51%), 101-250 mm^2 34/103 (33%), 251-2500 mm^2 16/103 (16%). Comparator group: N = 106; age (yrs) 61.9 ± 12.8; male 78/106 (74%); duration of diabetes (yrs) 15.8 ± 11.4; type 1 diabetes 21/106 (20%); insulin treatment 35/106 (33%); smokers 22/106 (21%); cerebro-vascular disease 9/106 (8%); cardiovascular disease 46/106 (43%); retinopathy 58/106 (55%); nephropathy 26/106 (25%); first ulcer 44/106 (42%); previous ulcer at same site 13/106 (12%); previous amputation 15/106 (14%); peripheral arterial disease: dorsalis pedis felt 90/106 (85%), posterior tibial felt 84/106 (79%); loss of sensation: under 1st metatarsal head 82/106 (77%), under 5th metatarsal head 71/106 (67%), plantar hallux 77/106 (73%), plantar heel 66/106 (62%), location of ulcer: toe 37/106 (35%), forefoot 44/106 (42%), hindfoot 22/106 (21%),	N = 103 Aquacel, a carboxymethyl cellulose hydrofibre dressing as primary dressing in addition to standard wound care.	N = 106 Standard wound care with initial debridement and using a simple non-adherent, knitted, viscose filament gauze dressing. All dressings were changed daily, on alternate days or three times a week depending on need and/or availability of professional staff.	Number of ulcers healed at 12 weeks Total 29/103 (28%) Ulcer area 25-100 mm^2 14/53 (26%) Ulcer area > 100 mm^2 15/50 (30%) Number of ulcers healed at 24 weeks Total 46/103 (45%) Ulcer area 25-100 mm^2 23/53 (43%) Ulcer area > 100 mm^2 23/50 (46%) Time to healing (days) 73.6 ± 45.3 SF36 scores Improvement in physical function scores at 24 weeks 5.7 Improvement in general health scores at 24 weeks 0.1	27/106 (25%) 16/50 (32%) 11/56 (20%) 41/106 (39%) 24/50 (48%) 17/56 (30%) 71.7 ± 37.3 -3.3 1.5	RR = 1.11 [95% CI 0.71, 1.73] RR = 0.82 [95% CI 0.45, 1.50] RR = 1.53 [95% CI 0.79, 3.01] RR = 1.16 [95% CI 0.84, 1.58] RR = 0.90 [95% CI 0.60, 1.38] RR = 1.52 [95% CI 0.93, 2.48] p = 0.83 p = NS p = NS

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
		malleolus 3/106 (3%); ulcer area: 25-100 mm^2 50/106 (47%), 101-250 mm^2 34/106 (32%), 251-2500 mm^2 22/106 (21%).			Incremental cost effectiveness ratio (ICER) £8.36 per 1% likelihood increase in healing using Aquacel rather than standard wound care		
(Ahroni 1997) USA	Level II RCT Good quality study	N = 39 diabetic patients with ulcers that penetrated the epidermis but did not significantly involve joint spaces, tendon or bone. Intervention group: N = 20; age (yrs) 61.2 ± 11.0; male 20/20 (100%); diabetes type 2 17/20 (85%); insulin therapy 14/20 (70%); diabetes duration (yrs) 15.6 ± 10.5; ex smoker 17/20 (85%); current smoker 1/20 (5%); % HbA_{1c} 12.4 ± 3.3; haematocrit 41.9 ± 5.1; total lymphocyte count 2248 ± 1337; creatinine 1.4 ± 0.6; blood urea nitrogen 22.6 ± 9.4; ulcer duration (days) 132.9 ± 320.6; chonic (>4 weeks) 12/20 (60%); partial thickness 2/20 (10%); full thickness 17/20 (85%); necrotic tissue 1/20 (5%); eschar 0/20 (0%); ulcer surface area (mm^2) 193.2 ± 346.4; total wound score 18.3 ± 6.6; ulcer cause: chronic pressure 11/20 (55%), dysvascular 5/20 (25%), other trauma 4/20 (20%); ulcer location: plantar forefoot 10/20 (50%), heel 7/20 (35%), dorsal toe 1/20 (5%), dorsal foot 2/20 (10%). Comparator group: N = 19; age (yrs) 65.4 ± 9.3; male 19/19 (100%); diabetes type 2 14/19 (74%); insulin therapy 13/19 (68%); diabetes duration (yrs) 17.2 ± 8.0; ex smoker 10/19 (53%); current smoker 2/19 (11%); % HbA_{1c} 13.1 ± 2.9; haematocrit 40.9 ± 4.5; total lymphocyte count 2160 ± 792; creatinine 1.6 ± 0.6; blood urea nitrogen 31.8 ± 27.2; ulcer duration (days) 74.9 ± 130.4; chonic (>4 weeks) 9/19 (47%); partial thickness 4/19 (21%); full thickness 12/19 (63%), necrotic tissue 2/19 (11%); eschar 1/19 (5%); ulcer surface area (mm^2) 166.7 ± 211.1; total wound score 20.4 ± 8.5; ulcer cause: chronic pressure 12/19 (63%), dysvascular 4/19 (21%), other trauma 3/19 (16%); ulcer location: plantar forefoot 10/19 (53%), heel 3/19 (16%), dorsal toe 2/19 (11%), dorsal foot 4/19 (21%).	N = 20. Sorbsan™ a calcium alginate dressing was applied to the wound (two layers) after sharp debridement and cleansing, as for comparator. Dressings were changed daily and received same treatment as comparator.	N = 19. Standard wound care, which included thorough sharp debridement, cleansing with half strength hydrogen peroxide and rinsing with normal saline. Wounds blotted dry and covered with a single layer of non-adherent dry fine maze gauze. The dressing was changed twice daily and held in place with gauze wrap. Antibiotics prescribed when soft tissue had been infected for 2 weeks.	Number of ulcers healed at 4 weeks 5/20 (25%) Number of patients that eventually required an amputation 2/20 (10%) Healing rate: Decrease in area (mm^2/day) 2.19±4.0 Decrease in linear advance of wound margin (mm/day) 0.094±0.147	7/19 (37%) 2/19 (11%) 2.04±2.61 0.084±0.100	RR = 0.70 [95% CI 0.26, 1.72] RR = 0.95 [95% CI 0.18, 5.17] p > 0.99 p = 0.87

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Piaggesi et al 2001) Italy	Level II RCT Good quality study	N = 20 diabetic patients, aged 18-75 years, with a foot ulcer deeper than 1 cm for > 3 weeks, and with good peripheral blood supply (palpable peripheral pulses) Intervention group: N = 10; age (yrs) 63.1 ± 4.6; diabetes type I 2/10 (20%); duration of diabetes (yrs) 14.8 ± 6.2; % HbA_{1c} 8.1 ± 2.7; ankle-brachial pressure index 1.1 ± 0.2; vibration perception threshold (V) 36.3 ± 9.9; ulcer duration (wks) 6.8 ± 2.6; maximum diameter (cm) 4.9 ± 2.4; maximum depth (cm) 2.3 ± 1.4; volume (cm^3) 22.6 ± 8.4. Comparator group: N = 10; age (yrs) 61.3 ± 7.5; diabetes type I 1/10 (10%); duration of diabetes (yrs) 16.1 ± 8.9; %HbA_{1c} 8.9 ± 3.1; ankle-brachial pressure index 1.0 ± 0.2; vibration perception threshold (V) 32.4 ± 12.8; ulcer duration (wks) 5.9 ± 1.3; maximum diameter (cm) 4.5 ± 1.9; maximum depth (cm) 2.9 ± 1.1; volume (cm^3) 19.2 ± 6.4.	N = 10. Aquacel, a carboxymethyl cellulose dressing was applied to the wound after surgical debridement and changed every second or third day, depending on the extent of exudates produced by the wound.	N = 10. Standard wound care which included initial surgical debridement, saline-moistened gauze, renewed twice a day with saline to prevent drying out. All patients in both groups received special post-operative shoes and crutches until complete re-epithelialisation.	Number of patients with ulcers that healed 10/10 (100%) Number of patients that required amputations 6/10 (60%) Number of patients that developed infections (harms) 1/10 (10%) Time to healing (days) 127±46	 9/10 (90%) 3/10 (30%) 3/10 (30%) 234±61	 RR = 1.11 [95% CI 0.94, 1.11] RR = 2.00 [95% CI 0.74, 5.66] RR = 0.33 [95% CI 0.05, 2.01] p < 0.001
(Lalau et al 2002) France	Level II RCT Average quality study	N = 77 diabetic patients, aged less than 75 years, with a foot ulcer having some granulation tissue and a surface area of 1-50 cm^2. Intervention group: N = 39; age (yrs) 60.8 ± 10.7; male 22/39 (56%); BMI (kg/m^2) 27.6 ± 5.11; diabetes type 1 15/39 (38%); duration of diabetes (yrs) 19.2 ± 11.8; % HbA_{1c} 7.6 ± 2.0; revascularisation procedures 13/39 (33%); $TcPO_2$ (mmHg) 44.6 ± 12.3; ulcer area (cm^2) 8.0 ± 10.5; ulcer duration (months) 4.9 ± 7.8; acute lesion 13/39 (33%); chronic lesion 26/39 (67%); acute ulcer duration (days) 37 ± 14; chronic ulcer duration (days) 205 ± 273; acute ulcer area (cm^2) 13.5 ± 15.5; chronic ulcer area (cm^2) 5.3 ± 5.4. Comparator group: N = 38; age (yrs) 63.5 ± 12.8; male 23/38 (61%); BMI (kg/m^2) 27.3 ± 5.52; diabetes type 1 16/38 (42%); duration of diabetes (yrs) 16.9 ± 8.9; % HbA_{1c} 7.9±1.5; revascularisation procedures 4/38 (11%); $TcPO_2$ (mmHg) 42.6 ± 10.3; ulcer area	N = 39. Algosteril, a calcium alginate dressing, was applied directly on to wound to cover entire area. Dressings were changed every day initially until thorough debridement then every 2 to 3 days. No other local treatment permitted, except saline solution. Secondary dressing was sterile gauze.	N = 38. Vaseline gauze was applied directly on to wound to cover entire area. Dressings changed every day initially until thorough debridement then every 2 to 3 days. No other local treatment permitted, except saline solution. Secondary dressing was sterile gauze.	% ulcers healed (75% granulation tissue and/or 40% decrease in ulcer area) Total 43% Acute ulcers 55% Mean % reduction wound area 35.7±30.7	 29% 23% 34.9±41.1	 p = NS p = NS p = NS

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
		(cm^2) 8.8 ± 16.0; ulcer duration (months) 9.1 ± 13.1; acute lesion 14/38 (37%); chronic lesion 24/38 (63%); acute ulcer duration (days) 29 ± 16; chronic ulcer duration (days) 417 ± 589; acute ulcer area (cm^2) 11.6 ± 17.5; chronic ulcer area (cm^2) 7.2 ± 15.2.					
(Donaghue et al 1998) USA	Level II RCT Average quality study	N = 75 diabetic patients with a foot ulcer attending a foot clinic at Harvard Medical School, Boston, USA. Intervention group: N=50; age (yrs) 59 (30-81); male 33/50 (66%); duration of diabetes (yrs) 19 (4-47); Wagner grade 1 ulcer 8/50 (16%); grade 2 36/50 (72%); grade 3 6/50 (12%); duration of ulcer (days) 146 ± 73; ulcer size (cm^2) 2.6 ± 0.50; weight (lbs) 195 ± 45; retinopathy 28/50 (55%); creatinine (mg/dl) 1.2 ± 0.6; serum albumin (g/dl) 3.7 ± 0.1. Comparator group: N=25; age (yrs) 60 (33-79); male 21/25 (84%); duration of diabetes (yrs) 17 (2-25); Wagner grade 1 ulcer 1/25 (4%); grade 2 20/25 (80%); grade 3 4/25 (16%); duration of ulcer (days) 225 ± 104; ulcer size (cm^2) 3.0 ± 0.6; weight (lbs) 214 ± 49; retinopathy 19/25 (76%); creatinine (mg/dl) 1.1 ± 0.1; albumin (g/dL) 3.8 ± 0.1.	N=50, Fibracol Collagen-Alginate wound dressing changed as necessary which was assessed weekly in an outpatient clinic	N=25 Standard treatment with a saline-moistened gauze dressing which was changed frequently (not stated)	Mean % reduction in ulcer area 80.6 ± 6	61.1 ± 26	p = 0.47 Number of patients with ulcers that healed 24/50 (48%)
						9/25 (36%)	RR=1.33 [95% CI 0.77, 2.5] Time to complete healing (weeks) 6.2±0.4
						5.8±0.4	p = 0.015 Time to 75% healing (weeks) 2
						4	p = 0.2551 Number of patients that achieved 75% ulcer area reduction 39/50 (78%)
						15/25 (60%)	RR=1.3 [95% CI 0.06, 1.84]
(Blackman et al 1994) France	Level II RCT Average quality study	N = 18 diabetic patients with a partial or full thickness Wagner grade 1 and 2 open wound or foot ulcer, free of hard eschar. Intervention group: N = 11; age (yrs) 59 ± 5; male 11/11 (100%); duration of ulcer (wks) 25 ± 7; ulcer size (cm^2) 2.7 ± 1.2; % HbA_{1c} 8.4 ± 0.9. Comparator group: N = 7; age (yrs) 51 ± 4; male 6/7 (86%); duration of ulcer (wks) 28 ± 6; ulcer size (cm^2) 1.8 ± 0.8; % HbA_{1c} 9.5 ± 1.1.	N = 11. PolyMem, poly-urethane membrane dressing containing a starch co-polymer, which was applied to ulcer (after surgical debridement). No topical antibiotics, disinfectants or further debridement was permitted. Dressings were changed once daily.	N = 7. Standard wound care including surgical debridement when necessary, saline-soaked gauze dressings, off-loading by use of orthotic footwear Dressings were changed at least once per day.	Number of patients with ulcers that healed 3/11 (27%)	0/7 (0%)	RR not calculable % reduction in ulcer size 65 ± 16
						-5 ± 26 (increase)	p < 0.001

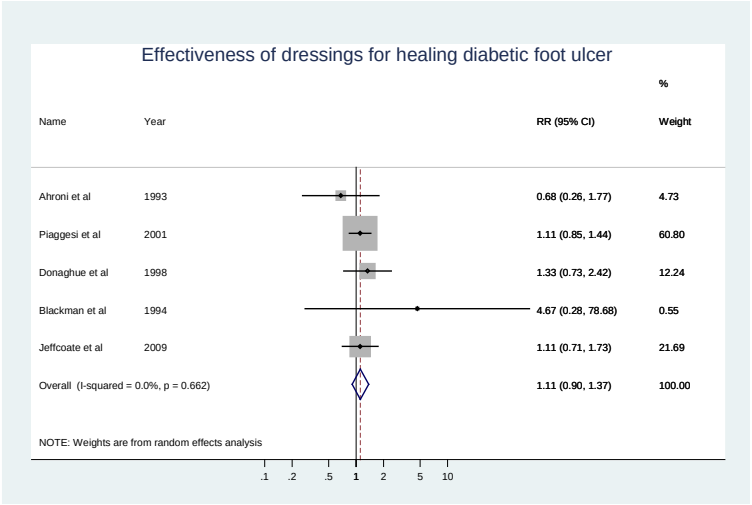
RR = relative risk; CI = confidence interval; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot. SF-36 form: Self report questionnaire (36 questions relating to 8 domains measuring health and well-being, a score of zero was associated with poor perceived health and a score of 100 as good health). Total wound score = composite scale of wound severity as described by (Knighton et al 1986).

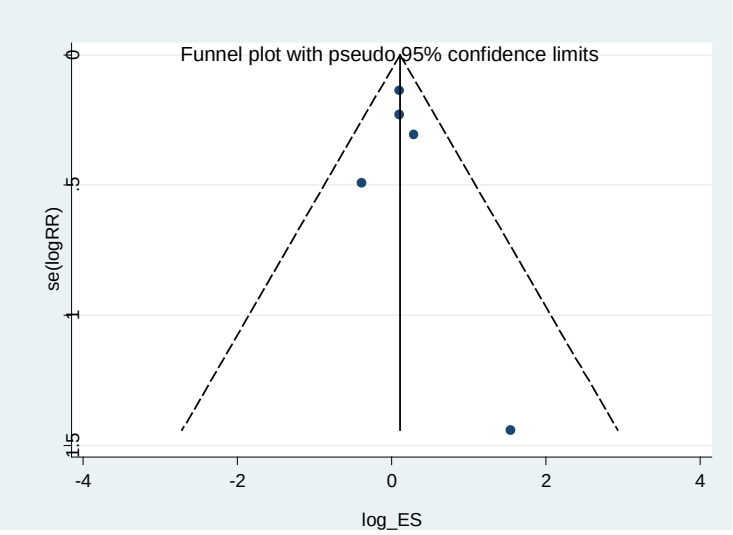
Figure 9 Meta-analysis of dressings for healing of diabetic foot ulcer

Study	RR	[95% Conf.	Interval]	% Weight
Ahroni et al	0.679	0.260	1.773	4.73
Piaggesi et al	1.105	0.846	1.445	60.80
Donaghue et al	1.333	0.734	2.422	12.24
Blackman et al	4.667	0.277	78.678	0.55
Jeffcoate et al	1.105	0.706	1.731	21.69
D+L pooled RR	1.114	0.904	1.373	100.00

Heterogeneity chi-squared = 2.40 (d.f. = 4) p = 0.662
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000

Test of RR=1 : z= 1.01 p = 0.311





Wound debridement comparing two different advanced moist wound debridement therapies

Three level II studies (one each of good, average and poor quality) compared the effectiveness of two different advanced moist wound therapies to treat diabetic foot ulcer (see Table 86). The effectiveness of using Aquacel-Ag (carboxymethyl cellulose hydrofibre dressing with 1.2% ionic silver; ER Squibb & Sons, USA) and Algosteril (calcium alginate dressing) as primary dressings for standard wound care were compared in one study (Jude et al 2007). Allevyn (hydrophilic polyurethane foam dressing; Smith & Nephew Medical, UK) and Kaltostat (sodium and calcium alginate dressing, ConvaTec Ltd, UK) were similarly compared in another study (Foster et al 1994). The third study investigates the effectiveness of using non-medicated industrial-grade polyurethane foam as a primary wound dressing compared to conventional techniques, including desloughing agents, hydrogel and a hydrocolloid dressing (Varma et al 2006).

Jude et al (2007) conducted a randomised controlled trial of good quality involving 134 diabetic patients with controlled diabetes and a Wagner grade 1 or 2 neuropathic or neuro-ischaemic foot ulcer. The patients were treated with standard wound care using either Aquacel-Ag or Algosteril as the primary dressing. Patients in both groups experienced a similar number of study-related adverse events (16% versus 13%; RR = 1.22 [95% CI 0.55, 2.73]). There were no statistically significant differences between the two groups for the time to healing or % reduction in ulcer size. There was a statistically significant reduction in ulcer depth for the patients using Aquacel-Ag compared with those using Algosteril (0.25 ± 0.49 cm compared to 0.13 ± 0.37 cm; p = 0.04), although the clinical importance of this difference is uncertain.

Varma et al (2006) conducted a randomised controlled trial of average quality involving 48 diabetes mellitus type II patients that presented with a lower limb wound to the Amrita Institute of Medical Sciences and Research Centre, Kochi, India, between January and July, in 2005. After randomisation, 58% of the intervention group and 75% of the control group had foot ulcers. Following surgical debridement, the patients were treated with standard wound care using either a polyurethane foam sheet (hardness of 10, pore diameter 0.4 mm with 65 pores per inch^2) as the primary dressing, or conventional techniques, including de-sloughing agents (collagenase, papain-urea, hyaluronidase ointment), hydrogels, hydrocolloid dressings, and topical antibiotics as deemed necessary. The authors found that all ulcers in both groups that were larger than 5 cm in diameter healed sufficiently for split-skin grafting. Of the ulcers that were less than 5 cm in diameter, all those treated with polyurethane foam and 42% of those treated with conventional techniques healed by re-epithelialisation of the wound (RR = 2.40 [95% CI 1.14, 2.40]). When all ulcers were taken into account, three patients would need to be treated with polyurethane foam instead of conventional techniques for one additional patient's ulcer to heal (NNT = 3 [95% CI 3, 10]). The time to healing was also shorter for the patients treated with polyurethane foam compared to those using conventional techniques (22.5 ± 15.4 versus 52.0 ± 22.7; p < 0.001). However, it is difficult to draw any clear conclusions from this data, as the precise treatment received by the 7 patients with ulcers that did not heal was not disclosed and may differ significantly to that received by the other 17 patients in the conventional therapy group. Also the location of the ulcers for these 7 patients was not disclosed. This may be important as not all ulcers in this study were foot ulcers.

Foster et al (1994) investigated the effectiveness of using Allevyn (hydrophilic polyurethane foam dressing) compared to Kaltostat (calcium-sodium alginate dressing) as the primary dressing in standard wound care for the treatment of diabetic foot ulcers. Thus, they conducted a randomised controlled trial involving 30 diabetic patients with a clean neuropathic or ischaemic foot ulcer. This poor quality study found no significant difference in the number of ulcers that healed or in the healing time between patients treated with Allevyn compared to

those treated with Kaltostat (Foster et al 1994). However, four patients being treated with Kaltostat had to be withdrawn from the study due to treatment-related adverse events, one due to severe pain, three due to the alginate plugging the lesion and preventing drainage of exudates, resulting in one case of cellulitis. In comparison, no patients treated with Allevyn suffered from an adverse event (RR = 0.00 [95% CI 0.00, 0.83]).

All three of the studies comparing different advanced moist wound therapies found a statistically significant and clinically important difference for at least one clinical outcome, but failed to show that any one dressing could consistently outperform another. The most alarming finding from these studies was the adverse events attributed to Kaltostat, the calcium-sodium alginate dressing. If this dressing can plug the lesion and prevent drainage of exudates from the wound, the potential harms caused by this dressing could outweigh any clinical benefits that may result from its use.

Box 123 Evidence statement matrix for comparison of two advanced moist wound therapies in addition to standard wound care

Component	Rating	Description
Evidence base	B	Three level II studies (1 with a low risk of bias and 2 with a high risk of bias)
Consistency	C	Some inconsistency, reflecting genuine uncertainty around question. All three of the studies found a statistically significant difference for at least one clinical outcome, but failed to show that any one dressing could consistently outperform another
Clinical impact	D	Slight clinical impact. The best quality study showed a statistically significant reduction in ulcer depth, although the clinical significance of the difference is uncertain. One found a statistically significant shortened time to healing and the third showed a statistically significant increase in adverse events for one treatment compared to another. However, given the quality of the latter two studies, it is uncertain whether these results were due to confounding from an unbalanced distribution of baseline characteristics between trail arms.
Generalisability	C	Two studies, including the better quality study, recruited diabetic patients with neuropathic or ischaemic foot ulcer, but the third study also allowed diabetic patients with leg and thigh ulcers to participate.
Applicability	C	Two studies were conducted in Europe (one in the UK, and one in the UK, France, Germany and Sweden), which has comparable healthcare for diabetic patients when compared to the Australian healthcare context. The other study was conducted in India, which has different healthcare for diabetic patients when compared to the Australian healthcare context.

Evidence statement

There is little evidence to suggest that one advanced moist wound debridement therapy can consistently outperform another when used in conjunction with standard wound care. (Grade C)

Table 86 Studies included which compared the effectiveness of two different advanced moist wound debridement therapies in the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Jude et al 2007) UK, France, Germany and Sweden	Level II RCT Good quality study	N = 134. Diabetic patients with Wagner grade 1 or 2 neuropathic or neuro-ischaemic foot ulcer, ≥ 1cm² in area, with controlled diabetes (HbA_{1c} ≤ 12.0%). Intervention group: N = 67; age (yrs) 58.9 ± 12.6; male 46/67 (69%); diabetes type I 23/67 (34%); serum creatinine (µmol/l) 90.5 ± 30.1; % HbA_{1c} 8.1 ± 1.9; ankle/brachial systolic blood pressure ratio 2.4 ± 9.7; Wagner grade I ulcer 53/76 (79%), neuropathic ulcer 54/67 (81%); plantar location 44/67 (66%); antibiotics prescribed 13/67 (19%); ulcer duration (yrs) 1.2 ± 2.1; ulcer depth (cm) 0.40 ± 0.45; ulcer area (cm²) 3.1 ± 4.1; epithelium (%) 7.9 ± 21.4; granulation (%) 76.8 ± 31.7; slough (%) 11.4 ± 22.6; eschar (%) 0.2 ± 1.3; sharp debridement (yes) 50/67 (75%); amount of exudates: none 3/67 (5%), minimal 27/67 (40%), moderate 33/67 (49%), heavy 4/67 (6%); condition of periulcer skin: normal 31/67 (46%), erythematous 18/67 (27%), macerated 22/67 (33%), callus 39/67 (58%), cellulitis 4/67 (5%). Comparator group: N = 67; age (yrs) 61.1 ± 11.4; male 53/67 (79%); diabetes type I 16/67 (24%); serum creatinine (µmol/l) 98.2 ± 30.8; % HbA_{1c} 7.9 ± 1.8; ankle/brachial systolic blood pressure ratio 1.1 ± 0.2; Wagner grade I ulcer 48/67 (72%); neuropathic ulcer 47/67 (70%); plantar location 47/67 (70%); antibiotics prescribed 8/67 (12%), ulcer duration (yrs) 1.4 ± 2.6; ulcer depth (cm) 0.40 ± 0.39; ulcer area (cm²) 4.2 ± 7.8; epithelium (%) 6.4 ± 14.2; granulation (%) 72.4 ± 31.6; slough (%) 15.9 ± 25.6; eschar (%) 0.2 ± 1.0; sharp debridement (yes) 54/67 (81%); amount of exudates: none 5/67 (8%), minimal 24/67 (36%), moderate 27/67 (40%), heavy 11/67 (16%), condition of periulcer skin: normal 31/67 (46%), erythematous 22/67 (33%), macerated 23/67 (34%), callus 37/67 (55%), cellulitis 3/67 (5%).	N= 67. Aquacel-Ag sodium carboxymethyl cellulose dressing with 1.2% ionic silver, in addition to standard wound care as for comparator. The primary Aquacel-Ag dressing was left for up to 7 days (changed as clinically indicated). Primary dressing was covered as for comparator.	N= 67. Algosteril, a non woven calcium alginate dressing, used in conjunction with standard wound care, which included surgical debridement at baseline and at subsequent dressing changes to remove callus and ensure there was no more than 5% slough or eschar on the ulcer. Wound cleansed with saline and covered with Algosteril and changed once daily on infected wounds. Primary dressing was covered by sterile, non adherent foam dressing. Footwear was accommodated where necessary.	Number of patients with ulcers that healed 21/67 (31.3%) Time to complete healing (days) 52.6 ± 1.8 Mean % reduction in ulcer area 58.1 ± 53.1 Ulcer depth reduction (cm) 0.25 ± 0.49 Number of study related adverse events 11/67 (16%)	15/67 (22.4%) 57.7 ± 1.7 60.5 ± 42.7 0.13 ± 0.37 9/67 (13%)	RR = 1.40 [95% CI 0.80, 2.48] p = 0.34 p = 0.95 p = 0.04 RR = 1.22 [95% CI 0.55, 2.73]
(Varma et al	Level II RCT	N = 48. Diabetes mellitus type II patients that	N = 24.	N = 24.	Number of patients with ulcers that healed		

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
2006) India	Poor quality study	presented with a lower limb wound to the Amrita Institute of Medical Sciences and Research Centre, Kochi, India, between January 1 2005 and July 31 2005. Intervention group: N = 24; age (yrs) 58.8 ± 9.4; duration of diabetes (yrs) 14 ± 8; exposed bone 16/24 (67%); peripheral occlusive vascular disease 8/24 (35%); neuropathy 15/24 (60%); blood urea nitrogen (mg%) 44.6 ± 28.3; serum creatinine (mg%) 1.7 ± 1.4; white blood cell count (cells/mm^3) 23.2 ± 8.5; ulcer area (cm^2) 208.9 ± 196.3; no. ulcers > 5 cm diameter 19/24 (79%); ulcer location: thigh 2/24 (8%), leg 8/24 (33%), foot 14/24 (58%). Comparator group: N = 24; age (yrs) 52.4 ± 7.4; duration of diabetes (yrs) 13 ± 7; exposed bone 12/24 (50%); peripheral occlusive vascular disease 9/24 (38%), neuropathy 6/24 (24%); blood urea nitrogen (mg%) 49.7 ± 43.2; serum creatinine (mg%) 1.4 ± 0.8; white blood cell count (cells/mm^3) 21.4 ± 7.2; ulcer area (cm^2) 198.3 ± 186.8; no. ulcers > 5 cm diameter 12/24 (50%); ulcer location: thigh 2/24 (8%), leg 4/24 (17%), foot 18/24 (75%).	Polyurethane foam sheet (Shore hardness of 10, pore diameter 0.4 mm with 65 pores per inch^2) was soaked in sterile saline and manually squeezed, then directly placed on the wound surface after surgical debridement as primary dressing. Sterile gamgee pads were placed over foam sheet and held in place with light compression bandage. No other topical treatments, such as antibiotics and de-sloughing agents, were used.	Standard wound care after initial surgical debridement. Wound was dressed daily using conventional techniques, including: topical antibiotics; desloughing agents (collagenase, papain-urea, hyaluronidase ointment, hydrogels, and hydrocolloid dressings as deemed necessary. In both groups, the limb was offloaded and sharp debridement was performed when necessary	24/24 (100%)	17/24 (29.9%)	RR = 1.41 [95% CI 1.13, 1.41] NNT = 3 [95% CI 3, 10]
					Number of ulcers that healed by primary intention (surgical intervention split-skin grafting)		
					19/19 (79.2%)	12/12 (100%)	RR not calculable
					Number of ulcers that healed by secondary intention (re-epithelialisation)		
					5/5 (100%)	5/12 (41.7%)	RR = 2.40 [95% CI 1.14, 2.40] NNT = 2 [95% CI 2, 13]
					Time to complete healing (days)		
					22.5 ± 15.4	52.0 ± 22.7	p < 0.001
(Foster et al 1994), UK	Level II RCT Poor quality study	N = 30. Diabetic patients with a clean neuropathic or ischaemic foot ulcer. Intervention group: N=15; age (yrs) 61; male 12/15 (80%); insulin dependent 6/15 (40%); duration of ulcer (days) 107; ulcer area (mm^2) 88. Comparator group: N=15; age (yrs) 70; male 8/15 (53%); insulin dependent 4/15 (27%), duration of ulcer (days) 170; ulcer area (mm^2) 79.	N=15. Allevyn, a hydrophilic polyurethane foam dressing which was changed weekly in addition to standard wound care	N=15. Kaltostat, a calcium-sodium alginate dressing which was changed weekly in addition to standard wound care	Number of patients with ulcers that healed		
					9/15 (60%)	8/15 (53%)	RR = 1.13 [95% CI 0.61, 2.10]
					Number of patients that had adverse events		
					0/15 (0%)	4/15 (27%)	RR = 0.00 [95% CI 0.00, 0.83]

RR = relative risk; CI = confidence interval; NNT = number needed to treat; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot.

Promogran versus wound care that does not inhibit protease activity

Promogran, consists of 55% collagen and 45% oxidised regenerated cellulose (Johnson & Johnson, USA), and has properties that aid wound healing in addition to creating a moist environment for natural debridement of the wound. The oxidised cellulose physically binds and inactivates matrix metalloproteases, which have a detrimental effect on wound healing by destroying various growth factors and other proteins (Lobmann et al 2006).

Two level II studies (one good and one average quality) investigated the effectiveness of using Promogran compared to using gauze as the primary dressing with standard wound care for treating diabetic foot ulcers. A third level II study of average quality compared Promogran with and without the addition of autologous platelet derived growth factors to another advanced moist wound therapy dressing, Tegaderm, a thin polyurethane membrane coated with a layer of an acrylic adhesive (3M Health Care Ltd), plus autologous platelet derived growth factors.

Veves et al (2002) compared the effectiveness of using Promogran compared to saline-moistened gauze as a primary wound dressing by conducting a randomised controlled trial of good quality. 276 diabetic patients with a Wagner grade 1-2 diabetic foot ulcer of at least 30 days duration, and with adequate perfusion, were treated using standard wound care with either Promogran or saline-moistened gauze as the primary dressing. The authors found that although more ulcers treated with Promogran healed than those treated with saline-moistened gauze, the difference was not statistically significant (37% versus 28%; RR = 1.31 [95% CI 0.93, 1.85]). There was also no difference in the % reduction of ulcer size between the two groups. However, the shorter time for ulcer healing in the Promogran group was statistically significant compared to ulcerw treated with saline-moistened gauze (7.0 ± 0.4 weeks versus 5.8 ± 0.4 weeks; $p < 0.001$).

Kakagia et al (2007) conducted a randomised controlled trial of average quality involving 51 diabetic patients, that attended a clinic in Greece from December 2004 to December 2006, with significant soft tissue defects of the foot that had been present for at least 3 months. Patients were randomly divided into three groups and their ulcers treated with standard wound care using Promogran as the primary dressing, either alone (group A) or with the addition of autologous platelet derived growth factors (group B). The outcomes for these two groups were compared to group C, whose ulcers were also treated with standard wound care, but using Tegaderm as the primary dressing, and also with the addition of autologous platelet derived growth factors. The number of patients with completely healed ulcers was the same in all three groups (RR for group A versus B and for group C versus B = 1.00 [95% CI 0.19, 5.40]). However, although the difference in the % reduction in ulcer dimensions (length, width and depth) was not statistically significant between groups A and B, there was a statistically significant greater reduction for group C compared to either group A or group B ($p < 0.001$).

Lobmann et al (2006) conducted a randomised controlled trial of average quality involving 33 diabetic patients with chronic diabetic foot lesions (University of Texas wound classification stage 2a). The aim was to compare the effectiveness of Promogran compared to a standard dressing (not specified), used as a primary dressing in standard wound care. Even though the study period was very short (8 days), there was a greater reduction in the wound area for ulcers treated with Promogran compared to those treated with the standard dressing ($p = 0.045$).

Overall, the two lower quality studies showed a statistically significant increase in the % reduction of ulcer size for ulcers treated with Promogran compared to those treated with standard wound care. The third good quality study showed that ulcers treated with Promogran

healed faster than when treated with standard wound care, although the absolute difference was small (mean 1.2 weeks).

A good quality systematic review by Chow et al (2008) identified an economic evaluation conducted by Ghatnekar et al (2002) that investigated the cost-effectiveness of Promogran in addition to standard wound care. Ghatnekar et al (2002) found that the costs per healed ulcer were higher for standard wound care than for Promogran plus standard wound care in France, Germany, Switzerland and the UK. Sensitivity analysis showed that the results were relatively sensitive to healing rates and the number of dressing changes. Increasing the number of dressing changes per week to five resulted in decreased cost savings in Switzerland and the UK and increased costs compared to standard wound care alone in Germany and France. Decreasing the dressing changes to three times per week resulted in increased cost savings in all four countries.

Box 124 Evidence statement matrix for advanced moist wound therapy dressings in addition to standard wound care

Component	Rating	Description
Evidence base	B	Three level II studies (1 with a low risk of bias, 2 with a moderate risk of bias)
Consistency	A	Two studies showed a statistically significant difference in the % reduction of ulcer size and the third better quality study showed a statistically significant difference in the time needed to heal.
Clinical impact	C	Moderate clinical impact. Although no study showed a statistically significant difference in the number of ulcers healed, all three studies showed statistically significant clinical outcomes for either time to healing or % reduction in ulcer size. However, only the outcome of reduction in ulcer size showed a clinically important difference as a consequence of Promogran use.
Generalisability	B	Population consisted of diabetic patients with chronic diabetic foot lesions mostly superficial, but some involving tendon, capsule or bone
Applicability	B	Two studies were conducted in Europe (one in Germany and one in Greece), which has comparable healthcare for diabetic patients when compared to the Australian healthcare context. The other study was conducted in the USA, which has similar healthcare for diabetic patients when compared to the Australian healthcare context.

Evidence statement

The use of Promogran wound dressing with or without the use of autologous platelet derived growth factors offers better clinical outcomes in terms of reduction in ulcer size and time to healing when treating diabetic foot ulcers compared to standard wound care. (Grade B)

Table 87 Studies which investigated the effectiveness of Promogran versus standard wound care with or without the addition of autologous platelet derived growth factors in the treatment of diabetic foot ulcer

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Chow et al 2008) France, Germany, Switzerland, UK	Level I SR Good quality study	Diabetic patients with deep foot ulcers (Ghatnekar et al 2002) Markov model for diabetic lower extremity ulcers	Promogran plus standard wound care	Standard wound care	No ICER reported Total treatment costs per healed ulcer were higher for SWC than for Promogran plus SWC in France, Germany, Switzerland and the UK. Sensitivity analysis: results were relatively sensitive to healing rates and number of dressing changes Increasing dressing changes to 5 per week: reduced cost savings in Switzerland and the UK and increased costs in Germany and France Decreasing dressing changes to 3 per week: greater increase in cost savings in all countries		
(Veves et al 2002) USA	Level II RCT. Good quality study	N = 276. Diabetic patients, aged 18 years or older, with a Wagner grade 1-2 diabetic foot ulcer of at least 30 days duration, and at least 1cm² in size, with adequate perfusion. Intervention group: N = 138; age (yrs) 58 (23-85); male 95/138 (69%); African-American 15/138 (11%); Native American 16/138 (12%); white 85/138 (62%); Hispanic 22/138 (16%); % HbA1c 8.6 (5.3-14.0); oscillometry (U) 4.4 (0.9-13.0); ulcer area (cm²) 2.5 (0.2-27.4); ulcer duration (months) 3 (1-84); history of foot ulcer 98/138 (71%). Comparator group: N = 138; age (yrs) 59 (37-83); male 108/138 (78%); African-American 12/138 (9%); Native American 16/138 (12%); white 88/138 (64%); Hispanic 22/138 (16%); % HbA1c 8.5 (4.9-13.1); oscillometry (U) 4.3 (0.9-12.0); ulcer area (cm²) 3.1 (0.1- 42.4); ulcer duration (months) 3 (1-144); history of foot ulcer 88/138 (63.8%).	N = 138 Promogran wound dressing cut to wound size and applied as primary dressing, secondary dressing and treatment same as for standard wound care.	N = 138 Standard wound care which included sharp debridement, saline-moistened gauze as primary dressing and covered with gauze a bandage and tape as secondary dressing	No. of patients with ulcers that healed Total 51/138 (37%) Ulcer duration < 6 months 43/95 (45.3%) Ulcer duration > 6 months 8/43 (18.6%) Wagner grade 1 25/56 (44.6%) Wagner grade 2 27/82 (32.9%)	 39/138 (28.3%) 29/89 (32.6%) 10/49 (20.4%) 20/63 (31.7%) 19/75 (25.3%)	 RR = 1.31 [95% CI 0.93, 1.85] RR = 1.39 [95% CI 0.96, 2.02] RR = 0.91 [95% CI 0.40, 2.06] RR = 1.41 [95% CI 0.89, 2.23] RR = 1.30 [95% CI 0.80, 2.14]

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
					Time to healing (weeks) Total 7.0 ± 0.4 Ulcer duration < 6 months 6.9 ± 0.4 % reduction of ulcer area 64.5%	5.8 ± 0.4 6.3 ± 0.4 63.8%	p < 0.001 p < 0.001 0.7% difference
(Kakagia et al 2007) Greece	Level II RCT Average quality study	N = 51. Diabetic patients, 43% male, that attended a clinic in Greece from December 2004 to December 2006, with significant soft tissue defects of the foot that had been present for at least 3 months (). Intervention group A: N = 17; age (yrs) 58 ± 10; leukocyte count (M/μl) 7.7 ± 1.9; haemoglobin (g/dl)	N = 17. Group A: Promogran, consisting of 45% oxidised regenerated cellulose and 55% collagen applied to	N = 17. Autologous platelet derived growth factors applied to the wound and covered with Tegaderm, a thin	No. of patients with ulcers that healed Group A, C 2/17 (12%) 2/17 (12%)	Group B 2/17 (12%)	RR = 1.00 [95% CI 0.19, 5.40]
		13.4 ± 1.9; HbA_{1c} (g/dl) 8.9 ± 3.1; platelet count (K/μl) 289 ± 63.5; sodium (mmol/l) 140 ± 1.6; potassium (mmol/l) 4.4 ± 0.4; glucose (mg/dl) 129 ± 69; creatinine (mg/dl) 1.6 ± 0.9; albumin (g/dl) 3.7 ± 0.7; ulcer duration (weeks) 17 ± 11; ulcer size (mm^2) 25.8 ± 15.2. Intervention group C: N = 17; age (yrs) 61 ± 9; leukocyte count (M/μl) 8.1 ± 1.3; haemoglobin (g/dl) 14.2 ± 1.5; HbA_{1c} (g/dl) 8.5 ± 4.0; platelet count (K/μl) 269 ± 96; sodium (mmol/l) 139 ± 2.2; potassium (mmol/l) 4.6 ± 0.3; glucose (mg/dl) 134 ± 72; creatinine (mg/dl) 2.0 ± 1.1; albumin (g/dl) 3.7 ± 0.6; ulcer duration (weeks) 19 ± 8; ulcer size (mm^2) 27.6 ± 17.5. Comparator group B: N = 17; age (yrs) 57 ± 12; leukocyte count (M/μl) 7.9 ± 1.7; haemoglobin (g/dl) 13.9 ± 1.2; HbA_{1c} (g/dl) 8.1 ± 2.8; platelet count (K/μl) 270 ± 101; sodium (mmol/l) 140 ± 1.7; potassium (mmol/l) 4.3 ± 0.6; glucose (mg/dl) 140 ± 67; creatinine (mg/dl) 1.3 ± 0.7; albumin (g/dl) 3.6 ± 0.9; ulcer duration (weeks) 20 ± 6; size (mm^2) 28.4 ± 13.6.	the wound as primary dressing in standard wound care. N = 17. Group C: Autologous platelet derived growth factors applied to the wound and covered with Promogran as the primary dressing in standard wound care.	polyurethane membrane coated with a layer of an acrylic adhesive. All patients had undergone debridement of the ulcer, followed by standard wound care with saline-moistened gauze for at least 4 weeks, resulting in no more than a 15% reduction in ulcer dimensions. All ulcers had to be> 2.5 cm in at least one dimension after debridement.	% reduction in ulcer dimensions Length: Group A 18.6±10.4 Group C 33.8±14.7 Width: Group A 3.9±10.8 Group C 46.1±13.1 Depth: Group A 35.6±10.6 Group C 55.1±10.8	Group B 14.3±7.1 Group B 17.4±8.0 Group B 34.9±9.9	p = 0.51 p < 0.001 p = 0.19 p < 0.001 p = 0.98 p < 0.001

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Lobmann et al 2006) Germany	Level II RCT Average quality study	N = 33. Diabetic patients with chronic diabetic foot lesions (University of Texas wound classification stage 2a). Intervention group: N = 18; age (yrs) 64 ± 11; duration of diabetes (yrs) 15 ± 11; % HbA_{1c} 7.4 ± 1.1; ulcer area (mm^2) 1237 (25-7200). Comparator group: N = 15; age (yrs) 62 ± 12; duration of diabetes (yrs) 16 ± 11; % HbA_{1c} 7.7 ± 1.9; ulcer area (mm^2) 1132 (360-3600).	N = 18. Promogran matrix wound dressing (protease inhibitor) applied directly on wound in addition to standard good wound care.	N = 15. Standard good wound care	% reduction in ulcer area 16	1.6	p = 0.045

RR = relative risk; CI = confidence interval; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot University of Texas Diabetic Foot Classification System: 01. A0 Pre – or post ulcerative lesion completely epithelialised, 02. A1 superficial wound not involving tendon, capsule or bone, 03. A2 Wound penetrating to tendon or capsule, 04. A3 wound penetrating to bone or joint, 05. B0 pre or post ulcerative lesion completely epithelialised with infection, 06. B1 superficial wound, not involving tendon, capsule or bone with infection, 07. B2 wound penetrating to tendon or capsule with infection, 08. B3 wound penetrating to bone or joint with infection, 09. C0 pre or post ulcerative lesion completely epithelialised with ischaemia, 10. C1 superficial wound not involving tendon, capsule or bone with ischaemia, 11. C2 wound penetrating to tendon or capsule with ischaemia, 12. C3 wound penetrating to bone or joint with ischaemia, 13. D0 pre or post ulcerative lesion completely epithelialised with infection and ischaemia, 14. D1 superficial wound not involving tendon, capsule or bone with infection and ischaemia, 15. D2 wound penetrating to tendon or capsule with infection and ischaemia, 16. D3 wound penetrating to bone or joint with infection and ischaemia; ICER = incremental cost-effectiveness ratio

Surgical debridement versus standard wound care

Piaggesi et al (1998) conducted a level II study of average quality involving 42 diabetic patients who presented to an outpatient clinic for the first time during 1995 with one or more painless neuropathic foot ulcers. The aim was to investigate the effectiveness of surgical debridement therapy in treating the ulcers (Table 88). The surgery described in this study involved the complete removal of the ulcer through conic ulcerectomy, including any segments of bone that might interfere with closure of the wound margins. The surgical wounds were closed with sutures and a drain which was removed after 48 hours. Thus, the ulcers treated using this surgical debridement method all healed by primary intention (surgical closure). This is a much more extreme debridement method than conventional sharp debridement which involves the removal of dead and necrotic tissue to restore a healthy wound bed which has the potential to heal by secondary intention (re-epithelialisation of the wound). The authors compared their surgical debridement method to conventional wound therapy after an initial debridement of lesions and elimination of surrounding hyperkeratosis. There was no statistically significant difference in the number of ulcers that healed, recurred, became infected or the number of patients that required an amputation between the two groups. However, there was a significant reduction in time to healing for the surgical debridement group compared to the comparator (46.7 ± 38.9 versus 128.9 ± 86.6 days; p = 0.001). Thus, this surgical debridement method does offer a marginal clinical benefit over conventional therapy in this study.

Box 125 Evidence statement matrix for surgical debridement in addition to standard wound care

Component	Rating	Description
Evidence base	C	One level II study with a moderate risk of bias
Consistency	N/A	There was only one study
Clinical impact	D	Slight clinical impact. Ulcers in the conventional therapy group took longer to heal compared to surgical debridement group, but there was no statistically significant difference between groups regarding the number of ulcers that healed completely, although it was trending that way.
Generalisability	B	Population consisted of diabetic patients with neuropathic foot ulcer of Wagner grade 1 or 2.
Applicability	B	This study was conducted in Italy, which has similar healthcare for diabetic patients when compared to the Australian healthcare context.

Evidence statement

Surgical debridement using conic ulcerectomy reduces the time for ulcer healing when compared to standard wound care using conventional sharp debridement for patients with diabetic foot ulcers. However, it is uncertain if it has any benefit for overall ulcer healing. (Grade C)

Table 88 Studies which investigated the effectiveness of surgical debridement in the treatment of diabetic foot ulcer

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Piaggesi et al 1998) Italy	II randomised controlled trial Average quality study	N = 42 patients with diabetes of not less than 5 years duration who presented to an outpatient clinic for the first time during 1995, with one or more painless neuropathic foot ulcers. Intervention group: N = 21 patients; n = 22 ulcers; age (yrs) 65.5 ± 9.9; duration of diabetes (yrs) 16.8 ± 10.6; diabetes type 2 19/21 (91%); BMI (kg/m^2) 28.1 ± 13.0; vibration perception threshold (V) at first toe 48.4 ± 24.2; at malleolus 43.2 ± 15.2; % HbA_{1c} 8.9 ± 2.2; ulcer duration (days) 39.4 ± 18.9; ulcer diameter (cm) 4.32 ± 1.95; ulcer depth (cm) 1.98 ± 1.1; location of ulcer: plantar 13/22 (59%); medial aspect of first metatarsal-phalangeal joint 5/22 (23%); lateral side of fifth metatarsal-phalangeal joint 4/22 (18%); upper side of toes 0/22 (0%); Wagner grade 1 14/22 (64%); grade 2 8/22 (36%). Comparator group: N = 21 patients; n = 24 ulcers; age (yrs) 63.2 ± 13.5; duration of diabetes (yrs) 18.2 ± 8.4; diabetes type 2 17/21 (81%); BMI (kg/m^2) 27.7 ± 9.4; vibration perception threshold (V) at first toe 46.1 ± 18.2; at malleolus 40.1 ± 11.9; % HbA_{1c} 9.5 ± 3.8; ulcer duration (days) 32.7 ± 19.3; ulcer diameter (cm) 4.25 ± 2.35; ulcer depth (cm) 1.58 ± 2.2; location of ulcer: plantar 16/24 (67%); medial aspect of first metatarsal-phalangeal joint 5/24 (21%); lateral side of fifth metatarsal-phalangeal joint 2/24 (8%); upper side of toes 1/24 (4%); Wagner grade 1 16/24 (67%); grade 2 8/24 (33%).	N = 21 patients, n = 22 ulcers. Surgical intervention that included conic ulcerectomy (debridement) including the removal of bone segments underlying the lesion, and surgical closure with stitches and relief from weight bearing for 4 weeks, plus irrigation of ulcers with povidone iodine 50% and saline 50%, twice weekly.	N = 21 patients, n = 24 ulcers. Conventional therapy consisting of relief from weight-bearing, and regular saline dressings every 24 hours after initial debridement and irrigation of ulcers with povidone iodine 50% and saline 50%.	Number of ulcers that healed completely		
					21/22 (96%)	19/24 (79%)	RR = 1.21 [95% CI 0.96, 1.51]
					Time to healing (days)		
					46.7 ± 38.9	128.9 ± 86.6	p = 0.001
					Number of ulcers the recurred		
					3/22 (14%)	8/24 (33%)	RR = 0.41 [95% CI 0.12, 1.35]
					Number of infections (harms)		
					1/22 (4.5%)	3/24 (12.5%)	RR = 0.36 [95% CI 0.05, 2.39]
					Number of amputations required		
					0/21 (0%)	1/21 (4.8%)	RR = 0.00 [95% CI 0.00, 3.78]

RR = relative risk; CI = confidence interval; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot

Wound debridement using larval therapy versus conventional debridement surgery

Three level III-2 studies of average quality investigated the efficacy of larval debridement therapy compared to conventional surgical debridement for treating diabetic foot ulcers (Table 89). The use of maggots to heal wounds was routine prior to the introduction of antibiotics and is increasing in popularity again (Sherman 2003). Maggot larvae secrete enzymes that selectively dissolve necrotic tissue, disinfect the wound, and stimulate wound healing. Two different maggot species have been used; *Lucilia sericata*, which is commercially available in the UK and the USA, and *Lucilia cuprina*, a tropical blowfly used in the Malaysian study. It is currently unknown if different species of maggot vary in their ability to perform debridement therapy.

Armstrong et al (2005) conducted a retrospective cohort study of 30 diabetic patients with a single foot ulcer and peripheral vascular disease. They were unable to walk without assistance and received maggot debridement therapy in addition to standard wound care. These cases were age and gender matched to a control group of 30 diabetic patients with the same disease criteria, but who received standard wound care (Table 89). The study was conducted at a large, referral-based diabetic foot clinic located in the Southern Arizona Veterans Affairs Medical Centre, in Tuscon. Although the standard wound care the patients received was not described, most standard care includes sharp debridement as needed. The species of maggot larvae involved was not disclosed, but was almost certainly *Lucilia sericata*, due to its availability in the USA. The authors did find a clinically important difference in the number of ulcers that healed after larval debridement therapy compared to standard wound care, although the result was not statistically significant (57% of cases compared to 33% controls healed; OR = 2.62 [95% CI 0.93, 7.37]). However, the time to healing reduced significantly from 22.4 ±4.4 weeks with standard wound care to 18.5 ± 4.8 weeks with larval therapy (p = 0.04). The likelihood of requiring an amputation also reduced significantly from 33% with standard wound care to 10% after larval therapy (OR = 0.22 [95% CI 0.06, 0.86]).

Paul et al (2009) conducted a non-randomised controlled trial to investigate the efficacy of maggot debridement therapy using *Lucilia cuprina* maggots (10/cm^2 ulcer area) compared to conventional surgical debridement. They investigated the number of patients with ulcers that healed and the number of patients that required amputations and found no statistically significant differences between the larval debridement and surgical debridement groups for either outcome. The analysis was not performed according to intention to treat and the ulcer grade was more severe in the maggot debridement group. However, the length of hospital stay was significantly shorter for the larval therapy patients than for those that had surgical debridement (p = 0.01, Table 89).

Sherman (2003) conducted a cohort study to investigate the efficacy of larval debridement therapy using *Lucilia sericata* maggots (5-8/cm^2 ulcer area) compared to conventional treatment which included surgical debridement as needed. The data presented in this study shows statistically significant differences for the weekly change in ulcer surface area and the ulcer healing rate at 4 and 8 weeks between the two groups (Table 89). Whereas the ulcers in the larval debridement therapy group decreased in size by an average of 2% per week, the ulcers in the conventional therapy group increased by an average of 27% per week (p < 0.05). However, there was no statistically significant difference between the two groups for the percent wound completely closed (36% [range 7-65] for larval therapy compared to 21% [range 0-44] for conventional treatment; p > 0.05) or the average time to healing (15 days [range 3-26] for larval therapy compared to 18 days [range 8-28] for conventional treatment; p > 0.05). The study had a small sample size and appears to have been underpowered. Additionally, the

ulcers appeared to be more severe (larger and more necrotic) in the group receiving larval debridement therapy.

Overall, larval debridement therapy appears to be as effective as standard care with surgical debridement and may have the additional benefit of shortening the time needed for the ulcer to heal. However, there are some logistical problems for effective implementation of this form of therapy. First, there is the distaste that many people feel for this form of treatment and the feeling of the maggot larvae moving over the ulcer area may not be bearable for some people. Secondly, for widespread use, the maintenance of sterile maggot populations that can be ready for use at a moment's notice requires additional resources that a treatment facility may not have. Currently, sterile *Lucilia sericata* maggots are available from the Department of Medical Entomology, Westmead Hospital in NSW.

Box 126 Evidence statement matrix for larval debridement therapy compared to conventional debridement surgery

Component	Rating	Description
Evidence base	D	Three level III-2 evidence studies with a moderate risk of bias
Consistency	A	All three studies showed consistent trends.
Clinical impact	C	Moderate clinical impact. All three studies reported shortened times to healing or hospital stays, but only two were statistically significant. Both studies that reported amputation rates showed a reduction in number of amputations after maggot therapy compared to conventional surgical debridement, but only one was statistically significant.
Generalisability	C	The population consisted of diabetic patients with non-healing foot and leg ulcers, with and without infections, with and without ischaemia
Applicability	C	Two studies were conducted in USA, which has similar healthcare for diabetic patients when compared to the Australian healthcare context. The third study took place in Malaysia, which has less similar healthcare for diabetic patients when compared to the Australian healthcare context. In Australia, sterile maggots are currently available from the Department of Medical Entomology, Westmead Hospital, NSW.

Evidence statement

Larval debridement therapy may improve foot ulcer healing time and prevent amputation when used in addition to standard wound care over standard wound care with surgical debridement alone in patients with severe diabetic foot ulcers. More research outside this setting is required. (Grade C).

Table 89 Studies which investigated the effectiveness of maggot debridement therapy in the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Armstrong et al 2005d) USA	III-2 retrospective cohort study Average quality study	N = 60. Diabetic patients unable to walk without assistance, with a single University of Texas grade C or D foot ulcer and diagnosed with peripheral vascular disease without surgical intervention, and at least 6 months of reliable follow-up information. Intervention group: N = 30, age (years) 71.7 ±6.8; male 26/30 (86.7%); duration of diabetes (years) 14.7 ± 8.4; wound size (cm^2) 11.8 ± 4.5; infections 24/30 (80%). Comparator group: N = 30 age and gender matched patients; age (years) 72.7 ±6.8; male 26/30 (86.7%); duration of diabetes (years) 16.3 ± 7.6; wound size (cm^2) 12.4 ± 6.7; infections 18/30 (60%).	N = 30 Maggot debridement therapy plus same standard wound care as control group.	N = 30 Standard wound care according to protocol followed in the high-risk diabetic foot clinic.	Number of patients with ulcers that healed 17/30 (57%)	10/30 (33%)	OR = 2.62 [95% CI 0.93, 7.37] RR = 1.79 [95% CI 0.96, 3.05]
					Time to healing (weeks) 18.5 ± 4.8	22.4 ±4.4	p = 0.04
					Number of patients that required amputation above foot 3/30 (10%)	10/30 (33%)	OR = 0.22 [95% CI 0.06, 0.86] RR = 0.30 [95% CI 0.09, 0.89]
(Paul et al 2009) Malaysia	III-2 non-randomised controlled trial Average quality trial	N = 59. Diabetic patients, aged 35-70 years, admitted to the orthopaedics wards in the Kuala Lumpur General Hospital for infected foot ulcers from December 2005 to May 2007 requiring debridement. All patients offered maggot debridement therapy and asked to sign consent form if agreeable. Intervention group – N = 29; mean age (yrs) 56.6 (30.0-75.0); male 18/29 (62%). 4 patients did not complete treatment. N = 25; age (yrs) 55.3 (30.0-69.2); peripheral neuropathy 11/25 (44%); antibiotic usage 24/25 (96%); serum albumin (g/dl) 35.4 (24.0-44.0); white cell count (x 10^9) 10.6 (7.6-17.6); % HbA_{1c} 10.0 (7.7-13.7); blood sugar (mmol/l) 11.1 (6.5-17.3); ankle-brachial systolic index 1.0 (0.81-1.86); University of Texas class 1B 4/25 (10%); class 2B 16/25 (30%); class 3B 5/25 (60%). Comparator group – N = 30; mean age (yrs) 55.6 (32.0-82.5); male 20/30 (66.7%). I patient did not complete treatment.	N = 25 *Lucilia cuprina* maggots were applied directly on the wound with a spatula (10/cm^2 ulcer area), covered with light gauze and then sealed with OpSite. Small fenestrations made to allow drainage of fluid. A gamgee was placed over this to absorb fluid and the entire foot was loosely bandaged with crepe, which was changed as necessary. A washout of the wound occurred after 48 h	N = 29 Surgical debridement was performed as required and wound dressing was performed daily with normal saline only.	No. patients with healed ulcers – per protocol Total 14/25 (56%)	18/29 (62%)	RR = 0.90 [95% CI 0.58, 1.39]
					UTMB class 1B 4/4 (100%)	6/8 (75%)	RR = 1.33 [95% CI 0.77, 1.33]
					UTMB class 2B 8/16 (50%)	4/8 (50%)	RR = 1.00 [95% CI 0.50, 2.54]
					UTMB class 3B 2/5 (40%)	8/13 (61.5%)	RR = 0.65 [95% CI 0.18, 1.52]
					Length of hospital stay (days) (range) 12.5 (2.0-32.0)	19.8 (3.0-47.0)	p = 0.01

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
		N = 29; age (yrs) 55.3 (32.0-82.5); peripheral neuropathy 10/29 (34.5%); antibiotic usage 28/29 (96.5%); serum albumin (g/dl) 37.4 (24.0-46.0); mean white cell count (x 10^9) 10.8 (7.5-18.0); % HbA_{1c} 10.8 (8.6-13.7); blood sugar (mmol/l) 9.8 (6.5-15.8); ankle-brachial systolic index 1.1 (0.90-1.50); University of Texas class 1B 8/29 (27.6%); class 2B 8/29 (27.6%); class 3B 13/29 (44.8%).	using normal saline. Maggots were reapplied if needed. If no change noticed after 3 applications then treatment was abandoned.		Number of amputations Total 5/25 (20%) Above ankle 1/25 (4%) Below ankle 4/25 (16%)	 11/29 (37.9%) 6/29 (20.7%) 5/29 (17.2%)	 RR = 0.53 [95% CI 0.21, 1.24] RR = 0.19 [95% CI 0.03, 1.11] RR = 0.93 [95% CI 0.29, 2.94]
(Sherman 2003) USA	III-2 cohort study Average quality study	N = 20. Diabetic patients with non-healing foot and leg ulcers referred to the maggot therapy service between 1990 and 1995, and were appropriate candidates. Intervention group: N = 14 (6 group 1 + 8 group 2 wounds); age (yrs) 63 (53-74); mean ideal body weight 129%; smoker 2/14 (14%); Hb (g/dl) 13.2; albumin (g/dL) 3.7; peripheral venous or arterial disease 13/14 (93%); receiving systemic antibiotics 3/14 (21%); neuropathic ulcer 9/14 (64%); ischaemic ulcer 1/14 (7%), mixed or undefined ulcer 4/14 (29%); duration of ulcer (weeks) 44 (4-318); size of ulcer (cm^2) 13.3 (0.9-42); circumference (cm) 13.5 (3.3-27.7); depth to peristeum or bone 21%; necrotic tissue (% total surface) 38 (0-90); granulation tissue (% total surface) 19 (0-100); Prior treatment with dry gauze, saline, petroleum, aloe, other gel 3/14 (21.4%); topical antimicrobial 1/14 (7.1%); chemical debridement agent 0/14 (0%); sharp debridement, incision and drainage, other surgical procedure 8/14 (57.1%); three or more different nonsurgical methods2/14 (14.3%). Comparator group: N = 14 (6 control + 8 group 2 wounds); age (yrs) 68 (53-82); mean ideal body weight 114%; smoker 3/14 (21%); Hb (g/dl) 12.4; albumin (g/dL) 3.7; peripheral venous or arterial disease 9/14	N = 14 (group 1 + group 2) Group 1, N = 6 Maggot (*Lucilia sericata*) therapy. Group 2, N = 8 Standard therapy first, followed by maggot therapy. Maggot therapy involved applying 5-8 disinfected fly larvae per cm^2 to the wound within a cage-like dressing which was left in place for 48 h. Maggots were then removed by wiping up the larvae with a wet gauze pad. 1-2 cycles were applied each week and saline- or 0.125% sodium	N = 14 (control + group 2) N = 6 Standard therapy. Patients received the conventional surgical or non-surgical therapy selected by their primary care staff.	% wound completely closed (range) 36% (7-65) Weekly % change in ulcer surface area (range) -2% (-22 to 18) Mean (range) healing rate (change in surface area divided by the mean circumference over time) at: 4 weeks 0.08 (0.2-0.14) 8 weeks 0.07 (0.04-0.11) Ave. Time (weeks) to healing (range) 15 (3-26)	 21% (0-44) +27% (4.1 to 50) -0.08 (-0.15 to -0.00) -0.02 (-0.08 to 0.04) 18 (8-28)	 p > 0.05 p < 0.05 p < 0.05 p < 0.05 p > 0.05

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
		(64%); receiving systemic antibiotics 2/14 (14%); neuropathic ulcer 12/14 (86%); ischaemic ulcer 1/14 (7%); mixed or undefined ulcer 1/14 (7%); duration of ulcer (weeks) 40 (4-312); size of ulcer (cm^2) 6.3 (0.5-15.5); circumference (cm) 9.4 (2.5-16.6); depth to peristeum or bone 14%; necrotic tissue (% total surface) 44 (0-100); granulation tissue (% total surface) 18 (0-90); prior treatment with dry gauze, saline, petroleum, aloe, other gel 3/14 (21.4%); topical antimicrobial 1/14 (7.1%); chemical debridement agent 1/14 (7.1%); sharp debridement, incision and drainage, other surgical procedure 5/14 (35.7%); three or more different nonsurgical methods 4/14 (28.5%).	hypochlorite-moistened gauze dressings were applied between treatments.				

OR = odds ratio; RR = relative risk; CI = confidence interval; University of Texas Diabetic Foot Classification System: 01. A0 Pre – or post ulcerative lesion completely epithelialised, 02. A1 superficial wound not involving tendon, capsule or bone, 03. A2 Wound penetrating to tendon or capsule, 04. A3 wound penetrating to bone or joint, 05. B0 pre or post ulcerative lesion completely epithelialised with infection, 06. B1 superficial wound, not involving tendon, capsule or bone with infection, 07. B2 wound penetrating to tendon or capsule with infection, 08. B3 wound penetrating to bone or joint with infection, 09. C0 pre or post ulcerative lesion completely epithelialised with ischaemia, 10. C1 superficial wound not involving tendon, capsule or bone with ischaemia, 11. C2 wound penetrating to tendon or capsule with ischaemia, 12. C3 wound penetrating to bone or joint with ischaemia, 13. D0 pre or post ulcerative lesion completely epithelialised with infection and ischaemia, 14. D1 superficial wound not involving tendon, capsule or bone with infection and ischaemia, 15. D2 wound penetrating to tendon or capsule with infection and ischaemia, 16. D3 wound penetrating to bone or joint with infection and ischaemia

In Indigenous populations

Professional foot care interventions versus standard medical care

Two level III-3 average quality studies investigated the effectiveness of professional foot care in preventing foot amputations in Indigenous populations in the USA (Table 90).

Schraer et al (2003) conducted a historically controlled study to investigate the effectiveness of the introduction of a specialty foot service to the Alaskan Native Medical Centre in early 1999 at reducing the number of lower-extremity amputations among the Indigenous Alaskan diabetic population. This service included a field component of itinerant services to rural hospitals and clinics and training for village health workers and community-based para-professionals. The number of Native Alaskans with diabetes was derived from the patient registry of the Alaskan Native Medical Centre and from computerised databases at each regional tribal health facility. Comparison data was collected from 1996-1998, pre-introduction of the specialty foot service and post-intervention data was collected from 1999-2001. The authors found that there was a significant reduction in the amputation rate after the specialty foot service was introduced compared to before their introduction (64%, $p < 0.001$). The largest decrease was among the Eskimo and Aleut diabetic populations (70%, $p = 0.047$ and 82%, $p < 0.001$, respectively). The reduction in amputation rates among the Alaskan Native Indian diabetic population was not statistically significant ($p = 0.94$).

Rith-Najarian et al (1998) conducted a historically controlled study to compare the effectiveness of two different foot care management programs, introduced in 1990 and 1994, in reducing amputation rates among 639 Chippewa Indians with diabetes in a rural primary care clinic in northern Minnesota. Data was collected for two different management periods; the public health period (1990–1993), when diabetic patients were screened for foot problems and high-risk individuals received foot care education and protective foot wear, and the staged management period (1994–1996), when comprehensive guidelines for diabetic foot management were implemented by primary care clinicians. The amputation rates during these two periods were compared to an earlier period of standard foot care (1986–1989), when foot care was at the discretion of the primary care provider. The authors found that the amputation rates did not significantly decrease during the public health period compared to the preceding standard care period (28% reduction; $p = 0.20$). In contrast, the overall amputation rate decreased significantly during the staged management period compared to the standard care period, especially the rate for first amputations (48% reduction; $p = 0.016$ and 71% reduction; $p = 0.0006$, respectively). The rate for major amputations did not decrease significantly when comparing either the staged management or the public health period with an earlier period of standard foot care (27% reduction; $p = 0.49$).

Both these studies showed that the introduction of specialist foot care management programs results in a lower incidence of amputations per 1000 diabetic person-years than standard care at the discretion of the primary care provider. However, the comparison of the comprehensive staged foot care management period with the public health period, when diabetic patients were screened for high-risk foot problems, showed no statistically significant differences.

Box 127 Evidence statement matrix for professional foot care versus standard medical care

Component	Rating	Description
Evidence base	D	Two level III-3 studies with a moderate risk of bias
Consistency	A	Both studies showed a statistically significant difference in the incidence of amputations per 1000 diabetic person-years between specialist foot care management programs and standard care at the discretion of the primary care provider.
Clinical impact	B	There is a statistically significant decrease in the incidence of amputations per 1000 diabetic person-years when patients are treated by a specialist foot care management program compared with standard care treatment at the discretion of the primary care provider.
Generalisability	A	The population consisted of Native Alaskans with diabetes in one study and Chippewa Indians with diabetes in the other.
Applicability	C	Both of these studies were conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia.

Evidence statement

Treatment of diabetic foot ulcers according to the protocols of professional management programs, instead of standard care at the discretion of the primary care provider, reduces the likelihood that the Native Alaskan and Chippewa Indians with diabetes will require an amputation. (Grade C)

Table 90 Studies which evaluated the effectiveness of professional foot care versus standard medical care

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Schraer et al 2004) Alaska, USA	III-3 historically controlled study Average quality study	N = 10134.5 diabetic person-years. Native Alaskans with diabetes derived from the patient registry of the Alaskan Native Medical Centre, ascertained from computerised databases at each regional tribal health facility. Intervention group: Native Alaskans with diabetes between 1999 and 2001. Comparator group: Same population base: Native Alaskans with diabetes, but different time period (between 1996 and 1998).	N = 5908 diabetic person-years. Introduction of specialty foot services to the Alaskan Native Medical Centre in early 1999, and this included a field component of itinerant services to rural hospitals and clinics and training for village health workers, community-based para-professionals. Data was collected from 1999–2001.	N = 4226.5 diabetic person-years. Pre-introduction of the specialty foot services. Data collected from 1996-1998. .	Number of amputation per diabetic person-years (incidence per 1000 p-y): For any duration of diabetes Eskimo 4/1979.5 (2.0) Indian 8/2655.5 (3.0) Aleut 4/1273 (3.1) All Natives 16/5908 (2.7) For diabetes of > 10 years duration Eskimo 4/501.5 (8.0) Indian 6/742 (8.1) Aleut 1/384.5 (2.6) All Natives 11/1628 (6.8)	% reduction 9/1355 (6.6) 7/1950 (3.6) 16/921.5 (17.4) 32/4226.5 (7.6) % reduction 7/405.5 (17.3) 7/610.5 (11.5) 8/326 (24.5) 22/1342 (16.4)	 70% p = 0.047 16% p = 0.94 82% p < 0.001 64% p < 0.001 54% p = 0.235 29% p = 0.722 89% p = 0.01 59% p = 0.021

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Rith-Najarian et al 1998) USA	III-3 historically controlled study Average quality study	N = 639. Chippewa Indians with diabetes in a rural primary care clinic in northern Minnesota Intervention group 1: N = 475; 1313 diabetic person-years; age (years) 54.2 ± 13.0; male 205/475 (43.2%); duration of diabetes (years) 9.7 ± 7.2. From a sample of medical records (142/475): % HbA_{1c} 9.6 ± 2.1; arterial pressure (mmHg) 136 ± 13; serum creatinine (mg/dl) 1.3 ± 1.2; serum cholesterol (mg/dl) 210 ± 42; past or current tobacco use 119/142 (84%); proteinuria > trace 55/142 (39%). Intervention group 2: N = 449; 1543 diabetic person-years; age (years) 53.6 ± 13.1; male 194/449 (43.2%); duration of diabetes (years) 8.5 ± 6.4. From a sample of medical records (129/449): % HbA_{1c} 9.4 ± 2.2; arterial pressure (mmHg) 132 ± 16; serum creatinine (mg/dl) 1.2 ± 1.2; serum cholesterol (mg/dl) 206 ± 48; past or current tobacco use 101/129 (78%); proteinuria > trace 62/129 (48%). Comparator group: N = 428; 1464 diabetic person-years; age (years) 53.9 ± 12.9; male 195/428 (45.6%); duration of diabetes (years) 8.3 ± 6.5.	N = 474. Staged diabetes management period (SDM; 1994-1996) Comprehensive guidelines for diabetic foot management were implemented by primary care clinicians in an Indian Health Service facility in northern Minnesota. N = 449. Public health period (PH; 1990-1993). Diabetic patients were screened for foot problems and high-risk individuals received foot care education and protective foot wear.	N = 428. Standard care period (SC; 1986-1989). Foot care at the discretion of the primary care provider.	Number of lower extremity amputations (LEA) per diabetic person-years (Incidence LEA/1000 p-y) Any LEA SDM 20/1313 (15) PH 33/1543 (21) SDM 20/1313 (15) First LEA SDM 7/1246 (6) PH 18/1467 (12) SDM 7/1246 (6) Major LEA SDM 11/1313 (8) PH 12/1543 (8) SDM 11/1313 (8)	 % reduction SC 42/1464 (29) 28%; p = 0.20 PH 33/1543 (21) SC 30/1414 (21) 43%; p = 0.06 PH 18/1467 (12) SC 16/1464 (11) 27%; p = 0.37 PH 12/1543 (8)	 48%; p = 0.016 29%; p = 0.27 71%; p = 0.0006 50%; p = 0.11 27%; p = 0.49 0%; p = 1.0

SDM = staged diabetes management; PH = public health; SC = standard care.

0.

Effectiveness of surgical treatment of hallux limitus

Daniels (1989) conducted a case series (level IV intervention evidence) of average quality to investigate the effectiveness of surgical correction of hallux limitus in healing and preventing recurrence of foot ulcers (Table 91). Seven American Indian diabetic patients with hallux limitus and central ulcers plantar to the proximal phalangeal heads of the great toes were treated by surgically correcting the foot deformity caused by hallux limitus. The authors found that the ulcers healed for all seven patients and did not recur after an average follow-up period of 28.8 months.

This study shows that all patients healed after surgery to correct foot deformity however, it is uncertain if similar results for healing and recurrence could be obtained from other less invasive interventions.

Box 128 Evidence statement matrix for surgical treatment of hallux limitus

Component	Rating	Description
Evidence base	D	One level IV study with moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	D	Although the effect of surgery was substantial, without a comparator group it is not possible to determine whether these patients would have healed without surgical intervention.
Generalisability	B	These results are likely to be generalisable to all ethnic groups with foot deformities and foot ulcers.
Applicability	B	This study was conducted in the USA (Phoenix Medical Center) and is likely to be applicable to the Australian healthcare context with few caveats

Evidence statement

There is evidence to suggest that surgical correction of foot deformity may increase healing of foot ulcer and prevent recurrence however, it is not known whether this intervention is more effective than others in this population for these outcomes (Grade C).

Table 91 Included study for the evaluation of surgical treatment of hallux limitus

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Dannels 1989) USA	Level IV case series Average quality study	N = 7. American Indian type 2 diabetic patients with hallux limitus and central ulcers plantar to the proximal phalangeal heads of the great toes. Intervention group: N = 7; male 4/7 (57%) with 6/8 (75%) affected feet; duration of diabetes (yrs) 14.25; affected limbs with medical arterial calcification 10/10 (100%); protective sensation 0/10 (0%); osteomyelitis 0/10 (0%); interphalangeal sesamoids 0/10 (0%); palpable dorsalis pedis and posterior tibial pulses 10/10 (100%); normal subpapillary venous plexus filling time in toes 10/10 (100%).	N = 10 affected feet (in 7 patients) Surgical correction of hallux limitus, a deformity of the first metatarsophalangeal joint. Osteotomies were through a dorsolinear incision over the first metatarsophalangeal joint and the wounds were closed primarily.	None	Number of feet with ulcers that healed 10/10 (100%) Number of feet whose ulcer recurred 0/10 (0%)		

Skin replacement therapies

Twenty published articles (one average quality level I evidence, three good quality level II evidence, twelve average quality level II evidence, one poor quality level II evidence, three average quality level III-2 evidence) investigated the effectiveness of skin replacement therapies in treating diabetic foot ulcers. There were several different types of skin replacement therapies identified. Three studies investigated three different methods of skin grafting: split-skin grafting, meshed skin grafting, and grafting epidermal sheets from suction blisters (Table 61 to Table 94). Two studies investigated the use of cultured keratinocytes, one with autologous cells and the other using allogenic cells, and another study investigated the use of cultured allogenic fibroblasts (Table 95). Ten studies investigated the use of cultured skin equivalents (Table 96), and three studies investigated the use of acellular dermal tissue matrixes (Table 98, Table 99). One study compared the use of a cultures skin equivalent and an acellular dermal tissue matrix (Table 97).

Split-skin grafting versus standard wound care

Mahmoud et al (2008) conducted an average quality non-randomised controlled study (level III-2 intervention evidence) to investigate the effectiveness of split-skin grafting compared to standard wound care in treating diabetic foot ulcers (Table 61). The study population consisted of 100 consecutive patients with diabetic foot ulcers > 2 cm diameter, and an ankle-brachial index of > 0.4 who were attending either the Jabir Abu Eliz Diabetic Centre or the Soba University Hospital. Patients were offered split-skin grafting or standard wound care. Patients were followed until complete healing (complete epithelialisation) occurred and the intervention group were followed for a further year to determine if ulcers recurred. The authors found that both the time to healing and the length of hospital stay was statistically significantly shorter after split-skin grafting compared to standard wound care ($p < 0.05$). However, the study design has substantial potential for introducing bias as a result of the process for allocating treatment Patients with more severe ulcers, or ulcers of a longer duration are likely to chose split-skin grafting over standard wound care. It is possible therefore, that this is a conservative estimate of the treatment effect.

Box 129 Evidence statement matrix for split-skin grafting versus standard wound care

Component	Rating	Description
Evidence base	D	One level III-2 study with a moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	B	Moderate clinical impact. The study showed a statistically significant difference in time to healing of ulcer and the length of hospital stay.
Generalisability	B	The population consisted of diabetic patients with foot ulcers greater than 2 cm diameter.
Applicability	D	The study was conducted in Sudan, which has different healthcare for diabetes patients compared to the Australian healthcare context.

Evidence statement

Split-skin grafting is likely to reduce the time for ulcer healing and length of hospital stay when compared to standard wound care for patients with diabetic foot ulcers. (Grade D)

Table 92 Studies which evaluate the effectiveness of split-skin grafting for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Mahmoud et al 2008) Sudan	Level III-2 Prospective cohort study Average quality study	N = 100. Consecutive patients with diabetic foot ulcers and an ankle brachial index of > 0.4, attending the Jabir Abu Eliz Diabetic Centre or the Soba University Hospital between November 2004 and July 2006. Intervention group – N = 50; age (yrs) 51 ± 10; male 29/50 (58%); type 2 diabetes 43/50 (86%); ulcer size 2-5 cm^2 5/50 (10%); 5-10 cm^2 30/50 (60%); >10 cm^2 15/50 (30%); ulcer duration < 1 month 6/50 (12%); 1-2 months 14/50 (28%); 2-3 months 18/50 (36%); > 3 months 12/50 (24%); location: dorsum 12/50 (24%); plantar 11/50 (22%); heel 8/50 (16%); interdigital 4/50 (8%); stump 9/50 (18%); other site 6/50 (12%). Comparator group(s) – N = 50; age (yrs) 51 ± 7; male 30/50 (60%); type 2 diabetes 39/50 (78%); ulcer size 2-5 cm^2 7/50 (14%); 5-10 cm^2 26/50 (52%); >10 cm^2 17/50 (34%); ulcer duration < 1 month 5/50 (10%); 1-2 months 15/50 (30%); 2-3 months 20/50 (40%); > 3 months 10/50 (20%); location: dorsum 14/50 (28%); plantar 15/50 (30%); heel 6/50 (12%); interdigital 3/50 (6%); stump 7/50 (14%); other site 5/50 (10%).	N = 50. Split-skin grafting All patients offered skin grafting, those that refused given standard wound care. Debridement and skin grating undertaken by same plastic surgeon. Dressings as for control group, and first changed on the 5ht post-operative day and then twice weekly.	N = 50. Standard wound care All patients underwent surgical debridement. Multilayered dressings comprised of paraffin gauze, diluted povidone-iodine soaked gauze, sterile gauze, and a roll bandage. Dressings were changed twice weekly. Patients also received off-loading as required	Time to healing (days) 28 ± 5 Length of hospital stay (days) 6 ± 2 Number of patients with ulcers that recurred 4/50 (8%)	 122 ± 7 18 ± 9 Not measured	 p < 0.05 p < 0.05

Meshed skin grafting versus split-skin grafting

Puttirutvong (2004) conducted a level II study of average quality involving 80 diabetic patients with infected ulcers of the lower legs or feet who attended Taksin Hospital (Table 93). Ulcers included severe wounds with deep abscesses, gangrene of the toes or feet, and necrotising fasciitis of the lower legs. The aim of the randomised controlled trial was to compare the effectiveness of meshed skin grafting and split-skin grafting in addition to standard wound care for healing and time to healing over a 6 month follow-up period. Some minor infections caused a few graft losses and longer healing times in the split-skin group, in addition to one case of recurrent ulcer and one of toe contracture. No adverse events were recorded for the meshed skin group. The authors found that all ulcers in both groups healed and there was no difference in the time taken to heal, but there was a trend towards better graft outcomes (efficacy of treatment score) with meshed skin grafts compared to split-skin grafts, although this did not reach statistical significance.

Box 130 Evidence statement matrix for meshed skin grafting compared to split-skin grafting

Component	Rating	Description
Evidence base	C	One level II study with a moderate risk of bias.
Consistency	N/A	Only one study.
Clinical impact	D	Slight clinical impact. The study showed no statistically significant differences between the two skin grafting methods.
Generalisability	C	The population consisted of diabetic patients with infected foot ulcers of any severity.
Applicability	D	The study was conducted in Thailand, which has different healthcare for diabetes patients compared to the Australian healthcare context.

Evidence statement

There is no evidence to suggest that there is any difference in clinical outcomes after meshed skin grafting compared to split-skin grafting for people with chronic diabetic foot ulcers. (Grade D)

Table 93 Study which evaluated the effectiveness of meshed skin grafting compared to split-skin grafting for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Puttirutvong 2004) Thailand	Level II RCT Average quality study	N = 80. Diabetic patients with infected ulcers of the lower extremities or feet that attended Taksin Hospital between January 2002 and June 2003. Wounds included deep abscesses, gangrene of the toes or feet, and necrotising fasciitis of the lower legs; haematocrit > 30%; rare bacterial colonisation <10^5/g tissue. Intervention group: N = 38; age (yrs) 56.84 ± 8.96; size of ulcer (cm^2) 104.24 ± 152. Comparator group: N = 42; age (yrs) 55.02 ± 10.12; size of ulcer (cm^2) 82.00 ± 73.21.	N = 38. Meshed skin graft (expansion of split-skin graft by meshing) Used expansion ratio of 1:3 Wounds treated the same in both groups. Wounds underwent debridement and standard wound care with wet-to-dry saline gauze until they were covered with granulation tissue and suitable for grafting.	N = 42. Split thickness skin graft Thighs were used as donor site. After skin graft coverage was established, the dressings consisted of non-adhesive gauze, saline-soaked swab, and mild pressure outer layer. Dressings were changed every day.	Number of patients with ulcers that healed		
					38/38 (100%)	42/42 (100%)	RR = 1
					Time to healing (days)		
					19.84 ± 7.37	20.36 ± 7.21	p = 0.282
					Efficacy of treatment score		
					Excellent		
					19/38 (50%)	17/42 (40.5%)	RR = 1.24 [95% CI 0.76, 1.99]
					Good		
					12/38 (31.6%)	18/42 (42.9%)	RR = 0.74 [95% CI 0.41, 1.30]
					Fair		
					7/38 (18.4%)	5/42 (11.9%)	RR = 1.55 [95% CI 0.56, 4.37]
					Poor		
					0/38 (0%)	2/42 (4.8%)	RR not calculable

RR = relative risk; CI = confidence interval; Efficacy of treatment score = Excellent: skin grafts epithelialised or healed 95% within 14 days with a smooth scar; Good: skin grafts epithelialised or healed 95% within 21 days, hypertrophic scar subsided within 6 months; Fair: skin grafts epithelialised or healed 95% within 21 days, prone to abrasion from minor trauma, minor infected wound, obvious hypertrophic scar after 6 months; Poor: skin grafts epithelialised or healed 95% within 28 days, keloid, contracture of toes or joint, recurrent ulcer..

Epidermal grafting versus conventional treatment methods

Yamaguchi et al (2004) conducted a non-randomised controlled trial (level III-2 intervention evidence) of average quality involving 38 Asian patients with intractable diabetic foot ulcers attending Osaka University Hospital (Table 94). Intractable ulcers were defined as those that did not respond to conservative treatments for more than 2 months. All patients were given the treatment options and allowed to choose their preferred method. After sharp en bloc debridement, the patients were classified according to the presence of exposed bone and were offered appropriate treatment options. Although patients chose the treatment option, the authors indicated that they attempted to match patients on age, sex, wound size, wound infection, wound duration and osteomyelitis. This suggests that there may be some selection bias in the study design.

Patients without exposed bone were offered either epidermal grafting using epidermal sheets obtained from suction blisters, or standard wound care. Of 18 patients, 10 opted for the grafting. The authors found a statistically significant reduction in the time needed for ulcer healing after epidermal grafting when compared to standard wound care (4.3 ± 0.6 weeks compared to 11.6 ± 3.4 weeks for standard wound care; $p = 0.04$).

Patients with exposed bone wore offered either a novel method or conventional treatment methods including covering the bone with adjacent muscle and/or skin grafts. Of 20 patients, 9 chose conventional methods. The novel method involved shaving the bone with a bone scraper until it bled from the bone marrow, and then covering with Tegaderm (a thin polyurethane membrane iodine; 3M Health Care, USA) for 3-8 days to prepare a wound bed prior to an epidermal graft. Although there was no statistically significant difference in the time needed for the ulcers to heal between the two groups, there was a statistically significant reduction in the number of amputations required after bone scraping and epidermal grafting compared to conventional treatment methods (0% compared to 89%; $p < 0.0001$).

Box 131 Evidence statement matrix for epidermal grafting compared to conventional treatment methods

Component	Rating	Description
Evidence base	D	One level III-2 study with a moderate risk of bias.
Consistency	N/A	There was only one study.
Clinical impact	C	Moderate clinical impact. There was a statistically significant difference in time to healing for ulcer without exposed bone, and for the number of amputations required by patients with ulcers where the bone is exposed.
Generalisability	B	Asian patients with diabetic foot ulcers that have not responded to conservative treatments for more than 2 months.
Applicability	C	The study was conducted in Japan, which has similar healthcare for diabetes patients compared to the Australian healthcare context.

Evidence statement

There is evidence to suggest that epidermal grafts improve the time to healing for people with chronic diabetic foot ulcers without exposed bone, and that bone scraping plus epidermal grafts reduces the risk of amputation for people with chronic diabetic foot ulcers that are exposed to the bone (Grade C) .

Table 94 Studies which evaluate the effectiveness of epidermal grafting for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Yamaguchi et al 2004) Japan	Level III-2 non-randomised study Average quality study	N = 38 Asian patients with intractable (> 2 months duration) diabetic foot ulcers attending Osaka University Hospital from 17 December 1998 to 17 March 2002. Patients were stratified depending on the presence of exposed bone after sharp *en bloc* debridement and they chose their treatment. Patients without exposed bone: N = 18 Intervention group – N = 10; age (yrs) 60.3 ± 4.4; gender: male 5/10 (50%); female 5/10 (50%); ulcer size (cm^2) 4.7 ± 1.1; ulcer duration (months) 2.8 ± 0.3; infected 8/10 (80%); bone exposure 0/10 (0%). Comparator group(s) – N = 8; age (yrs) 58.9 ± 5.0; gender: male 5/8 (63%); female 3/8 (37%); ulcer size (cm^2) 6.5 ± 2.7; ulcer duration (months) 4.6 ± 1.4; infected 7/8 (88%); bone exposure 0/8 (0%). Patients with exposed bone: N = 20 Intervention group – N = 11; age (yrs) 58.1 ± 4.9; gender: male 8/11 (73%); female 3/11 (27%); ulcer size (cm^2) 5.6 ± 2.1; ulcer duration (months) 12.3 ± 7.6; infected 8/11 (72%); bone exposure 11/11 (100%). Comparator group(s) – N = 9; age (yrs) 64.8 ± 3.8; gender: male 7/9 (78%); female 2/9 (22%); ulcer size (cm^2) 3.4 ± 0.9; ulcer duration (months) 6.6 ± 1.2; infected 7/9 (78%); bone exposure 9/9 (100%).	Patients without exposed bone: N = 10. After debridement, wound was covered with an occlusive dressing (Tegaderm plus) for up to 2 weeks, until granulation tissue formed, then covered with an epidermal graft. Epidermal sheets were obtained from suction blisters harvested under local anaesthetic from donor skin (abdomen of inner thigh). Patients with exposed bone: N = 11. Bone was shaved with a bone scraper until bleeding from the bone marrow was observed, and then wound was covered with Tegaderm Plus for 3-8 days. Finally, epidermal grafts were applied to the prepared wound bed.	N = 8. Standard wound care, including sharp debridement, bed rest, special casts and antibiotics as needed. N = 9. Conventional treatment, which includes covering bone with adjacent muscle and/or skin grafts, or leave as is.	Time to healing of ulcer (weeks) No exposed bone: 4.3 ± 0.6 Exposed bone: 5.1 ± 0.7 Number of patients that required amputations No exposed bone: 0/10 (0%) Exposed bone: 0/11 (0%)	 11.6 ± 3.4 6.2 ± 2.5 1/8 (13%) 8/9 (89%)	 p = 0.04 p = 0.86 p = 0.26 p < 0.0001

Cultured keratinocytes or fibroblasts versus placebo carrier

Two level II studies of average quality investigated the use of cultured keratinocytes, one with autologous cells and the other using allogenic cells, and a level III-2 study of average quality investigated the use of cultured allogenic fibroblasts (Table 95). All three studies used different delivery methods for the cultured cells. The allogenic keratinocytes were loaded onto micro-carriers produced from polyethylene and silica, whereas the autologous keratinocytes were seeded onto Myskin dressings (medical grade PVC with a plasma polymerised acrylic acid layer; Celltran Ltd, UK); both were applied directly onto the wound after debridement and combined with standard wound care (Bayram et al 2005; Moustafa et al 2007). The cultured allogenic fibroblasts were dispersed directly over the debrided wound and sealed with thrombin, then a layer of Tegaderm (a thin polyurethane membrane; 3M Health Care, USA) was applied over the wound (Han et al 2009).

Bayram et al (2005) conducted a randomised controlled trial involving 40 diabetic patients with foot ulcers to investigate the effectiveness of using allogenic keratinocytes compared with the placebo carrier to treat ulcers. They found that there was a statistically significant reduction in ulcer area and in time to healing for the patients treated with cultured keratinocytes compared to those that received the placebo ($p < 0.001$). Moustafa et al (2007) also conducted a randomised controlled trial, but it was very small, involving only 16 diabetic patients that had at least one chronic Wagner grade 1 foot ulcer and attended one of four diabetic outpatient clinics in the UK. Of these 16 patients, only 12 completed the study and were included in the final analysis. Although the results showed a trend towards more ulcers healed after treatment with cultured autologous keratinocytes compared to the placebo, it did not reach statistical significance (57% compared to 20%; RR = 2.86 [95% CI 0.64, 17.44]).

The non-randomised study conducted by Han et al (2009) involved 55 patients with a diabetic foot ulcer that had not displayed signs of healing for 1 month. Patients were provided information about the cultured allogenic fibroblast treatment and allowed to choose between this treatment and a control treatment with fibrinogen and thrombin but no cells. The authors reported that there was a statistically significant increase in the number of ulcers healed after 8 weeks of treatment with cultured fibroblasts compared to the control (83.8% and 50% respectively; RR = 1.68 [95% CI 1.12, 2.56]). Three patients would need to be treated with cultured fibroblasts compared to control for one additional patient's ulcer to heal (NNT = 3 [95% CI 2, 12]). There was also a statistically significant decrease in the time to healing; from 47.2 ± 7.8 days for the control group, to 30.9 ± 10.1 days for the fibroblast treated group ($p < 0.05$).

Another cultured skin equivalent used in one study consisted of HYAFF 11-based autologous cultured dermal and epidermal grafts. Initially, keratinocytes and fibroblasts were cultured from a skin biopsy taken from the patient and then seeded onto two distinct HYAFF 11 scaffolds made of a benzylic ester of hyaluronic acid. First, autologous fibroblasts grown on Hyalograft 3D was applied to the ulcer followed 7-10 days later with autologous keratinocytes grown on Laserskin.

Caravaggi et al (2003) conducted an average quality trial to investigate the effectiveness of HYAFF 11-based autologous cultured dermal and epidermal grafts in addition to standard wound care compared to standard wound care alone. Included in the study were 79 diabetic patients with a Wagner grade 1-2 ulcer on the plantar surface or dorsum of foot, without signs of healing for 1 month, and with adequate perfusion to the limb. There were 22 adverse events reported, equally distributed between the two groups, and considered not to be related to study treatments. The most common events were infection, inflammation and worsening of ischaemia. The difference in the number of patients that healed after treatment with the HYAFF 11-based grafts compared to standard wound care was not statistically significant for plantar

ulcers, but it was for dorsal ulcers (67% compared to 31%; RR = 2.04 [95% CI 1.00, 4.50]). Three patients with dorsal ulcers would need to be treated with HYAFF 11-based grafts in addition to standard wound care compared to standard wound care alone for one additional patient's ulcer to heal (NNT = 3 [95% CI 2, 533]). There was also a statistically significant reduction in ulcer size for patients with dorsal ulcers that did not heal after treatment with HYAFF 11-based grafts (68.0 ± 37.3%) compared to standard wound care (32.9 ± 35.1%; p = 0.072), but not for plantar ulcers (p = 0.823).

Box 132 Evidence statement matrix for cultured keratinocytes or fibroblasts compared to placebo

Component	Rating	Description
Evidence base	C	Three level II studies with a moderate risk of bias and one level III-2 study with a moderate risk of bias
Consistency	B	Three studies found statistically significant differences in ulcer area, time to healing and/or number of ulcers healed. A third study was underpowered but showed similar trends.
Clinical impact	C	Moderate clinical impact. One study reported a reduction in ulcer area, two studies reported a reduction in time to healing, and one study reported an increased number of healed ulcers that were all statistically significant. One study also reported a statistically significant number of healed dorsal ulcers but not for plantar ulcers.
Generalisability	B	Population consisted of patients with chronic diabetic foot ulcers
Applicability	C	One study was conducted in the UK and another in Itlay, where the care of diabetic foot ulcers is likely to be similar to Australia. The other two studies were conducted in Turkey and Korea, where health care is likely to be provided differently to patients with diabetic foot ulcers than in Australia.

Evidence statement

Treatment with cultured keratinocytes or fibroblasts, when compared with placebo or control, was found to reduce the ulcer size, decrease the time required to heal, and increase the number of ulcers that healed completely for people with chronic diabetic foot ulcers. (Grade C)

Table 95 Studies which evaluate the effectiveness of cultures keratinocytes or fibroblasts for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Bayram et al 2005) Turkey	Level II RCT Average quality study	N = 40. Diabetic patients with grade 2-3 (assessment method not stated) diabetic foot ulcers. Intervention group: N = 20; ulcer area (cm^2) 10.3 ± 4.0. Comparator group: N = 20; ulcer area (cm^2) 8.8 ± 4.0.	N = 20. Cultured allogenic keratinocyte-loaded microcarriers (produced from polyethylene and silica). Following serial debridement of the wound a single layer of the microcarriers (with or without loaded keratinocytes) were applied onto the wound (~75/cm^2) and covered with petroleum jelly gauze.	N = 20. Placebo - microcarrier Same treatment as intervention group. The dressing was renewed every three days for up to 30 days.	Reduction in ulcer area: 92% Time to complete healing: Number of dressing changes needed before healing (changed every third day) 9.2 ± 3.2 Wound score: 17.15 ± 2.7	32% 16.5 ± 2.0 9.05 ± 3.0	p < 0.001 p < 0.001 p < 0.001
(Moustafa et al 2007) UK	Level II RCT Average quality study	N = 16 diabetic patients that attended diabetic outpatient clinics in the Northern General Hospital, Royal Hallamshire Hospital, Leeds General Infirmary, and Nottingham City Hospital; age 52.4 (24-78); ulcer duration (months) 14 (2-28); type 1 diabetes 10/16 (62.5%); duration (years) 12-34; type 2 diabetes 6/16 (37.5%); duration (years) 0.75-16; % HbA_{1c}, 7-14%; all index ulcers were Wagner grade 1. Intervention group: N = 9; withdrew prior to treatment 2/9 (22%); % HbA_{1c}, 10.55 ± 1.43. Comparator group: N = 7; withdrew prior to treatment 1/7 (14%); withdrew due to infection in week 8 1/7 (14%); % HbA_{1c}, 9.55 ± 1.24.	N = 9 patients (11 ulcers). Myskin dressings (medical grade PVC with a plasma polymerised acrylic acid layer) was used as a carrier, and was seeded with autologous keratinocytes plus standard wound care All patients underwent a 4 week lead-in period with standard wound care and optimal off-loading prior to recruitment. A split-thickness skin biopsy	N = 7 patients (13 ulcers). Placebo Myskin dressing (without keratinocytes) plus standard wound care After debridement and cleaning of ulcer, the Myskin dressings (active or placebo) were applied once per week for 6 weeks, then all patients received active treatment for an additional 6 weeks. Myskin dressing was covered with Lyofoam or Allevyn dressing, semi-compressed	Number of patients with ulcers that healed (per protocol): 4/7 (57%) Number of patients with ulcers that improved by > 50%: 7/7 (100%) Number of patients with ulcers that recurred: 3/4 (75%)	1/5 (20%) 5/5 (100%) 0/1 (0%)	RR = 2.86 [95% CI 0.64, 17.44] RR = 1 RR = not calculable

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
			(2 x 2 cm; 0.4-0.6 mm thick) was taken (usually from thigh) at -2 weeks. Keratinocytes from skin biopsy were cultured and seeded onto carrier dressing	felt, and a second layer of Lyofoam or Allevyn, and taped into position. Control patients were offered an additional 6 weeks active treatment if ulcers were not healed after the initial 12 week period.			
(Han et al 2009) Korea	Level III-2 non-randomised study Average quality study	N = 55 patients with type 1 or 2 diabetes and a foot ulcer that had not displayed signs of healing for 1 month. Intervention group – N = 37, mean age (yrs) 63.9 ± 8.2, gender: 20/37 (54%) male, 17/37 (46%) female, mean ulcer size (cm^2) 4.6 ± 1.7, duration of ulcer (weeks) 13.2 ± 5.5, ulcer with exposed bone 20/37 (54%). Dorsal ulcers 19/37 (51%): forefoot 8/19 (42%), heel 2/19 (11%), toe 9/19 (47%). Plantar ulcers 18/37 (49%): forefoot 9/18 (50%), heel 5/18 (28%), toe 4/18 (22%). Comparator group(s) – N = 18, mean age (yrs) 59.8 ± 5.8, gender: 11/18 (61%) male, 7/18 (39%) female, mean ulcer size (cm^2) 4.3 ± 1.9, duration of ulcer (weeks) 12.4 ± 5.1, ulcer with exposed bone 8/18 (44%). Dorsal ulcers 9/18 (50%): forefoot 5/9 (56%), heel 0/9 (0%), toe 4/9 (44%). Plantar ulcers 9/18 (50%): forefoot 5/9 (56%), heel 1/9 (11%), toe 3/9 (33%).	N = 37. Patients underwent debridement as necessary. Fresh cultured fibroblasts were then dispersed over the wound and sealed with thrombin. Tegaderm was applied to the graft site and changed 5 days later. Patients returned every 3-7 days to have the dressings changed and the wound examined.	N = 18. Treatment and wound management was the same as for the intervention group except that only fibrinogen and thrombin without cells was applied to the wound. Pressure from ulcer site was off-loaded for all patients using foam dressings with a hole at ulcer site and appropriate footwear.	Number of patients with ulcers that healed: 31/37 (83.8%) Time to healing (days): 30.9 ± 10.1	9/18 (50%) 47.2 ± 7.8	RR = 1.68 [95% CI 1.12, 2.56] NNT = 3 [95% CI 2, 12] p < 0.05
(Caravaggi et al 2003) Italy	Level II RCT Average quality study	N = 79 diabetic patients with a Wagner grade 1-2 ulcer on the plantar surface or dorsum of foot, of > 2 cm^2 and without signs of healing for 1 month and with adequate perfusion to the limb. Intervention group: N = 43; diabetes type 1 9/43 (20.9%); $TcPO_2$ (mmHg) 48.0 (interquartile range 24.0); ankle-brachial index 0.7 ± 0.3; % HbA_{1c} 7.9 ± 2.13; ulcer area (cm^2) 5.3 ± 6.76; depth of ulcer (mm) 6.1 ± 5.68; duration of ulcer (months) 4.0	N = 43. HYAFF-11-based autologous grafts. A skin biopsy (1-2 cm^2, 0.8 mm deep) was taken and sent to the TissueTech Autograft Laboratory	N = 36 Initially subjected to extensive debridement. The ulcers were covered with non-adherent paraffin gauze and a secondary dressing of sterile cotton pads	Number of patients with ulcers that healed: Plantar 12/22 (55%) Dorsal 14/21 (66.7%)	 10/20 (50%) 5/16 (31.3%)	 RR = 1.09 [95% CI 0.62, 1.95] RR = 2.04 [95% CI 1.00, 4.50] NNT = 3

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
		(interquartile range 10.0); localisation of ulcer: forefoot 31/43 (72.1%); midfoot 7/43 (16.3%); hindfoot 3/43 (7.0%); not specified 2/43 (4.7%). Comparator group: N = 36; diabetes type 1 3/36 (8.0%); $TcPO_2$ (mmHg) 48.5 (interquartile range 20.5); ankle-brachial index 0.7 ± 0.22, % HbA_{1c} 8.1 ± 2.25; ulcer area (cm^2) 6.2 ± 7.58; depth of ulcer (mm) 8.0 ± 5.46; duration of ulcer (months) 4.0 (interquartile range 6.0); localisation of ulcer: forefoot 24/36 (66.7%); midfoot 7/36 (19.4%); hindfoot 2/36 (5.6%); not specified 3/36 (8.3%).	in Italy for fibroblast and keratinocyte cell culturing. The cells were then seeded on two distinct biodegradable scaffolds composed of a benzylic ester of hyaluronic acid. Patients first received autologous fibroblasts on Hyalograft 3D applied over ulcer after extensive debridement and cleansing. This was then covered as for control patients, if a second graft was required, the wound was cleansed prior to application. After 7-10 days the autologous keratino-cytes grown on laserskin was applied to the ulcer, dressed and covered as before. A second graft was permitted if required.	and gauze. Visits and dressing changes were same for both groups. Secondary dressing could be changed after 3 days (earlier if needed). After 7 days the non-adherent paraffin gauze was changed every 2 days after cleansing the ulcer with physiologic solution. Antibiotics prescribed if needed. All patients provided with non-removeable fibreglass cast)plantar ulcera) or therapeutic shoe (dorsal ulcers) for off-loading.	[95% CI 2, 533] Mean % reduction in ulcer size for non-healed ulcers: Plantar 61.1 ± 26.0 64.7 ± 34.7 p = 0.823 Dorsal 68.0 ± 37.3 32.9 ± 35.1 p = 0.072 Median time to complete healing (days): Plantar 57 58.5 Dorsal 63 77 Total 57 77		

RR = relative risk; CI = confidence interval; NNT = number needed to treat; Wound score considers granulation formation, epithelisation, contraction, and amount of discharge, each scored 0-5; 20 = completely healed; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localized gangrene of forefoot or heel, Grade 5 = gangrene of entire foot.

Cultured skin equivalents versus standard wound care

One systematic review of average quality identified five level II studies that reported ulcer healing by skin replacement therapies. Four of these studies (2 of good quality and 2 of average quality) reported additional outcomes and are also reported below (Table 96).

A further three level II studies investigated the use of different cultured skin equivalents to treat diabetic foot ulcers.

Four studies used Dermagraft (Smith and Nephew, USA), a cryo-preserved living dermal substitute containing dermal collagen, matrix proteins, growth factors, and cytokines secreted by cultured fibroblasts

Three studies used Apligraf (or Graftskin; Organogenesis, USA), a living bilayered cultured skin equivalent containing both a dermal layer composed of fibroblasts in a bovine collagen lattice including matrix proteins and cytokines, and an epidermal layer formed by keratinocytes with a well differentiated stratum corneum .

One study used OrCel (Ortec, Israel), a bilayered cellular matrix in which fibroblasts are cultured on and within the porous sponge side of the collagen matrix while keratinocytes are cultured on the coated, non-porous side.

The average quality systematic review (level I evidence) by Blozik and Scherer (2008) identified five randomised controlled trials that investigated the effectiveness of using cultured skin equivalents in addition to standard wound care compared to standard wound care alone. Three studies used Dermagraft, one used Apligraft, and the fifth study used HYAFF 11-based autologous cultured dermal and epidermal grafts (Table 96). The authors conducted a meta-analysis of these studies for the number of ulcers that healed completely and found that there was a statistically significant increased number of healed ulcers after using cultured skin equivalents in addition to standard wound care (43% compared to 29%; RR_p = 1.46 [95% CI 1.21, 1.76]). Seven patients would need to be treated with cultured skin equivalents in addition to standard wound care for one additional patient's ulcer to heal (NNT_p = 7 [95% CI 5, 14]). Additional outcomes from these five level II studies are discussed below and reported in Table 96.

Four randomised controlled trials investigated the effectiveness of using Dermagraft in addition to standard wound care (Table 96). Two of these studies were included in the meta-analysis by Blozik and Scherer (2008) and will not be discussed further (Gentzkow et al 1996; Marston et al 2003).

A third study of average quality by Pollak et al (1997) reported on the outcomes of the same randomized controlled trial as Naughton et al (1997), which was included in the meta-analysis by Blozik and Scherer (2008). The results of Pollak et al (1997) have therefore not been included in the meta-analysis below. The authors reported that 281 diabetic patients with neuropathic full-thickness plantar surface foot ulcers of the forefoot or heel, and with adequate perfusion were randomised to receive either Dermagraft in addition to standard wound care or standard wound care alone. Of these patients 235 were evaluable for the primary endpoint. During the course of the trial, investigators discovered that not all batches of Dermagraft had biological activity within the therapeutic range (Naughton et al (1997) investigated the reasons for the loss of biological activity, whereas Pollak et al (1997) provided more detail about the trial and its outcomes.). The Dermagraft group was analysed by subgroups according to the number of biologically active Dermagraft applications they received. The increased number of healed ulcers after receiving Dermagraft in addition to standard wound care compared to standard wound care alone (as reported in the meta-analysis; Blozik and Scherer, 2008) was

not statistically significant. However, the increased number of ulcers that healed by week 12 for the Dermagraft subgroups that received either half or all active applications (51% and 54%, respectively) was statistically significant compared to the standard care group (32%; RR = 1.60 [95% CI 1.11, 2.24]). Four patients would need to be treated with active Dermagraft in addition to standard wound care for one additional patient's ulcer to heal (NNT = 4 [95% CI 3, 23]). By week 32 there was no statistically significant difference between the Dermagraft subgroups, but there was a statistically significant increase in the number of ulcers healed for all patients that received Dermagraft in addition to standard wound care compared to those that received standard wound care alone (58% compared to 42%; RR = 1.36 [95% CI 1.01, 1.82]). The reduction in median healing time for the Dermagraft group (13 weeks) was statistically significant when compared to the standard wound care alone group (28 weeks; $p < 0.05$).

Hanft and Surprenant (2002) also conducted an average quality trial that investigated the effectiveness of using Dermagraft in addition to standard wound care compared to standard wound care alone (Table 96). A total of 46 diabetic patients with a full-thickness plantar foot ulcer present for at least 2 weeks, with no sign of clinical infection and with adequate circulation to the foot were randomised to receive either Dermagraft in addition to standard wound care or standard wound care alone. The authors found that the increased number of ulcers that healed in the Dermagraft group (62.5%) compared to the standard wound care group (27.3%) was statistically significant (RR = 2.29 [95% CI 1.15, 4.77]). Three patients would need to be treated with Dermagraft in addition to standard wound care for one additional patient's ulcer to heal (NNT = 3 [95% CI 2, 15]). If the ulcer was located on the forefoot or toe, or of >6 weeks duration, the statistically significant difference between the two groups was even greater (RR = 4.55 [95% CI 1.45, 15.64] and 5.0 [95% CI 1.67, 17.6], respectively). Only two patients with ulcers located on the forefoot or toe, or of >6 weeks duration would need to be treated with Dermagraft in addition to standard wound care for one additional patient's ulcer to heal (NNT = 2 [95% CI 1, 7] and 2 [95% CI 1, 5], respectively). The mean per cent wound closure by week 12 for ulcers of >6 weeks duration treated with Dermagraft plus standard wound care (98 ± 5.2%) was statistically significant compared to those treated with standard wound care alone (48.2 ± 93%; $p = 0.002$).

Two systematic reviews identified two studies which conducted economic evaluations of using Dermagraft in addition to standard wound care (Chow et al 2008; Langer & Rogowski 2009). One study by Segal and John (2002) investigated its use within the Australian healthcare context using effectiveness data from Naughton et al (1997) and found that the incremental cost of Dermagraft versus standard wound care per additional healed week was A$383. The second economic study, Allenet et al (2000), modelled the cost effectiveness of Dermagraft versus standard wound care in the French healthcare setting and found the incremental cost of Dermagraft in addition to standard wound care was €5,913per additional ulcer healed . Sensitivity analysis found that variations in the number of Dermagraft applications, weekly cost for healed state, the number of amputations and the rehabilitation time post-amputation did not affect the cost-effectiveness of Dermagraft.

Three randomised controlled trials investigated the effectiveness of using Apligraf (Graftskin) in addition to standard wound care compared to standard wound care alone (Table 96). Only one study by Veves et al (2001) was included in the meta-analysis by Blozik and Scherer, 2008) and will not be discussed further. Additionally, the poor quality study by Sabolinski and Veves (2000) has been included in Table 96, but not the meta-analysis as it is highly probable that it is a single center report from the multi-centered study reported by Veves et al (2001).

Edmonds et al (2009) conducted an average quality trial involving 72 diabetic patients with a neuropathic ulcer limited to the plantar region of the forefoot (through the dermis but without

sinus tract, bone or tendon exposure) that has been present for at least 2 weeks and with adequate vascular supply. The patients were randomised into two groups to receive either treatment with Apligraf (Graftskin) in addition to standard wound care or standard wound care alone. There were no adverse events reported that were considered to result from the treatment. However, three events were localised to the ulcer, one patient's ulcer became infected, another developed osteitis and required an amputation, and the third had a squamous cell carcinoma. There were no statistically significant differences in the number of ulcers that recurred or the median time to healing between the two groups, but there was a statistically significant increase in the number of ulcers that healed after treatment with Apligraf in addition to standard wound care (51.5% compared to 25.6%; RR = 2.01 [95% CI 1.10, 3.73]). Four patients would need to be treated with Apligraf in addition to standard wound care compared to standard wound care alone for one additional patient's ulcer to heal (NNT = 4 [95% CI 2, 29]).

The previously mentioned systematic reviews also identified two studies that studied the cost-effectiveness of Apligraft (Chow et al 2008; Langer & Rogowski 2009). Steinberg et al (2002), using effectiveness data from Veves et al (2001), found that the incremental cost of Apligraf in addition to standard wound care per ulcer-free month gained was US$6,683, in the USA. They also reported that the incremental cost of Apligraf versus standard wound care per amputation or resection avoided was US$86,226. The major driver of this result was the cost of Apligraf. The authors found that when the number of Apligraf applications was reduced to 1.5 per patient (the average number of applications considered to be used in routine practice), the cost per amputation avoided decreased to $US30, 403.

Lipkin et al (2003) conducted a randomised controlled trial of good quality to investigate the effectiveness of OrCel, a bi-layered cellular matrix in addition to standard wound care compared to standard wound care alone. A population of 40 diabetic patients with peripheral neuropathy and a University of Texas grade 1A ulcer on the plantar surface of the foot that had been present for at least 30 days and with adequately perfusion in the limb were randomised into the two treatment arms. There were no statistically significant differences in the number of ulcers that healed or the number that became infected between the two groups. However, the faster rate of wound closure for the patients that received OrCel in addition to standard wound care (1.8 ± 2.5%/day) compared to those that received standard wound care alone (1.1 ± 1.9%/day) was statistically significant (p = 0.009), especially for ulcers that were less than 6 cm^2 in size (2.2 ± 2.8%/day compared to 1.1 ± 2.0%/day; p = 0.001).

Pooled analysis of the seven randomised controlled trials (Figure 10), comparing the number of patients with ulcers that healed after using cultured skin equivalents and receiving standard wound care compared to standard wound care alone indicates that there is a statistically significant benefit in using cultured skin equivalents (pooled RR = 1.53 [95% CI 1.27, 1.84]). However, the funnel plot suggests that there is the potential for publication bias to have an impact on the pooled estimate.

Thus, there is adequate evidence to suggest that the use of cultured skin equivalents in addition to standard wound care offers better clinical outcomes for treating diabetic foot ulcers compared to standard wound care alone. Overall, each of these studies have shown at least one statistically significantly clinical benefit for using cultured skin equivalents with standard wound care over using standard wound care alone.

Box 133 Evidence statement matrix for cultured skin equivalents compared to standard wound care

Component	Rating	Description
Evidence base	B	One level I study with a moderate risk of bias and nine level II studies (3 with a low risk of bias, 5 with a moderate risk of bias, and 1 with a high risk of bias.
Consistency	A	All studies showed either trends towards or statistically significant differences between the two groups for all outcomes reported.
Clinical impact	B	Substantial clinical impact. Meta-analysis showed a statistically significant increase in the number of ulcers that healed after treatment with cultured cell equivalents compared to standard wound care alone. All studies showed either trends towards or statistically significant differences between the two groups for all outcomes reported in favour of using cultures skin equivalents.
Generalisability	A	Population consisted of diabetic patients with chronic, non-healing, full-thickness, foot ulcers with adequate perfusion.
Applicability	B	Three studies were conducted in Europe (one multicentre trial also in Australia), where the care of diabetic foot ulcers is likely to be comparable to Australia. Seven studies were conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia.

Evidence statement

There is substantial evidence to suggest that clinical outcomes are significantly improved for people with chronic diabetic foot ulcers with adequate perfusion, treated with cultured skin equivalents and standard wound care compared to standard wound care alone. (Grade B)

Table 96 Studies which evaluate the effectiveness of cultured skin equivalents for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Chow et al 2008; Langer & Rogowski 2009) Australia	Level I systematic review Good quality study	Diabetic patients with chronic full-thickness foot ulcers. (Segal & John 2002) Price year = 2000 efficacy data from Naughton et al (1997) and Pollak et al (1997)	Cultured skin equivalents plus standard wound care Dermagraft plus standard wound care	Standard wound care Standard wound care	ICER per additional healed week = A$383		
France		(Allenet et al 2000) Efficacy data from Naughton et al (1997) and Pollak et al (1997	Dermagraft plus standard wound care	Standard wound care	ICER per additional ulcer healed = FF38,784 (€5,913) Sensitivity analysis: variations in the number of Dermagraft applications, weekly cost for healed state, the number of amputations and rehabilitation time post-amputation did not affect cost-effectiveness of Dermagraft		
USA		(Steinberg et al 2002) Efficacy data from Veves at al (2001)	Apligraf plus standard wound care	Standard wound care	ICER = US$6,683 per ulcer-free month gained ICER = US$86,226 per amputation or resection avoided Significantly higher mean total costs seen in the Apligraf group than the SWC group (US$7,366 vs US$2,020; p < 0.001) Major driver is cost of Apligraf applications – contributes 76% to total costs Mean costs for severe adverse event: lower for Apligraf than SWC (US$1,232 vs US$1,335; p = 0.136) Sensitivity analysis: number of apligraf applications and the cost of Apligraf impacted on the ICER		
The Netherlands		(Redekop et al 2003) Efficacy data from Veves at al (2001)	Apligraf plus standard wound care	Standard wound care	No ICER reported The cost of Apligraf vs SWC for the number of ulcer-free months gained was found to be cost saving in the Netherlands. After 4 weeks the cost of treatment with Apligraf plus		

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
					SWC was 253% higher than for SWC alone After 24 weeks the cost of treatment with Apligraf plus SWC was 1% lower (€3828 vs €3853) After 52 weeks the cost of treatment with Apligraf plus SWC was 12% lower Sensitivity analysis: cost difference was sensitive to the number of Apligraf applications		
(Blozik & Scherer 2008) Germany	Level I systematic review Average quality study	N = 5 randomised controlled clinical trials with participants having diabetic foot ulcers, and that compared bioengineered skin with standard wound care. Gentzkow et al (1996) Diabetic patients, full-thickness foot ulcer on the plantar surface of the forefoot or heel, ulcer area > 1 cm^2. Naughton et al (1997) Diabetic patients, full-thickness chronic foot ulcer on the plantar surface of the forefoot or heel, ulcer area > 1 cm^2. Veves et al (2001) diabetic patients, full-thickness neuropathic ulcer on the dorsum of foot, ulcer area > 1 cm^2, ulcer duration > 2 weeks. Caravaggi et al (2003) diabetic patients, Wagner grade 1-2 foot ulcer on plantar surface or dorsum, ulcer area > 2 cm^2, ulcer duration > 1 month. Marston et al (2003) diabetic adults, foot ulcer on the plantar surface of the forefoot or heel, ulcer area 1-20 cm^2, ulcer duration > 2 weeks.	N = 406. Skin replacement therapies N = 12. Dermagraft applied weekly for 8 weeks plus standard care N = 109 Up to 8 applications of Dermagraft plus standard care N = 112 Graftskin applied weekly for up to 5 times N = 43 Autologous fibro-blasts on Hyalograft scaffold (2nd graft if required). 7-10 days later, autologous keratinocytes grown on Laserskin N = 130 Dermagraft applied weekly for 7 weeks plus standard care	N = 386 N = 13 Standard wound care N = 126 Standard wound care N = 96 Standard wound care N = 36 Standard wound care N = 115 Standard wound care	Number of patients with ulcers that healed Gentzkow et al, 1996 6/12 (50%) 1/13 (8%) RR = 6.50 [95% CI 1.29, 39.71] NNT = 2 [95% CI 2, 14] Naughton et al, 1997 42/109 (39%) 40/126 (32%) RR = 1.21 [95% CI 0.86, 1.72] Veves et al, 2001 63/112 (56%) 36/96 (38%) RR = 1.50 [95% CI 1.11, 2.04] NNT = 5 [95% CI 3, 19] Caravaggi et al, 2003 26/43 (60%) 15/36 (42%) RR = 1.46 [95% CI 0.92, 2.29] Marston et al, 2003 39/130 (30%) 21/115 (18%) RR = 1.64 [95% CI 1.03, 2.62] NNT = 9 [95% CI 5, 104] Pooled 176/406 (43%) 113/386 (29%) RR_p = 1.46 [95% CI 1.21, 1.76] NNT_p = 7 [95% CI 5, 14]		
(Marston et	Level II RCT	N = 245 diabetic patients, over 18 years, attending	N = 130.	N = 115.	Number of patients with ulcers that healed		

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
al 2003) USA	Good quality study	one of 35 clinics in the USA between December 1998 and March 2000, with a full-thickness plantar ulcer of at least 2 weeks duration (later revised to > 6 weeks) and at least 1 cm^2, with adequate perfusion in limb. Intervention group: N = 130; age (yrs) 55.8 (27-83); male 90/130 (69%); Caucasian 90/130 (69%);	Dermagraft skin replacement therapy, first application on day 0, then received up to 7 additional applications at weekly	Standard wound care, which included sharp debridement when necessary, wound dressings consisted of a non-	Forefoot ulcers 33/112 (29.5%)	20/102 (19.6%)	RR = 1.50 [95% CI 0.93, 2.45]
		non-Caucasian 40/130 (31%); type 1 diabetes 32/130 (25%); ulcer duration (weeks) 41; ulcer located on forefoot/toe 112/130 (86%); heel 18/130 (14%); ulcer area (cm^2) 2.31 (0.75-16.7). Comparator group: N = 115; age (yrs) 55.5 (31-79); male 91/115 (79%); Caucasian 87/115 (76%); non-Caucasian 28/115 (24%); type 1 diabetes 27/115 (23%); ulcer duration (weeks) 67; ulcer located on forefoot/toe 102/115 (89%); heel 13/115 (11%); ulcer area (cm^2) 2.53 (0.5-18.0).	intervals. Patients received the same standard wound care as control group. Before randomisation all patients received sharp debridement and saline-moistened gauze dressings.	adherent interface, saline-moistened gauze to fill ulcer, dry gauze, and adhesive fixation sheets. Patients were allowed to be ambulatory with extra-depth diabetic footwear with custom inserts or healing sandals.	Heel ulcers 6/18 (33%) % reduction in ulcer area 91 Number of patients with ulcers that became infected (harms) 31/163 (19%)	1/13 (8%) 78 48/151 (32%)	RR = 4.33 [95% CI 0.83, 26.82] p = 0.044 RR = 0.60 [95% CI 0.40, 0.88] NNT = 8 [95% CI 5, 32]
(Veves et al 2001) USA	Level II RCT Good quality study	Veves, 2001 N = 208 diabetic patients, aged over 18 years, with full-thickness neurpopathic ulcers with adequate perfusion in limb. Intervention group: N = 112, age (yrs) 58 ± 10; male 88/112 (79%); Caucasian 77/112 (69%); African-American 20/112 (18%); Hispanic 14/112 (13%); BMI (kg/m^2) 30.9 ± 6.54; % HbA_{1c} 8.6 ± 1.5; ankle brachial index 0.65-0.8 10/112 (8.9%); 0.8-1.00 50/112 (36%); > 1.00 59/112 (53%); ulcer duration (months) 11.5 ± 13.3; ulcer area (cm^2) 2.97 ± 3.10. Comparator group: N = 96; age (yrs) 56 ± 10; male 74/96 (77%); Caucasian 67/96 (70%); African-American 14/96 (15%); Hispanic 13/96 (14%); BMI (kg/m^2) 33.1 ± 7.72; % HbA_{1c} 8.6 ± 1.4; ankle brachial index 0.65-0.8 10/96 (10.4%); 0.8-1.00 29/96 (30.2%); > 1.00 54/96 (56.3%); ulcer duration (months) 11.1 ± 12.5; ulcer area (cm^2) 2.83 ± 2.45.	N = 112. Graftskin skin replacement therapy. After debridement, Graftskin was applied directly over the ulcer, then covered with saline-moistened Tegapore. The ulcer was then covered with dry gauze and then petroleum gauze and Kling. Graftskin applied weekly for up to 5 applications. Dressings were changed as for control group All patients used crutches or a	N = 96. Standard wound care After debridement, ulcer was covered with saline-moistened Tegapore and saline-moistened gauze, dry gauze, petroleum gauze, and wrapped in Kling. The patients changed the outer dressings twice daily for the first 5 weeks. The investigators changed inner dressings at twice weekly visits. After week 5, ulcers in both groups were covered with saline-	Median time to complete closure (days) 65 Number of patients that required an amputation 7/112 (6.3%) Number of patients with ulcers that became infected (harms) 25/112 (22.3%) Number of patients with ulcers that recurred 3/51 (5.9%)	90 15/96 (15.6%) 31/96 (32.3%) 4.31 (12.9%)	p = 0.0026 RR = 0.40 [95% CI 0.17, 0.91] NNT = 11 [95% CI 6, 103] RR = 0.69 [95% CI 0.44, 1.08] RR = 0.45 [95% CI 0.12, 1.74]

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
			wheelchair for first 6 weeks. Also provided with customised tridensity sandals to be worn throughout study period.	moistened gauze and petroleum gauze, and wrapped in Kling. Dressings were changed twice daily til study week 12.			
(Lipkin et al 2003) USA	Level II RCT Good quality study	N = 40 diabetic patients between 18 and 85 years, with peripheral neuropathy and a University of Texas grade 1A ulcer on the plantar surface of the foot that has been present for at least 30 days and is between 1 and 12 cm^2 in size, Diabetes must be controlled and the limb adequately perfused. Intervention group – N = 20; age (yrs) 57.4 ± 10.6; Gender: male 18/20 (90%); female 2/20 (10%); Race: Caucasian 15/20 (75%); African-American 3/20 (15%); other 2/20 (10%); % HbA_{1c} 8.39 ± 1.4; ulcer duration (months) 12.2 ± 10.8; ulcer area (cm^2) 6.0 ± 7.6; ulcers < 6 cm^2 15/20 (75%); ulcers < 6 cm^2 area (cm^2) 2.8 ±1.5; ulcers > 6 cm^2 5/20 (25%); ulcers > 6 cm^2 area (cm^2) 15.7 ±10.4. Comparator group(s) – N = 20, Age (yrs) 59.0 ± 12.7, Gender: male 14/20 (70%), female 6/20 (30%), Race: Caucasian 17/20 (85%), African-American 2/20 (10%), Other 1/20 (5%), % HbA_{1c} 8.97 ± 2.08, Ulcer duration (months) 11.9 ± 11.8, Ulcer area (cm^2) 5.5 ± 4.3, Ulcers < 6 cm^2 13/20 (65%), ulcers < 6 cm^2 area (cm^2) 2.9 ±1.5, Ulcers > 6 cm^2 7/20 (35%), ulcers > 6 cm^2 area (cm^2) 10.3 ±3.6.	N = 20. Bilayered cellular matrix (BCM) is a porous collagen sponge containing co-cultured allogenic keratinocytes and fibroblasts harvested from human neonatal foreskin was applied weekly for up to six total applications. After initial 2-week screening period with standard wound care, BCM was applied to ulcer and covered with a non-adherent dressing and gauze wrap. The gauze wrap was changed every 2-3 days, as required. After 6 weeks, standard care alone was given.	N = 20. Standard wound care Consists of sharp debridement, covering with moist saline gauze, then a layer of transparent adhesive dressing and gauze wrap. This dressing was changed twice daily. Provided with a pressure relief walker and encouraged to limit mobility.	Number of patients with ulcers that healed Total 7/20 (35%) Ulcers < 6 cm^2 7/15 (47%) Ulcers > 6 cm^2 0/5 (0%) Rate of wound closure (%/day) Total 1.8 ± 2.5 Ulcers < 6 cm^2 2.2 ± 2.81 Ulcers > 6 cm^2 0.8 ± 1.19 Number of patients with ulcers that became infected (harms) 2/20 (10%)	4/20 (20%) 3/13 (23%) 1/7 (14.3%) 1.1 ± 1.9 1.1 ± 2.03 1.2 ± 1.61 4/20 (20%)	RR = 1.75 [95% CI 0.64, 5.05] RR = 2.02 [95% CI 0.72, 6.33] RR = not calculable p = 0.0087 p = 0.001 p = 0.248 RR = 0.5 [95% CI 0.11, 2.13]
(Pollak et al 1997) USA	Level II RCT Average quality study	N = 333 diabetic patients with neuropathic full-thickness plantar surface foot ulcers of the forefoot or heel, > 1 cm^2 in size, with adequate perfusion controlled diabetes. Intervention group DG: N = 109; age (yrs) 55.3; male 80/109 (73%); insulin dependent 80/109 (73%);	N = 109. Dermagraft applied weekly for up to 8 applications in addition to the same standard wound care	N = 126. Standard wound care with debridement and infection control, ulcer covered with a non-adherent interface,	Number of ulcers that healed by week 12 DG-½TR 31/61 (51%)	40/126 (32%)	RR = 1.60 [95% CI 1.11, 2.24] NNT = 5 [95% CI 3, 24]

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
		% HbA_{1c} 10.8; ankle-arm index 1.1; ulcer area (cm^2) 2.9; ulcer duration (weeks) 44.4. Intervention group DG-½TR: N = 61; age (yrs) 57.1; male 44/61 (72%); insulin dependent 43/61 (70%); % HbA_{1c} 10.9; ankle-arm index 1.1; ulcer area (cm^2)	as control patients. Discovered some patients did not receive Dermagraft that was metabolically active	then with saline-soaked gauze to fill ulcer, and secured with an adhesive covering. and off-loading with special	DG-ATR 20/37 (54%)		RR = 1.70 [95% CI 1.12, 2.41] NNT = 4 [95% CI 3, 23]
		2.9; ulcer duration (weeks) 56.6. Intervention group DG-ATR: N = 37; age (yrs) 57.5; male 26/37 (70%); insulin dependent 24/37 (65%); % HbA_{1c} 10.8; ankle-arm index 1.1; ulcer area (cm^2) 3.0; ulcer duration (weeks) 60.7. Comparator group: N = 126; age (yrs) 55.5; male 91/126 (72%); insulin dependent 87/109 (69%); % HbA_{1c} 11.6; ankle-arm index 1.1; ulcer area (cm^2) 2.8; ulcer duration (weeks) 46.5.	(within therapeutic range). DG-½TR: N = 61. Received active product first 2 apps and at least half of all apps. DG-ATR: N = 37. Received active product for all apps.	shoes and inserts.	Number of ulcers that healed by week 32 DG 50/87 (58%) DG-½TR 30/52 (58%) DG-ATR 19/32 (59%) Median time to healing (weeks) 13 Median time to ulcer recurrence (weeks) 12 Number of patients with an ulcer that developed an infection (harm) 29/139 (21%)	39/92 (42%) 28 7 34/142 (24%)	RR = 1.36 [95% CI 1.01, 1.82] NNT = 7 [95% CI 3, 235] RR = 1.36 [95% CI 0.97, 1.86] RR = 1.40 [95% CI 0.94, 1.94] p < 0.05 RR = 0.87 [95% CI 0.56, 1.35]
(Caravaggi et al 2003) Italy	Level II RCT Average quality study	N = 79 diabetic patients with a Wagner grade 1-2 ulcer on the plantar surface or dorsum of foot, of > 2 cm^2 and without signs of healing for 1 month and with adequate perfusion to the limb. Intervention group: N = 43; diabetes type 1 9/43 (20.9%); $TcPO_2$ (mmHg) 48.0 (interquartile range 24.0); ankle-brachial index 0.7 ± 0.3; % HbA_{1c} 7.9 ± 2.13; ulcer area (cm^2) 5.3 ± 6.76; depth of ulcer (mm) 6.1 ± 5.68; duration of ulcer (months) 4.0	N = 43. HYAFF-11-based autologous grafts. A skin biopsy (1-2 cm^2, 0.8 mm deep) was taken and sent to the TissueTech Autograft Laboratory in Italy for fibroblast	N = 36 Initially subjected to extensive debridement. The ulcers were covered with non-adherent paraffin gauze and a secondary dressing of sterile cotton pads	Number of patients with ulcers that healed Plantar 12/22 (55%) Dorsal 14/21 (66.7%)	10/20 (50%) 5/16 (31.3%)	RR = 1.09 [95% CI 0.62, 1.95] RR = 2.04 [95% CI 1.00, 4.50] NNT = 3

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
		(interquartile range 10.0); localisation of ulcer: forefoot 31/43 (72.1%); midfoot 7/43 (16.3%); hindfoot 3/43 (7.0%); not specified 2/43 (4.7%). Comparator group: N = 36; diabetes type 1 3/36 (8.0%); $TcPO_2$ (mmHg) 48.5 (interquartile range	and keratinocyte cell culturing. The cells were then seeded on two distinct biodegradable	and gauze. Visits and dressing changes were same for both groups. Secondary dressing			[95% CI 2, 533] Mean % reduction in ulcer size for non-healed ulcers: Plantar 61.1 ± 26.0 64.7 ± 34.7 p = 0.823
		20.5); ankle-brachial index 0.7 ± 0.22, % HbA_{1c} 8.1 ± 2.25; ulcer area (cm^2) 6.2 ± 7.58; depth of ulcer (mm) 8.0 ± 5.46; duration of ulcer (months) 4.0 (interquartile range 6.0); localisation of ulcer: forefoot 24/36 (66.7%); midfoot 7/36 (19.4%); hindfoot 2/36 (5.6%); not specified 3/36 (8.3%).	scaffolds composed of a benzylic ester of hyaluronic acid. Patients first received autologous fibroblasts on Hyalograft 3D applied over ulcer after extensive debridement and cleansing. This was then covered as for control patients, if a second graft was required, the wound was cleansed prior to application. After 7-10 days the autologous keratino-cytes grown on laserskin was applied to the ulcer, dressed and covered as before. A second graft was permitted if required.	could be changed after 3 days (earlier if needed). After 7 days the non-adherent paraffin gauze was changed every 2 days after cleansing the ulcer with physiologic solution. Antibiotics prescribed if needed. All patients provided with non-removeable fibreglass cast)plantar ulcera) or therapeutic shoe (dorsal ulcers) for off-loading.			Dorsal 68.0 ± 37.3 32.9 ± 35.1 p = 0.072 Median time to complete healing (days): Plantar 57 58.5 Dorsal 63 77 Total 57 77
(Edmonds et al 2009) European Union and Australia	Level II RCT Average quality study	N = 72 diabetic patients aged 18 to 80 years, with a neuropathic ulcer limited to the plantar region of the forefoot (through the dermis but without sinus tract, bone or tendon exposure) that has been present at least 2 weeks and with adequate vascular supply to target extremity. Intervention group – N=33; age (yrs) 56.4 ± 11.6; male 29/33 (87.9%); weight (kg) 98.1 (63-145); height	N = 33. Apligraf was placed directly on bed of target ulcer, then Mepitel (a porous flexible polyamide wound contact layer) was applied as a	N = 39. Standard wound care consistent with international guidelines: sharp debridement, saline-moistened dressings, a non-weight bearing	Number of patients with ulcers that healed completely by 12 weeks 17/33 (51.5%)	10/39 (25.6%)	RR = 2.01 [95% CI 1.10, 3.73] NNT = 4 [95% CI 2, 29]
					Median time to healing (days) 84	ND	p = 0.059

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
		(cm) 177.9 ± 7.7; duration of diabetes (yrs) 15.7 ± 9.2; type 1 16/33 (48.5%); duration of ulcer (yrs) 2.0 ± 2.3; ulcer size (cm^2) 3.0 ± 2.1. Comparator group(s) – N=39; age (yrs) 60.6 ± 9.8; male 33/39 (84.6%); weight (kg) 97.9 (65-173); height	primary non-adherent dressing. Secondary dressings and standard wound care as for control.	regime. The same primary and secondary dressings (saline-moistened gauze, dry gauze,	(<50% healed) Recurrence of ulceration at 12 weeks after healing 1/15 (7%)	1/10 (10%)	RR = 0.67 [95% CI 0.07, 6.23]
		(cm) 177.5 ± 10.0; duration of diabetes (yrs) 16.0 ± 9.1; type 1 13/39 (33.3%); duration of ulcer (yrs) 1.7 ± 1.8; ulcer size (cm^2) 3.0 ± 2.1.	Additional applications of Apligraf at 4 and 8 weeks if the wound was judged to be not healing.	and bandage to hold in place) were used as for intervention group. Both groups had the same off-loading requirements.			
(Gentzkow et al 1996) USA	Level II RCT Average quality study	N = 50 diabetic patients under reasonable glycaemic control, with full-thickness diabetic ulcers of the plantar surface or heel suitable for a skin graft, and with adequate perfusion. Intervention group A: N = 12; age (yrs) 62.7; male 8/12 (75%); insulin dependent 7/12 (58%); % HbA_{1c} 8.0; ankle-arm index 1.0; area of ulcer (cm^2) 2.2; duration of ulcer (weeks) 50.4. Intervention group B: N = 14; age (yrs) 66.2; male 11/14 (79%); insulin dependent 9/14 (64%); % HbA_{1c} 8.2; ankle-arm index 1.1; area of ulcer (cm^2) 2.3; duration of ulcer (weeks) 40.7. Intervention group C: N = 11; age (yrs) 62.7; male 7/11 (64%); insulin dependent 9/11 (82%); % HbA_{1c} 8.4; ankle-arm index 0.9; area of ulcer (cm^2) 3.3; duration of ulcer (weeks) 43.2. Comparator group D: N = 13; age (yrs) 53.8; male 9/13 (69%); insulin dependent 10/13 (77%); % HbA_{1c} 9.1; ankle-arm index 1.0; area of ulcer (cm^2) 1.9; duration of ulcer (weeks) 87.0.	Dermagraft was applied directly on wound after sharp debridement, and received treatment as for standard wound care. Group A: N = 12. 1 piece of Dermagraft applied weekly, total of 8 pieces Group B: N = 14. 2 pieces of Dermagraft applied 2-weekly, total of 8. Group C: N = 11. 1 piece of Dermagraft applied 2-weekly, total of 4.	Group D: N = 13. Standard wound care which included sharp debridement to remove all necrotic tissue and callous, covered with a non-adherent interface, then with saline-soaked gauze, and secured with an adhesive covering. Patients were provided with high-quality therapeutic shoes for off-loading.	Number of patients with ulcers that healed completely Group B 3/14 (21.4%) Group D 1/13 (7.7%) RR = 2.79 [95% CI 0.44, 18.00] Group C 2/11 (18.2%) RR = 2.36 [95% CI 0.33, 17.56] Number patients with ulcers with 50% closure Group A 9/12 (75%) Group D 3/13 (23.1%) RR = 3.25 [95% CI 1.31, 7.96] Group B 7/14 (50%) RR = 2.17 [95% CI 0.78, 6.69] Group C 2/11 (18.2%) RR = 0.79 [95% CI 0.17, 3.48] Median time to complete closure (weeks) Group A 12 Group D > 12 p = 0.056 Group B > 12		

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
					Group C > 12 Median time to50% closure (weeks) Group A 2.5	 Group D > 12	 p = 0.0047
					Median % decrease in wound volume Group A 88.9%	 Group D 0%	 p = 0.017
					Number of ulcers that became Infected (harms) Group A 2/12 (17%)	 Group D 3/13 (23%)	 RR = 0.72 [95% CI 0.16, 3.22]
					Group B 4/14 (29%)		 RR = 1.24 [95% CI 0.36, 4.43]
					Group C 3/11 (27%)		 RR = 1.18 [95% CI 0.31, 4.49]
(Hanft & Surprenant 2002) USA	Level II RCT Average quality study	N = 46 diabetic patients aged 18 years or over, with a full-thickness plantar foot ulcer present for at least 2 weeks, with no sign of clinical infection and adequate circulation to the foot. N = 28 patients with ulcer > 6 weeks duration Intervention group: N = 14; age (yrs) 54.1 ± 15.6; male 92.9%; Caucasian 57.1%; smoker 28.6%; alcohol use 28.6%; type 1 diabetes 7.1%; BMI (kg/m^2) 29.95 ± 7.35; $\%HbA_{1c}$ 7.95 ± 2.5; albumin (g/dl) 3.99 ± 0.41; ankle-arm index 1.07 ± 0.2; duration of ulcer (weeks) 21.0 ± 18.2; ulcer area (cm^2) 1.56 ± 0.83; ulcer location: forefoot or toe 71.4%; heel 28.6%. Comparator group: N = 14; age (yrs) 58.2 ± 10.8; male 92.9%; Caucasian 57.1%; smoker 14.3%;	N = 24 N = 14 > 6 weeks duration. Dermagraft applied directly on wound after sharp debridement at day 0 and up to 7 additional applications over course of study. Standard wound care same as for control group.	N = 22 N = 14 > 6 weeks duration. Standard wound care included sharp debridement, non-adherent interface, saline-moistened gauze, dry gauze, and adhesive tape, and prescribed orthotics to avoid weight-bearing.	Total number of ulcers healed by week 12 15/24 (62.5%)	 6/22 (27.3%)	 RR = 2.29 [95% CI 1.15, 4.77] NNT = 3 [95% CI 2, 15]
					Number of forefoot or toe ulcers healed by week 12 7/10 (70%)	 2/13 (15%)	 RR = 4.55 [95% CI 1.45, 15.64] NNT = 2 [95% CI 1, 7]
					Number of >6 week duration ulcers healed by wk 12 10/14 (71.4%)	 2/14 (14.3%)	 RR = 5.0 [95% CI 1.67, 17.6] NNT = 2 [95% CI 1, 5]
					Mean % wound closure by wk 12 (>6 week duration)		

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
		alcohol use 42.9%; type 1 diabetes 21.4%; BMI (kg/m^2) 32.64 ± 9.21; $\%HbA_{1c}$ 7.96 ± 1.9; albumin (g/dl) 3.88 ± 0.35; ankle-arm index 1.10 ± 0.27; duration of ulcer (weeks) 80.8 ± 188.9; ulcer area (cm^2) 1.54 ± 0.81; ulcer location: forefoot or toe 92.9%; heel 7.1%.			98 ± 5.2	48.2 ± 93	p = 0.002
(Sabolinski & Veves 2000) USA	Level II RCT Poor quality study	N = 33 diabetic patients that attended the Foot Centre and had an ulcer for at least 2 weeks prior to the start of the study. Ulcers were subjected to aggressive debridement followed by standard wound care (according to the American Diabetes Association) for one week and patients with ulcers that did not respond adequately to treatment were included in the study. Baseline characteristics of intervention and comparator groups were not provided.	N = 16. Graftskin applied to ulcers once a week for up to 5 applications in addition to standard wound care.	N = 17. Standard wound care (according to the American Diabetes Association): including woven gauze dressings kept moist by saline and changed twice per day.	Number of patients with ulcers that healed within 12 weeks		
					12/16 (75%)	7/17 (41%)	RR = 1.82 [95% CI 1.00, 3.04]
					Median time to healing (days)		
					38.5	91	p = 0.01

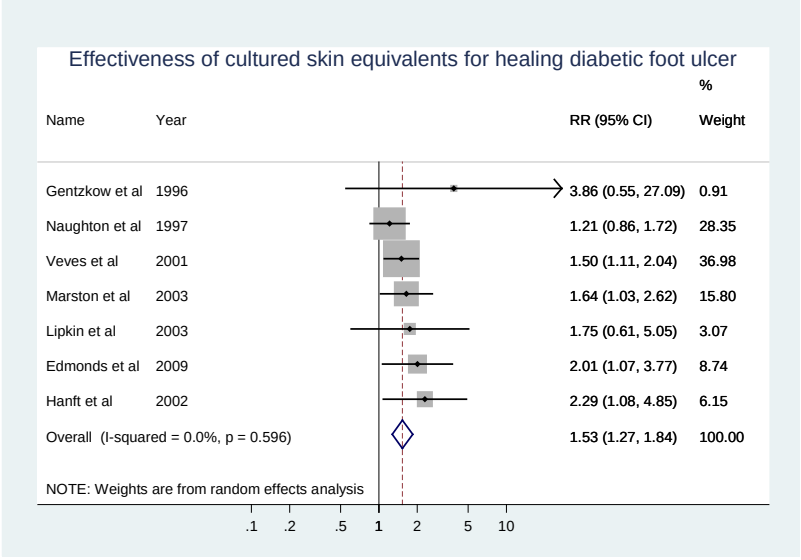
RR = relative risk; CI = confidence interval; NNT = number needed to treat; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot; ICER = incremental cost-effectiveness ratio; SWC – standard wound care.

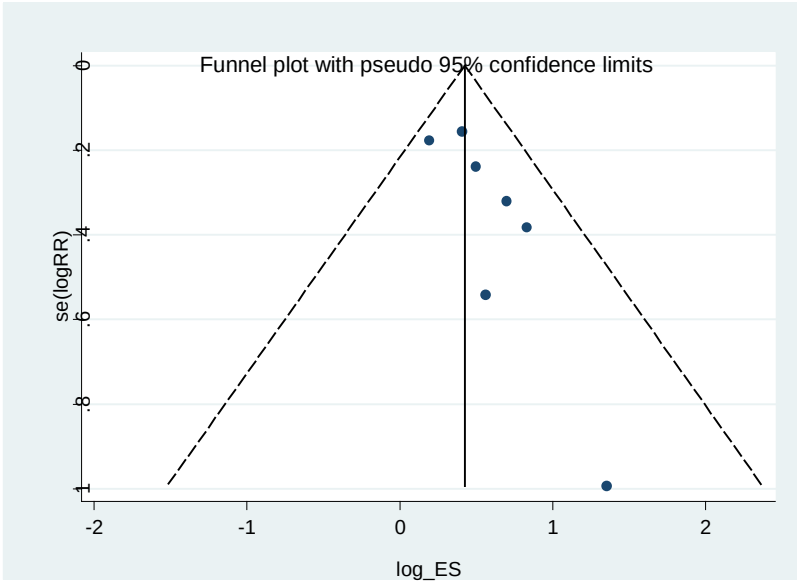
Figure 10 Meta-analysis of cultured skin equivalents for healing of diabetic foot ulcer

Study	RR	[95% Conf.	Interval]	% Weight
Gentzkow et al	3.865	0.551	27.087	0.91
Naughton et al	1.214	0.856	1.721	28.35
Veves et al	1.500	1.105	2.036	36.98
Marston et al	1.643	1.029	2.622	15.80
Lipkin et al	1.750	0.606	5.054	3.07
Edmonds et al	2.009	1.071	3.767	8.74
Hanft et al	2.292	1.083	4.849	6.15
D+L pooled RR	1.529	1.270	1.841	100.00

Heterogeneity chi-squared = 4.60 (d.f. = 6) p = 0.596
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000

Test of RR=1 : z= 4.48 p = 0.000





Cultured skin equivalent versus acellular wound matrix

One level II study of average quality compared the use of Dermagraft, a cultured skin equivalent with OASIS wound matrix (Healthpoint, USA), an acellular collagen-based tissue matrix derived from porcine intestinal submucosa, in addition to standard wound care (Table 97). Landsman et al (2008) conducted an average quality randomised controlled trial involving 26 diabetic patients, with a full-thickness ulcer of at least 4 weeks duration that did not extend to bone or tendons, and had a viable wound bed with granulation tissue. They found that there was little difference in the number of patients with ulcers that healed between the two groups (85% for Dermagraft group compared to 80% for OASIS group; RR = 0.91 [95% CI 0.70, 1.27]). Similarly there was no statistical difference for the time to healing for the two groups (p = 0.73).

Box 134 Evidence statement matrix for a cultured skin equivalent compared to an acellular dermal tissue matrix

Component	Rating	Description
Evidence base	C	One level II study with a moderate risk of bias.
Consistency	N/A	There was only one study
Clinical impact	D	Slight clinical impact. There were no statistically significant differences for either the number of healed ulcers or the time to healing.
Generalisability	C	Population consisted of diabetic patients with a full-thickness ulcer of at least 4 weeks duration that did not extend to bone or tendons, and had a viable wound bed with granulation tissue
Applicability	C	The study was conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia.

Evidence statement

The evidence presented in this study suggests that there is no statistical or clinical advantage when using either Dermagraft or OASIS wound matrix in addition to standard wound care for people with chronic diabetic foot ulcers. (Grade C)

Table 97 Study which compared the use of a cultured skin equivalent with an acellular dermal tissue matrix for the treatment of diabetic foot ulcer

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Landsman et al 2008) USA	Level II RCT Average quality study	N = 26 diabetic patients, over 18 years, with a full-thickness ulcer that does not extend to bone or tendons, has a viable wound bed with granulation tissue, and is of at least 4 weeks duration. Intervention group: N = 13; age (yrs) 62.2 ± 12.2; male 10/13 (77%); ulcer area (cm^2) 1.85 ± 1.83. Comparator group: N = 13; age (yrs) 63.4 ± 9.84; male 8/13 (62%); ulcer area (cm^2) 1.88 ± 1.39.	N = 13. Dermagraft applied directly to wound, could be reapplied twice more, as an adjunct to standard wound care. Standard wound care consisted of debridement, saline-moistened gauze dressings, and off-loading	N = 13. OASIS Wound Matrix (acellular collagen-based bioactive wound matrix) as an adjunct to standard wound care. Applied to wound, could be reapplied if not adhering to the wound (up to 8 times)	Number of patients with ulcers that healed 11/13 (85%) Time to healing (days) 40.9 ± 32.3	10/13 (80%) 35.7 ± 41.5	RR = 0.91 [95% CI 0.70, 1.27] p = 0.73

RR = relative risk; CI = confidence interval.

Acellular wound matrix versus moist wound therapy

One randomised controlled study of average quality investigated the use of GraftJacket (Wright Medical Technology, USA) an acellular wound matrix in addition to moist wound therapy compared to moist wound therapy alone (Table 98). GraftJacket is processed from donated human skin to remove epidermal and dermal cells while preserving the remaining bioactive components and structure of the dermis.

Reyzelman et al (2009) conducted a trial that compared the effectiveness of GraftJacket in addition to moist wound therapy in 85 diabetic patients with an uninfected University of Texas grade 1 or 2 diabetic foot ulcer, and with adequate perfusion to the affected limb. Before randomisation, all patients were surgically debrided. The group that were treated with GraftJacket used Silverlon (Arggentum Medical, USA), a silver-based non-adhesive dressing, and secondary dressings including hydrogels or moist gauze. The control group that received only moist wound therapy were treated with alginates, foams, hydrocolloids or hydrogels. The authors found that the increased number of patients with ulcers that healed in patients treated with GraftJacket, silver dressings and moist wound therapy compared to patients treated with moist wound therapy alone was statistically significant (69.6% compared to 46.2%; RR = 1.51 [95% CI 1.04, 2.18]). Four patients would need to be treated with the GrafJacket intervention for one additional patient's ulcer to heal (NNT = 4 [95% CI 2, 42]). However, for the ulcers that did not heal completely, there was no statistical difference in the percent reduction in ulcer size between the two groups.

Box 135 Evidence statement matrix for acellular wound matrixes compared to moist wound therapy

Component	Rating	Description
Evidence base	C	One level II study with a moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	C	Moderate clinical impact. Reyzelman et al (2009) reported an increased number of healed ulcers that was statistically significant.
Generalisability	B	Population consisted of diabetic patients with a University of Texas grade 1 or 2 diabetic foot ulcer with no signs of infection, and with adequate perfusion to affected limb.
Applicability	C	The study was conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia.

Evidence statement

The use of GraftJacket wound matrix with Silverlon may increase the likelihood of ulcers healing when used in addition to moist wound therapy in diabetic patients with chronic foot ulcers (Grade C).

Acellular wound matrix versus moist wound therapy plus sharp debridement

Brigido et al (2004) also conducted a randomised controlled trial involving 40 diabetic patients that presented to a medical centre with a chronic, non-healing, full-thickness ulcer of the lower extremity (leg or foot) of at least 6 weeks duration (Table 98). The aim was to compare the effectiveness of GraftJacket, covered with a mineral oil-soaked fluff compressive dressing to maintain a moist wound environment, compared to moist wound therapy using Curasol Hydrogel (Healthpoint, USA), a clear, viscous, non-drying hydrogel polymer, gauze dressings, and sharp debridement. The GraftJacket matrix was applied surgically after debridement to remove all necrotic tissue. Adverse events were reported for five grafted patients, four experienced drying of a superficial portion of the graft due to insufficient moisture and one patient developed a seroma which was aspirated. In all five patients, the grafts incorporated

with the host tissue and were not considered to be failures. The authors found that the 73% reduction in ulcer size after treatment with GraftJacket when compared to 34% in those treated with Curasol was statistically significant (p = 0.001).

Box 136 Evidence statement matrix for acellular wound matrixes compared to moist wound therapy plus sharp debridement.

Component	Rating	Description
Evidence base	C	One level II study with a moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	D	Moderate clinical impact. Brigido et al (2004) reported a greater reduction in ulcer size with the intervention compared to the control. This difference was reported to be statistically significant.
Generalisability	B	Population consisted of diabetic patients with a chronic, non-healing, full-thickness ulcer of the lower extremity (leg or foot) least 6 weeks duration.
Applicability	C	The study was conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia.

Evidence statement

The use of GraftJacket wound matrix may aid in reducing the size of ulcers when used in addition to moist wound therapy in diabetic patients with surgically debrided chronic foot ulcers (Grade C).

Table 98 Studies which evaluate the effectiveness of acellular wound matrixes for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Reyzelman et al 2009) USA	Level II RCT Average quality study	N = 85 diabetic patients, aged over 18 years, with a University of Texas grade 1 or 2 diabetic foot ulcer of 1-25 cm^2, with no signs of infection, and with adequate perfusion to affected limb. Intervention group: N = 46; age (yrs) 55.4 ± 9.6; BMI (kg/m^2) 33.1 ± 6.7; diabetes type 1 5/46 (10.9%); % HbA_{1c} 8.2 ± 2.0; ulcer duration (weeks) 23.3 ± 22.4; ulcer size (cm^2) 3.6 ± 4.3; ulcer located on toe 15/46 (32.6%); foot 15/46 (32.6%); heel 4/46 (8.7%); other 5/46 (10.9%). Comparator group: N = 39; age (yrs) 58.9 ± 11.6; BMI (kg/m^2) 34.6 ± 8.5; diabetes type 1 2/39 (5.1%); % HbA_{1c} 7.6 ± 1.6; ulcer duration (weeks) 22.9 ± 29.8; ulcer size (cm^2) 5.1 ± 4.8; ulcer located on toe 5/39 (12.8%); foot 17/39 (43.6%); heel 8/39 (20.5%); other 3/39 (7.7%).	N = 46. GraftJacket (a human acellular dermal regenerative tissue matrix) was sutured or stapled in place after surgical debridement, then covered with a silver-based non-adherent dressing. Secondary dressings (hydrogel or moist gauze) were applied as for control group.	N = 39. Moist wound therapy, which consisted of application of alginates, foams, hydrocolloids or hydrogels to ulcer, and dressings were changed daily. Off-loading for all patients with removable cast walker. Antibiotics were prescribed as needed.	Number of patients with ulcers that healed 32/46 (69.6%) Time to healing (weeks) 5.7 ± 3.5 For ulcers that did not heal: Number that reduced in size 12/14 (85.7%) % reduction in ulcer size 49.1 ± 35.9	18/39 (46.2%) 6.8 ± 3.3 15/21 (71.4%) 47.2 ± 52.0	OR = 2.67 [95% CI 1.10, 6.44] RR = 1.51 [95% CI 1.04, 2.18] NNT = 4 [95% CI 2, 42] p = 0.28 RR = 1.20 [95% CI 0.83, 1.48] p = 0.91
(Brigido et al 2004) USA	Level II RCT Average quality study	N = 40 diabetic patients that presented to a medical centre between April 7 2003 and June 27 2003, with a chronic, non-healing, full-thickness ulcer of the lower extremity (leg or foot), of at least 1 cm^2 in size and at least 6 weeks duration; age (years) 58 (43-70); male 31/40 (77.5%); insulin therapy 24/40 (60%). Intervention group: N= 20; ulcer duration (weeks) 25; ulcer length (mm) 32.5; ulcer width (mm) 21.0; ulcer area (cm^2) 9.7; ulcer depth (mm) 8.5. Comparator group: N= 20; ulcer duration (weeks) 27; ulcer length (mm) 26.7; ulcer width (mm) 18.6; ulcer area (cm^2) 5.4; ulcer depth (mm) 6.0.	N = 20. Surgical application of GraftJacket tissue matrix at day 0, then covered with a mineral oil-soaked fluff compressive dressing to maintain moist wound environment and changed on days 5, 10 and 15. Then used a dry sterile dressing.	N = 20. Moist wound therapy with sharp debridement and Curasol Hydrogel and gauze dressings. Standardised off-loading for both groups.	% reduction in ulcer size Length 50.9% Width 49.6% Depth 89.1% Area 73.1%	 15.4% 22.9% 25.0% 34.2%	 p = 0.001 p = 0.001 p = 0.001 p = 0.001

OR = odds ratio; RR = relative risk; CI = confidence interval; NNT = number needed to treat; University of Texas Diabetic Foot Classification System: 01. A0 Pre – or post ulcerative lesion completely epithelialised, 02. A1 superficial wound not involving tendon, capsule or bone, 03. A2 Wound penetrating to tendon or capsule, 04. A3 wound penetrating to bone or joint, 05. B0 pre or post ulcerative lesion completely epithelialised with infection, 06. B1 superficial wound, not involving tendon, capsule or bone with infection, 07. B2 wound penetrating to tendon or capsule with infection, 08. B3 wound penetrating to bone or joint with infection, 09. C0 pre or post ulcerative lesion completely epithelialised with ischaemia, 10. C1 superficial wound not involving tendon, capsule or bone with ischaemia, 11. C2 wound penetrating to tendon or capsule with ischaemia, 12. C3 wound penetrating to bone or joint with ischaemia, 13. D0 pre or post ulcerative lesion completely epithelialised with infection and ischaemia, 14. D1 superficial wound not involving tendon, capsule or bone with infection and ischaemia, 15. D2 wound penetrating to tendon or capsule with infection and ischaemia, 16. D3 wound penetrating to bone or joint with infection and ischaemia

Acellular wound matrix versus Regranex gel with recombinant human platelet derived growth factor

A randomised controlled trial (level II intervention evidence) of average quality was conducted by Niezgoda et al (2005) to investigate the effectiveness of the OASIS acellular wound matrix, used in conjunction with a dressing to protect the healing environment in addition to standard wound care, compared to Regranex Gel, a sodium carboxymethyl cellulose gel with 0.01% recombinant human platelet derived growth factor (rhPDGF), in addition to standard wound care (Table 99). The investigators randomised 98 diabetic patients with chronic, non-healing, full-thickness, University of Texas grade 1A ulcers of more than 1 month duration, and with a viable wound bed with granulation tissue. Of the patients randomised only 73 completed the study and were included in the final analysis. Adverse events were reported for 17 patients that received the OASIS wound matrix treatment and 10 patients that received the Regranex gel treatment. These events included pain/discomfort and/or infection of the wound as well as some events that were not related to treatment. Although there was an increase in the number of ulcers that healed and a decrease in the time to healing after treatment with OASIS wound matrix (49%) compared to Regranex gel treatment (28%), these differences did not reach statistical significance. According to the per protocol analysis however, for patients with type 2 diabetes or plantar ulcers, the difference was statistical significant (RR = 2.21 [95% CI 1.14, 4.07] and 3.63 [95% CI 1.37, 10.98], respectively. Three patients with type 2 diabetes or plantar ulcers would need to be treated with OASIS acellular wound matrix in conjunction with a dressing to protect the healing environment and standard wound care, compared to Regranex Gel for one additional patient's ulcer to heal (NNT = 3 [95% CI 2, 17] and 3 [95% CI 2, 9], respectively). At 6 month follow-up of patients with ulcers that had healed, there were no statistically significant differences between the two groups for the number of ulcers that had recurred.

Box 137 Evidence statement matrix for an acellular wound matrix versus Regranex gel

Component	Rating	Description
Evidence base	C	One level II study with a moderate risk of bias.
Consistency	N/A	There was only one study.
Clinical impact	D	Slight clinical impact. The difference in the number of ulcers that healed did not reach statistical significance for all patients, only for subgroups of patients with either type 2 diabetes or plantar ulcers.
Generalisability	D	Population consisted of diabetic patients with chronic, non-healing, full-thickness, University of Texas grade 1A ulcers of more than 1 month duration, and with a viable wound bed with granulation tissue. However, given the per protocol analysis it is uncertain whether the results are generalisable to other populations with similar characteristics.
Applicability	B	The study was conducted in the USA and Canada, where the care of diabetic foot ulcers is likely to be similar to Australia.

Evidence statement

OASIS acellular wound matrix, used in conjunction with a dressing to protect the healing environment and standard wound care may improve healing in patients with type 2 diabetes and/or plantar ulcers when compared to Regranex Gel, a sodium carboxymethyl cellulose gel with 0.01% recombinant human platelet derived growth factor (rhPDGF), in addition to standard wound care. (Grade D)

Table 99 Study which evaluated the effectiveness of an acellular wound matrix compared to Regranex gel for the treatment of diabetic foot ulcer

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Niezgoda et al 2005) USA and Canada	Level II RCT Average quality study	N = 98 diabetic patients, at least 18 years of age, with chronic (> 1 month duration), non-healing, full-thickness (University of Texas classification grade 1 A) ulcers, with a viable wound bed with granulation tissue. Intervention group: N = 37; age (yrs) 58 ± 2.3; male 23/37 (62%); type 1 diabetes 18/37 (49%); BMI (kg/m^2) 31.7 ± 7.6; % HbA_{1c} 7.9 ± 1.8; $TcPO_2$ (mmHg) 63.2 ± 3.4; albumin (g/dl) 3.9 ± 0.9; toe-brachial index 1.06 ± 0.07; ulcer size (cm^2) 5.0 ± 1.4 (range 1.0-40.0); plantar location 27/37 (72%); duration: 1-3 months 17/37 (46%); 4-6 months 8/37 (22%); 7-12 months 5/37 (13%); > 12 months 7/37 (19%). Comparator group: N = 36; age (yrs) 57 ± 1.9; male 21/36 (58%); type 1 diabetes 8/36 (22%); BMI (kg/m^2) 33.4 ± 7.4; % HbA_{1c} 8.8 ± 2.4; $TcPO_2$ (mmHg) 62.7 ± 13.7; albumin (g/dl) 3.8 ± 0.5; toe-brachial index 0.94 ± 0.07; ulcer size (cm^2) 3.2 ± 0.5 (range 1.0-20.0); plantar location 21/36 (58%); duration: 1-3 months 19/36 (53%); 4-6 months 4/36 (11%); 7-12 months 6/36 (17%); > 12 months 7/36 (19%).	N = 50. OASIS Wound Matrix (acellular collagen-based extracellular matrix derived from pig small intestine submucosa) was cut slightly larger than the ulcer, placed on the wound bed and moistened with sterile normal saline. A secondary dressing was then applied. Pressure-relief shoes were provided, although best method of off-loading was at the discretion of the clinician.	N = 48. Regranex Gel (becalpermin or rhPDGF-BB) was applied daily by patient according to insert, covered with saline-moistened gauze dressing for 12 hours before removing gel with saline and redressing the wound. Patients that were not healing after 12 weeks were offered the opportunity to cross-over into other treatment arm. If wound area reduced by 50% in 4 weeks, could continue treatment until healed for up to 8 weeks.	Number of patients with ulcers that healed completely by week 12 – <u>per protocol</u> All ulcers 18/37 (49%) Plantar ulcers 14/27 (52%) Type 1 diabetes patients 6/18 (33%) Type 2 diabetes patients 12/19 (63%) Time to healing (days) 67 6-month follow-up: Number that were healed at 12 weeks 8/19 (42%) Number that remain healed 6/19 (32%) Number of ulcers that recurred 2/8	10/36 (28%) 3/21 (14%) 2/8 (25%) 8/28 (29%) 73 6/18 (33%) 4/18 (22%) 2/6	 RR = 1.75 [95% CI 0.96, 3.27] RR = 3.63 [95% CI 1.37, 10.98] NNT = 3 [95% CI 2, 9] RR = 1.33 [95% CI 0.41, 5.36] RR = 2.21 [95% CI 1.14, 4.07] NNT = 3 [95% CI 2, 17] p = 0.245 RR = 1.26 [95% CI 0.56, 2.94] RR = 1.42 [95% CI 0.50, 4.21] RR = 0.75

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
					(25%)	(33%)	[95% CI 0.16, 3.70]

RR = relative risk; CI = confidence interval; NNT = number needed to treat; University of Texas Diabetic Foot Classification System: 01. A0 Pre – or post ulcerative lesion completely epithelialised, 02. A1 superficial wound not involving tendon, capsule or bone, 03. A2 Wound penetrating to tendon or capsule, 04. A3 wound penetrating to bone or joint, 05. B0 pre or post ulcerative lesion completely epithelialised with infection, 06. B1 superficial wound, not involving tendon, capsule or bone with infection, 07. B2 wound penetrating to tendon or capsule with infection, 08. B3 wound penetrating to bone or joint with infection, 09. C0 pre or post ulcerative lesion completely epithelialised with ischaemia, 10. C1 superficial wound not involving tendon, capsule or bone with ischaemia, 11. C2 wound penetrating to tendon or capsule with ischaemia, 12. C3 wound penetrating to bone or joint with ischaemia, 13. D0 pre or post ulcerative lesion completely epithelialised with infection and ischaemia, 14. D1 superficial wound not involving tendon, capsule or bone with infection and ischaemia, 15. D2 wound penetrating to tendon or capsule with infection and ischaemia, 16. D3 wound penetrating to bone or joint with infection and ischaemia

Radiowave or electric therapy

Electrical stimulation versus standard wound care

One good and two average quality studies evaluated the use of electrical stimulation in addition to standard wound care for ulcer healing (Baker et al 1997; Lundeberg et al 1992; Peters et al 2001).

The studies were conducted on patients attending medical centres for the treatment of non-healing foot ulcers. Patients received various treatment regimens of electrical stimulation in addition to standard wound care. No statistically significant results were reported for ulcer healing in any of the studies (Table 100).

In the study by Peters et al (2001) electrical stimulation was provided by a small electrical stimulation device to a Dacron mesh silver nylon stocking at night. The placebo group in this trial also wore the stockings at night and used a device which appeared to be a small electrical stimulation device however, this device did not deliver any electrical stimulation. As the current was delivered at a subsensory level and all patients had sensory neuropathy, it is unlikely that any patient could determine into which treatment group they had been allocated.

Baker et al (1997) applied electrical stimulation with conventional carbon rubber electrodes which were placed on intact skin near the edges of the ulcer. There were three intervention groups which each received a different program of electrical stimulation. Two groups were treated with currents which had been assumed to be of therapeutic benefit, the third group received current which had been considered to be sub-therapeutic however, subsequent analysis led the authors to consider that there may have been some benefit although no statistically significant effect was noted.

Lundeberg et al (1992) provided electrical stimulation by applying alternating constant current pulses near the ulcer surface area at such an intensity to evoke tingling or numbness at the site. This was performed for 20 minutes twice daily for one week. After 12 weeks, the direction of the treatment effect showed a benefit in terms of ulcer healing however this was not of statistical significance.

Meta-analysis was performed however; the pooled estimate can not be relied upon as there was statistically significant heterogeneity which was largely to due to true variation in the effect size (data not shown).

Peters et al (2001) also reported on the time to healing, but did not found a statistically significant difference between the intervention and control group.

The results indicate that there is no evidence to support electric stimulation in addition to standard treatment for diabetic foot ulcers. Box 138 summarises the body of evidence according to the NHMRC grading criteria.

Box 138 Evidence matrix for electric stimulation for the treatment of diabetic foot ulcer

Component	Rating	Description
Evidence base	C	One level II study with low risk of bias and two level II studies with moderate risk of bias.
Consistency	D	Although all studies were underpowered to detect a significant difference, the direction of the treatment effect differed in the study by Baker et al (1997).
Clinical impact	D	There was no statistically significant clinical impact of the intervention on ulcer healing.
Generalisability	B	The studies were mostly homogenic, patients were recruited from an outpatient clinic or a department of an university hospital, where they were treated for diabetic foot ulceration. Two studies included more males than females and one study had a high proportion of Hispanic patients.
Applicability	C	The studies took place in the USA and Sweden, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.

Evidence statement

There is no evidence to suggest that electric stimulation provides any additional benefit with regard to healing compared to standard wound care alone for diabetic foot ulceration (Grade C).

Table 100 Studies included which compare electric stimulation to standard treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
(Peters et al 2001) USA	Level II RCT Good quality study	Patients attending university medical centre for non-healing ulcer Intervention group: N = 20; mean age (yrs) 59.9 ± 7.0; male 80% (n = 16); mean DM duration (yrs) 17 ± 7.5; neuropathy 100% (n = 20) Comparator group: N = 20; mean age (yrs) 54 ±1 2; male 95% (n = 19); mean DM duration (yrs) 16 ± 12; neuropathy 100% (n = 20).	N = 20, patients received standard wound care which included weekly debridement, topical hydrogel and off loading with removable cast walker. In addition the patients received electric stimulation through microcomputer every night for 8 hours.	N = 20, patients received standard wound care which included weekly debridement, topical hydrogel and off loading with removable cast walker. In addition the patients received sham electric stimulation, which did not give a current, through microcomputer every night for 8 hours.	Ulcers healed		
					Intervention 13/20 (65%)	Control 7/20 (35%)	Effect size [95% CI] RR 1.9 [0.96, 12]
					Infection		
					Intervention 2/20 (10%)	Control 2/20 (10%)	ns
					Mean time to complete wound closure (weeks)		
					Intervention 6.8±3.4	Control 6.9±2.8	ns
(Baker et al 1997) USA	Level II RCT Average quality study	Patients attending medical centre for non-healing foot ulcer. Intervention group A: N = 21 (33 ulcers); mean age (yrs) 58 ± 2; male 76% (n = 16); ethnicity: non Hispanic white 43% (n = 9), Hispanic or other 57% (n = 12). Intervention group B: N =20 (28 ulcers); mean age (yrs) 58 ± 2; male 76% (n=16); ethnicity: non Hispanic white 30% (n=6), Hispanic or other 70% (n=14). Intervention group C: N = 19 (28 ulcers); mean age (yrs) 51 ± 2; male 74% (n=14); ethnicity: non Hispanic white 11% (n=2), Hispanic or other 89% (n=17). Comparator group: N = 20 (25 ulcers); mean age (yrs) 52 ± 2; male 70% (n=14); ethnicity: non Hispanic white 10% (n=2), Hispanic or other 90% (n = 18).	N = 21, asymmetric biphasic stimulation and standard treatment	N = 20. sham electric stimulation (no current through electrodes) and standard treatment	Ulcers healed		
					Intervention 15/33 (45%)	Control 12/25 (48%)	Effect size [95% CI] RR 0.9 [0.3, 2.5]
			N = 20, symmetric biphasic stimulation and standard treatment		Ulcers healed		
					Intervention 8/28 (29%)	Control 12/25 (48%)	Effect size [95% CI] RR 0.9 [0.3, 2.3]
			N = 19, micro current stimulation and standard treatment		Ulcers healed		
					Intervention 10/28 (36%)	Control 12/25 (48%)	Effect size [95% CI] RR 0.7 [0.4, 1.4]

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
(Lundeberg et al 1992) Sweden	Level II RCT Average quality study	Patients attending hospital department of internal medicine and surgery for diabetic leg ulcer. Intervention group: N = 20; mean age (yrs) 59.9 ± 7.0; male 80% (n = 16); mean DM duration (yrs) 17 ± 7.5; neuropathy 100% (n = 20). Comparator group: N = 20; mean age (yrs) 54 ± 12; male 95% (n = 19); mean DM duration (yrs) 16 ± 12; neuropathy 100% (n = 20).	N = 20, patients were treated with electronic nerve stimulation (ENS) and standard treatment	N = 20, patients treated with sham electronic nerve stimulation and standard treatment.	Healing at week 12		
					Intervention 10/32 (31%)	Control 4/32 (13%)	Effect size [95% CI] RR 2.5 [0.9, 7.1]

RCT= randomized controlled trial; DM= diabetes mellitus; RR= relative risk

Non-contact normothermic wound therapy versus standard wound care

Three average quality randomised controlled trials evaluated the effectiveness of non contact normothermic wound therapy in addition to standard wound care for the treatment of diabetic foot ulcer (Table 101). Non contact normothermic wound therapy involved application after debridement and cleansing of an adhesive wound chamber, a warming card and a temperature control unit.

After conducting a meta-analysis of the two studies which reported healed ulcers, the results indicate that those ulcers treated with additional non-contact normothermic wound therapy were twice as likely to heal compared to standard wound care by itself over a follow up of 2 to 3 months (RR=2.2 [95%CI 1.2, 3.9]) (Figure 11).

McCulloch et al (2002) also reported that there was a statically significant difference in the rate of healing between the intervention and standard wound care ($p<0.05$), but not for the time to wound closure ($p=0.57$).

The result suggests that non-contact normothermic wound therapy in addition to standard wound care is more effective in healing foot ulcers than standard wound care by itself.

Another study by Alvarez et al evaluated the effectiveness of normothermic wound therapy for the treatment of neuropathic foot ulcers compared to standard wound care (Alvarez et al 2003).

The study sample was recruited from a university wound care centre and randomised into either the intervention (n=25) or control group (n=24). Patients in the intervention group received the same intervention as the 2003 study and similarly for the control group. There were no statistically significant differences between the two groups for baseline characteristics.

Over a 12 week period, the authors found that there was a mean percentage wound closure of 11% in the intervention group versus 35% in the control group. This indicated that ulcers treated with additional non contact normothermic wound therapy were approximately 3 times more likely to reduce in wound size than ulcers treated with standard wound care alone (HR= 3.2, $p=0.011$). Furthermore, the authors reported that the intervention group needed approximately 25 days to achieve 50% wound healing, while the control group needed approximately 43 days, which was found to be a statistically significant difference in healing speed ($p= 0.031$). Some slight to moderate skin maceration was reported in 40% of the intervention group, but this did not result in serious adverse events.

The results suggest that non-contact normothermic wound therapy in addition to standard wound care was more effective in reducing wound size area over 12 weeks than standard wound care alone. However, there is some risk of side effects like skin maceration.

Box 139 summarises the body of evidence according to the NHMRC grading criteria.

Box 139 Evidence matrix for comparison of non-contact normothermic therapy for the prevention of diabetic foot complications

Component	Rating	Description
Evidence base	C	Three level II studies with moderate risk of bias.
Consistency	B	Although one study was underpowered, the direction of the treatment effects was consistent for healing of ulcers.
Clinical impact	C	The meta analysis indicates a moderate clinical impact with a relative risk of 2.2 [95% CI 1.2, 3.9].
Generalisability	C	The studies were homogenic, Patients were recruited from an outpatient clinic, where they were treated for chronic diabetic foot ulceration.
Applicability	C	The studies took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.

Evidence statement

The evidence suggests that non contact normothermic wound therapy in addition to standard wound care is more effective at healing foot ulcers than standard wound care by itself (Grade C).

Figure 11 Non-contact normothermic wound therapy for diabetic foot ulcer

```
          Study     |     RR    [95% Conf. Interval]     % Weight
--------------------+---------------------------------------------------
McCullock et al     |  2.600       1.170     5.775         53.77
Alvarez et al       |  1.750       0.740     4.139         46.23
--------------------+---------------------------------------------------
D+L pooled RR       |  2.165       1.206     3.887        100.00
--------------------+---------------------------------------------------

  Heterogeneity chi-squared =   0.44 (d.f. = 1) p = 0.505
  I-squared (variation in RR attributable to heterogeneity) =   0.0%
  Estimate of between-study variance Tau-squared =  0.0000

  Test of RR=1 : z=   2.59 p = 0.010
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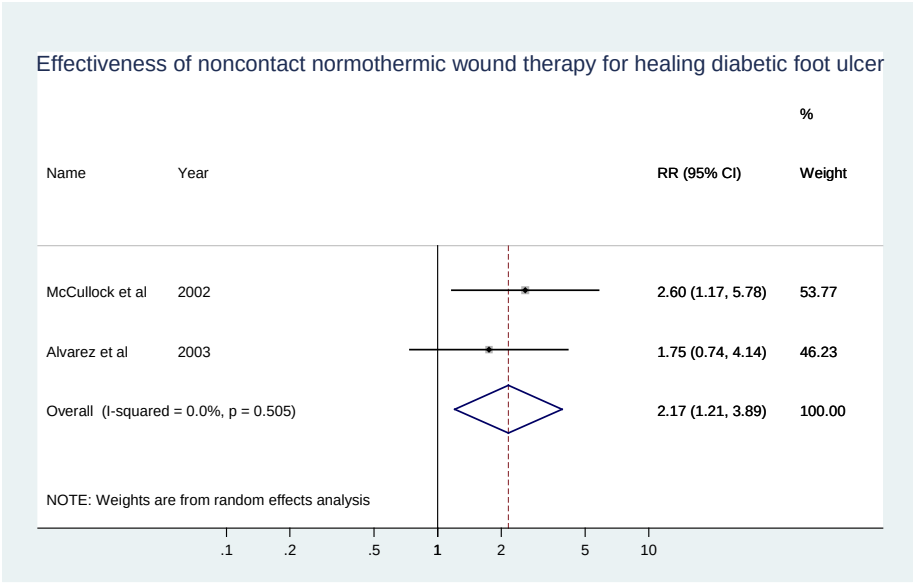


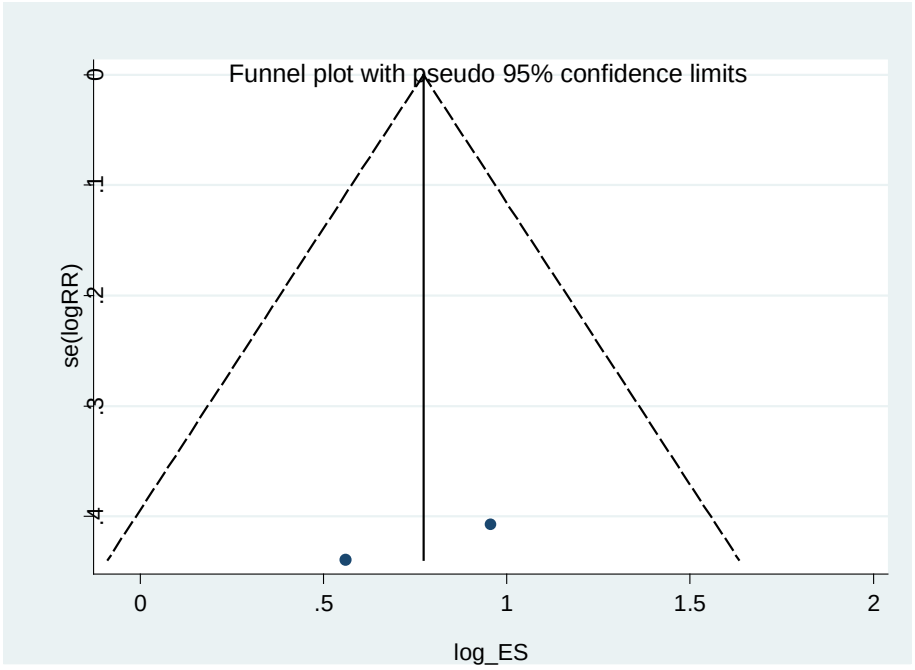


Table 101 Studies included which compare normothermic wound therapy to standard care for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
(McCulloch & Knight 2002) USA	Level II RCT Average quality study	Patients attending outpatient clinic for non-healing ulcer Intervention group: N = 18; mean age (yrs) 55.5 ± 12.8; ulcer location of plantar aspect of toes or metatarsal heads 76%; ulcer surface area (cm²) 2.02 ± 1.54; mean blood glucose (mg/dl) 139±25.7. Comparator group: N = 18; mean age (yrs) 52.5 ± 12.1; ulcer location of plantar aspect of toes or metatarsal heads 78% ulcer surface area (cm²) 2.58±12.8 mean blood glucose (mg/dl) 136±27.9.	N = 18, patients cleansed wounds with saline followed by application of warming system comprised of no contact foam dressing, warming card, temperature control unit and AC adaptor. Treatment was conducted daily for 3 hours, 5 days a week. After treatment wounds were covered with alginate and semi permeable foam dressing and offloading	N = 18, patients cleansed wounds with saline followed by application of appropriate moisture-retentive dressing and received offloading device (calcium alginate combined with thin, semipermeable foams). Patients received instruction in daily wound care.	Healed ulcer at 2 months		
					Intervention 13/18 (72%)	Control 5/18 (28%)	Effect size [95% CI] RR 2.6 [1.3, 5.3] NNT 2 [1, 8]
					mean healing rate (cm²/day)		
					Intervention 0.02 ± 0.02	Control 0.008 ± 0.009	p = 0.049
					Mean time to complete wound closure (days)		
					Intervention 32.6 ± 17.1	Control 27.6 ± 13.7	p = 0.57
(Alvarez et al 2003) USA	Level II RCT Average quality study	Patients attending medical centre for non-healing foot ulcer. Intervention group: N = 10; mean age (yrs) 61 (38–75); male 60%; mean ulcer surface area (mm²) 346; ulcer location forefoot 70% (n=7); other location 30% (n=3); more than one ulcer 40% (n=4); medical history of non healing <1 yr 70% (n=7); 1-3 yrs 30% (n=3); type II DM 80% (n=8); insulin dependent DM 50% (n=5). Comparator group: N = 10; mean age (yrs) 61 (38–75) ; male 60% (n=6) ; mean ulcer surface area (mm²) 346; ulcer location forefoot 70% (n=7) ; other location 30% (n=3) ; more than one ulcer 40% (n=4) ; medical history of non healing <1 yr 70% (n=7) ; 1-3 yrs 30% (n=3) ; type II DM 80% (n=8) ; insulin dependent DM 50% (n=5).	N = 10, after debridement and callus removal patients received negative normothermic wound therapy for 1 hours three times daily and fitted with a therapeutic healing sandal with plastizote inserts.	N = 10, after debridement patients received saline dressing and fitted with a therapeutic healing sandal with plastizote inserts.	Ulcers healed at 12 weeks		
					Intervention 7/10 (70%)	Control 4/10 (40%)	Effect size [95% CI] RR 1.75 [0.74, 4.14] p = 0.069
(Alvarez et al	Level II RCT	Diabetic patients with neuropathic foot ulcer.	N = 25, after	N = 24, after	Mean wound closure		

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
2006)	Average quality	Patient characteristics were not reported by treatment group however, authors reported no differences between group in patient demographics, baseline ulcer size or ulcer duration.	debridement and callus removal patients received negative normothermic wound therapy for 1 hours three times daily and fitted with a therapeutic healing sandal with plastizote inserts.	debridement patients received saline dressing and fitted with a therapeutic healing sandal with plastizote inserts.	11%	35%	HR 3.2 p = 0.011
					Time to 50% wound closure		
					25 days	43 days	p = 0.031

RCT = randomised controlled trial; DM = diabetes mellitus; RR = relative risk; NNT = number needed to treat; CI = confidence interval; HR = hazard ratio

Local heat versus global heat

One average quality randomised controlled trial evaluated the effectiveness of local heat for the treatment of chronic wounds in diabetic patients (Petrofsky et al 2007). A study sample of 29 subjects were randomised into three groups; intervention with local heat (n=9), global heat (n=10) and a control group that only received standard ulcer care (n=10). Both interventions were given in addition to standard wound care.

Local heat was applied with an infrared heat lamp for 20 minutes, while global heat was applied for 20 minutes in a room of 32°C. All patients received electric stimulation with a current controlled Challenge 8000 powered muscle stimulator with a frequency of 30Hz. The interventions were conducted 3 times per week over a 4 week period. Patients in the control group only received standard ulcer care and no electric stimulation or heat application.

The authors reported that the reduction in ulcer area was a mean 70 ± 17% for global heat and 55 ± 31% for local heat, while the ulcer area in the control group increased with by a mean of 4 ± 8%. This indicates that both local and global heat significantly increased ulcer healing in comparison to the control group ($p=0.0001$ and $p<0.0001$ respectively). Furthermore, additional global heat application was found to be more effective for ulcer healing than additional local heat application ($p<0.05$). There were no adverse events reported.

These results suggest that global heat application in addition to electric stimulation and standard wound care is more effective than additional local heat or standard wound. Both global and local heat increased ulcer healing compared to standard care alone. Box 140 summarises the body of evidence according to the NHMRC grading criteria.

Box 140 Evidence matrix for comparison of global heat versus local heat for the treatment of diabetic foot ulcer

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	C	The results presented a significant clinical impact of the intervention.
Generalisability	B	The study sample consisted of patients attending a wound care centre for chronic diabetic foot ulceration.
Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.

Evidence statement

The evidence suggests that global heat in addition to electric stimulation and standard wound care is more effective than additional local heat or standard wound care alone (Grade C).

Application of heat, either global or local, in addition to electric stimulation and standard wound care is more effective at reducing wound area than standard wound care alone (Grade C).

High voltage pulsed current versus placebo / standard care

Two average quality studies evaluated the effectiveness of high voltage pulsed current (HVPC) in addition to standard wound care for the treatment of chronic foot ulcer (Table 102).

The average quality randomised controlled trial of Houghton et al (2003) reported on the reduction in ulcer surface area over an 8 week follow-up period. The authors found that 32% of the ulcer wound surface area in the HVPC group had decreased versus 16% in the control group. No additional information was provided to determine whether this was a statistically significant difference.

In the study, the effect of treatment on the ulcer was also evaluated by using the Pressure Score Status Tool (PSST). A low score on the scale indicates a better wound appearance. Over an 8 week period, the authors reported a total PSST score of 32 in the intervention group and 28 in the control group, indicating that the ulcers in the control group appeared better than the intervention group. However, this was not found to be a statistically significant difference.

The results indicated that HVPC in addition to standard wound care is not more effective than standard care alone in reducing wound surface area or increasing the PSST appearance of the wound. However, the HVPC did increase the proportion of healed ulcers over 1 year compared to standard wound care. Box 141 summarises the body of evidence according to the NHMRC grading criteria.

Box 141 Evidence matrix for high voltage pulsed current for the prevention of diabetic foot ulcer

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study available.
Clinical impact	D	No statistically significant effect was seen between the two groups.
Generalisability	C	The studies included patients attending a hospital division of vascular surgery and outpatient foot clinics, which is generalisable to the target population with some caveats.
Applicability	B	The study took place in Canada, which has a similar health care for diabetes patients compared to the Australia health care context with few caveats.

Evidence statement

There is no evidence to support high voltage pulsed current in addition to standard wound care for ulcer healing in patients with chronic leg ulcers (Grade C).

Table 102 Studies included which compare high voltage pulsed current to standard care for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
(Houghton et al 2003) Canada	Level II RCT Average quality study	Patients attending outpatient clinic for chronic leg ulcer Intervention group: N = 14; male 64% (n=9), mean age (yrs) 66 ± 4.8, duration of DM (yrs) 3.0 ± 1.4, ulcer size (cm^2) 6.4 ± 1.9, ulcer location foot 71% (n=10), neuropathy 43% (n=6), infected ulcer 57% (n=8), diabetic foot ulcer 14% (n=2), arterial/venous 64% (n=9), mixed 21% (n=3) Comparator group: N = 13, male 62% (n=8), mean age (yrs) 62 ± 5.6, duration of DM (yrs) 4.6 ± 2.4, ulcer size (cm^2) 5.5 ± 2.0, ulcer location foot 77% (n=10), neuropathy 54% (n=7), infected ulcer 31% (n=4), diabetic foot ulcer 23% (n=3), arterial/venous 46% (n=8), mixed 23% (n=3)	N = 14, patients treated with high voltage pulsed current (HVPC) for 45 minutes, 3 times a week for 4 weeks and standard care	N = 13, patients treated with sham treatment for 45 minutes, 3 times a week for 4 weeks and standard care.	Wound area reduction at 8 weeks		
					Intervention 32%	Control 16%	Not reported
					Total Pressure Sore Status Tool (PSST)		
					Intervention 31.7±1.55	Control 82.8±2.1	p=ns

RCT= randomised controlled trial; DM= diabetes mellitus; RR= relative risk; ns = not significant.

Shock wave therapy versus standard wound care

One average quality randomised controlled trial evaluated the effectiveness of shock wave therapy compared to standard care for the treatment of neuropathic foot ulcers in diabetic patients (Moretti et al 2009).

The study sample was recruited from a diabetic ambulatory of endocrinology unit of a university and randomised into two groups that both received standard care in the form of debridement, Silvercell dressing and therapeutic foot wear. The intervention group (n=15) received an additional therapy of three applications of external shock wave therapy at 72 hour intervals. The shocks were applied directly around the wound perimeter with 100 pulses per 1cm² of the wound, delivered at a flux density of 0.03mJ/mm².

The authors reported that 53% of the ulcers in the intervention group had healed versus 33% in the control group, which was not found to be a statistically significant decrease in ulceration risk (RR=1.6 [95%CI 0.7, 3.7]). However, for re-epithelisation the authors reported a statistically significant difference as the intervention group showed a mean 2.97 ± 0.34 mm²/die and the control group 1.3±0.26 mm²/die over a 20 week follow up period (p<0.001). Furthermore, the results indicated that the ulcers in patients receiving shock wave therapy in addition to standard wound care healed quicker than those in the control group (61 ± 4.7 days versus 82 ± 4.7 days, p<0.001).There were only two adverse events reported, one in the control and one in the intervention group who developed infection of the wound.

The results suggest that there is insufficient evidence to support shock wave therapy in addition to standard wound care does for the healing of ulcers. However, the therapy may accelerate the healing process and increase re-epithelisation significantly more than standard wound care alone. Box 142 summarises the body of evidence according to the NHMRC grading criteria

Box 142 Evidence matrix for shock wave therapy for the prevention of diabetic foot complications

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	C	The results indicated that there was no significant effect for the additional intervention on the ulcer healing, but did show an increase in re-epithelisation and acceleration of healing for the intervention group compared to standard wound care alone.
Generalisability	B	The study included patients from a diabetic ambulatory endocrinology unit of a university with neuropathic foot ulcers, which makes the sample generalisble to the target population.
Applicability	C	The study took place in the Italy, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.

Evidence statement

There is insufficient evidence that shock wave therapy in addition to standard wound care is more effective than standard care alone for the healing of neuropathic foot ulcers in diabetic patients. However, the therapy may accelerate the healing process and increase the re-epithelisation of the neuropathic foot ulcer compared to standard wound care alone in diabetic patients (Grade C)

Shockwave therapy versus hyperbaric oxygen therapy

One average quality randomised controlled trial evaluated the effectiveness of shock wave therapy for the treatment of chronic diabetic foot ulcers compared to hyperbaric oxygen therapy over an average 12 month follow-up period (Wang et al 2009).

The study sample (n=70) consisted of outpatients visiting a hospital in Taiwan for chronic diabetic foot ulcers care. Subjects were randomised into either the intervention group (n=34) or

control group (n=36) and all patients received standard wound care which consisted of offloading, wound cleansing with normal saline solution and application of silver sulfadiazine cream. The intervention group received an additional three sessions of shockwave therapy at fortnightly intervals. The application of shockwave was 300 plus100cm² impulses at a flux density of 0.11mJ/cm². The control group received hyperbaric oxygen therapy 5 times per week for 20 weeks, which consisted of 90 minutes of enclosure in a sealed chamber with a 2.5 ATA air pressure and inhalation of 100% medical grade oxygen through a mask.

After the 20 week treatment period 29% of the ulcers in the intervention group had healed compared to 21% in the control group. The number of healed foot ulcers in the shock wave therapy was not found to be statistically significant compared to hyperbaric oxygen therapy (RR=1.38 [95%CI 0.63, 3.0]). Similarly, there was no statistically significant increase in the likelihood of achieving more than 50% improvement in ulcers for the intervention group compared to the control group (RR=1.2 [95%CI 0.76, 1.8]). No adverse events were reported.

The results were underpowered to detect a difference between shock wave therapy in addition to standard wound care and hyperbaric oxygen therapy in addition to standard wound care. Box 143 summarises the body of evidence according to the NHMRC grading criteria

Box 143 Evidence matrix for comparison of shock wave therapy for the prevention of diabetic foot complications

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study available
Clinical impact	D	The results indicated that there were no statistically significant effects in the intervention group relative to the comparator.
Generalisability	C	The study included a sample of outpatients attending a hospital for chronic diabetic foot ulcers, which makes the sample generalisable to the target population.
Applicability	D	The study took place in the Taiwan, which has different health care for diabetes patients compared to the Australia health care context.

Evidence statement

There is no evidence to support the use of shock wave therapy over hyperbaric oxygen therapy in addition to standard wound care for ulcer improvement or healing (Grade C).

Ultrasound therapy versus placebo

One good quality randomised controlled trial evaluated the effectiveness of ultrasound therapy in addition to standard wound care for the treatment of chronic diabetic foot ulcer (Ennis et al 2005).

After recruitment, a total of 133 patients who attended outpatient hospital clinics or private wound clinics for the treatment of chronic diabetic foot ulcer were randomised into either the intervention (n=70) or control group (n=63). The intervention involved treatment with an active ultrasound device, three times a week for four minutes. The control group received the same treatment except for the use of a sham device. All patients received standard wound care, which consisted of debridement and saline moistened gauze covered with dry gauze or Vaseline gauze. Dressing changes occurred three times a week at the clinic.

The authors reported that those ulcers treated with ultrasound in addition to standard wound care were approximately 3 times more likely to heal than in the control group over a 12 week follow up period (RR=2.85 [95CI 1.1, 7.9]). The estimated number of treated patients required to obtain one case of ulcer healing was 4 (NNT=4 [95%CI 2, 34]). For time to healing, the authors reported a mean of 9.12 ± 0.58 weeks for the intervention group versus a 11.7 ± 0.22 weeks for the controls, $p<0.02$. Furthermore, no statistically significant difference was found for re-ulceration between the two groups (9% in the intervention group versus 0% in the control group, p=0.533). With regard to adverse events of the treatment, the authors reported 81% mild, 66% moderate and 11% severe adverse events in the intervention group versus 60%, 51% and 19% in the control group, respectively. The authors only found a statistically significant increased risk for mild adverse events in the intervention group compared to the control group (RR=1.4 [95%CI 1.1, 1.7]).

The results suggest that ultrasound in addition to standard wound care is more effective for the treatment of foot ulcer than standard care. Interestingly, the study had large losses to follow up of 61% in the intervention and 56% in the control group, although reasons for this have not been provided. Box 144 summarises the body of evidence according to the NHMRC grading criteria

Box 144 Evidence matrix for ultrasound for the treatment of diabetic foot ulceration

Component	Rating	Description
Evidence base	C	One level II study with low risk of bias.
Consistency	N/A	Only one study available
Clinical impact	B	The results indicate that there is statistically significant clinical effect on the healing of ulcers for the intervention compared to the control group.
Generalisability	C	The study included patients attending hospital clinics and private wound clinics. A third of the population consisted of black or Hispanic ethnicity which makes the study sample generalisable to the target population with some caveats.
Applicability	C	The study took place in the USA and Canada, which has a health care for diabetes patients compared to the Australia health care context with some caveats.

Evidence statement

The evidence suggests that ultrasound in addition to standard care is more effective at healing diabetic foot ulcer than standard care by itself. However, it should be taken in account that there is an increased risk for mild adverse events with the additional ultrasound treatment (Grade C).

Foot compression versus placebo

One good quality randomised controlled trial evaluated the effectiveness of functional foot compression for the treatment of infected diabetic foot wounds (Armstrong & Nguyen 2000).

From a university teaching hospital, 115 patients were randomised into either the intervention group (n= 59) or control group (n=56). The intervention group received incision and debridement followed by foot compression, which was applied with a pneumatic device considered to reduce oedema in infected diabetic foot ulcers. The device inflated to approximately 160mmHg for 2 seconds before deflating and was used for approximately 8 hours per day. The control group received a sham foot compression treatment following sharp debridement. All patients were instructed to cleanse wounds twice daily with sterile isotonic sodium chloride solution and then pat dry while wearing disposable glove. Over a period of 12 weeks, 75% of the ulcers in the intervention group had healed versus 51% in the control group, indicating that treatment with foot compression increased the likelihood of foot ulcer healing compared to standard wound care (OR=2.9 [95%CI 1.2, 6.8]). There were two adverse events reported in both the intervention and control group that consisted of irritation to the dorsal surface of the foot.

The result suggests that there may be a benefit for foot compression over standard care alone in the healing of infected diabetic foot ulcers. Box 145 summarises the body of evidence according to the NHMRC grading criteria

Box 145 Evidence matrix for foot compression for the treatment of diabetic foot

Component	Rating	Description
Evidence base	B	One level II study with low risk of bias.
Consistency	N/A	Only one study.
Clinical impact	B	The result indicates that there is a statistically significant clinical impact for the treatment.
Generalisability	C	The study sample consisted of patients with chronic diabetic foot wounds and consisted of mainly Mexican Americans. This makes the sample generalisable to the target population with some caveats.
Applicability	C	The studies took place in USA, which have similar health care for diabetes patients compared to the Australia health care context

Evidence statement

The evidence suggests that foot compression in addition to standard wound care is more effective for healing of infected diabetic foot ulcers than standard care alone (Grade C).

Radiotherapy versus placebo

One average quality randomised controlled trial evaluated the effectiveness of palliative radiotherapy in addition to standard wound care for the treatment of acute osteoarthropathy of diabetic feet (Chantelau & Schnabel 1997).

The study sample (n=12) was recruited from the department of nutrition and metabolic diseases, where patients presented with acute diabetic osteoarthropathy of the feet. All subjects received standard care which involved off-loading and oral antibiotics and a low dose of heparin. In addition to standard care, the intervention group received radiotherapy consisting of 6 sessions conducted in one week (n=6). The authors reported that the time to healing in the radiotherapy group was a mean 7 days (4-10), while in the control group a mean 9.7 days (4-15). However, this was not found to be a statistically significant difference. No adverse events were reported and there was complete follow up.

Box 146 summarises the body of evidence according to the NHMRC grading criteria

Box 146 Evidence matrix for radiotherapy for the treatment of diabetic foot osteoarthropathy

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study.
Clinical impact	D	The result indicates that there is no statistically significant difference.
Generalisability	C	The study sample consisted for patients with severe diabetic foot complications. This makes the sample generalisable to the target population with some caveats.
Applicability	C	The studies took place in Germany, which have similar health care for diabetes patients compared to the Australia health care context

Evidence statement

There is insufficient evidence to suggest that radiotherapy in addition to standard care is better than standard care by itself for the treatment of diabetic foot osteoarthropathy (Grade C).

Interventions to improve the clinical management of diabetic foot ulcers

Six studies of average quality (two studies of level II intervention evidence, one level III-2 study, and three level III-3 studies) investigated the effectiveness of better management of diabetic foot ulcer care compared to standard care. Three studies (one level III-2 and two level III-3) investigated the effectiveness of staged multidisciplinary care compared to standard care at the discretion of the attending physician (Table 103). One study (level III-3) investigated the effectiveness of a GP training program in a historical cohort study (Table 104). A level II study investigated the effectiveness of treating diabetic foot ulcers using digital imaging and a remote expert consultant compared to standard care with a local physician (Table 105). The sixth study (level II evidence) investigated the effectiveness of providing prognostic data to clinicians compared to standard care in treating diabetic foot ulcers (Table 106).

Staged multidisciplinary management of diabetic foot ulcer care versus standard care

Three studies of average quality (one level III-2 and two level III-3) investigated the effectiveness of a multidisciplinary, staged management care program compared to standard care (Table 103). Multidisciplinary diabetic foot care teams often include: endocrinologists, orthopaedists, plastic and vascular surgeons, infectious disease specialists, radiologists, rehabilitation specialists, diabetes educators, wound care nurses and footwear technicians. The evidence-based staged management of diabetic foot ulcers is implemented via detailed algorithms according to guidelines for assessment and treatment, which provided standardised treatment protocols for each risk category. Standard care is usually an uncoordinated approach at the discretion of the attending physician, and usually includes debridement, moist wound care, infection control, and off-loading.

Horswell et al (2003) conducted a retrospective cohort study (level III-2 intervention evidence) involving 214 patients with a diabetic foot ulcer and investigated the effectiveness of the outpatient, multidisciplinary, staged management Diabetes Foot Program (DFP) in Baton Rouge compared to standard care in any of 9 Louisiana State University Health Care Services Division hospitals. The hospital visits and amputation rates of 45 diabetic patients whose foot ulcers were treated by the DFP were compared to 169 diabetic patients with an active foot ulcer who attended outpatient clinics. The length and the rate of foot-related hospital stay were four times shorter ($p = 0.0002$) and five times less frequent ($p = 0.029$) respectively, for patients

treated by the multidisciplinary, staged management DFP than those treated with standard care. While the rate of emergency department visit in patients treated with the DFP was half of that compared to those treated with standard care (0.6 visit per DFP patient compared to 1.2 visits per standard care patient; p = 0.004), DFP patients were three times more likely to attend the outpatient clinic than patients treated with standard care (25 visits per DFP patient compared to 8 visits per standard care patient; p < 0.001). Patients treated with the DFP were also about five times less likely to have an amputation-related hospital admission (0.04 admission per patient) than those treated with standard care (0.19 admission per patient; p = 0.035).

Yesil et al (2009) conducted a historical control study (level III-3) involving 574 patients with diabetic foot ulcers who were admitted to Dokuz Eylul University Hospital in Turkey between January 1999 and January 2008. In January 2002, a multidisciplinary diabetic foot care team was established at this hospital and a staged management care program was implemented. Thus, the 137 patients treated from 1999 to 2001 received standard uncoordinated care; whilst the 437 patients treated since January 2002 received multidisciplinary, staged management care. There were no statistically significant differences in the proportion of ulcers that healed and in the number of patients that required minor amputations between the two groups. The time spent in hospital was shortened from 39.5 days under standard care to 26.9 days under multidisciplinary, staged management care (p < 0.001). The difference in the rate of patients that required major amputations was also statistically significant and in favour of multidisciplinary, staged management care (12.6% compared to 20.4% for standard care; RR= 0.62 95% CI 0.41, 0.93]). Thirteen patients would need to be treated with multidisciplinary, staged management care, rather than standard care, in order to save one patient from major amputation surgery (NNT = 13 [95% CI 6, 100]).

Rerkasem et al (2009) also conducted an historical control study to investigate the effectiveness of the establishment of a multidisciplinary diabetic foot care team and the implementation of a staged management care program in August 2005 at the Chiang Mai University Hospital in Thailand. One hundred and seventy-one diabetic patients that attended this hospital between August 2003 and July 2006 with a foot ulcer requiring treatment were included in this study. Those treated between August 2003 and July 2005 formed the historical control group (standard care group, n=61), and patients treated after that received multidisciplinary, staged management care (n=110). There was a statistically significant reduction in the rate of patients that required minor or major amputations after multidisciplinary, staged management care compared to standard care (RR for all amputation = 0.24 [95% CI 0.09, 0.60]). Five patients need to be treated with multidisciplinary, staged management care, instead of standard care, to save one additional patient from an amputation surgery (NNT = 5 [95% CI 4, 11]). There were 56 patients in the multidisciplinary, staged management care group and 40 patients in the standard care group agreed to complete the SF-36 questionnaire. The scores in patients receiving multidisciplinary, staged management care were statistically significantly higher than those in patients that received standard care in the domains of Physical functioning, Physical role limitation, and Emotional role limitation, as well as for the total SF-36 score (54.7 ± 21.6 compare to 46.0 ± 16.5; p = 0.03) indicating a better quality of life.

All three studies have shown a statistically significant reduction in the amputation rate for patients who were treated with multidisciplinary, staged management care compared to those receiving standard care.

Box 147 Evidence statement matrix for staged multidisciplinary care versus standard care

Component	Rating	Description
Evidence base	D	One level III-2 study and two level III-3 studies with a moderate risk of bias
Consistency	B	The studies were mostly consistent in finding a statistically significant reduction in the amputation rate.
Clinical impact	B	Overall, the studies have shown a statistically significant reduction in the amputation rate favouring multidisciplinary, staged management care over standard care. One study also found that the length and the rate of foot-related hospital stays were shorter and less frequent, respectively, for patients treated by the multidisciplinary, staged management care than for those treated with standard care. The SF-36 scores for patients that had received multidisciplinary, staged management care were statistically significantly higher than for patients that received standard care.
Generalisability	A	Population consisted of diabetic patients with foot ulcers
Applicability	C	One study was conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia. The other two studies were conducted in Thailand and Turkey, which has different healthcare for diabetes patients compared to the Australian healthcare context.

Evidence statement

There is some evidence to suggest that multidisciplinary, staged management care reduces the risk of amputation rate for patients with diabetic foot ulcers compared to standard care. (Grade C)

Table 103 Studies which evaluate the effectiveness of staged multidisciplinary care for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Horswell et al 2003) USA	Level III-2 non-randomised retrospective study Average quality study	N = 214 Intervention group: N = 45 diabetic patients with active foot ulcer that had visited the Diabetic Foot Program (DFP) (in the Louisiana State University Health Care Services Division) between March and December, 1998. Patients also must have had a non-DFP outpatient visit at any time at any of the State hospitals in both the baseline and follow-up period. Age (yrs) 55.4; female 27/45 (60%); African American 33/45 (73%); Rate per patient (based on 8 months baseline before treatment) for: comorbid vascular disease 0.20, comorbid neurologic disease 0.11, comorbid renal disease 0.16, comorbid eye disease 0.47, foot related hospitalizations 0.31, foot related inpatient days 3.36, amputation hospitalizations 0.18, outpatient visits 4.32, emergency department visits 0.82. Comparator group: N = 169 diabetic patients with an outpatient foot ulcer diagnosis (code 707.1 of the International Statistical Classifications of Diseases, 9th Revision, Clinical Classifications (ICD-9-CM) between March and December 1998 from any of the 9 Louisiana State University Health Care Services Division hospitals. Patients must not have visited the DFP at any time between March 1998 and December 1999 and must have had a non-DFP outpatient visit at any time at any of the State hospitals in both the baseline and follow-up period. Age (yrs) 53.8; female 90/169 (53%); African American 122/169 (72%); Rate per patient (based on 8 months baseline before treatment) for: comorbid vascular disease 0.24, comorbid neurologic disease 0.14, comorbid renal disease 0.10, comorbid eye disease 0.38, foot related hospitalizations 0.32, foot related inpatient days 1.97, amputation hospitalizations 0.18, outpatient visits 3.85, emergency department visits 0.77.	N = 45. Foot ulcers were treated with a multidisciplinary, staged management foot care program, which consisted of devices to offload pressure; self-care education; and, after healing, monitored progressive ambulation, and custom-fabricated footwear.	N = 169. Foot ulcers were treated with standard foot care: uncoordinated treatment that included wound care, antibiotics, and self-care education. Offloading devices for ulcer healing were generally not available for this group.	Foot-related hospitalisation rate (admissions per patient): 0.09 Length of hospital stay (days per patient): 0.91 Amputation-related hospitalisation rate (admissions per patient): 0.04 Number of emergency department visits per patient: 0.60 Number of outpatient visits per patient: 24.91	0.50 3.97 0.19 1.22 8.04	p = 0.0002 p = 0.029 p = 0.035 p = 0.004 p < 0.001

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Yesil et al 2009) Turkey	Level III-3 historical control study Average quality study	N = 574 patients with diabetic foot ulcers who were admitted to Dokuz Eylul University Hospital in Turkey between January 1999 and January 2008. Intervention group: N = 437; age (yrs) 62.3 ± 10.3; males 306/437 (70%); duration of diabetes (yrs) 16.3 ± 9.6; type 2 diabetes 420/437 (96%); insulin use 295/437 (68%); smokers 166/437 (38%); BMI (kg/m^2) 26.6 ± 4.5; % HbA_{1c} 9.1 ± 2.3; retinopathy 278/437 (63%); nephropathy 236/437 (54%); neuropathy 360/437 (82%); limb ischaemia 250/437 (57%); ulcer located on toe 198/437 (45%), forefoot 94/437 (22%), midfoot 39/437 (9%), hindfoot 64/437 (15%), leg 42/437 (10%); Wagner: grade 1 46/437 (11%); grade 2 155/437 (36%); grade 3 125/437 (29%); grade 4 103/437 (24%); grade 5 8/437 (2%); osteomyelitis 174/437 (40%); antibiotic treatment 408/437 (93%). Comparator group: N = 137; age (yrs) 63.8 ± 11.4; males 85/137 (62%); duration of diabetes (yrs) 14.6 ± 7.8; type 2 diabetes 134/137 (98%); insulin use 81/137 (59%); smokers 69/137 (50%); BMI (kg/m^2) 26.0 ± 4.8; % HbA_{1c} 8.5 ± 1.7; retinopathy 85/137 (62%); nephropathy 66/137 (48%); neuropathy 123/137 (90%); limb ischaemia 71/137 (52%); ulcer located on toe 65/137 (47%), forefoot 35/137 (26%), midfoot 10/137 (8%), hindfoot 21/137 (15%), leg 6/137 (4%); Wagner: grade 1 12/137 (9%); grade 2 52/137 (38%); grade 3 39/137 (29%); grade 4 30/137 (22%); grade 5 4/137 (3%); osteomyelitis 56/137 (41%); antibiotic treatment 127/137 (93%).	N = 437. Diabetic patients admitted to hospital between January 2002 and January 2008. Treatment was managed by a multidisciplinary diabetic foot care team that included endocrinologists, orthopaedist, plastic and vascular surgeons, infectious disease specialists, radiologists, rehabilitation specialists, diabetes education, wound care nurses and a footwear technician. All patients received standard care that included wound care, bed rest, offloading, IV antibiotics and debridement or amputation when indicated.	N = 137. Diabetic patients admitted to the endocrinology clinic between January 1999 and December 2001. Treatment was managed by the attending physician. All patients received standard care that included wound care, bed rest, offloading, IV antibiotics and debridement or amputation when indicated.	Number of patients with ulcers that healed without requiring an amputation: 220/437 (50.3%) Length of hospital stay (days): 26.9 ± 21.3 Number of patients requiring an amputation: Minor 103/437 (23.6%) Major 55/437 (12.6%) Total 158/437 (36.2%)	60/137 (43.8%) 39.5 ± 28.3 27/137 (19.7%) 28/137 (20.4%) 55/137 (40.1%)	RR = 1.15 [95% CI 0.94, 1.43] p < 0.001 RR = 1.19 [95% CI 0.83, 1.76] RR= 0.62 95% CI 0.41, 0.93] NNT = 13 [95% CI 6, 100] RR = 0.90 [95% CI 0.72, 1.15]
(Rerkasem et al 2009; Rerkasem et al 2007) Thailand	Level III-3 historical control study Average quality study	N = 171 diabetic patients that attended Chiang Mai University Hospital between August 2003 and July 2006 with a foot ulcer needing treatment. Intervention group: N = 61; age (yrs) 57.8; males 20/61 (32.8%); hypertension 42/61 (68.9%); history of smoking 26/61 (42.6%); hyperlipidaemia 27/61 (44.3%). Intervention subgroup: N = 56; age (yrs) 61.3 ±	N = 61. Patients with diabetic foot ulcers attending Chiang Mai University Hospital between August 2005 and July 2006. Treated by a	N = 110. Patients with diabetic foot ulcers attending Chiang Mai University Hospital between August 2003 and July 2005. Prior to August 2005,	Number of patients that required a minor amputation: Toe 2/61 (3.3%) Total 2/61 (3.3%)	10/110 (9.1%) 15/110 (13.6%)	RR = 0.36 [95% CI 0.09, 1.40] RR = 0.24 [95% CI 0.06, 0.89] NNT = 10 [95% CI 7, 87]

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
		1.6; males 24/56 (42.9%); number of outpatient visits 8.0 ± 5.7; mean stay in hospital (days) 7.1 ± 13.5. Comparator group: N = 110; age (yrs) 60.6; males 37/110 (33.6%); hypertension 49/110 (44.6%); history of smoking 55/110 (50%); hyperlipidaemia 73/110 (66.4%). Comparator subgroup: N = 40; age (yrs) 62.5 ± 2.1; males 20/40 (50%); number of outpatient visits 3.7 ± 4.0; mean stay in hospital (days) 8.7 ± 12.8.	dedicated diabetic foot team (consisting of endocrinologists, a rehabilitation physician, a family doctor, nurses, and plastic and vascular surgeons) using standardised ulcer assessment and management protocols and preventative services were provided routinely, including self-care education, palliative foot care, and provision of protective footwear. N = 56. Patients that participated in an interview and filled out a questionnaire.	patients received standard care, such as debridement. There were no detailed guidelines for specific services. Consultations and preventative measures were undertaken at the discretion of the attending physician. N = 40. Patients that participated in an interview and filled out a questionnaire.	Number of patients that required a major amputation: Below knee 2/61 (3.3%) Above knee 0/61 (0%) Total 2/61 (3.3%) Total number of all amputations: 4/61 (6.6%) SF-36 questionnaire scores: 1. Physical functioning 37.6 ± 33.9 2. Physical role limitation 45.1 ± 42.5 3. Emotional role limitation 57.2 ± 45.7 Physical health dimension 45.7 ± 23.5 Total SF-36 score 54.7 ± 21.6	12/110 (10.9%) 3/110 (2.7%) 15/110 (13.6%) 30/110 (27.3%) 18.9 ± 23.4 27.5 ± 40.4 32.5 ± 43.7 37.0 ± 18.4 46.0 ± 16.5	RR = 0.30 [95% CI 0.08, 1.14] RR = not calculable RR = 0.24 [95% CI 0.06, 0.89] NNT = 10 [95% CI 7, 87] RR = 0.24 [95% CI 0.09, 0.60] NNT = 5 [95% CI 4, 11] p < 0.01 p = 0.04 p < 0.01 p = 0.05 p = 0.03

RR = relative risk; CI = confidence interval; NNT = number needed to treat; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localized gangrene of forefoot or heel, Grade 5 = gangrene of entire foot; SF-36 score: Self report questionnaire (36 questions relating to 8 domains measuring health and well-being, a score of zero was associated with poor perceived health and a score of 100 as good health). Total wound score = composite scale of wound severity as described by (Knighton et al 1986).

GP training program versus standard care

One historically controlled study (level III-3) by Benotmane et al (2004) investigated the effectiveness of a GP training program compared to standard care (Table 104). The GP training program, which provided information about treatment and patient referral, was introduced in 1994. A total of 176 diabetic patients with a foot ulcer admitted to the Endocrinology service of the University Hospital of Oran from that time to December 1998 were treated by trained GPs. The charts of these patients were compared to the charts of 132 diabetic patients with a foot ulcer who were admitted to the hospital from January 1989 to December 1993, before the training program was implemented, and therefore, received standard care at the discretion of the GP. There were no differences in the mortality rates and the rates of patients requiring an amputation between the two groups.

Box 148 Evidence statement matrix for GP training program versus standard care

Component	Rating	Description
Evidence base	D	One level III-3 study with a moderate risk of bias.
Consistency	N/A	Only one study
Clinical impact	D	Slight/restricted impact. No differences were found between the two groups for either the mortality rate or the rate of patients that required amputations.
Generalisability	A	Population consisted of diabetic patients with a foot ulcer
Applicability	D	The study was conducted in Algeria, which has different healthcare for diabetes patients compared to the Australian healthcare context.

Evidence statement

There is insufficient evidence that a GP training program has had any impact on the mortality and amputation rates in patients with diabetic foot ulcers. (Grade D)

Table 104 Study which evaluated the effectiveness of a GP training program for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Benotmane et al 2004) Algeria	Level III-3 historical control study Average quality study	N = 308 diabetic patients with a foot ulcer admitted to the Endocrinology service of the University Hospital of Oran from 1st January 1989 to 31st December 1998. Intervention group: N = 176; N = 183 ulcers; age (yrs) 58.3 ± 13.1; male 102/176 (58%); local residents 131/176 (74.4%); type 2 diabetes 158/176 (89.8%); duration of hospital stay (days) 42.5 ± 34.9; Wagner: grade 1 or 2 67/183 (36.6%), grade 3 46/183 (25.1%), grade 4 or 5 70/183 (38.3%). Comparator group(s): N = 132, N = 163 ulcers; age (yrs) 59.6 ± 17.7; male 88/132 (66.7%); local residents 102/132 (77.3%); type 2 diabetes 118/132 (89.4%); duration of hospital stay (days) 44.5 ± 37.0; Wagner: grade 1 or 2 60/163 (36.8%); grade 3 28/163 (17.2%); grade 4 or 5 75/163 (46%).	N = 176 patients admitted from 1st January 1994 to 31st December 1998. Post-GP training program. A GP training program to improve diabetic foot ulcer management was implemented in 1994.	N = 132 patients admitted from 1st January 1989 to 31st December 1993. Pre-GP training programme. All diabetic patients with a foot ulcer received standard care at the discretion of the GP	Number of patients deaths 15/176 (8.5%) Number of patients that required a major amputation 29/176 (16.5%) Number of patients that required a minor amputation 20/176 (11.4%)	12/132 (9.1%) 21/132 (15.9%) 19/132 (14.4%)	 RR = 0.94 [95% CI 0.46, 1.92] RR = 1.04 [95% CI 0.62, 1.73] RR = 0.79 [95% CI 0.44, 1.41]

RR = relative risk; CI = confidence interval; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localized gangrene of forefoot or heel, Grade 5 = gangrene of entire foot; SF-36 score: Self report questionnaire (36 questions relating to 8 domains measuring health and well-being, a score of zero was associated with poor perceived health and a score of 100 as good health). Total wound score = composite scale of wound severity as described by (Knighton et al 1986).

Remote expert consultation using digital imaging versus standard care

One level II study investigated the effectiveness of digital imaging and a remote expert consultant compared to digital imaging and standard care by the local physician in the treatment of lower extremity ulcers (Table 105). A randomised controlled trial was conducted by Santamaria et al (2004). It involved 93 patients who had a chronic ulcer of various aetiologies on the lower extremity and attended Broome, Derby, Kununurra and Wyndham hospitals. Only 36 (39%) of these patients had diabetic ulcers. All patients received standard wound care as determined by the local clinician and had their wound photographed and measured at each visit. The four treatment centres were randomised to electronically transfer the wound images and measurements to a wound care consultant in Perth every 2 weeks and receive treatment advice, or to not receive any external consultation. By randomising centres instead of patients, possible confounding due to the local clinician's increased knowledge level arising from expert consultant advice was avoided. However, this resulted in large differences in the baseline characteristics for age, gender and the number of diabetic ulcers between the two groups (Table 105). The authors found that there was a statistically significant increase in the ulcer healing rate for patients treated by local clinicians receiving expert advice (6.82% size reduction per week) compared to patients relying on the local clinician alone (-4.90 % size reduction per week; p = 0.012). There was also a statistically significant decrease in the rate of patients requiring an amputation from the centres receiving expert advice compared to centres not receiving remote consultation (2% compared to 14%; RR = 0.14 [95% CI 0.02, 0.86]). Eight patients would need to be treated by local clinicians receiving expert advice, instead of local clinicians alone, to save one patient from an amputation (NNT = 8 [95% CI 6, 85]).

Box 149 Evidence statement matrix for remote expert consultation versus standard care

Component	Rating	Description
Evidence base	C	One level II study with a moderate risk of bias.
Consistency	N/A	Only one study
Clinical impact	A	Very large impact. There were statistically significant differences between the two groups for the ulcer healing rate (% size reduction per week) the rate of patients that required amputations.
Generalisability	C	Population consisted of patients with chronic ulcers of various aetiologies on the lower extremity.
Applicability	A	The study was conducted in Australia, and therefore is directly applicable.

Evidence statement

Digital imaging of the wound, electronically transferring those images to a remote expert consultant and receiving treatment advice increase the ulcer healing rate and decrease the rate of amputation surgery when compared to treatment at the discretion of the local clinician for patients with lower extremity ulcers, including diabetic foot ulcers. (Grade C)

Table 105 Study which evaluatef the effectiveness of a remote expert consultation for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Santamaria et al 2004) Australia	Level II randomised controlled trial Average quality study	N = 93 patients with a chronic ulcer of the lower extremity; attending Broome, Derby, Kununurra and Wyndham hospitals. N = 36 patients with diabetic ulcers. Intervention group: N = 50; age (yrs) 63.5; male 24/50 (48%); ulcer site: leg 21/50 (42%), foot 29/50 (58%); ulcer aetiology: venous 7/50 (14%), arterial 1/50 (2%), mixed 1/50 (2%), diabetic 25/50 (50%), traumatic 6/50 (12%), surgical 5/50 (10%), pressure 3/50 (6%), burn 2/50 (4%). Comparator group: N = 43; age (yrs) 49.5; male 27/43 (63%); ulcer site: leg 14/43 (33%), foot 39/43 (67%); ulcer aetiology: venous 1/43 (2%), arterial 2/43 (5%), mixed 4/43 (9%), diabetic 11/43 (26%), traumatic 12/43 (28%), surgical 0/43 (0%), pressure 11/43 (26%), burn 2/43 (5%).	N = 50. Standard wound care as determined by the local wound care clinician. Their wounds were photographed and measured at each clinic attendance. These images and measurements were electronically transferred every 2 weeks to a wound care consultant located in Perth. These were then returned to the treating clinician with wound management advice.	N = 43. Standard wound care as determined by the local wound care clinician. Their wounds were photographed and measured at each clinic attendance	Healing rate (% ulcer size reduction per week) 6.82 Number of patients that required an amputation 1/50 (2%)	-4.90 6/43 (14%)	p = 0.012 RR = 0.14 [95% CI 0.02, 0.86] NNT = 8 [95% CI 6, 85]

RR = relative risk; CI = confidence interval; NNT = number needed to treat.

Providing prognostic data to improve care versus standard care

One randomised controlled trial (level II) by Kurd et al (2009) investigated the effectiveness of providing prognostic data to clinicians compared to standard care in treating diabetic foot ulcers (Table 106). A total of 74 wound care centres in the USA, involving 1810 patients with diabetic neuropathic foot ulcers that attended these centres, were randomised into four groups to receive different prognostic information derived from the electronic database from Curative Health Services, which was common to all of the participating wound care centres. The centres were partially blinded in that, although they knew that they might receive different information from usual, they did not know different centres received different information. The centres received baseline prognostic information, week 4 prognostic information, both baseline and week 4 prognostic information, or no prognostic information, without receiving any guidance or educational information about prognostic models. The baseline prognostic algorithm for diabetic foot ulcer was based on wound duration, wound size and anatomic depth (or grade) of ulcer, and the week 4 prognostic algorithm was based on per cent change in area, log healing rate, and log area ratio.

There were no statistically significant differences in the rate of ulcer healing by week 20 among the centres receiving baseline prognostic information, both baseline and week 4 prognostic information, and no prognostic information. However, there was a statistically significant higher ulcer healing rate in centres receiving week 4 prognostic information compared to those receiving no prognostic information, after adjusting for age, gender, ulcer area and ulcer duration (adjusted OR = 1.50 [95% CI 1.05, 2.14]). Eleven patients would need to be treated in centres receiving week 4 prognostic information, instead of in those receiving no prognostic information, for one ulcer to heal (NNT = 11 [95% CI 6, 39]). The authors were uncertain about the reason for the difference in outcomes for the centres that received week 4 prognostic information and those that received both baseline and week 4 prognostic information. They suggested that this may be due to disregarding the second report because care had already been based on baseline data or may be related to not receiving any guidance on the use of prognostic information.

Box 150 Evidence statement matrix for providing prognostic data versus standard care

Component	Rating	Description
Evidence base	C	One level II study with a moderate risk of bias.
Consistency	N/A	Only one study
Clinical impact	C	Moderate clinical impact. There was a statistically significant difference for the rate of ulcers healed between centres receiving week 4 prognostic information and those receiving none.
Generalisability	A	Population consisted of diabetic patients with a neuropathic foot ulcer.
Applicability	C	The study was conducted in the USA, which has similar healthcare for diabetes patients compared to the Australian healthcare context.

Evidence statement

There is some evidence to suggest that supplying week 4 prognostic algorithms to treatment centres increases the rate of neuropathic foot ulcers that heal compared to supplying no prognostic algorithms (Grade C).

Table 106 Study which evaluated the effectiveness of providing prognostic data for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Kurd et al 2009) USA	Level II randomised controlled trial Average quality study	N = 74 centres; N = 1810 patients with diabetic neuropathic foot ulcers that attended participating centres. Intervention group 1: N= 19 centres; N = 424 patients; age (yrs) 64.1 ± 14.3; males 230/424 (54.2%); ulcer area (cm^2) 4.9 ± 13.4; duration of ulcer (months) 4.3 ± 15.2; wound grade > 2 84/424 (19.8%). Intervention group 2: N= 17 centres; N = 366 patients; age (yrs) 63.0 ± 14.2; males 211/366 (57.6%); ulcer area (cm^2) 6.8 ± 22.7; duration of ulcer (months) 4.0 ± 15.6; wound grade > 2 86/366 (23.5%). Intervention group 3: N= 18 centres; N = 499 patients; age (yrs) 63.1 ± 14.4; males 251/499 (50.5%); ulcer area (cm^2) 6.4 ± 28.7; duration of ulcer (months) 6.7 ± 16.1; wound grade > 2 96/499 (19.2%). Comparator group: N= 20 centres; N = 521 patients; age (yrs) 61.6 ± 14.1; males 281/521 (53.9%); ulcer area (cm^2) 6.2 ± 33.8; duration of ulcer (months) 3.2 ± 11.7; wound grade > 2 101/521 (19.4%).	Provision of prognostic information by using the electronic database from Curative Health Services, that was common to all of the participating wound care centres. Group 1 N= 19 centres N = 424 patients Received baseline prognosis information Group 2 N= 17 centres N = 366 patients Received week 4 prognosis information Group 3 N= 18 centres N = 499 patients Received both baseline and week 4 prognosis information	N= 20 centres N = 521 patients No prognostic information provided. Baseline algorithm based on wound duration wound size and anatomic depth (or grade) of ulcer. Week 4 algorithm based on % change in area, log healing rate, and log area ratio.	Number of ulcers healed by week 20 Group 1 221/424 (52.1%)	255/521 (48.9%)	OR = 1.14 [95% CI 0.81, 1.58] OR* = 1.18 [95% CI 0.80, 1.73] RR = 1.07 [95% CI 0.94, 1.21]
					Group 2 213/366 (58.2%)		OR = 1.45 [95% CI 1.04, 2.02] OR* = 1.50 [95% CI 1.05, 2.14] RR = 1.19 [95% CI 1.05, 1.34] NNT = 11 [95% CI 6, 39]
					Group 3 265/499 (53.1%)		OR = 1.18 [95% CI 0.81, 1.58] OR* = 1.18 [95% CI 0.85, 1.63] RR = 1.09 [95% CI 0.96, 1.22]

RR = relative risk; CI = confidence interval; NNT = number needed to treat; OR = odds ratio; OR* = odds ratio adjusted for age, gender, ulcer area and ulcer duration; Wound grade = a progressive scale used in the Curative Health Services as described by: wound grade I, a partial thickness wound involving only dermis and epidermis; wound grade 2, a full thickness wound that may extend into subcutaneous tissues; wound grade 3, all those that have exposed tendons, ligament and/or joint; wound grade 4, the subset of wound grade 3 that have an abscess and/or osteomyelitis; wound grade .5, the subset of wound grade 3 that are covered by necrotic tissue; and wound grade 6, all wounds that contain gangrene in the wound and surrounding tissue.

Orthotics

Off-loading versus standard wound care

Total contact cast versus traditional dressing treatment

One level II RCT of average quality compared the use of a total contact cast (TCC) with traditional dressing treatment (TDT). Mueller et al (1989) reported that more ulcers healed (χ^2=12.4, p<0.05) and less infections developed (χ^2=4.1, p<0.05) in the TCC group than in the TDT group. Five participants in the TDT group required hospitalisation due to infection and two subsequently required amputations. None of the TCC group were hospitalised during the study period of 6 weeks. The authors recommend changing the cast more frequently in patients with vascular disease, fragile skin or leg oedema and suggest that TCC is contraindicated in patients with severe lower limb oedema, severe vascular disease (with an ankle brachial index < 0.4) or who have active gross infection (≥ grade 3 ulcer).

This evidence is summarised in Box 151 according to NHMRC criteria.

Table 107 Total contact cast versus traditional dressing treatment

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
(Mueller et al 1989) USA	Level II RCT. Average quality study	N = 43 diabetic patients with a current plantar ulcer Intervention group: n=21, age 54 ± 10 years, male 62% (n=13), insulin dependent 24% (n=5), duration of diabetes (yrs) 17 ± 6, ulcer duration (days) 155 ± 195, ulcer size: area (cm^2) 1.8 ± 2.5, depth (mm) 3.6 ± 3.2, Grade (assessment method not stated), I 71% (n=15), II 29% (n=6), sensation (Semmes-Weinstein monofilament): intact 0%, decreased 0%, severely decreased 29% (n=6), absent 71% (n=15), vascular disease: ankle/brachial ratios 0.5-0.99 10% (n=2), ankle/brachial ratios <0.5 0.5% (n=1) Control group: n=22, age 55 ± 12 years, male 74% (n=14), insulin dependent 32% (n=6), duration of diabetes (yrs) 17 ± 9, ulcer duration (days) 175 ± 200, ulcer size: area (cm^2) 2.8 ± 3.4, depth 2.4±0.9, ulcer grade (assessment method not stated) I 68% (n=13), II 32% (n=6), sensation (Semmes-Weinstein monofilament): intact 0%, decreased 5% (n=1), severely decreased 32% (n=6), absent 63% (n=12), vascular disease: ankle/brachial ratios 0.5-0.99 16% (n=3), ankle/brachial ratios <0.5 5% (n=1)	N = 21 Total contact casting (TCC) for off-loading pressure to ulcerated foot and instruction to limit ambulation to ≈33% of usual activity	N = 19 Traditional dressing treatment (TDT) which consisted of dressing changes and accommodative footwear with instructions to limit weight bearing on the involved extremity	**Patients healed** Intervention: 90% (19/21) Control: 32% (6/19) Effect size [95% CI]: RR = 2.9 [1.5, 5.6] **Healing time (days)** Intervention: 42 ± 29 Control: 65 ± 29 Effect size [95% CI]: Mean difference = 23 [4.4, 41.6] **Complications** Intervention Infection: 14.3% (3/21) Control Infection: 26.3% (5/19) Effect size [95% CI]: RR = 0.54 [0.15, 1.97] Amputation: 0% Amputation: 10.5% (2/19) ARR = 0.11 [-0.07, 0.31]

Felted foam dressing versus standard wound care

One level II RCT of average quality compared felted foam dressing with standard wound care (Zimny et al 2003). All participants were given standard wound care which included debridement, antibiotic cover as required and daily wound dressings (Table 108). Pressure relief was provided using a half shoe and wound healing was assessed fortnightly using planimetric measurements. Measured outcomes included healing time (days) and reduction in wound radius (mm). The use of felted foam dressings reduced the time to ulcer healing (75 days (67–84) versus 85 days (79–92), p=0.03) and increased the rate of wound radius reduction per week (0.48mm/week (0.42–0.56) versus 0.39mm/week (0.35–0.42), p=0.005) compared to standard wound dressings. However, a difference of wound radius reduction of less than one tenth of a millimetre each week is of questionable clinical significance.

This evidence is summarised in Box 151 according to NHMRC criteria.

Table 108 Felted foam dressing versus standard wound care

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
(Zimny et al 2003) Germany	Level II RCT. Average quality study	N=54 diabetic patients with neuropathic plantar forefoot ulcer Wagner Grade I or II **Intervention group:** n=24, mean age 62.1 ± 13.0 years, male 54.2% (n=13), BMI 27.4 ± 4.9, duration of diabetes (yrs) 18.2 ± 7.6, type I diabetes 29% (n=7), HbA_{1c} 7.9 ± 0.6%, $TcPO_2$ (kPa) 8.9 ± 1.3, ankle brachial index 1.0 ± 0.1, ulcer localisation metatarsal head I-III 79% (n=19), IV-V 21% (n=5), ulcer area (mm^2) 102.3 ± 45.3, Wagner Grade I 25% (n=6), II 75% (n=18) **Control group:** n=30, mean age 62.1 ± 10.8, male 56.7% (n=17), BMI 28.5 ± 4.3, duration of diabetes (yrs) 22.1 ± 11.8, type I diabetes 43% (n=13), HbA_{1c} 7.5 ± 1.2%, $TcPO_2$ (kPa) 8.7 ± 1.0, ankle brachial index 1.0 ± 0.2, ulcer localisation metatarsal head I-III 80% (n=24), IV-V 20% (n=6), ulcer area (mm^2) 112.5 ± 50.8, Wagner Grade I 23% (n=7), II 77% (n=23)	n=24 Standard wound care including debridement, antibiotics as required, and use of a half shoe. Plus felted foam dressing used to provide pressure relief, rubber foam 0.64cm thick with a layer of felt glued with rubber glue, cut to size of ulcer and wrapped in gauze to hold in place, then covered with saline soaked sponge. Wound changed daily.	n=30 Standard wound care including debridement, antibiotics as required, and use of a half shoe. Wounds were assessed daily and every fortnight healing was assessed using planimetric measurements	Mean wound radius reduction (mm/week)		
					Intervention 0.48 [95% CI 0.42, 0.56]	Control 0.39 95% CI 0.35, 0.42]	p = 0.005
					Time to healing (days)		
					Intervention 75.2 [95% CI 67, 84]	Control 85.2 [95% CI 79, 92]	p = 0.03

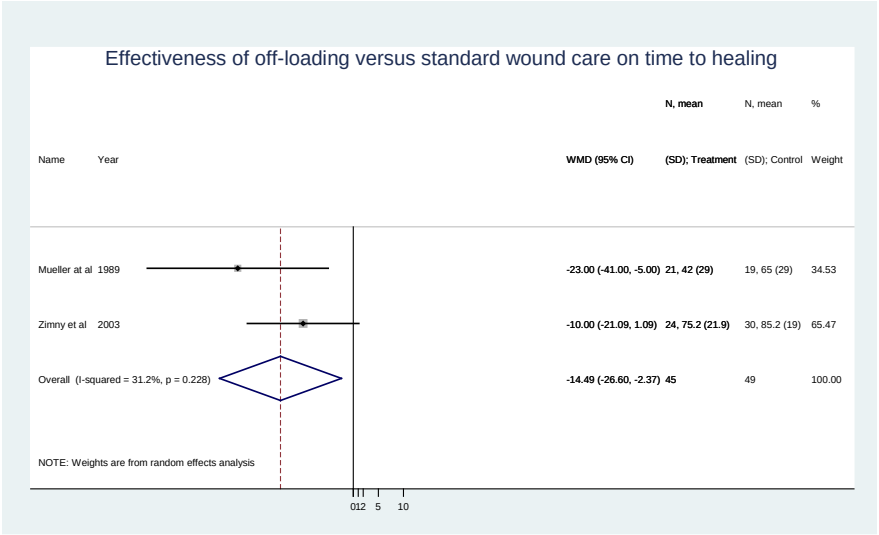
Meta-analysis of off-loading interventions indicates that there is a statistically significant difference in time to healing compared to standard wound care (Figure 13). Although only two studies were included in the analysis, it is apparent that there is a significant reduction of 14.5 days with the addition of off-loading to standard wound care.

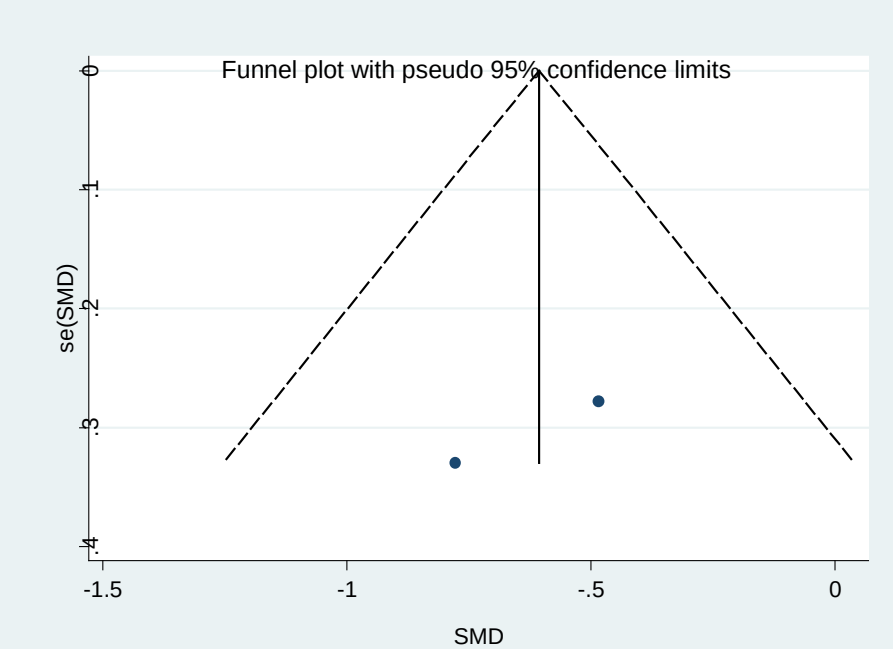
Figure 12 Meta-analysis of off-loading interventions versus standard wound care

```
           Study     |     WMD   [95% Conf. Interval]     % Weight
---------------------+-------------------------------------------------
Mueller at al        |-23.000     -40.997    -5.003         34.53
Zimny et al          |-10.000     -21.090     1.090         65.47
---------------------+-------------------------------------------------
D+L pooled WMD       |-14.489     -26.603    -2.374        100.00
---------------------+-------------------------------------------------

  Heterogeneity chi-squared =   1.45 (d.f. = 1) p = 0.228
  I-squared (variation in WMD attributable to heterogeneity) =  31.2%
  Estimate of between-study variance Tau-squared = 26.3361

  Test of WMD=0 : z=   2.34 p = 0.019
```





Box 151 Evidence statement matrix for off-loading versus standard wound care

Component	Rating	Description
Evidence base	B	Two average quality level II RCTs with moderate risk of bias.
Consistency	B	Although one study did not detect a statistically significant difference in time to healing, both studies reported that the intervention group healed quicker than the standard wound care groups.
Clinical impact	C	With a weighted mean difference of 14.5 days the reduction in time to healing with off-loading would provide a moderate clinical impact.
Generalisability	B	Evidence directly generalisable to target population of diabetic patients with chronic foot ulcers
Applicability	B	Evidence applicable to the Australian healthcare context with few caveats

Evidence statement:

There is evidence to suggest that off-loading interventions in addition to standard wound care will significantly reduce the time to healing relative to standard wound care alone in people with diabetic plantar foot ulcers (Grade B).

Comparison of off-loading interventions

Total contact cast versus removable cast walker

Two average quality RCTs compared Total Contact Cast (TCC) versus Removable Cast Walker (RCW) for the treatment of diabetic foot ulcers (Table 109). Armstrong et al (2005) devised an 'instant' TCC and compared it with a standard RCW. Initial findings suggest there was a significant benefit for the number of ulcers healed using an iTCC (82.6%, 19/23) compared to the control group using a RCW (51.9%, 14/27, RR=1.59, 95% CI [1.07, 2.12], p = 0.04). In addition, the difference in time to healing between the two groups was significant (41.6 ± 18.7 days for the intervention group versus 58.0 ± 15.2 days for the control group, p = 0.02). However the participants in the intervention group also had a statistically significant higher occurrence of peri-wound maceration (68.2%, 15/23) than participants in the control group (37.5%, 9/27) (RR = 1.96, 95% CI [1.09, 3.43], p = 0.05). In an earlier study by Armstrong et al (2001), TCC was compared with RCW to identify improvements in number of ulcers healed and

time to heal. Findings suggest that the use of TCC is superior to the use of RCW however positive trends did not reach statistical significance.

Although positive trends did not reach statistical significance in several of the studies, advantages of using an RCW have been identified. A cast that can be removed to allow wound assessment and inspection improves patient care and reduces cost and inconvenience for the patient. Rather than having the whole cast removed and replaced at each assessment it can simply be reapplied after inspection by the health professional. Financial saving such as plaster technician's time to put on new cast and equipment cost of materials are also significantly reduced when a cast can be easily reused.

These studies have been included in meta-analyasis of data regarding the comparison of non-removable devices, including instant total contact casts, with removable off-loading devices (Figure 13).

Box 152 Evidence statement matrix for total contact cast versus removable cast walker

Component	Rating	Description
Evidence base	B	Two average quality level II RCTs with low risk of bias
Consistency	B	Most studies are consistent in their findings and any inconsistency can be explained
Clinical impact	D	Slight clinical impact in relation to number of ulcers healed and time to heal however positive trends did not always reach statistical significance
Generalisability	C	Likely generalisable to the population of diabetic patients with chronic foot ulcers
Applicability	B	Although studies were from the USA and Italy, evidence is probably applicable to the Australian healthcare context with some caveats

Evidence statement

Evidence suggests that use of a total contact cast versus removable cast walker shows a positive trend towards improving clinical outcomes for patients with chronic diabetic foot ulcers in relation to number of ulcers healed and time to heal. Findings however did not always reach clinical significance (Grade B).

Table 109 Total contact cast versus removable cast walker

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
(Armstrong et al 2005b) USA	Level II RCT. Average quality study	n=50 diabetic patients with a neuropathic plantar ulcer at least Grade 1A (University of Texas Diabetic Foot Wound Classification System). Intervention group: n=23, age 66.9±10.1 years, male 87% (n=20), BMI (kg/m^2) 33.3 ± 6.8, wound area 2.7 ± 1.3, vibration perception threshold 37±8.1 volts, HbA_{1c} 8.5 ± 1.5%. Control group: n=27, age 64.6±9.8 years, male 89% (n=24), BMI (kg/m^2) 33.5 ± 6.2, wound area 2 ± 1.1cm^2, vibration perception threshold 37.3 ± 7 volts, HbA_{1c} 8 ± 1.4%.	n=23 Standard wound care including inspection and debridement weekly. Plus treatment with a removable cast walker wrapped with a cohesive bandage rendering it irremovable by the patient thereby becoming an iTCC ('Instant' total contact cast).	n=27 Standard wound care including inspection and debridement weekly. Plus use of a removable cast walker.	Patients healed		
					Intervention 82.6% (19/23)	Control 51.9% (14/27	Effect size [95% CI] RR=1.59 [1.07, 2.12] p=0.04
					Ulcer healing time (days)		
					Intervention 41.6 ± 18.7	Control 58.0 ± 15.2	p=0.02
(Armstrong et al 2001), USA	Level II RCT. Average quality study	n=39 diabetic patients with a neuropathic plantar ulcer at least Grade 1A (University of Texas Diabetic Foot Wound Classification System). Intervention group: n=19, male 74% (n=14), duration of diabetes (yrs) 17.8 ± 8.7, $TcPO_2$ 60.7 ± 9.0, ulcer area 1.3 ± 0.8 cm^2, ulcer duration 4.3 ± 5.7 months, vibration perception threshold 41.5 ± 10.5 volts. Control group: n=20, 90% (n=18) male, duration of diabetes (yrs) 18.2±10.1, $TcPO_2$ 62.0±16.3, ulcer area 1.4±1.4cm^2, ulcer duration 5.6±6.2 months, VPT 46.7±4.8 volts.	n=19 Standard wound care including weekly inspection, debridement and measuring of wound. Participants wore a pedometer to measure number of steps and a total contact cast (TCC). These were changed weekly or as necessary.	n=20 Standard wound care including weekly inspection, debridement and measuring of wound. Participants wore a pedometer to measure number of steps and a removable cast walker (RCW) and were instructed to use it whenever ambulant.	Proportion of patients with ulcer healed		
					Intervention 89.5% (17/19)	Control 65% (13/20)	Effect size [95% CI] RR=1.38 [0.98, 1.67] p=0.13
					Healing time (days)		
					Intervention 33.5 ± 5.9	Control 50.4 ± 7.2	p=0.07

iTCC=instant total contact cast; RCW=removable cast walker; TCC=total contact cast; University of Texas Diabetic Foot Wound Classification System= 01. A0 Pre – or post ulcerative lesion completely epithelialised, 02. A1 superficial wound not involving tendon, capsule or bone, 03. A2 wound penetrating to tendon or capsule, 04. A3 wound penetrating to bone or joint, 05. B0 pre or post ulcerative lesion completely epithelialised with infection, 06. B1 superficial wound, not involving tendon, capsule or bone with infection, 07. B2 wound penetrating to tendon or capsule with infection, 08. B3 wound penetrating to bone or joint with infection, 09. C0 pre or post ulcerative lesion completely epithelialised with ischaemia, 10. C1 superficial wound not involving tendon, capsule or bone with ischaemia, 11. C2 wound penetrating to tendon or capsule with ischaemia, 12. C3 wound penetrating to bone or joint with ischaemia, 13. D0 pre or post ulcerative lesion completely epithelialised with infection and ischaemia, 14. D1 superficial wound not involving tendon, capsule or bone with infection and ischaemia, 15. D2 wound penetrating to tendon or capsule with infection and ischaemia, 16. D3 wound penetrating to bone or joint with infection and ischaemia; VPT=vibration perception threshold

Total contact cast versus instant total contact cast

Two average quality studies provided evidence regarding the comparison of total contact casts and instant total contact casts (Table 110)

Katz et al (2005) reported on the number of ulcers healed and median time to healing when the use of RCW which was rendered irremovable by fibreglass casting material (iTCC) was compared to a standard TCC. Although there is some uncertainty regarding the reporting of the data as continous outcomes, findings suggest that the use of an 'instant' TCC is comparable in terms of healing time and number of ulcers healed but is less expensive and easier to apply. Further, the number of complications were reduced using the iTCC although this positive trend did not reach statistical significance (p=0.09).

Piagessi et al (2007) also compared an instant contact cast called the Optima Diab Molliter which was rendered immovable by the use of a plastic lace. Healing rate and median healing time of ulcers were comparable to the use of a TCC but statistical significance was not reached for either outcome (healing rate at 12 weeks, RR=0.89 [0.82, 1.09]).

No meta-analysis of these data was performed as a result of the reporting of proportion of ulcers healed as a continuous outcome by Katz et al (2005).

This evidence has been summarised in Box 153 according to NHMRC criteria.

Box 153 Evidence statement matrix for total contact cast versus instant total contact casts

Component	Rating	Description
Evidence base	C	Two average quality level II RCTs with moderate risk of bias
Consistency	B	Most studies are consistent in their findings and any inconsistency can be explained
Clinical impact	D	No statistically significant difference was detected for ulcer healing and healing time.
Generalisability	B	Likely generalisable to the population of diabetic patients with chronic foot ulcers
Applicability	B	Although studies were from the USA and Italy, evidence is probably applicable to the Australian healthcare context with some caveats

Evidence statement

There was no evidence to suggest that there were any differences in the proportion of ulcers which healed, or the healing time of ulcers between total contact casts and instant total contact casts in patients with diabetic foot ulcers (Grade C).

Table 110 Instant total contact cast versus total contact cast walker

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data iTCC	Effect size [95% CI} TCC
(Katz et al 2005) USA	Level II RCT. Average quality study	n=41 diabetic patients with a chronic Grade 1A or IIA ulcer (University of Texas Diabetic Foot Wound Classification System) for at least 7 days. Intervention group: n=21, age 50.7 (29-65) years, male 71% (n=15), race: white 14% (n=3), black 29% (n=6), Hispanic 62% (n=13), type II diabetes 95% (n=20), duration of diabetes (yrs) 14 (5-33), current smoker 14% (n=3), ever smoked 52% (n=11), insulin use 38% (n=8), neuropathy disability score 9.2 (7-10), vibration perception threshold 47 (44-51) volts, ulcer surface area (median, 1st and 3rd quartile) 3.1 (1.6, 0.9-3.4) cm^2, ulcer duration (median, 1st and 3rd quartile) 228 (55, 14-260) days. Control group: n=20, age 51 (23-65) years, male 65% (n=14), race: white 10% (n=2), black 40% (n=8), Hispanic 60% (n=12), type II diabetes 90% (n=18), duration of diabetes (yrs) 14.3 (2-27), current smoker 10% (n=2), ever smoked 35% (n=7), insulin use 55% (n=11), neuropathy disability score 9.2 (6-10), vibration perception threshold 45 (41-48) volts, ulcer surface area (median, 1st and 3rd quartile) 2.9 (1.9, 0.9-3.9), ulcer duration (median, 1st and 3rd quartile) 202 (76, 19-263) days.	n=21 Removable cast walker rendered irremovable by fibreglass casting material (iTCC).	n=20 Standard total contact cast	Proportion of ulcers healed: 80 ± 41% Median time to healing (1st and 3rd quartile) 4 weeks (3–7) Adverse events iTCC: 38% complications (after removing maceration from the results only 13% had complications) TCC: 54% complications (after removing maceration from the results 46% had complications) Relative risk reduction = 41% Absolute risk reduction = 27% [-4.3, 58]	74 ± 45% p = 0.7 5 weeks (3–7) p = 0.09

(Piaggesi et al 2007) Italy	Level II RCT. Average quality study	n=20 diabetic patients with a plantar ulcer of minimum 3 week duration with area >1 cm^2 and graded 1A or 2A (University of Texas Diabetic Foot Wound Classification System). Intervention group: n=20, age 61.1 ± 6.4 years, duration of diabetes (yrs) 13.4 ± 7.5, HbA_{1c} 7.6 ± 0.9%, vibration perception threshold 39.1±8.6 volts, area of foot lesions 3.9±1.8cm^2. Control group: n=20, age 59.8±8.2 years, duration of diabetes (yrs) 14.7 ± 11.1, HbA_{1c} 7.9 ± 1.1%, vibration perception threshold 36.8 ± 7.4 volts, area of foot lesions 3.7 ± 1.6 cm.	n=20 Optima Diab Molliter Walker, an instant contact casting device for off-loading pressure which is secured to make it non-removable by using a specialized plastic lace. Can be removed and repositioned at check-ups by using a new lace.	n=20 Conventional fibreglass total contact casting device. Repositioning is not possible and removal is necessary for check-ups using a oscillating saw.	Healing rate at 12 weeks: 17/20 (85%) 19/20 (95%) RR = 0.89 [0.82, 1.09] Healing time 6.7 ± 3.4 weks 6.5 ± 4.4 weeks Mean difference = 0.2 [-2.72, 2.32] p = 0.87

Non-removable cast versus half shoe

Three studies (2 level II RCTs and 1 prospective non-randomised study) all of average quality compared the use of non removable total contact casts with the use of a half shoe (Table 111).

In one RCT, Armstrong et al (2001) reported that ulcers are more likely to heal by 12 weeks in patients using a non-removable cast compared to those using a half shoe (89.5% versus 58.3%, RR = 3.29 [1.13, 12.14]) and the time taken for ulcers to heal (amongst ulcers that healed by 12 weeks) was significantly less (33.5 ± 5.9 days versus 61.0 ± 6.5 days, p = 0.005).

In another RCT, Van De Weg et al (2008) reported that time to healing was shorter for the patients using a non-removable cast compared with a custom made temporary shoe (59 days versus 90 days) however the differences were not statistically significant (p = 0.11). After adjustment for differences in baseline values, wound surface area reduction at 16 weeks was not different in the two groups (difference in wound surface area reduction in the TCC group versus the custom made shoe group was 0.10cm^2 [95% CI -0.92, 0.72]).

In a prospective, non-randomised study, Ha Van et al (2003) reported that the healing time of ulcers in patients using a non-removable cast was almost half that of patients using a half shoe (68.6 ± 35.1 days versus 134.2 ± 133.0 days, p = 0.02). Participants using the non-removable cast were less likely to develop secondary osteomyelitis compared with those using the half shoe (RR = 0.37 [95% CI 0.013, 0.88], p = 0.03). Understandably, compliance amongst patients using the non-removable cast was significantly greater than that of the half shoe group (97.6% versus 41.1%, p = 0.001). Five patients using non-removable casts developed a new ulcer during the study period compared with no patients in the half shoe group.

Ha Van et al (2003) postulated that one likely explanation for the observed improved outcomes in patients with non-removable casts compared with those using half shoes was that the study is confounded by treatment compliance. Patients with a non-removable cast are (largely) unable to remove it. No outcomes in compliant half shoe patients were reported to verify this hypothesis.

Box 154 Evidence statement matrix for non-removable cast versus half shoe

Component	Rating	Description
Evidence base	C	Two level II RCTS and one level III-2 prospective non randomized study all of average quality with moderate risk of bias
Consistency	B	Most studies are consistent and any inconsistencies can be explained
Clinical impact	B	Substantial clinical impact in relation to time to healing of ulcers, number of ulcers healed and reduction in secondary infections
Generalisability	B	Evidence directly generalisable to target population of diabetic patients with chronic foot ulcers
Applicability	C	Studies were from the USA, Netherlands and France which although not the same as the Australian healthcare context are probably applicable with some caveats

Evidence statement:

The use of a non-removable cast is effective in increasing the likelihood that an ulcer heals, reducing the time it takes for an ulcer to heal and decreasing the risk of developing osteomyelitis compared to the use of a half shoe in patients with foot ulcers (Grade C).

Table 111 Non-removable cast versus half shoe

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
(Armstrong et al 2001) USA	Level II RCT. Average quality study	N = 43, diabetic patients with loss of protective sensation (>25 volts) using a vibration perception threshold (VPT) meter, at least one palpable foot pulse and a plantar ulcer corresponding to 1A on the University of Texas Diabetic Foot Wound Classification System Intervention group: n = 19, male 73.7% (n = 19), duration of diabetes (yrs) 17.8 ± 8.7, $TcPO_2$ 60.7 ± 9.0, ulcer area (cm^2) 1.3 ± 0.8, ulcer duration (months) 4.3 ± 5.7, VPT (volts) 41.5 ± 10.5 Control group: n=24, male 83.3% (n=20), duration of diabetes (yrs) 15.3±7.9, $TcPO_2$ 58.6±10.4, ulcer area (cm^2) 1.3±1.2, ulcer duration (months) 5.5±7.1, VPT (volts) 45.4±7.7	N = 19 Standard wound care including weekly inspection, debridement and measuring of wound. Participants wore a pedometer to measure number of steps and a non-removable total contact cast (TCC). These were changed weekly or as necessary	N = 24 Standard wound care including weekly inspection, debridement and measuring of wound. Participants wore a pedometer to measure number of steps and use a half shoe whenever ambulant	Proportion of patients with ulcer healing at 12 weeks Intervention: 89.5% (17/19) | Control: 58.3% (14/24) | Effect size [95% CI]: RR = 3.29 [1.13, 12.14] Healing time (days) amongst ulcers healed by 12 weeks Intervention: 33.5 ± 5.9 | Control: 61.0 ± 6.5 | p = 0.005
(Van De Weg et al 2008) Netherlands	Level II RCT. Average quality study	N = 43 diabetic patients with sensory neuropathy and a plantar ulcer of Wagner Grade I or II Intervention group: n = 23, mean age 64.8 ± 10.8 years, male 68% (n = 16), duration of diabetes (yrs) 12 (IQR 6.20), HbA_{1c} 7.8 ± 0.3%, ankle arm index 0.69 ± 0.25, antibiotics 41% (n = 9), duration of ulcer (weeks) 4 (IQR 3, 8), mean wound surface area (cm^2) 4.2 ± 3.1, Wagner grade I 9% (n = 2), II 91% (n = 21), forefoot location 87% (n = 20) Control group: n = 20, mean age 58.1 ± 11.1 years, male 90% (n = 18), duration of diabetes (yrs) 12 (IQR 7.17), HbA_{1c} 8.7 ± 2.2%, ankle arm index 0.65 ± 0.21, antibiotics 45% (n = 9), duration of ulcer (weeks) 5 (IQR 4,8), mean wound surface area (cm^2) 3.0 ± 3.1, ulcer grade I 10% (n = 2), II 90% (n = 18), forefoot location 90% (n = 18)	N = 23 Debridement of wound then aquacell wound dressing applied. Adhesive foam used over bony prominences. A well moulded cast which maintained contact with the planar aspect was applied then a cast shoe with a polyplastic rocker added. Cast changed weekly for duration of study up to 16 weeks	N = 20 Same wound care as for intervention plus a custom made felt shoe was supplied with a rigid leather socket stiffened with Rhenoflex. Insoles were made of cork and a plastazote covering. Patients were instructed to wear them whenever ambulating	Number of patients healed by 16 weeks Intervention: 6/23 (26.1%) | Control: 6/20 (30%) | p = 0.775 (Chi Square) Time to healing (days) of healed ulcers Intervention: 59 ± 39 | Control: 90 ± 12 | p = 0.11 (t-test) Mean size of unhealed ulcers (cm^2) at baseline and 16 weeks Intervention: Baseline 4.2 ± 3.1, 16 weeks 1.5 ± 1.6 | Control: Baseline 3.0 ± 3.1, 16 weeks 1.1 ± 1.2 Average % reduction in ulcer size at 16 weeks Intervention | Control

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
					35.7% | 36.7%
(Ha Van et al 2003) France	Level III-2 prospective non-randomised average quality study	N = 93 diabetic patients with neuropathy and a University of Texas Grade 1A plantar ulcer Intervention group: n = 42, mean age 58 ± 11 years, male 90.5% (n = 38), duration of diabetes (yrs) 17 ± 11, type I diabetes 14.3% (n = 6), BMI 28.55 ± 3.42, retinopathy 74% (n = 31), peripheral arterial disease 55% (n = 23), neuropathy 100%, HbA_{1c} 7.85 ± 2.7%, creatinine (µmo/l) 119 ± 205, duration of ulcer (days) 395 ± 560, duration > 6 months 48% (n = 20), ulcers size (mm): length 20.43 ± 12.06, width 13.8 ± 7.71, depth 5.42 ± 5.35, under forefoot 83% (n = 35), under midfoot (Charcot) 10% (n = 4), under hindfoot 7% (n = 3) Control group: n = 51, mean age 62 ± 7 years, male 78.4% (n = 40), duration of diabetes (yrs) 15 ± 10, type I diabetes 23.5% (n = 12), BMI 29.06 ± 4.76, retinopathy 73% (n = 37), peripheral arterial disease 43% (n = 22), neuropathy 96% (n = 49), HbA_{1c} 8.18 ± 1.6%, creatinine (µmo/l) 163 ± 200, duration of ulcer (days) 134 ± 272, duration > 6 months 18% (n= 9), ulcer size (mm): length 15.61 ± 12.31, width 10.21 ± 9.12, depth 3.37 ± 3.16, under forefoot 96% (n = 49), under midfoot (Charcot) 0%, under hindfoot 4% (n = 2)	N = 42 Standard wound care plus off-loading by a non-removable fibreglass cast boot with a window cut over the ulcer. Daily care at home by nurse (cleaning with saline, petroleum jelly saturated gauze), fortnightly clinic examinations for monitoring and wound debridement	N = 51 Standard wound care plus off-loading with either the Barouk half shoe for patients with ulcers under the forefoot or the Sanital heel-relief shoe for patients with ulcers under the hindfoot. Daily care and clinic examinations as for intervention group	Mean time to healing (days) Intervention 68.6 ± 35.1 | Control 134.2 ± 133.0 | p = 0.02 Number of ulcers healed Intervention 34/42 (80.9%) | Control 36/51 (70.6%) | Age adjusted hazard ratio healing (cast boot) = 1.68 [95% CI 1.04, 2.7] Secondary osteomyelitis Intervention 3/42 (7%) | Control 13/51 (25%) | Effect size [95% CI] RR = 0.37 [0.013, 0.88] p = 0.03

IQR = interquartile range; University of Texas Diabetic Foot Wound Classification System = University of Texas Diabetic Foot Wound Classification System = 01. A0 Pre – or post ulcerative lesion completely epithelialised, 02. A1 superficial wound not involving tendon, capsule or bone, 03. A2 wound penetrating to tendon or capsule, 04. A3 wound penetrating to bone or joint, 05. B0 pre or post ulcerative lesion completely epithelialised with infection, 06. B1 superficial wound, not involving tendon, capsule or bone with infection, 07. B2 wound penetrating to tendon or capsule with infection, 08. B3 wound penetrating to bone or joint with infection, 09. C0 pre or post ulcerative lesion completely epithelialised with ischaemia, 10. C1 superficial wound not involving tendon, capsule or bone with ischaemia, 11. C2 wound penetrating to tendon or capsule with ischaemia, 12. C3 wound penetrating to bone or joint with ischaemia, 13. D0 pre or post ulcerative lesion completely epithelialised with infection and ischaemia, 14. D1 superficial wound not involving tendon, capsule or bone with infection and ischaemia, 15. D2 wound penetrating to tendon or capsule with infection and ischaemia, 16. D3 wound penetrating to bone or joint with infection and ischaemia; VPT = Vibration Perception Threshold; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot.

Non-removable cast versus therapeutic shoe

One average quality, level II RCT compared the use of a non-removable cast and a specially designed therapeutic shoe for the treatment of chronic diabetic foot ulcers (Table 112). Caravaggi et al (2000) used two types of bandages in construction of the non-removable cast. One provided flexibility and resistance (Softcast 3M) while the other providing higher resistance and off-loading (Scotchcast 3M). The cloth shoe had a rocker-bottom sole with a cushioned insole with an area of off-loading in the area around the ulcer. After 30 days of treatment, 8.3% (n = 2) of the therapeutic shoe group had an increase in ulcer size while no participants in the non-removable cast group experienced an increase in ulcer size. Patients treated with a non-removable cast with 100% reduction in surface area at 30 days was 50% (n =13) versus 21% (n = 5) amongst patients treated with a therapeutic shoe ($\chi^2 = 4.61$, p=0.03). Patients treated with a non-removable cast experienced a more rapid reduction of ulcer size than patients treated with a therapeutic shoe ($z = 3.53$, p = 0.0004). The authors do not state whether complete healing had occurred, only that the surface area had been reduced.

No adverse effects were reported by either group and the treatment was well accepted by participants in both groups (91.15 ± 9.9 in the therapeutic shoe group versus 88.33 ± 17.3 in the non-removable cast group, as measured by a visual analogue scale after the study). Caravaggi et al (2000) postulates that the use of fibreglass bandages to create the non-removable cast may reduce the side effects of friction associated with heavier casts which can lead to new ulcers developing.

Box 155 Evidence statement matrix for non-removable cast versus therapeutic shoe

Component	Rating	Description
Evidence base	C	One level II RCT with moderate risk of bias
Consistency	N/A	Only one study
Clinical impact	C	Moderate clinical impact in relation to reduction of surface area of ulcer
Generalisability	B	Evidence generalisable to the target population of diabetic patients with chronic foot ulcers
Applicability	C	The study was conducted in Italy which although not the same as the Australian healthcare context is probably applicable

Evidence statement:

Non-removable casts are moderately effective in reducing the surface area of ulcers at a faster rate compared to therapeutic shoes (Grade C).

Table 112 Non-removable cast versus therapeutic shoe

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
(Caravaggi et al 2000) Italy	Level II RCT. Average quality study	N = 50 diabetic patients with a neuropathic plantar ulcer and insensitivity to Semmes-Weinstein 5.07 monofilament, vibration perception threshold of 25 volts measured at the malleolus with a biothesiometer **Intervention group:** n = 26, age 60.5 ± 10.7 years, male 69% (n = 18), insulin 50% (n = 13), duration of diabetes (yrs) 17.3 ± 10.7, prior lesion 38% (n = 10), BMI (kg/m^2) 27 ± 1.6, smoking 19% (n = 5), hypertension 50% (n = 13), retinopathy 54% (n = 14), microalbuminuria 15% (n = 4), proteinuria 19% (n = 5), renal impairment 19% (n = 5), ankle brachial index 1.00 ± 0.7, transcutaneous oxygen tension on dorsum of foot 53.5 ± 12.6 **Control group:** n = 24, age 59.2 ± 9.9 years, male 67% (n = 16), insulin 50% (n = 12), duration of diabetes (yrs) 16.2 ± 9.1, prior lesion 38% (n = 9), BMI (kg/m^2) 27.3 ± 2.5, smoking 42% (n = 10), hypertension 46% (n = 11), retinopathy 54% (n = 13), microalbuminuria 16% (n = 4), proteinuria 13% (n = 3), renal impairment 8% (n = 2), ankle brachial index 1.03 ± 0.8, transcutaneous oxygen tension on dorsum of foot 52.6 ± 11.6	N = 26 All participants received standard wound care including debridement as necessary, medication with a paraffin gauze dressing and dressings changed every 2 days. Wounds were assessed at weekly clinic visits. Plus use of a non-removable off-bearing fibreglass cast with a window directly above the ulcer to allow examination and dressing of the ulcer	N = 24 Standard wound care including debridement as necessary, medication with paraffin gauze dressing and dressings changed every 2 days. Wounds were assessed at weekly clinic visits. Plus use of a specialised cloth shoe with a rigid sole and an unloading alkaform insole area around the ulcer	**Trend in ulcer area reduction (quintiles)** Intervention / Control 1.00: 50% (n = 13) / 20.8% (n = 5) 0.75: 26.9% (n = 7) / 12.5% (n = 3) 0.50: 19.2% (n = 5) / 25% (n = 6) 0.25: 3.8% (n = 1) / 8.3% (n = 2) 0.00: 0 / 25% (n = 6) -0.25: 0 / 8.3% (n = 2) **Effect size for percentage of healing of the ulcer surface [95% CI]** RR = 2.4 [1.07, 5.76]

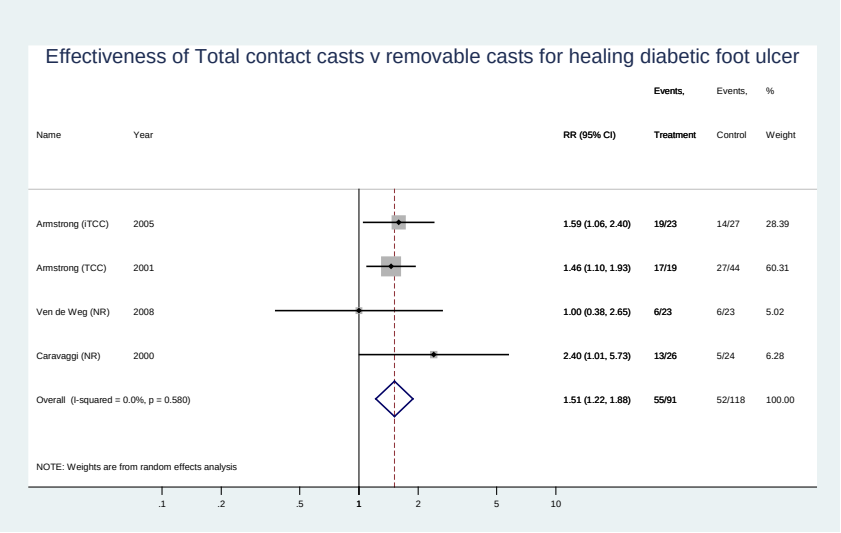
Meta-analysis of appropriate RCTs which compared non-removable devices, including instant total contact casts, with removable off-loading devices suggests that non-removable off-loading devices are more effective at achieving complete healing of diabetic foot ulcers than removable devices (RR = 1.51 [95% CI 1.22, 1.88]) (Figure 13). Despite the different devices included in the analysis, the reasonable measure for heterogeneity provides support that pooling of these data is appropriate. The results of this meta-analysis are summarised in Box 156 according to NHMRC criteria.

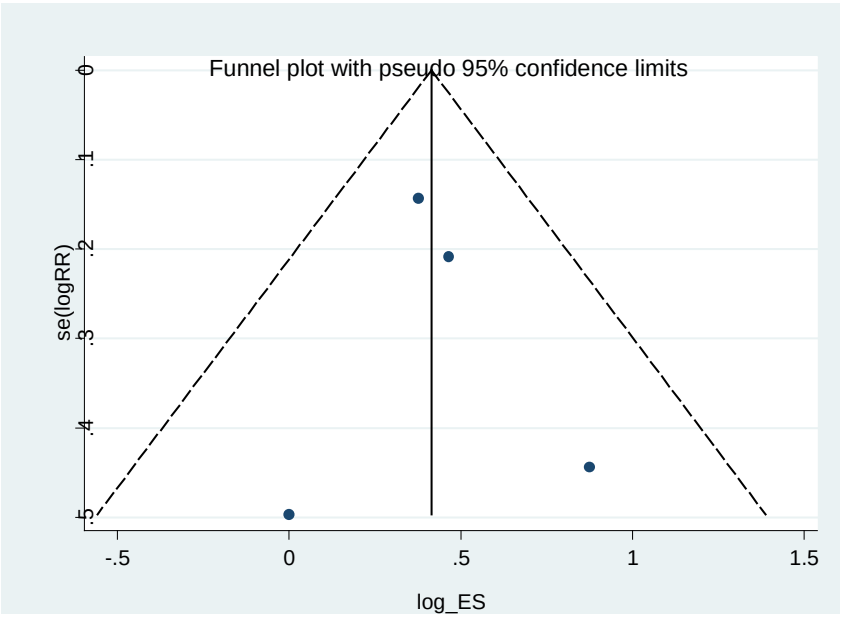
Figure 13 Meta-analysis of non-removable casts versus removable casts for ulcer healing

Study	RR	[95% Conf.	Interval]	% Weight
Armstrong (iTCC)	1.593	1.058	2.398	28.39
Armstrong (TCC)	1.458	1.101	1.930	60.31
Ven de Weg (NR)	1.000	0.378	2.645	5.02
Caravaggi (NR)	2.400	1.006	5.726	6.28
D+L pooled RR	1.514	1.217	1.882	100.00

Heterogeneity chi-squared = 1.96 (d.f. = 3) p = 0.580
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000

Test of RR=1 : z= 3.73 p = 0.000





Box 156 Evidence statement matrix for non-removable casts versus removable casts

Component	Rating	Description
Evidence base	C	Four level II RCTs with moderate risk of bias
Consistency	B	Most studies consistent and inconsistency may be explained.
Clinical impact	C	Moderate clinical impact in relation to ulcer healing.
Generalisability	B	Evidence generalisable to the target population of diabetic patients with chronic foot ulcers
Applicability	B	The studies were conducted in a number of countries in Europe and also in the USA suggesting that these results are applicable to the Australian healthcare context with few caveats.

Evidence statement:

Non-removable off-loading devices are more effective for ulcer healing in patients with diabetic plantar foot ulcers with regard to complete ulcer healing compared with removable off-loading devices (Grade C).

Topical treatments

Topical treatment with zinc hyaluronic acid versus standard wound care

One average and one poor quality level II studies considered the use of zinc hyaluronic acid as a topical treatment for diabetes foot ulcer and reported outcomes on ulcer healing and time to heal (Table 70).

The average quality study by Tankova et al (2002) reported that only one of the two measured outcomes reached statistical significance. No clinically relevant difference in the proportion of healed ulcer (for neuropathic, neuroischaemic or Wagner grades 1 – 4 ulcers) was found between the two interventions. The authors did find that treatment with zinc hyaluronic acid in addition to standard wound care improved time to healing significantly (74 ± 31 days versus 92 ± 25 days, p = 0.008). In addition, the poor quality study by Ramos Cueva et al (2007) reported a decrease in healing time for the intervention compared to the control group (7.8 ± 3.5 versus >12 weeks, respectively). However, this did not reach statistical significance.

The use of zinc hyaluronic acid in addition to standard wound care did not increase the number of diabetic foot ulcers that healed compared to standard wound care alone, but it is likely to shorten the healing time of those that did.

Box 157 Evidence matrix for comparison of for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	C	One level II studies with moderate risk of bias and on level II study with high risk of bias.
Consistency	C	The direction of the treatment effect was consistent, although one study did not reach significance.
Clinical impact	C	Moderate clinical impact. Tankova et al (2007) reported a substantial clinical impact of the intervention on time to healing. Though, Ramos Cuevas et al (2007) did not find a significant clinical effect. For ulcer healing no significant results were reported.
Generalisability	A	The studies included a sample population attending outpatient hospital foot or diabetes clinics, which makes them generalisable to the target population.
Applicability	D	One study took place in Bulgaria, and other in Mexico, where the care of diabetic foot ulcers is likely to be different for diabetes patients compared to the Australian healthcare context.

Evidence statement

The use of zinc hyaluronic acid may provide some benefit in reducing ulcer healing time when used in conjunction with standard wound care to treat diabetic foot ulcers (Grade C).

Table 113 Studies which compare zinc hyaluronate acid to standard wound care for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Tankova et al 2002) Bulgaria	Level II RCT Average quality study	Diabetic patients with foot ulcers attending a diabetes foot clinic located in teaching hospital. Intervention group: N = 35, n = 43 ulcers, neuropathic 27/43 (63%), neuroischaemic 16/43 (37%), infection present 29/43 (67%), Wagner grade: W1 21/43 (49%), W2 16/43 (37%), W3 5/43 (12%), W4 1/43 (2%), ulcer area (cm^2) 10.32 ± 4.61, ulcer depth (mm) 9.3 ± 3.1. Comparator group: N = 24, n = 28 ulcers, neuropathic 17/28 (61%), neuroischaemic 11/28 (39%), infection present 20/28 (71%), Wagner grade: W1 14/28 (50%), W2 10/28 (36%), W3 3/28 (11%), W4 1/28 (4%), ulcer area (cm^2) 11.46 ± 5.39, ulcer depth (mm) 8.5 ± 5.3.	N=35, standard wound care: debridement, local antiseptics, immobilisation of foot, and antibiotics if necessary plus Hyaluricht (zinc hyaluronate) applied daily at a dose of 2-4 drops onto the ulcer.	N=20, standard wound care: debridement, local antiseptics, immobilisation of foot, and antibiotics if necessary.	Mean time to healing (days)±SD		
					74 ± 31	92 ± 25	p = 0.008
					Number of healed ulcers		
					Neuropathic		
					27/27 (100%)	16/17 (94%)	RR = 1.06 [95% CI 0.94, 1.20]
					Neuroischaemic		
					13/16 (81%)	7/11 (64%)	RR = 1.28 [95% CI 0.83, 1.94]
					Wagner grade 1		
					20/20 (100%)	13/13 (100%)	RR not calculable
					Wagner grade 2		
					16/16 (100%)	9/10 (90%)	RR = 1.11 [95% CI 0.90 1.37]
					Wagner grade3		
					4/5 (80%)	1/3 (33%)	RR 2.4 [95%CI 0.75, 9.9]
					Wagner grade 4		
					0/2 (0%)	0/2 (0%)	RR not calculable

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Ramos Cuevas et al 2007), Mexico	Level II RCT Poor quality study	Diabetic patients attending tertiary care centre and diabetic foot clinic Intervention group: N = 25, male 56% (n = 14), average age (yrs) 56.76 ± 8.78, duration Type II DM (yrs) 14.74 ± 6.72, oral hypoglycaemic agents n = 16, insulin use n = 8, diet n = 1, average glycaemia (mg/dl) 163.64 ± 86.4, peripheral neuropathy diagnosis 100% (n = 25), average AAI (mmHg) 1.06 ± 0.18, SO_2 (%) 82-100. Comparator group: N = 25, male 56% (n = 14), average age (yrs) 60.12 ± 8.42, duration Type II DM (yrs) 16.40 ± 5.8, oral hypoglycaemic agents n = 15, insulin use n = 9, diet n = 1, average glycaemia (mg/dl) 182.4 ± 68.3, peripheral neuropathy diagnosis 96% (n = 25), average AAI (mmHg) 0.96 ± 0.15, SO_2 (%) 92-99.	N=25, treatment with zinc hyaluronic acid, application once a day, plus conventional care	N=25, conventional treatment with daily care at the assigned clinic and/or patient 's home	Average closure time of ulcer (weeks) 7.8 ± 3.5	>12 (one 7 wks, one 9 wks)	p = NS

AAI = Ankle Arm index; DM = diabetes mellitus; NS = non significant; RCT = randomised controlled trial; RR = relative risk; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localized gangrene of forefoot or heel, Grade 5 = gangrene of entire foot.

Topical phenytoin treatment versus standard care

One level II study and one level III-2 study, both of average quality, considered the use of phenytoin powder as a topical treatment for diabetic foot ulcer and reported the effect on ulcer healing and wound area reduction (Table 114).

The randomised controlled trial by Pai et al (2001) compared the effectiveness of topical phenytoin in addition to standard wound care compared to a placebo plus standard wound care for treating diabetic patients foot ulcers that were hospitalised in 1 of 3 teaching hospitals. Two (2/20; 10%) phenytoin-treated deep ulcers healed compared to eight (8/25; 32%) placebo-treated deep ulcers over the six-week period. The relative risk of healing suggests that the use of phenytoin powder decreases the number of deep ulcers healed compared to standard care, however this was not a statistically significant difference (RR = 0.31 [95%CI 0.07, 1.3]). A greater proportion of patients did not complete the study from the phenytoin-treated group compared to the placebo group due to treatment failure (14% compared to 3%; RR = 4.72 [95% CI 0.78, 30.2]). The authors suggested that this may be caused by the presence of an irritant, which may have been either an additive or the phenytoin itself. They also measured wound size and found a higher reduction in those patients receiving phenytoin powder compared to placebo over a 6 week period (8.47 ± 1.6 cm^2 versus 7.82 ± 1.52 cm^2, respectively). Although, again this was not statistically significant (mean difference = -0.65 [95%CI -1.5, 0.17]).

A non-randomised control trial conducted by Muthukumarasamy et al (1991) reported no statistically significant clinical difference for ulcer healing or ulcer improvement (defined by healthy granulation) after the use of phenytoin powder as a topical treatment in addition to standard wound care compared to standard wound care alone for diabetic patients with a foot ulcer admitted to a tertiary care centre (RR = 1.67 [95% CI 0.93, 3.04] and RR = 1.69 [95% CI 0.98, 2.98], respectively). Though, there were some benefits of phenytoin powder use over standard care earlier in the treatment period, at day 14 for ulcer healing and days 14, 21 and 28 for wound size reduction. When the authors combined ulcer healing with ulcer improvement as an outcome, the results indicated a statistically significant benefit of phenytoin powder over standard care (84% compared to 50%; RR = 1.7 [95% CI 1.3, 2.1]). Three patients would need to be treated with phenytoin powder in addition to standard wound care for one additional patient to benefit (NNT=3 [95%CI 2, 6]).

These studies were underpowered to detect a difference between phenytoin powder in addition to standard wound care and standard wound care for the outcomes of ulcer healing, ulcer improvement, or wound size reduction. However, in one study the combined outcome of ulcer healing and improvement was statistically significant. Box 158 summarises the body of evidence according to the NHMRC grading criteria.

Box 158 Evidence matrix for comparison of phenytoin powder for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias and on level III-2 study with moderate risk of bias.
Consistency	C	Both studies were underpowered to detect a difference. Uncertainty regarding the effect of phenytoin powder remains.
Clinical impact	D	Both studies reported non-significant results for ulcer healing. Muthukumarasamy et al (1991) also reported non-significant results for ulcer improvement (granulation), but did find a moderate effect when two outcomes were combined (healing and improvement). There was no significant clinical impact of the intervention for wound size reduction.
Generalisability	B	The studies included a sample population that were inpatients in hospital for foot ulcers, which makes them generalisable to the target population.
Applicability	C	One study took place in India, and one study in the USA, which might be applicable to the Australian context with some caveats.

Evidence statement

The use of phenytoin powder in addition to standard wound care for patients hospitalised with diabetic foot ulcers is not effective for ulcer healing, ulcer improvement or wound size reduction (Grade C).

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Table 114 Studies included which compare phenytoin powder to standard care for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Pai et al 2001) USA	Level II RCT average quality study	Diabetic patients with grade I and II foot ulcers according to Meggitts clinical classification, hospitalised in 1 of 3 teaching hospitals. Intervention group: N = 36, male 69% (n=25), female 41% (n=11), medium age (yrs) 55.5, average duration DM (yrs) 8.7, Pedal pulse detected 81% (n=29), pedal pulse diminished 19% (n=7), peripheral neuropathy changes 36% (n=13), neuroischaemic changes 14% (n=5) Comparator group: N = 34, male 65% (n=22), female 35% (n=12), medium age (yrs) 60.0, average duration DM (yrs) 9, Pedal pulse detected 71% (n=24), pedal pulse diminished 29% (n=10), peripheral neuropathy changes 41% (n=14), neuroischaemic changes 29% (n=10)	N=36, surgical debridement when necessary followed by wound measurement. Gentle saline cleaning, topical phenytoin and a sterile dressing was applied daily for up to 6 weeks or until healed. Powder quantity depended on surface area: 0-5 cm^2 = 100mg; 5.1-9 cm^2 = 150mg; 9.1-15cm^2= 200mg; >15 cm^2= 300mg	N=34, surgical debridement when necessary followed by wound measurement. Gentle saline cleaning, placebo (combination of talc and colloidal silicon dioxide) applied to wound and covered with a sterile dressing daily for up to 6 weeks or until healed. Powder quantity dusted was same as for intervention	Number of deep ulcers healed at 6 weeks 2/20 (10%)	8/25 (32%)	RR 0.31 [95% CI 0.07, 1.3] Mean difference in wound area at 6 weeks (cm^2) (n=50 completed study) 8.47 ± 1.58 vs 7.82 ± 1.52; -0.65 [-1.5, 0.17] Number of patients that did not complete study 5/36 (14%) vs 1/34 (3%); RR = 4.72 [95% CI 0.78, 30.2]
(Muthukumaras amy et al 1991) India	Level III-2 nonrandomised controlled trial average quality study	Diabetic with a foot ulcer of Meggitts clinical classification grade 1 or 2, admitted to a tertiary care centre Intervention group: N = 50; age: 40-50 yrs 12/50 (24%), 51-60 yrs 19/50 (38%), 61-70 yrs 15/50 (30%), 71-80 yrs 4/50 (8%); male 27/50 (54%); ulcer duration: 3 weeks 2/50 (4%), 4 weeks 7/50 (14%), 5 weeks 4/50 (8%), 6 weeks 10/50 (20%), 7 weeks 8/50 (16%), 8 weeks 9/50 (18%), 9 weeks 5/50 (10%), 10 weeks 5/50 (10%); size of ulcer: 30 cm^2 18/50 (36%), 31-60 cm^2 13/50 (26%), 61-90 cm^2 11/50 (22%), >90 cm^2 8/50 (16%). Comparator group: N = 50; age: 40-50 yrs 12/50 (24%), 51-60 yrs 19/50 (38%), 61-70 yrs 15/50 (30%), 71-80 yrs 4/50 (8%); male 27/50 (54%); ulcer duration: 3 weeks 2/50 (4%), 4 weeks 7/50 (14%), 5 weeks 4/50 (8%), 6 weeks 10/50 (20%), 7 weeks 8/50 (16%), 8 weeks 9/50 (18%), 9 weeks 5/50 (10%), 10 weeks 5/50 (10%); size of ulcer: 30 cm^2 17/50	N = 50, topical application of phenytoin powder. Wounds underwent meticulous debridement and were cleaned with saline. Phenytoin powder was then applied in a thin uniform layer and a sterile dry dressing was applied. This was repeated daily.	N = 50, wounds underwent meticulous debridement and were cleaned with saline. Ulcer was covered with a sterile dry occlusive dressing, changed daily.	Number of ulcers healed 20/25 (40%)	12/50 (24%)	RR = 1.67 [95% CI 0.93, 3.04] Number of ulcers improved (healthy granulation) 22/50 (44%) vs 13/50 (26%); RR = 1.69 [95% CI 0.98, 2.98] Number of ulcers healed or improved ulcer 42/50 (84%) vs 25/50 (50%); RR = 1.68 [95% CI 1.27, 2.11] NNT = 3 [95% CI 2, 6]

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
		(34%), 31-60 cm^2 14/50 (28%), 61-90 cm^2 10/50 (20%), >90cm^2 9/50 (18%).					

CI = confidence interval; DM = diabetes mellitus; RCT = randomised controlled trial; RR = relative risk; Meggitts clinical classification: grade 1 = superficial ulcers, and grade 2 = deep ulcers with slough.

Total immersion in pH neutral superoxidised solution versus saline solution and povidone iodine spray

One good quality level II study considered the treatment of diabetic foot ulcer with pH neutral superoxidised solution (NpHSS) compared to saline solution followed by povidone iodine spray (Table 69). The intervention involved weekly to biweekly immersion of the affected foot in NpHSS for 15 to 20 minutes followed by daily cleansing with NpHSS spray. The control group received a similar treatment, except the affected foot was immersed in saline and a povidone iodine spray was used for cleansing.

Martínez De Jesús et al (2007) reported that the use of NpHSS reduced cellulitis, defined by a >50% reduction of erythaema at the wound area in 81% of patients, while the use of saline immersion and povidone iodine spray resulted in a reduction in cellulitis in 44% of patients (RR = 1.85 [95% CI 1.10, 2.97]). Three patients need to be treated with NpHSS rather than saline/povidone iodine for one additional patient to have a reduction in cellulitis (NNT = 3 [95% CI 2, 16]). Additionally, the number of patients with an absence of peri-ulcer skin conditions around the wound was significantly greater in the NpHSS group than the control group (90% versus 31%; RR = 2.90 [95% CI 1.61, 4.29]). Only two patients would need to be treated with with NpHSS compared to saline/povidone iodine for an absence of peri-ulcer skin conditions in one additional patient's ulcer (NNT = 2 [95% CI 1, 3]). Furthermore, the authors reported the difference in the number of ulcers with granulating tissue present in the wound after treatment with NpHSS compared to saline/povidone iodine was also statistically significant and providing a number needed to treat of 4 (90% compared to 62%; RR = 1.45 [95% CI 1.02, 1.81]; NNT 4 [95% CI 2, 88]). No adverse events were reported.

When considering the results, it should be taken in account that the study population of Martínez De Jesús et al (2007) involved patients with severe diabetic foot infections. The results suggest that immersion of the affected foot in NpHSS for 15 to 20 minutes followed by the NpHSS spray was more effective for the treatment of infected diabetic foot ulcers than immersion in saline followed by povidone iodine spray. Box 105 summarises the body of evidence according to the NHMRC grading criteria.

Box 159 Evidence matrix for the comparison of total foot immersion in pH neural superoxidised solution for the treatment of severely infected diabetic foot ulcers

Component	Rating	Description
Evidence base	B	One level II studies with low risk of bias
Consistency	N/A	Only one study.
Clinical impact	C	The results are substantial and show statistically significant differences in cellulitis and the condition of the wound. However, these are secondary outcomes and the relevance to primary ulcer healing outcomes is uncertain.
Generalisability	B	The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population. Though the study only included patient with severe diabetic foot infections.
Applicability	C	The study came from Mexico, which might be applicable to the Australian context with some caveats.

Evidence statement

Evidence suggests that immersion in pH neural superoxidised solution followed by the same spray is more effective at improving infection parameters e.g. increase granulating tissue, reduce cellulitis and improving the surrounding skin than immersion in saline followed by povidone iodine spray of severely infected diabetic foot ulcers (Grade C).

Table 115 Studies included which compare pH neutral superoxidised solution for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Martínez De Jesús et al 2007) Mexico	Level II RCT good quality study	Diabetic patients attending San Elian Diabetic Foot Salvage and Prevention Centre Intervention group – N= 21mean age (yrs) 61.9±11.9, male 45% (n=9), female 55% (n=12), mean diabetes duration (yrs) 16.4±8.1, mean HbA1c 7.1±2, mean fasting glucose (mg/dl) 163±59, obesity (chi-square and Yates correction) 30% (n=6), ulcer duration (wks) 13.7±24, B/A index (Yao) 0.9±0.5 Comparator group(s) – N=16, mean age (yrs) 67.8±11.6, male 50% (n=8), female 50% (n=8), mean diabetes duration (yrs) 17±10.2, mean HbA1c 6.7±1.8, mean fasting glucose (mg/dl) 152±65.8, obesity (chi-square and Yates correction) 25% (n=4), ulcer duration (wks) 15.1±16.3, B/A index (Yao) 1.14±0.7	N=21, initial 15 to 20 minutes immersion of affected foot in neutral pH superoxidised solution (NpHSS), repeated weekly or biweekly followed by NpHSS spray cleansing between immersions and to remove gauze.	N=16, initial 15 to 20 minutes immersion of affected foot in saline weekly or biweekly followed by povidone iodine spray cleansing between immersions. When infection resolved only surgical soap (Dermo Clean) with saline rinse was used	Number of ulcers with cellulitis reduction (effected area of erythaema) >50%		
					17/21 (81%)	7/16 (44%)	RR = 1.85 [95% CI 1.10, 2.97] NNT =3 [95% CI 2, 16]
					Number of ulcers with absence of peri-ulcer skin conditions around wound		
					19/21 (90%)	5/16 (31%)	RR = 2.90 [95% CI 1.61, 4.29] NNT 2 {95% CI 1, 3]
					Number of ulcers with granulation tissue wound bed		
					19/21 (90%)	10/16 (62%)	RR = 1.45 [95% CI 1.02, 1.81] NNT 4 [95% CI 2, 88]

RCT= randomized controlled trail; B/A index= brachial ankle index; ARR= absolute risk reduction

Povidone iodine dressing versus non-adherent, viscose filament gauze dressing or Aquacel moist wound dressing

Jeffcoate et al (2009) conducted a good quality randomised controlled trial (level II evidence) to investigate the effectiveness of using a povidone iodine dressing (Inadine©) compared to a simple non-adherent, knitted, viscose filament gauze dressing and Aquacel, an advanced moist wound dressing, as the primary dressings in standard wound care for the treatment of chronic foot ulcers in diabetes patients (Table 116). The authors reported that 44% of the ulcers healed in the Inadine group, compared to 39% and 45% of the ulcers in the gauze and Aquacel groups, respectively. Though, this was not found to be statistically significant (RR = 1.2 [95%CI 0.84, 1.6] and 0.99 [95% CI 0.74, 1.4], respectively). For the time to healing, ulcers treated using Inadine dressings healed in 78 ± 45 days, compared to 72 ± 37 days for those treated using gauze dressings and 74 ± 45 days with Aquacel dressings, but the differences were not statistically significant (p = 0.51 and p = 0.52). The author also measured the quality of life after 24 weeks with the SF-36 questionnaire, but indicated no statistically significant differences between the two groups. The number of adverse events for each group was also reported; ten ulcers treated with the Inadine dressings became infected compared to seven ulcers treated with simple gauze dressings and seven ulcers treated with aquacel (RR = 1.40 [95% CI 0.57, 3.57]).

The results suggest that the use of povidone iodine dressing compared to a non-adherent viscose gauze dressing or the Aquacel dressing, as the primary dressing in standard wound care provided no additional benefit for healing or accelerating the time to healing for chronic diabetic foot ulcers over a 24 week period. Box 160 provides an overview of the body of evidence for povidone iodine dressing according to the NHMRC criteria.

Box 160 Evidence matrix for comparison of povidone iodine dressing for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	B	One level II study with low risk of bias
Consistency	N/A	Only one study.
Clinical impact	D	The study did not report any clinically or statistically significant results.
Generalisability	B	The study included a sample population that attended clinic outpatient settings for foot ulcers, which makes them generalisable to the target population.
Applicability	B	The study took place in the UK, which might be applicable to the Australian context with few caveats.

Evidence statement

The results suggest that the use of povidone iodine dressing is as effective as a non-adherent viscose gauze dressing or the Aquacel moist wound dressing for the healing and time to healing in chronic diabetic foot ulcers (Grade C).

Table 116 Studies included which compare povidone iodine dressing versus non-adherent, viscose filament gauze dressing for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Jeffcoate et al 2009) UK	Level II RCT Good quality study	Diabetic patients attending clinic outpatient setting in 9 different centres. Intervention group: N = 108, age (yrs) 58.8 ± 13.2, male 75% (81), duration of diabetes (yrs) 15.3 ± 9.8, type 1 diabetes 23% (25), insulin treatment 41% (44), oral hypoglycaemic agents 31% (33), smokers 16% (17), cerebrovascular disease 6% (7), cardiovascular disease 37% (40), retinopathy 57% (62), nephropathy 18% (19), first ulcer 32% (35), previous ulcer at same site 19% (21), previous amputation 19% (21), peripheral arterial disease: dorsalis pedis pressure 86% (93), posterior tibial pressure 80% (86), loss of sensation: under 1st metatarsal head 81% (87), under 5th metatarsal head 75% (74), plantar hallux 79% (85), plantar heel 69% (74), location of ulcer toe 42% (45), forefoot 35% (38), hindfoot 21% (23), malleolus 2% (2); ulcer area: 25-100 mm^2 44% (48), 101-250 mm^2 33% (36), 251-2500 mm^2 22% (24). Comparator group: N = 106, age (yrs) 61.9 ± 12.8, male 74% (78), duration of diabetes (yrs) 15.8 ± 11.4, type 1 diabetes 20% (21), insulin treatment 33% (35), oral hypoglycaemic agents 34% (36), smokers 21% (22), cerebrovascular disease 8% (9), cardiovascular disease 43% (46), retinopathy 55% (58), nephropathy 25% (26), first ulcer 42% (44), previous ulcer at same site 12% (13), previous amputation 14% (15), peripheral arterial disease: dorsalis pedis pressure 85% (90), posterior tibial pressure 79% (84), loss of sensation: under 1st metatarsal head 77% (82), under 5th metatarsal head 67% (71), plantar hallux 73% (77), plantar heel 62% (66); location of ulcer toe 35% (37), forefoot 42% (44), hindfoot 21% (22), malleolus 3% (3), ulcer area: 25-100 mm^2 47% (50), 101-250 mm^2 32% (34), 251-2500 mm^2 21% (22).	N = 108, underwent initial debridement, povidone iodine dressings (Inadine) were changed daily, on alternate days or three times a week depending on need and/or availability of professional staff	N = 106, underwent initial debridement and applied a simple non-adherent, knitted, viscose filament gauze dressing that was changed daily, on alternate days or three times a week depending on need and/or availability of professional staff N=106, underwent initial debridement and applied Aquacel, a moist wound dressing, that was changed daily, on alternate days or three times a week depending on need and/or availability of professional staff	% ulcer healed at 24 weeks		
					Inadine 48/108 (44%)	Gauze 41/106 (39%) Aquacel 46/106 (45%)	RR = 1.2 [95% CI 0.84, 1.6] RR = 0.99 [95% CI 0.74, 1.4]
					Mean time to healing (days)±SD		
					Inadene 78 ± 45	Gauze 72 ±3 7 Aquacel 74 ± 45	p = 0.51 p = 0.52
					Mean physical function (SF-36) at 24 weeks		
					Inadene 40 ± 45	Gauze 40 ± 28 Aquacel 45 ± 32	p = ns p = ns
					Mean general health (SF-36) at 24 weeks		
					Inadene 43 ± 22	Gauze 44 ± 23 Aquacel 45 ± 25	p = ns p = ns
					Number of ulcers that became infected		
					Inadine 10/108 (9%)	Gauze 7/106 (7%) Aquacel 7/106	RR = 1.40 [95% CI 0.57, 3.57] RR = 1.40

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
						(7%)	[95% CI 0.57, 3.57]

RCT= randomised controlled trial; SD= standard deviation; RR= relative risk; ICER- incremental cost-effectiveness ratio

Cadexomer iodine ointment versus standard care

Apelqvist et al (1996) conducted an average quality randomised controlled trial (level II evidence) that investigated the effectiveness of using a slow iodine releasing ointment (Lodosorb®, Perstorp Pharma AB) compared to gentamicin solution (Garamycin®, Schering-Plough) and streptodornase/ strepto-kinase (varidase®, Lederle) as adjuncts to standard wound care using dry saline gauze (Mesalt®, Mölnlycke) for the treatment of foot ulcer (Table 117).

The author reported that 23% of the ulcers completely healed in the intervention group compared to 11% in the control group. The relative risk indicates that there was no statistically significant increase in complete healing for those receiving Lodosorb compared to those treated with gentamicin (RR=2.16 [95%CI 0.54, 9.27]). Similarly, for improvement of the ulcer, defined by a reduction of more than 50% of the initial ulcer area or an improvement in Wagner grade, the authors found that those treated with lodosorb were no more likely to have a benefit than those who received gentamicin treatment (RR=0.80 [95%CI 0.52, 1.30]). The lack of statistically significant effect is likely to be due to the study being underpowered to detect a significant difference.

The results suggest that there might be a trend towards cadexomer iodine ointment being beneficial compared to standard wound care with gentamin solution. Box 161 provides an overview of this body of evidence according to the NHMRC criteria.

Box 161 Evidence matrix for comparison of cadexomer iodine ointment for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	C	One level II studies with moderate risk of bias
Consistency	N/A	Only one study.
Clinical impact	D	The study did not report significant results, therefore the clinical impact would be slight.
Generalisability	B	The study included a sample population that attended a clinic outpatient setting for foot ulcers, which makes them generalisable to the target population.
Applicability	B	The study took place in the Sweden, which might be applicable to the Australian context with few caveats.

Evidence statement

The evidence suggests that the use of cadexomer iodine ointment is as effective as gentamicin solution for the healing or reduction of wound area of diabetic foot ulcer (Grade C).

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Table 117 Included study of cadexomer iodine ointment versus standard care for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Apelqvist & Tennvall 1996) Sweden	Level II RCT Average quality study	Diabetic patients attending clinic outpatient setting Intervention group: N = 22 Comparator group: N = 19 Inclusion criteria: diabetes Caucasian patients, aged over 40 years, with an exudative foot ulcer of Wagner grade 1 or 2 and > 1 cm^2 (length x width), systolic toe pressure of > 30 mmHg or a systolic ankle pressure of > 80 mmHg Exclusion criteria: patients with ulcers larger than 25 cm^2, with a deep abscess, osteomyelitis of gangrene, undergoing investigations of the thyroid gland, inability to adhere to study protocol. Patients were withdrawn from study for non-compliance, hospitalisation, ulcer grade deterioration to Wagner grade 3-4, > 100% increase in ulcer area, adverse reaction to topical treatment.	N=22, basic treatment (foot wear correction, oral antibiotics, ulcers cleaned with sterile saline) dressing of cadexomer iodine ointment (Iodosorb©).	N=19, basic treatment (foot wear correction, oral antibiotics, ulcers cleaned with sterile saline) dressing of gentamicin solution, streptodornase/strepto-kinase, dry saline gauze.	% completely healed foot ulcer 5/22 (23%) % improved (reduction of >50% of initial ulcer area or improvement of Wagner grade) 12/22 (55%)	2/19 (11%) 13/19 (68%)	RR = 2.16 [95% CI 0.54, 9.27] RR = 0.80 [95% CI 0.52, 1.30]

CI = confidence interval; RCT= randomised controlled trial; RR= relative risk; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot

Zinc oxide tape dressing versus hydrocolloid dressing

A good quality randomised controlled trial (level II evidence) by Apelqvist et al (1990) evaluated the use of a zinc oxide tape dressing (MeZinc©, Mölnlycke Health Care, Sweden) for the topical treatment of necrotic foot ulcer in diabetes patients (Table 118). All patients in the study received standard wound care including corrective foot wear for offloading when necessary. Patients in the intervention group were treated using an adhesive zinc oxide tape dressing, which was changed daily in the first week and then every 3 days. Patients in the control group were treated using an occlusive hydrocolloid dressing (DuoDerm© Granuflex© or Varhesive©, ConVatec, USA) with a similar changing schedule as the intervention group.

Apelqvist et al (1990) found that after a 5-week treatment period, 41% of the ulcers being treated in the intervention group had complete absence of necrosis in their wound compared to 23% in the control group (RR = 1.80 [95% CI 0.75, 4.54]). Additionally, 23% of the intervention group had more than 50% reduction in necrotic area in the wound, compared to 5% of the control group (RR = 5.00 [95% CI 0.86, 31.8]). Although, there was no statistically significant difference for either outcome, when the outcomes were combined the authors reported that patients who received the adhesive zinc oxide tape were 53% more likely to have complete or more than 50% decrease in necrosis in their wound than those treated with occlusive hydrocolloid dressing (RR = 2.33 [95% CI 1.17, 4.81]) Three patients would need to be treated with zinc oxide tape compared an occlusive hydrocolloid dressing for one additional patient to benefit (NNT = 3 [95% CI 2, 13]). Though there seems to be some benefit in the intervention, the authors also reported an increase of necrosis of more than 25% of the wound area for 5 patients (23%) in the intervention group and 10 patients (46%) in the control group which was associated with pain and oedema. Other adverse events reported were maceration of the skin edges in both groups and one patient treated with DuoDerm showed signs of cellulitis as a result of a *Staphylococcus aureus* infection.

The evidence suggests that the use of adhesive zinc oxide tape would decrease necrosis of the wound by more than 50% of the wound area over a 5 week period compared to treatment with occlusive hydrocolloid dressing. Box 162 summarises the body of evidence according to the NHMRC grading criteria.

Box 162 Evidence matrix for comparison of zinc oxide tape for the treatment of necrotic diabetic foot ulcers

Component	Rating	Description
Evidence base	B	One level II study with low risk of bias
Consistency	N/A	Only one study.
Clinical impact	D	The study did not report significant results for the separate outcomes. Though for the combined outcome the intervention has a moderate clinical impact, as there are also risks involved in the use of zinc oxide tape.
Generalisability	C	The study included a sample population that attended a clinic outpatient setting for foot ulcers. All subjects had necrotic diabetic foot ulcers which makes them generalisable to the target population with some caveats.
Applicability	B	The study took place in the Sweden, which might be applicable to the Australian context with few caveats.

Evidence statement

The use of adhesive zinc oxide tape in the treatment of necrotic diabetes foot ulcer might be beneficial for the reduction of initial necrosis, though this treatment still involves risks. Further research would be necessary (Grade C)

Table 118 Studies included which compare zinc oxide tape versus standard care for the treatment of necrotic diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Apelqvist et al 1990b) Sweden	Level II RCT Good quality study	Diabetic patients attending diabetes outpatient combined foot care team Intervention group: N = 22; age (yrs) 63 ± 13; male 45% (n=10);, duration of diabetes (yrs) 22 ± 15; diet 5% (n=1); oral hypoglycaemic agents 18% (n=4); insulin 77% (n=17); systolic blood pressure (mmHg) 66 ± 33; systolic ankle pressure (mmHg) 104 ± 41; fB-glukos (mmol/l) 9.1 ± 4.8; HbA1c (%) 8.4 ± 1.4; zinc (µg/ml) 0.74 ± 0.05; ulcer area (cm^2) 2.2 (1-10.5); necrotic area (cm^2) 1.5 (0.5-10.5); dry necrotic ulcer 68% (n=15); wet necrotic ulcer 32% (n=7); localisation: digit I 23% (n=5), digit II-V 14% (n=3), plantar surface 5% (n=1), dorsal area 5% (n=1), malleolus 32%(n=7), heel 23% (n=5). Comparator group: N = 22; age (yrs) 62 ± 18; male 73% (n=16); duration of diabetes (yrs) 19 ± 12; diet 0% (n=0); oral hypoglycaemic agents 18% (n=4); insulin 82% (n=18); systolic blood pressure (mmHg) 68 ± 32; systolic ankle pressure (mmHg) 114 ± 52; fB-glukos (mmol/l) 9.0 ± 4.0; HbA1c (%) 8.0 ± 2.1; zinc (µg/ml) 0.76 ± 0.05; ulcer area (cm^2) 2.2 (0.9-20.4); necrotic area (cm^2) 1.6 (0.9-19.2); dry necrotic ulcer 73% (n=16); wet necrotic ulcer 27% (n=6); localisation: digit I 18% (n=4), digit II-V 14% (n=3), plantar surface 0% (n=0), dorsal area 9% (n=2), malleolus 36%(n=8), heel 23% (n=5).	N=22, corrective foot wear when necessary and relief of external pressure on the ulcer. Ulcers were cleaned with sterile saline and dressed with adhesive zinc oxide tape (MeZinc) (Mölnlycke Health Care, Sweden). Dressing changed daily in first week followed by every 3 days.	N=22, corrective foot wear when necessary and relief of external pressure on the ulcer. Ulcers were cleaned with sterile saline and dressed occlusive hydrocolloid dressing (DuoDerm or Granuflex or Varhesive) (ConVatec, USA). Dressing changed daily in first week followed by every 3 days.	Number of ulcers where necrotic area has totally dissolved or decreased by > 50% 1422 (67%) Number of ulcers with a complete absence of necrosis 9/22 (43%) Number of ulcers with a > 50% decrease in necrotic area 5/22 (23%)	6/22 (29%) 5/22 (23%) 1/22 (5%)	RR = 2.33 [95% CI 1.17, 4.81] NNT = 3 [95% CI 2, 13] RR = 1.80 [95% CI 0.75, 4.54] RR = 5.00 [95% CI 0.86, 31.8]

CI = confidence interval; RCT= randomised controlled trial; RR= relative risk; NNT= number needed to treat

Tretinoin solution versus saline solution

One good quality randomised, double blinded controlled trial evaluated the use of topical tretinoin therapy for diabetic foot ulcers (Table 119). Short-contact daily application of tretinoin is reported to improve healing by stimulating the formation of new granulation tissue, new vascular tissue and new collagen formation. All patients followed the same protocol, except intervention group received a 0.05% tretinoin solution and the control group a placebo saline solution of similar colour. This solution was applied to the wound for 10 minutes. The wound was then rinsed with normal saline solution and cadexomer iodine gel was applied and left until the next day. This protocol was repeated once a day for four weeks.

Tom et al (2005) reported that in the control group 46% of the ulcers had completely healed versus 18% of the ulcers in the control group after 16 weeks. Though, this was not found to be a statistically significant difference (RR = 2.54 [95% CI 0.74, 10.05]). There was a statistically significant increase in the number of ulcers that decreased in area by more than 50% after treatment with tretinoin solution compared to those treated with saline solution (85% versus 45%; RR = 1.86 [95% CI 1.02, 2.88]). Similarly, there was a significantly greater percentage change in wound depth in the intervention group compared to the control group (60 ± 14% versus 30 ± 13%; p = 0.02). The adverse events reported were mild to moderate pain and burning sensation in 3 patients in the intervention group. Pain was also reported in one patient in the control group and another experienced erythaema and oedema.

The evidence provided above suggests that 0.05% tretinoin solution therapy of 10 minutes was more beneficial for wound area and depth reduction in diabetic foot ulcers than saline therapy, even though some mild to moderate adverse events were associated with this treatment. However, the study sample was small and therefore the study was underpowered to detect a difference in complete ulcer healing. Box 163 summarises the body of evidence according to the NHMRC grading criteria.

Box 163 Evidence matrix for tretinoin solution for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	B	One level II study with low risk of bias
Consistency	N/A	Only one study.
Clinical impact	C	The study reported significant results for wound area and depth, indicating a moderate clinical impact of the treatment with tretinoin solution. Still some mild adverse events are involved. The study might be underpowered for complete ulcer healing due to the small sample size.
Generalisability	C	The study included a sample population that attended a Veteran outpatient clinic for foot ulcers. Though the subjects were mainly males, they are likely to be generalisable to the target population with some caveats.
Applicability	C	The study took place in the USA, which might be applicable to the Australian context with some caveats.

Evidence statement

The evidence suggests that the use of 0.05% tretinoin solution therapy for 10 minutes in addition to standard care is beneficial for reduction in wound area and depth. Though some mild to moderate adverse effects are involved (Grade C)

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Table 119 Included study for tretinoin solution versus saline solution for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Tom et al 2005) USA	Level II RCT Good quality study	Diabetic patients attending outpatient clinic at Veterans Affairs Medical Centre. Intervention group: N = 12, age (yrs) 58.3 ± 1.5, duration of ulcer (months) 6.3 ± 2.0, plantar surface ulcer 12, dorsum foot 1, mean ulcer baseline surface area (cm^2) 0.87 ± 0.26, baseline ulcer depth (cm) 0.24 ± 0.05, duration of diabetes (yrs) 14.8 ± 2.3, HbA_{1c} level (%) 7.7 ± 0.4. Comparator group: N = 10, age (yrs) 58.3 ± 1.5, duration of ulcer (months) 6.3 ± 2.0, plantar surface ulcer 12, dorsum foot 1, mean ulcer baseline surface area (cm^2) 0.87 ± 0.26, baseline ulcer depth (cm) 0.24 ± 0.05, duration of diabetes (yrs) 14.8 ± 2.3, HbA_{1c} level (%) 7.7 ± 0.4.	N=13 ulcers. Administration of topical 0.05% tretinoin solution on foot ulcers in diabetics + standard treatment	N=11 ulcers. Treatment with placebo saline solution the same colour as the tretinoin solution + standard treatment	Number of ulcers that healed completely		
					6/13 (46%)	2/11 (18%)	RR = 2.54 [95% CI 0.74, 10.05]
					Number of ulcers with >50% reduction in surface wound area of wound		
					11/13 (85%)	5/11 (45%)	RR = 1.86 [95% CI 1.02, 2.88]
					% Change in depth of foot ulcer mean ± SD)		
					60 ±14	30 ±13	p = 0.02

CI = confidence interval; RCT= randomised controlled trial; RR= relative risk; SD = standard deviation.

Argidene Gel versus saline dressing

The good quality double blinded randomised trial by Steed et al (1995) evaluated the use of Argidene gel for the healing of diabetic foot ulcer (see Table 120). Argidene gel is an arginine-glycine-aspartic (RGD) peptide matrix conjugated with sodium hyaluronate in a viscous gel. The RGD peptide matrix contains the cell recognition sequence and facilitates rapid re-population of the site by endothelial cells, fibroblasts and kerationocytes by providing attachment sites.

Steed et al (1995) compared the use of Argidene gel with a normal saline soaked dressing and found that 35% of the ulcers in the intervention group had healed versus 8% in the control group, indicating that those receiving Argidene gel were almost 4.5 times more likely to heal than those receiving saline soaked gauze (RR = 4.38 [95%CI 1.29, 16.80]). The estimated number of patients who needed to be treated with Argidene gel in addition to standard wound care rather than standard wound care alone for one additional patient to benefit was 4, (NNT = 4 [95%CI 3, 17]). The confidence intervals for both results are rather wide, indicating some uncertainty around the estimates.

Similar results were reported for greater than 50% healing of the ulcer. For those receiving Argidene gel, 75% of patients had ulcers that healed by more than 50% over 10 weeks compared to 48% of the patients in the control group. There was a statistically significant healing benefit in the intervention group compared to the control group, as shown by the relative risk of 1.6 (RR = 1.56 [95%CI 1.05, 2.39]) The number needed to treat with Argidene gel to benefit an additional patient compared to saline soaked gauze was 4 [95%CI 2, 33].

Additionally, the wound area size was also statistically significantly reduced in the intervention group compared to the control group (72 ± 6.8% versus 30 ± 27%; $p < 0.01$). In the intervention group, three events of cellulitis were reported, while four events (malodorous exudate, inflammation, increased erythaema, and cellulitis) were reported in the control group. All these were possibly related to the study treatment and all seven resolved without surgery or long term antibiotics.

The results suggest that the use of Argidene gel in addition to standard care was effective in healing and improving ulcers. Though, some caution is advised, as some of the confidence intervals were rather wide, indicating that the estimate has some uncertainty.

Box 164 Evidence matrix for Argidene gel for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	B	One level II study with low risk of bias
Consistency	N/A	Only one study.
Clinical impact	B	The results indicate a moderate to substantial clinical impact as the relative risk are 1.6 and 4.4 for complete healing and ulcer improvement, respectively. Furthermore, the NNT indicated that the treatment is very effective.
Generalisability	C	The study included a sample population that attended outpatient clinics for their foot ulcers. There was a slight overrepresentation of males in the sample, which makes the sample generalisable to the target group with some caveats.
Applicability	C	The study took place in the USA, which might be applicable to the Australian context with some caveats.

Evidence statement

The evidence suggests that the use of Argidene gel in addition to standard wound care results in a greater reduction in wound area, and greater healing (> 50% healing or completely healing) of diabetic foot ulcers compared to standard care alone (Grade C).

Table 120 Included study for Argidene Gel versus saline dressing for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Steed et al 1995) USA	Level II RCT Good quality study	Diabetic patients attending outpatient clinic at multiple sites (6) Intervention group: N = 40; age (yrs) 61.8 ± 1.9; male 29/40 (72.5%); ulcer duration (months) 16.5 ± 2.7; ulcer area (cm^2) 3.5 ± 0.5; ulcer location on plantar surface 25/40 (62%); toes 7/40 (18%); lateral, medial or dorsal aspects 8/40 (20%). Comparator group: N = 25; age (yrs) 61.0 ± 2.2; male 20/25 (80%); ulcer duration (months) 19.0 ± 3.5; ulcer area (cm^2) 3.5 ± 0.6; ulcer location on plantar surface 17/25 (68%); toes 4/25 (16%); lateral, medial or dorsal aspects 4/25 (16%).	N = 40, ulcers were treated with standard wound care, cleaned with saline, underwent debridement as needed followed by twice weekly change of Argidene Gel covered with petroleum-impregnated gauze, followed by a non-adherent dressing, and finally a gauze wrap. Patients were given shoes for off-loading on first visit	N = 25, ulcers were treated with standard wound care, cleaned with saline, underwent debridement as needed followed by twice weekly change of saline soaked gauze covered with petroleum-impregnated gauze, followed by a non-adherent dressing, and finally a gauze wrap. Patients were given shoes for off-loading on first visit	Number of ulcers that healed completely 14/40 (35%) Number of ulcers with >50% healing at 10 weeks 30/40 (75%) % reduction in ulcer size 720 ± 6.8	2/25 (8%) 12/25 (48%) 30 ± 27	RR = 4.38 [95% CI 1.29, 16.8] NNT = 4 [95% CI 3, 17] RR = 1.56 [95% CI 1.05, 2.39] NNT = 4 [95% CI 2, 33] p < 0.0001

CI = confidence interval; RCT= randomised controlled trial; RR= relative risk; SD = standard deviation.

Doxycycline hydrogel versus the hydrogel alone

Doxycycline, an antibiotic belonging to the tetracycline family, is also an inhibitor of matrix metalloproteinases. Inhibiting metalloproteinases is thought to be important for improving the healing parameters of chronic wounds by preventing the inactivation of various growth factors and preventing activation of pro-inflammatory factors. Thus, the delivery of doxycycline via a hydrogel vehicle creates a moist environment free of metalloproteinase activity that is conducive to healing.

Chin et al (2003) conducted an average quality randomised, double-blinded controlled trial (level II intervention evidence) that evaluated the once daily application of 1% doxycycline hydrogel compared to hydrogel alone, on chronic foot ulcers in diabetic patients (Table 121). In very small sample size, the authors found that 100% (4/4) of the patients treated with 1% doxycycline hydrogel for foot ulcer healed, while 33% (1/3) of the patients treated with a the hydrogel alone healed over a 20 week period, which was statistically significant ($p = 0.05$). Furthermore, the intervention group had a mean ulcer duration of 3 months (range 2 to 5 months), while the control group had a mean duration of 12.3 months (range 5 to 24 months), which is likely to have resulted in an overestimate of the treatment effect. Similarly, age also varied significantly between the groups. The use of 1% doxycycline hydrogel was safe as no adverse events were reported.

The result above suggest that the use of 1% doxycycline hydrogel on chronic foot ulcer would improve the healing of foot ulcers in diabetes patients significantly better than hydrogel alone. As the two groups had significant difference at baseline, the result should be interpreted with caution. Box 165 summarises the body of evidence according to the NHMRC grading criteria.

Box 165 Evidence matrix for comparison of doxycycline hydrogel for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study.
Clinical impact	D	The study reported a significant difference in healing of foot ulcer. Caution should be used with these results as the two groups had significant difference at baseline.
Generalisability	C	It is unclear where the subjects were recruited, though the patient characteristics indicate diabetic patients treated in a medical centre. Most of the subjects were male and had coronary artery disease as a comorbidity.
Applicability	C	The study took place in the USA, which might be applicable to the Australian context with some caveats.

Evidence statement

The evidence suggests that the use of 1% doxycycline hydrogel on chronic foot ulcer would improve the healing of foot ulcers in diabetes patients compared to a vehicle hydrogel. Though, further research should be conducted (Grade C)

Table 121 Studies included which compare doxycycline hydrogel versus vehicle hydrogel for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Chin et al 2003), USA	Level II RCT Average quality study	N = 7 diabetic patients with full-thickness, lower extremity ulcers of > 4 weeks duration and with adequate perfusion. Intervention group: N = 4, age (yrs) 56.75 (46-68), male 3/4 (75%), duration of diabetes (yrs) 10.25 (5-20), smoking 1/4 (25%). Co-morbidities: hypertension 4/4 (100%), coronary artery disease 2/4 (50%), cerebral vascular disease 1/4 (25%), congestive heart failure 1/4 (25%), chronic obstructive pulmonary disease 1/4 (25%), end-stage renal disease 0/4 (0%), atrial fibrillation 1/4 (25%), hyperlipidemia 0/4 (0%), obesity 1/4 (25%), previous amputation 0/4 (0%), ulcer: size (cm^2) 5.33 ± 4.59, duration (months) 3 (2-5). Comparator group: N = 3, age (yrs) 69.67 (64-78), male 3/3 (100%), duration of diabetes (yrs) 10.67 (6-19), smoking 1/3 (33.3%). Co-morbidities: hypertension 2/3 (66.7%), coronary artery disease 1/3 (33.3%), cerebral vascular disease 0/3 (0%), congestive heart failure 1/3 (33.3%), chronic obstructive pulmonary disease 0/3 (0%), end-stage renal disease 1/3 (33.3%), atrial fibrillation 0/3 (0%), hyperlipidemia 1/3 (33.3%), obesity 1/3 (33.3%), previous amputation 2/3 (66.7%), ulcer: size (cm^2) 3.47 ± 3.48, duration (months) 12.3 (5-24).	N=4, Once-daily topical application of 1% doxycycline hydrogel and standardised wound care. Hydrogel spread to 2 mm thickness over wound, covered with dry gauze pads and secured with soft outer wrap. Patients were then fitted with off-loading shoe.	N=3, Same treatment using vehicle hydrogel. Treatment continued until ulcer healed or for 20 weeks.	Number of ulcers that healed by week 20 4/4 (100%) Mean time to healing (days) 16.25	1/3 (33%) > 22.7	p = 0.05 RR = 3.00 [95% CI 0.61, 14.86] Mean difference = > 6.45 days

CI = confidence interval; RCT= randomised controlled trial; RR = relative risk

Ketanserin versus Saline

Martínez de Jesús et al (1997) evaluated the use of 2% ketanserin ointment in addition to standard wound care compared to standard wound care alone for the treatment of diabetic foot ulcers using a randomised controlled trial study design of average quality (Table 122). The ointment consisted of a hydrophilic polyethyleneglycol base with 2% ketanserin, which is a serotonergic-receptor antagonist that inhibits platelet aggregation, blocks vasoconstriction and improves tissue perfusion. Standard wound care consisted of cleaning the wound with normal saline and using dry gauze dressings, debridement when necessary, and antibiotic therapy when required.

After 12 weeks, the authors found a statistically significant ($p < 0.001$) reduction in the wound area of patients treated with ketanserin ointment compared to the control group (87% versus 63% reduction, respectively). No adverse events were reported for both groups.

The evidence provided above suggests that the use of ketanserin ointment in the treatment of diabetic foot ulcers is more effective in reducing the area of the wound than normal saline. Though, the study might be subjected to information bias as the investigators were not blinded to the treatment. Box 166 summarises the body of evidence according to the NHMRC grading criteria.

Box 166 Evidence matrix for ketanserin hydrogel for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study.
Clinical impact	B	The results indicated that there is a substantial clinical impact on wound area reduction when using ketanserin ointment compared to normal saline. However, it is uncertain whether this translates into ulcer healing.
Generalisability	B	The study sample was patient admitted to hospital for several diabetic foot related problems, which makes them generalsible to the target population.
Applicability	C	The study took place in Mexico, which might be applicable to the Australian context with some caveats.

Evidence statement

The evidence suggests that the use of ketanserin in addition to standard wound care was more effective at reducing the area of the foot ulcer than the use of normal saline in diabetic patients hospitalised for foot problems (Grade C).

Table 122 Included study of ketanserin versus saline for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Martínez-de Jesús et al 1997) Mexico	Level II RCT Average quality study	Diabetic patients with a non-healing Wagner grade 2 or 3 foot ulcer that required hospital care. Intervention group: N = 69, age (yrs) 59.7 ± 10.7, male 31/69 (44.9%), duration of diabetes (yrs) 23 ± 26.5, smoker 39/69 (56.5%), obesity 20/69 (28.9%), number of previous amputations 0.5 ± 0.6, Wagner grade 2 44/69 (63.7%), grade 3 25/69 (36.3%), ulcer area (cm^2) 44.75 ± 20.8. Comparator group: N = 71, age (yrs) 60.7 ± 12.1, male 28/71 (39.4%), duration of diabetes (yrs) 21.7 ± 9.5, smoker 27/71 (38%), obesity 23/71 (32.3%), number of previous amputations 0.6 ± 0.7, Wagner grade 2 50/71 (70.4%), grade 3 21/71 (29.6%), ulcer area (cm^2) 39.70 ± 17.9.	N = 69, debridement, systemic antibiotics, foot rest and daily application of 2% ketanserin ointment (Sufrexal©, Janssen Pharmaceuticals) covered with dry gauze dressing.	N = 71, debridement, systemic antibiotics, foot rest and daily application of saline covered with dry gauze dressing.	Mean reduction in ulcer area (cm^2) at week 12 (% reduction from baseline at week 0) 6.8 ± 6.5 (87%)	15 ± 10 (63%)	p < 0.001

RCT= randomised controlled trial; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot

Dimethylsulphoxide versus standard care

The average quality study pseudo-randomised controlled trial (level III-1 evidence) by Lishner et al (1985) evaluated the use of dimethylsulphoxide (DSMO) in the treatment of diabetic foot ulcers (Table 123). All patients underwent debridement and slough was removed with a chlorinated lime (1.25%) and boric acid (1.25%) solution in water followed by application of a dry dressing and broad spectrum antibiotics when cellulitis was present. Furthermore, patients were advised to wear appropriate soft foot wear to minimise pressure on the affected area. In addition to this standard wound care, the intervention group received a daily soaking of the affected foot in 500ml of 25% DSMO in normal saline solution for 20 minutes. When the ulcer was infected, 80mg of garamycin was added to the solution. A fresh solution was prepared every 3 days. If after 6 weeks, healing was unsatisfactory, the solution was upgraded to 50% DMSO in normal saline.

The authors reported that in the intervention group ulcers had healed in 70% of the patients over 20 weeks compared to 10% in the control group. This indicates that those patients receiving treatment with DMSO in addition to standard wound care were 7 times more likely to heal than those receiving only standard wound care (RR = 7.00 [95% CI 2.30, 25.35]). The estimated number of ulcers that need to be treated with DSMO in addition to standard wound care for one additional ulcer to heal was 2 (NNT = 2 [95% CI 1, 3]).

For the outcome of ulcer improvement, the authors found similar results. Patients who received DMSO in addition to standard wound care were 2.6 times more likely to improve than those receiving only standard wound care (RR = 2.57 [95% CI 1.54, 3.46]). The NNT indicated that 2 patients would be needed to treat for 1 case to benefit (NNT = 2 [95% CI 1, 4]). There was no clear definition given for ulcer improvement. There were no adverse events reported for the 25% DMSO solution. Some patients who received 50% DMSO solution reported local irritation of the skin and a burning sensation that occasionally necessitated a temporary interruption of the treatment for 2 to 4 days.

Though the results suggest the treatment with DMSO solution is effective and safe, it has to be noted that the study only included diabetic patients with neuropathy and chronic ulcers. Also it is unclear how many patients required 50% DMSO solution after 6 weeks. Box 167 summarises the body of evidence according to the NHMRC grading criteria.

Box 167 Evidence matrix for comparison of DMSO solution for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	C	One level III-1 study with moderate risk of bias
Consistency	N/A	Only one study.
Clinical impact	A	For both outcomes the results indicate a substantial clinical impact, as the relative risks are both above 2 and the NNT's are small with a narrow confidence interval.
Generalisability	B	The study included patients with neuropathy and a non healing foot ulcer.
Applicability	C	The study took place in the Israel, which might be applicable to the Australian context with some caveats.

Evidence statement

The evidence suggests that soaking the affected foot in 25% or 50% dimethylsulphoxide solution in addition to standard care was more effective in healing and improving foot ulcer than standard care on itself in diabetic patients with chronic foot ulcers (Grade C).

Table 123 Included study for DMSO in addition to standard wound care for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Lishner et al 1985) Israel	Level III-1 pseudo-randomised controlled trial Average quality study	Diabetic patients with neuropathy and non-healing foot ulcers, hospitalised after failure of conventional treatment for 4 months. Intervention group: N = 20; age (yrs) 67; male 12/20 (60%); duration of diabetes (yrs) 14; insulin therapy 12/20 (60%); nephropathy 11/20 (55%); neuropathy 20/20 (100%); retinopathy 20/20 (100%); peripheral vascular disease 14/20 (70%); duration of ulcer (months) 16. Comparator group: N = 20; age (yrs) 64; male 10/20 (50%); duration of diabetes (yrs) 15.5; insulin therapy 14/20 (70%); nephropathy 14/20 (70%); neuropathy 20/20 (100%); retinopathy 20/20 (100%); peripheral vascular disease 12/20 (60%); duration of ulcer (months) 14.	N = 20, underwent debridement, slough removed with a chlorinated lime (1.25%) and boric acid (1.25%) solution in water, dry dressing was applied and broad spectrum antibiotics were given systematically when cellulitis was present. In addition, patients received 20 minutes soak of the affected foot in 500ml of 25% DSMO in normal saline solution, every day. When infection was present, additional 80mg garamycin added. After 6 weeks no progress in healing, DMSO solution to 50%.	N = 20, underwent debridement, slough removed with a chlorinated lime (1.25%) and boric acid (1.25%) solution in water, dry dressing was applied and broad spectrum antibiotics were given systematically when cellulitis was present.	Number of patients with ulcers that healed 14/20 (70%) Number of patients with ulcers that improved 18/20 (90%)	2/20 (10%) 7/20 (35%)	RR = 7.00 [95% CI 2.30, 25.35] NNT = 2 [95% CI 1, 3] RR = 2.57 [95% CI 1.54, 3.46] NNT = 2 [95% CI 1, 4]

CI = confidence interval; DMSO = dimethylsulphoxide; RR= relative risk; NNT= number needed to treat

Iamin gel versus placebo

Iamin gel (ProCyte Corporation, USA) contains 2% of the peptide-copper complex Glycyl-$_L$ –histidyl-$_L$ – lysine: copper (GHK-Cu) and 3% hydroxypropylmethylcellulose (HPMC). The peptide is reported to be a strong chemo-attractant for cells critical in the healing process, and the copper complex has been shown to be angiogenic. GHK-Cu has been demonstrated to stimulate the formation of granulation tissue in rats and collagen accumulation in pigs (Mulder et al 1994).

Mulder et al (1994) evaluated the effectiveness of Iamin gel for the closure of diabetic foot ulcer compared to placebo (Table 124). In the average quality randomised controlled trial patients received an 8-week treatment with either Iamin gel or placebo (3% HPMC gel), applied directly after initial sharp debridement. The authors indicated that the ulcer treated with Iamin gel had a 99% median wound area reduction compared to 61% of the wound area in the placebo group, which is a statistically significant difference ($p < 0.05$). There was also a difference in the number of plantar ulcers that healed (> 98% wound closure) between the two groups but this did not reach statistical significance (54% in the intervention group versus 31% in the control group; RR = 1.71 [95% CI 0.94, 3.14]).

When the ulcers in the population were stratified by size, the Iamin treatment group did not differ significantly from the placebo group for either median wound closure or number of wounds that healed in the small ulcer category. For large ulcers (> 100 mm² at baseline), there was a statistically significant difference between the two groups, in median wound area reduction (89% reduction in the Iamin group compared with an 11% increase in the placebo group; $p < 0.01$), and in the number of ulcers that healed (43% compared to 6%; RR = 6.86 [95% CI 1.31, 42.26]). The authors also reported that the mean rate of wound closure for ulcers treated with Iamin gel was statistically significantly greater than for the placebo group (70 ± 10 mm/day and 10 ± 21 mm/day respectively; $p < 0.05$).

To determine the effect of the Iamin gel following a 4 week delay in application after debridement, the authors included a second and third intervention group that were treated with 2% and 4% Iamin gel, respectively, and were followed for 12 weeks. The authors did not find a statistically significant difference in the wound closure rate between the second or third intervention groups and the placebo group ($p > 0.05$).This indicates that a delayed application of Iamin gel was no more effective than the standard care.

The difference in the number of adverse events (infections) for the immediate Iamin treatment group compared to the placebo group was statistically significant, with only 7% of the intervention group developing an infection compared to 34% of the placebo groups (RR = 0.21 [95% CI 0.05, 0.73]). Four patients with plantar ulcers would need to be treated with Iamin gel to save one additional patient's ulcer from becoming infected (NNT = 4 [95% CI 3, 15]). No other adverse events were reported in any of the four groups.

The results above suggest that immediate use of 2% Iamin gel is more effective than standard wound care, for the median area of wound closure and for the number of ulcers that healed, particularly for ulcers larger than 100 mm². Delaying the use of Iamin gel (either 2% or 4% gel) was no more effective than standard wound care for the rate of wound closure. Therefore, it could be suggested that the effectiveness of 2% Iamin gel is reliant on sharp debridement and application should be commenced immediately afterwards. Box 168 summarises the body of evidence according to the NHMRC grading criteria.

Box 168 Evidence matrix for comparison of Iamin gel for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study.
Clinical impact	B	The results indicate that there is a substantial clinical impact for 2% Iamin gel in reducing wound area and in wound closure, but only if applied immediately after sharp debridement.
Generalisability	B	The study sample consisted of patients with plantar ulcers of various sizes, attending specialist clinics in several medical centres. Therefore, they are generalisable to the target population with few caveats.
Applicability	C	The study took place in the USA, which might be applicable to the Australian context with some caveats.

Evidence statement

The evidence suggests that immediate application of 2% Iamin gel after sharp debridement in addition to standard wound care is more effective than standard wound care alone, particularly in large ulcers. Delayed application of either 2% or 4% Iamin gel after sharp debridement provides no additional benefit to standard wound care for the treatment of diabetic foot ulcer (Grade C).

Table 124 Included study which compared lamin gel versus placebo for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Mulder et al 1994) USA	Level II RCT Average quality study	N = 181 diabetic patients with adequately controlled diabetes and a full-thickness ulcer of the lower extremity, below the knee. Minimum ulcer size on two longest axes 0.5 x 0.5 cm (25 mm^2) and maximum ulcer size approximately 2700 mm^2. Doppler blood pressure ≥ 40 mmHg. Baseline characteristics: N = 181; age (yrs) 60; duration of diabetes (yrs) 15, type 2 diabetes 137/181 (76%); insulin dependent 114/181 (63%), plantar foot ulcer 145/181 (80%), other lower extremity ulcer 36/181 (20%). Outcomes only reported for patients with plantar ulcers. Intervention group 1: N = 28 patients with plantar foot ulcers. Intervention group 2: N = 39 patients with plantar foot ulcers. Intervention group 3: N = 42 patients with plantar foot ulcers. Comparator group: N = 32 patients with plantar foot ulcers.	Intervention 1. N = 28, Immediate treatment for 8 weeks with Iamin 2% Gel (2% GHK -Copper, 3% HPMC) after initial sharp debridement. Gel is applied once daily by patient. Intervention 2. N = 39 delayed treatment with Iamin gel. After sharp debridement, there was an initial 4 week treatment with placebo prior to treatment for an additional 8 weeks with Iamin 2% gel applied once daily by patient. Intervention 3. N = 42, delayed treatment with Iamin gel. After sharp debridement, there was an initial 4 week treatment period with placebo prior to treatment for an additional 8 weeks with Iamin 4% gel applied once daily by patient.	N = 32, 8 weeks treatment with vehicle after initial sharp debridement. Placebo gel (3%HPMC) was applied once daily by patient.	Median area of wound closure (%) Intervention 1 All plantar ulcers: 98.5% 60.8% p < 0.05 Small ulcers: 100% 99.6% p > 0.05 Large ulcers: 89% -11% p < 0.01 **Number of ulcers with:≥ 98% wound closure** Intervention 1 All plantar ulcers: 15/28 (54%) 10/32 (31%) RR = 1.71 [95% CI 0.94, 3.14] small ulcers: 9/14 (64%) 9/16 (56%) RR = 1.14 [95% CI 0.64, 1.93] Large ulcers: 6/14 (43%) 1/16 (6%) RR = 6.86 [95% CI 1.31, 42.26] Wound closure rate (mm/day) mean ± SD Intervention 1 70 ±10 10 ± 21 p < 0.05 Intervention 2 31 ± 10 p > 0.05 Intervention 3 34 ± 13 p > 0.05 Number of ulcers that became infected (harms)		

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
					2/28 (7%)	11/32 (34%)	RR = 0.21 [95% CI 0.05, 0.73] NNT = 4 [95% CI 3, 15]

CI = confidence interval; GHK-Cu= Glycyl-$_L$ –histidyl-$_L$ –lysine peptide-copper complex; HPMC= hydroxypropylmethylcellulose; NNT = number needed to treat; RCT= randomised controlled trail; RR = relative risk; SD= standard deviation

Local insulin treatment in addition to standard wound care

Razzak et al (1997) evaluated the use of local insulin therapy in addition to standard wound care in diabetic foot ulcer of patients admitted to hospital (Table 125). In this average quality randomised controlled trial, standard wound care involved antibiotic therapy, control of hypoglycaemia and local surgery (drainage of abscesses, wound debridement or local amputation of gangrenous toe). The difference between the intervention and control group was the application of 5 -10 units of insulin locally via a saline soaked gauze, while the control group was treated with gauze soaked with diluted povidone solution (0.05%).

The authors found that the ulcers of patients receiving local insulin treatment healed significantly quicker than the control group, with the average length of hospital stay for the intervention group being 20 days compared to 54 days for the control group ($p < 0.001$). It should be noted that the control group included more severe lesions, having more gangrene and abscesses than the intervention group, than in the intervention (25% and 58% versus 17% and 17%, respectively). Therefore, the treatment effect may be overestimated. There were more infected ulcers in the intervention group, than the control group (67% versus 33%, respectively).

These results suggest that the use of local insulin in addition to standard wound care is more effective than standard care with diluted povidone solution for healing of foot ulcers. Box 169 summarises the body of evidence according to the NHMRC grading criteria.

Box 169 Evidence matrix for comparison of local insulin for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study.
Clinical impact	B	The results indicate that there is a significant effect of local insulin used in addition to standard wound care, however it is possible the effect size has been overestimated.
Generalisability	C	The study sample consisted of patients admitted to hospital for diabetic foot complications. There were more males included than females. Therefore, they are generalisable to the target population with some caveats.
Applicability	D	The study took place in Saudi-Arabia, which might not be directly applicable to the Australian context.

Evidence statement

The evidence suggests that, in addition to standard wound care, local insulin therapy is effective in reducing hospital stays in complicated diabetic foot ulcer (Grade C).

Table 125 Included study for local insulin versus diluted povidone for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Razzak et al 1997) Saudi Arabia	Level II RCT Average quality study	Patients admitted to a general surgery department for diabetic foot complications. Intervention group: N = 12; mean age (yrs) 58.3; mean duration of diabetes (yrs) 16.4; insulin dependent 5/12 (42%); mean blood sugar on admission (mmol) 17.1; neuropathy 6/12 (50%); distal pulses present 6/12 (50%); ankle-brachial index < 1 5/12 (42%); type of lesion: infected ulcer 8/12 (67%), abscess 2/12 (17%), gangrene 2/12 (17%). Comparator group: N = 12; mean age (yrs) 61.1; mean duration of diabetes (yrs) 8; insulin dependent 2/12 (17%); mean blood sugar on admission (mmol) 13.8; neuropathy 4/12 (33%); distal pulses present 8/12 (67%); ankle-brachial index < 1 5/12 (42%); type of lesion: infected ulcer 4/12 (33%), abscess 7/12 (58%), gangrene 3/12 (25%).	N = 12. Foot was dressed daily with saline soak impregnated with 5-10 units of insulin (depending on size of the ulcer) and standard wound care as for control group.	N = 12. Foot was dressed daily with diluted povidone solution and standard wound care including antibiotic therapy, control of hyperglycaemia, local surgical treatment (drainage of abscess, wound debridement or local amputation of gangrenous toe).	Average duration of hospital stay (days) (range) 20 (15-35)	54 (33-71)	p < 0.001

RCT= randomised controlled trial

Talactoferrin gel versus placebo

Talactoferrin gel is a recombinant lactoferrin, iron binding glycoprotein, known to have anti-infective and anti- inflammatory properties. Furthermore, it stimulates the production of polymorphonuclear cells and macrophages to the wound area. An average quality randomised controlled trial conducted by Lyons et al (2007) reported the effectiveness of 2.5% and 8.5% talactoferrin in an aqueous carbopol gel for the complete or greater than 75% closure of diabetic foot ulcer (Table 126).

All patients in the study received standard wound care which involved periodic sharp debridement as needed, and twice daily dressing changes, offloading using standard devices and infection control. The subjects were randomised into three different groups; the control group was treated using a placebo carbopol gel, and two intervention groups that were treated with 2.5% or 8.5% talactoferrin gel for 12 weeks. After treatment patients were followed for up to 90 days.

The authors reported that there were no statistically significant differences in the proportion of ulcers that healed completely between either the 2.5% or 8.5% talactoferrin group compared to the control group at the end of the 12 week treatment period (RR = 1.07 [95%CI 0.27, 4.22] and RR = 1.07 [95%CI 0.27, 4.22], respectively). Treatment with talactoferrin also did not produce a statistically significant effect at 90 days after treatment (RR = 1.42 [95%CI 0.40, 5.17] and RR = 1.78 [95%CI 0.55, 6.09], respectively). Similarly, when the subjects were stratified into four groups by ulcer duration and size, the results for each group did not indicate that treatment with either 2.5% or 8.5% talactoferrin gel was more beneficial than placebo for achieving 75% or greater wound closure. There were 82 adverse events reported, with 26, 31 and 25 occurring in the placebo, 2.5% and 8.5% talactoferrin groups, respectively. The most frequent events were cellulitis, arthralgia, and localised infections, however, as the frequency was similar for all three groups, they were not considered to be related to the treatment received. Only one adverse event was considered to be related to the treatment, an episode of grade 1 burning sensation in a patient in the placebo group. 14 of these adverse events were serious and occurred in 13 patients but all were unrelated to the talactoferrin treatment. One placebo patient died due to renal failure, eight patients needed hospital treatment for ulcer-related wound infections and five required hospitalisation for other medical conditions.

The results indicate that there is no benefit from using talactoferrin gel in addition to standard wound care for the treatment of diabetic foot ulcer. A total of 18 patients withdrew from the study prior to completion, of these 8 patients (7 from the intervention group and 1 from the control group) withdrew even though their ulcer was improving, potentially adversely affecting the study outcomes. Box 170 summarises the body of evidence according to the NHMRC grading criteria.

Box 170 Evidence matrix for talactoferrin gel for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study.
Clinical impact	D	The results indicate that there was no significant effect of talactoferrin gel in addition to standard care for ulcer healing.
Generalisability	B	The study sample consisted of patients visiting outpatients settings and had an over representation of females. Therefore the sample is generalisable to the target population with few caveats.
Applicability	C	The study took place in the USA, which might be applicable to the Australian context with some caveats.

Evidence statement

The evidence indicates that the use of talactoferrin in addition to standard wound care is no more beneficial than standard wound care alone for healing of severe diabetic foot ulcer (Grade C).

Table 126 Studies included which compare talactoferrin gel versus placebo for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Lyons et al 2007) USA	Level II RCT Average quality study	Diabetic patients with a full-thickness neuropathic foot ulcer at or below the ankle that had not decreased in size by more than 30% in the last 4 weeks. Intervention group 1: N = 15; age (yrs) 58 ± 10; male 14/15 (93%); race: Caucasian 14/15 (93%), African-American 1/15 (7%), Hispanic 0/15 (0%); type 1 diabetes 4/15 (27%); BMI (kg/m^2) 37.8 ± 9.0; % HbA_{1c} 8.2 ± 1.9; ulcer duration (months) 9.7 ± 8.4; ulcer area (cm^2) 2.6 ± 1.8. Intervention group 2:N = 15: age (yrs) 53 ± 15: male 12/15 (80%); race: Caucasian 10/15 (67%), African-American 4/15 (27%), Hispanic 1/15 (7%); type 1 diabetes 3/15 (20%); BMI (kg/m^2) 33.0 ± 7.6; % HbA_{1c} 8.7 ± 1.6; ulcer duration (months) 9.6 ± 11; ulcer area (cm^2) 3.0 ± 2.0. Comparator group: N = 16; age (yrs) 56 ± 14; male 9/16 (56%); race: Caucasian 13/16 (81%), African-American 1/16 (6%), Hispanic 2/16 (13%); type 1 diabetes 4/16 (25%); BMI (kg/m^2) 30.1 ± 4.5; % HbA_{1c} 8.6 ± 1.9; ulcer duration (months) 8.9 ± 7.7; ulcer area (cm^2) 1.9 ± 1.1.	N = 15, After sharp debridement the 2.5% talactoferrin (TF) gel was applied topically twice daily for 12 weeks with standard care. N= 15, After sharp debridement the 8.5% talactoferrin gel was applied topically twice daily for 12 weeks with standard care.	N = 12, Standard care consisted of periodic sharp debridement, as needed, twice daily saline dressing changes, off-loading using standardised devices, and systemic control of infection	**Number of ulcers that healed completely at end of 12 week treatment period**		
					2.5% TF 3/15 (20%) 8.5% TF 3/15 (20%)	3/16 (19%)	RR = 1.07 [95% CI 0.27, 4.22] RR 1.07 [95% CI 0.27, 4.22]
					Number of ulcers that healed completely at 30 days post-treatment		
					2.5% TF 5/15 (33%) 8.5% TF 5/15 (33%)	3/16 (19%)	RR = 1.78 [95% CI 0.55, 6.09] RR = 1.78 [95% CI 0.55, 6.09]
					Number of ulcers that healed completely at 90 days post-treatment		
					2.5% TF 4/15 (27%) 8.5% TF 5/15 (33%)	3/16 (19%)	RR = 1.42 [95% CI 0.40, 5.17] RR = 1.78 [95% CI 0.55, 6.09]
					Number of ulcers that were < 2 cm^2 area and < 6 months duration, and achieved >75% closure		

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
					2.5% TF 1/3 (33%) 8.5% TF 3/4 (75%)	I 1/3 (33%)	RR = 1.00 [95%CI 0.12, 8.12] RR = 2.25 [95% CI 0.62, 9.66]
					Number of ulcers that were < 2 cm^2 area and > 6 months duration, and achieved >75% closure		
					2.5% TF 1/1 (100%) 8.5% TF 0/1 (0%)	1/4 (25%)	RR = 4.00 [95%CI 0.73, 21.8] RR = not calculable
					Number of ulcers that were > 2 cm^2 area and < 6 months duration, and achieved >75% closure		
					2.5% TF 0/3 (0%) 8.5% TF 2/2 (100%)	1/2 (50%)	RR = not calculable RR = 2.00 [95% CI 0.50, 8.00]
					Number of ulcers that were > 2 cm^2 area and > 6 months duration, and achieved >75% closure		
					2.5% TF 1/3 (33%) 8.5% TF 3/4 (100%)	1/3 (33%)	RR = 1.00 [95%CI 0.12, 8.12] RR = 2.25 [95% CI 0.62, 9.66]

CI = confidence interval; RCT= randomised controlled trial; RR= relative risk; TF = talactoferrin

Thrombin peptide Chrysalin® treatment versus saline placebo

Chrysalin® is a 23-amino acid peptide which represents the thrombin-binding domain of thrombin receptors found on fibroblasts and other cells. It has been shown that a number of cellular events involved in tissue repair and wound healing are activated by the binding of thrombin derivatives (Fife et al 2007). One average quality randomised controlled trial by Fife et al (2007) evaluated the use of Chrysalin® to determine its effect on healing and healing time of diabetic lower extremity (below the knee) Wagner grade 1-3 ulcers of more than 8 weeks duration (Table 127). Patients were randomised into three groups to receive either 1μg, 10μg Chrysalin® in 0.1 ml saline or a 0.1 ml saline placebo applied directly to the wound in addition to standard wound care.

Fife et al (2007) found that 52% and 61% of the ulcers in the 1 μg and 10 μg Chrysalin® groups healed completely compared to 48% in the placebo group after the 20 week treatment period but this difference was not statistically significant. When only those patients with foot ulcers were analysed (as opposed to other lower extremity ulcers) the difference became statistically significant for foot ulcers in the 1 μg Chrysalin® group (75% healed) compared to the placebo group (48% healed), indicating that patients treated with 1 μg Chrysalin® in addition to standard care were approximately two and half times more likely to heal (RR = 2.44 [95%CI 1.10, 4.97]). The estimated number of patients who needed to be treated with 1 μg Chrysalin® in addition to standard wound care for one additional patient's foot ulcer to heal was 3, indicating high effectiveness of the treatment (NNT = 3 [95%CI 1, 20]). However, the difference between the number of foot ulcers that healed in the 10 μg Chrysalin® group compared to the placebo group did not reach statistical significance 70% compared to 48%; RR = 2.28 [95% CI 0.96, 4.82]). This is likely to be due to inadequate power to detect a difference, but also possibly as a result of the smaller size of the foot ulcers in the 1 μg Chrysalin® group compared to the 10 μg Chrysalin® and placebo groups (2.4 ± 2.5 cm^2, compared to 3.6 ± 3.8 cm^2 and 3.7 ± 3.2 cm^2, respectively). The authors also reported that there was a statistically significant difference in the number of patients with heel ulcers (which are known to be difficult to treat) treated with either 1μg or 10μg Chrysalin® in addition to standard wound care that healed completely compared to placebo (86% compared to 0%; $p < 0.03$).

The authors also reported the median time for wound closure and found that there was no statistical difference between the 1 μg or 10 μg Chrysalin® groups compared to the placebo groups. However, for patients with only foot ulcers, the 10 μg Chrysalin® group healed quicker than the control group (94 days for 1 μg intervention group, 72 days for combined intervention group versus >140 days in the control group; p = < 0.05). There was a statistically significant difference in the linear rate of wound healing between the foot ulcers in the 10 μg Chrysalin® group compared to placebo (0.104 mm/day compared to 0.058 mm/day; $p < 0.05$) but not for foot ulcers in the 1 μg Chrysalin® group (0.089 mm/day).

Adverse events in the form of pain, oedema and erythaema were reported in 24% of the placebo group, 22% in the 10 μg group and 20% in the1 μg group. Overall 14 patients from the primary study population reported serious side effects such as infection, osteomyelitis and other general problems. The investigators reported that none of the serious side effects seemed drug-related.

The results suggest that Chrysalin® in addition to standard wound care is effective in complete healing and accelerates healing of diabetic foot ulcers. However, the results were not always consistent between the two doses suggesting that further research may be required. Box 171 summarises the body of evidence according to the NHMRC grading criteria.

Box 171 Evidence matrix for Chrysalin® treatment of diabetic leg, foot and heel ulcers

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study.
Clinical impact	C	The results indicate that Chrysalin may be effective in the treatment of diabetic foot and heel ulcers however, further research may be required.
Generalisability	C	The study population consisted of diabetic patients with a lower extremity, Wagner grade 1-3 ulcer (below the knee) of more than 8 weeks duration. Therefore the results are generalisable to the target population with some caveats.
Applicability	C	The study took place in the USA, which might be applicable to the Australian context with some caveats.

Evidence statement

There is some evidence to suggest that 1 µg and 10 µg Chrysalin® in addition to standard wound care is effective in healing and accelerating the healing process of diabetic foot and heel ulcers compared to standard wound care alone. Further research may be required (Grade C).

Table 127 Studies included which compare Chrysalin® dressing versus saline dressing for the treatment of diabetic foot and heel ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Fife et al 2007) USA	Level II RCT Average quality study	Diabetic patients with a lower extremity Wagner grade 1-3 ulcer (below the knee) of more than 8 weeks duration. Intervention group 1: N = 20; male 14/20 (70%); Caucasian 12/20 (60%), Black 4/20 (20%); Hispanic 4/20 (20%); other ethnicity 0/20 (0%), age (yrs) 59.3 ± 6.4; weight (lbs) 206.5 ± 41.8; ulcer area (cm²) 3.59 ± 5.31. Intervention subgroup 1.1: N = 12 patients with foot ulcers; male 11/12 (91%); age (yrs) 59.4 ± 7.1; ulcer area (cm²) 2.4 ± 2.5. Intervention subgroup 1.2: N = 3 patients with heel ulcers; age (yrs) 55.7 ± 10.3; ulcer area (cm²) 3.62. Intervention group 2: N = 18; male 14/18 (78%); Caucasian 11/18 (61%); Black 2/18 (11%); Hispanic 5/18 (28%); other ethnicity 0/18 (0%); age (yrs) 53.4 ± 10.5; weight (lbs) 229.5 ± 58.8; ulcer area (cm²) 3.15 ± 3.20. Intervention subgroup 2.1: N = 10 patients with foot ulcers; male 8/10 (80%); age (yrs) 50.1 ± 10.7; ulcer area (cm²) 3.6 ± 3.8. Intervention subgroup 2.2: N = 4 patients with heel ulcers; age (yrs) 51.48 ± 10.26; ulcer area (cm²) 6.19. Comparator group: N = 21; male 15/21 (71%); Caucasian 11/21 (52%); Black 6/21 (29%); Hispanic 3/21 (14%), other ethnicity 1/21 (5%), age (yrs) 55.7 ± 12.8; weight (lbs) 196.3 ± 77.3; ulcer area (cm²) 4.11 ± 5.99. Comparator subgroup 1: N = 13 patients with foot ulcers; male 10/13 (77%); age (yrs) 54.6 ± 111; ulcer area (cm²) 3.7 ± 3.2. Comparator subgroup 2: N = 5 patients with heel ulcers; age (yrs) 53.6 ± 14.3; ulcer area (cm²) 5.32.	Group 1 N = 20 patients with ulcers. N = 12 foot ulcers Patients underwent sharp debridement as needed, the ulcer was irrigated with saline and blotted with gauze. Then 1 μg Chrysalin® in 0.1 ml saline was applied to the wound and left for 1 minute. The wound was then covered with Cutinova Foam© (Beiersdorf, Germany) and bandaged. Off-loading prescribed as necessary. Bandages were removed and the ulcer treated as above at twice weekly clinic visits for up to 20 weeks. Group 2 N= 18 patients with ulcers. N= 13 foot ulcers Same treatment as for group 1 except a 10 μg Chrysalin® was used. Subgroup 3 N = 7 heel ulcers	N = 21 patients with ulcers. N = 13 foot ulcers N = 5 heel ulcers Same treatment as for intervention groups except a saline placebo instead of study drug.	Number of patients with ulcers that healed completely by week 20		
					All ulcers: Group 1 11/20 (52%) Group 2 11/18 (61%) Foot ulcers: Subgroup 1.1 9/12 (75%) Subgroup 2.1 7/10 (70%) 1.1 +2.1 16/22 (73%) Heel ulcers: Subgroup 1.2 3/3 (100%)	10/21 (48%) 4/13 (38%) 0/5 (0%)	RR = 1.16 [95% CI 0.64, 2.07] RR = 1.28 [95% CI 0.72, 2.20] RR = 2.44 [95% CI 1.10, 4.97] NNT = 3 [95% CI 1, 20] RR = 2.28 [95% CI 0.96, 4.82] RR = 2.36 [95% CI 1.15, 4.48] NNT = 2 [95% CI 1, 13] RR not calculable RR not calculable

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
					Subgroup 2.2 3/4 (75%) 1.2 + 2.2 6/7 (86%)		RR not calculable p < 0.03
					Median time to 100% ulcer closure (days)		
					All ulcers: Group 1 122 Group 2 87 Foot ulcers: Subgroup 1.1 94 Subgroup 2.1 71.5	>140 >140 	p > 0.05 p > 0.05 p > 0.05 p < 0.05
					Linear rate of foot ulcer closure (mm/day)		
					Foot ulcers: Subgroup 1.1 0.089 Subgroup 2.1 0.104 Heel ulcers: 1.2 + 2.2 0.106	0.058 0.040	p > 0.05 p < 0.05 p < 0.02

RCT= randomised controlled trial; RR= relative risk; ns= non significant; WHR= wound healing rate; ARR= absolute risk ratio; NNT= number needed to treat

Ozone treatment in addition to standard wound care

One average quality randomised controlled trial evaluated the effectiveness of ozone therapy in addition to standard care for the treatment of diabetic foot ulcers in patients hospitalised for foot complications (Table 128). The patients randomised to the intervention group were treated daily with 10 mg ozone (generated by OZOMED equipment, Cuba) by rectal insufflations as well as locally. Local ozone treatment required that the lesion was covered with a plastic bag sealed to the leg and put under vacuum to eliminate the air; the bag was then refilled with ozone concentration of 60 mg/l. The patients remained with the bag for 1 hour before the bag was removed and the lesion was covered with ozonised sunflower oil (Oleozone©). Patients in the control group were treated with standard wound care including conventional antibiotic therapy for 20 days.

Martinez-Sanchez et al (2005) reported that after a 20 day follow up period, 78% of the ulcers in the ozone group were healed compared to 69% in the control group. However, this difference was not statistically significant (RR = 1.10 [95% CI 0.87, 1.38]). This might be explained by the relatively short follow up of 20 days, as there was a significant difference between the perimeter (cm) and wound area (cm^2) reduction of the wound over 20 days (42 ± 0.25% for the ozone versus 27 ± 0.17% for the control group ($p < 0.01$) and 75 ± 0.35% for ozone versus 50 ± 0.17% in the control group ($p < 0.02$), respectively). Furthermore, the results indicated that the wound would improve more quickly with ozone than with the conventional treatment, as the mean healing rate with respect to area (cm^2) and perimeter (cm) for the ozone group was 2.7 ± 0.05 cm^2/day and 0.34 ± 0.0 cm/day compared to 1.2 ± 0.01 cm^2/day and 0.24 ± 0.0 cm/day in the control group. The mean difference was statistically significant for both outcomes ($p < 0.01$ and $p = 0.04$, respectively). The quicker recovery was also reflected in the statistically significant duration of hospital stay between the two groups (mean 26 days (range 5-58 days) for the ozone patients compared to a mean 34 days (range 7-383 days) for the control patients; $p = 0.01$). There were no adverse events reported by the authors.

The results suggest that treatment with ozone in addition to standard wound care accelerates the recovery of diabetic foot ulcers compared to standard wound care with conventional antibiotic therapy. Though, there were no adverse events, the treatment itself might be uncomfortable for the patient. Box 172 summarises the body of evidence according to the NHMRC grading criteria.

Box 172 Evidence matrix for ozone therapy for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias
Consistency	N/A	Only one study.
Clinical impact	C	The results indicated that there was a substantial clinical impact of the ozone treatment compared to conventional therapy. The non significant result on the number of ulcers healed can be explained by the short follow up.
Generalisability	C	The study sample consisted of patients hospitalised for diabetic foot complications. Furthermore, the sample included a third of black or other ethnicity in the sample and therefore are generalisable to the target population with few caveats.
Applicability	D	The study took place in Cuba, which differs in health care for diabetic patients compared to that in Australia.

Evidence statement

The evidence suggest that the use of ozone in addition to standard care was not more effective in ulcer healing than conventional therapy, but did accelerate the time to healing and reduces the days of hospitalisation (Grade C).

Table 128 Included study which compares ozone therapy versus standard wound care for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Martínez Sánchez et al 2005) Cuba	Level II RCT Average quality study	Patients diagnosed with neuroinfectious diabetes foot, were suffering from ulcers of the feet and lower extremities, and hospitalised in the Institute of Angiology and Vascular surgery for diabetic foot related complications. Intervention group: N = 51; 20-40 years of age 9% (n = 5); 40-60 years of age 32% (n = 17); ≥60 years of age 57% (n = 30); white 75% (n = 39); black 13% (n = 7); mixed ethnicity 11% (n = 6); male 50% (n = 26); hypertension 38% (n = 20); renal dysfunction 3% (n = 2); cardiovascular disease 19% (n = 10). Comparator group: N = 49; 20-40 years of age 14% (n = 7); 40-60 years of age 40% (n = 20); ≥60 years of age 44% (n = 22); white 61% (n = 30); black 16% (n = 8); mixed ethnicity 22% (n = 11); male 61% (n = 30); hypertension 46% (n = 23); renal dysfunction 4% (n = 2); cardiovascular disease 14% (n = 7).	N = 51, patients treated daily with ozone (generated by OZOMED equipment, Cuba), 20 sessions, by rectal insufflations (with ozone dose of 10 mg, ozone concentration: 50 mg/l) and locally. For local ozone treatment, the lesion was covered with a plastic bag for 1 hour, sealed at the leg and in vacuum and filled with ozone concentration of 60 mg/l. After treatment the lesion was covered with ozonised sunflower oil (Oleozone©) plus debridement and gauze dressing	N = 49, patients were treated with systemic antibiotic therapy (according to microbe present), using conventional method for treatment, with topical application to the lesion (for 20 days) plus debridement and gauze dressing	Number of patients with healed ulcers		
					39/51 (78%)	34/49 (69%)	RR = 1.10 [95% CI 0.87, 1.38]
					Mean % wound area (cm²) reduction		
					75 ± 0.35	50 ± 0.17	p < 0.02
					Perimeter (cm) reduction		
					42 ± 0.25	27 ± 0.17	p < 0.01
					Healing rate with respect to area (cm²/day)		
					2.7 ± 0.05	1.2 ± 0.01	p < 0.01
					Healing rate with respect to perimeter (cm/day)		
					0.34 ± 0.0	0.24 ± 0.0	p = 0.04
					Length of hospitalisation (days		
					26 ± 13	34 ± 18	p = 0.01

RCT= randomised controlled trial; RR= relative risk; SD= standard deviation

Bensal HP versus silver sulphadiazine

One poor quality randomised controlled trial conducted by Jacobs and Tomczak (2008) reported on the effectiveness of Bensal HP versus silver sulphadiazine cream, both were applied to the wound every 12 hours and covered with gauze and used in conjunction with standard wound care for the treatment of diabetic foot ulcer (Table 129).

Bensal HP consisted of 6% benzoic acid and 3% salicylic acid in a polyethylene glycol and 3% *Quercus rubra* bark extract (QRB7). Its mechanism of action is unknown, but antimicrobial and anti-inflammatory responses have been demonstrated. Silver is used in wound care for its antimicrobial properties. In both treatment groups, patients received debridement when necessary and were treated by offloading. After a 6 week treatment period, 40% of the ulcers in the Bensal HP group were healed compared to 30% in the silver sulphadiazine group. This was not found to be statistically significant (RR = 1.33 [95% CI 0.58, 3.15]). For the percentage reduction in wound diameter, the authors reported 73% reduction in the Bensal HP group versus 55% in the silver sulphadiazine group, which was statistically significant (p = 0.016). No adverse events were reported for either Bensal HP or silver sulphadiazine cream.

The results suggest that the use of Bensal HP resulted in a faster rate of wound healing than the use of silver sulphadiazine cream in addition to standard wound care. Even so, this did not result in a significant greater number of healed ulcers, which can be explained by the rather short follow-up of 6 weeks. It should be noted that the study did not describe the patient characteristics which makes it hard to either compare both groups or generalise the results to the target population. Box 173 summarises the body of evidence according to the NHMRC grading criteria.

Box 173 Evidence matrix for Bensal HP for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	C	One level II study with a high risk of bias
Consistency	N/A	Only one study.
Clinical impact	C	The results indicate that there is a significant clinical impact on the reduction of ulcer diameter, but no effect on ulcer healing. This may be explained by the relatively short follow-up of 6 weeks. It is unclear if the two groups were comparable.
Generalisability	D	The study population consisted of diabetic patients with a Wagner grade 1 or 2 ulcer on the plantar aspect of the foot, visiting an outpatient clinic. There were no baseline characteristics given, except ulcer grade, size and location, which makes it difficult to generalise to the target population.
Applicability	D	The study took place in Dutch Antilles, which may not be applicable to the Australian healthcare context.

Evidence statement

There is insufficient evidence to suggest that Bensal HP in addition to standard care is more effective than silver sulphadiazine cream for the treatment of diabetic foot ulcer (Grade D).

Table 129 Included study which compared Bensal HP versus silver sulphadiazine for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Jacobs & Tomczak 2008) Netherlands' Antilles	Level II RCT Poor quality study	Diabetic patients with a Wagner grade 1 or 2 ulcer on the plantar aspect of the foot, visiting an outpatient clinic. Intervention group N = 20, ulcer diameter (cm) 1.9 ± 0.76, Wagner: grade 1 6/20 (30%), grade 2 14/20 (70%). Comparator group(s) – N = 20, ulcer diameter (cm) 1.6 ± 0.78, Wagner: grade 1 11/20 (55%), grade 2 9/20 (45%).	N = 20, standard care with topical treatment with Bensal HP [6% benzoic acid and 3% salicylic acid in a polyethylene glycol and 3% Quercus rubra bark extract (QRB7)] as an adjunctive treatment.	N = 20, standard care with topical application of silver sulphadiazine cream as an adjunctive treatment	Number of patients with ulcers that were healed at 6 weeks		
					8/20 (40%)	6/20 (30%)	RR = 1.33 [95% CI 0.58, 3.15]
					% reduction in ulcer diameter		
					73%	55%	p = 0.016

CI = confidence interval; RCT = randomised controlled trial; RR = relative risk; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot

Lyophilised Collagen versus hyaluronic acid

Di Mauro et al (1991) conducted a poor quality randomised controlled trial that evaluated the effectiveness of lyophilised collagen applied directly onto the surface of the ulcer compared to a hyaluronic acid medicated gauze for the treatment of diabetic foot ulcer (Table 130). Both of these treatment were in addition to standard wound care.

Lyophilised collagen stimulates the wound healing by promoting platelet adhesion and aggregation and attracts macrophages necessary for wound healing. Hyaluronic acid is thought to play important roles in the formation of granulation tissue and in the re-epithelialisation process. The authors reported that application of lyophilised collagen onto the wound, instead of using a hyaluronic acid medicated dressing, accelerated the mean time to healing (32 ± 8.6 days versus 49 ± 11 days, $p < 0.001$). No adverse events were reported. Furthermore, of the 20 ulcers, 19 were foot ulcers and one was a wrist ulcer.

Even though this result is statistically significant, there is insufficient information provided on patient characteristics and sample sizes. This reduces the generalisablility of the target population. Box 174 summarises the body of evidence according to the NHMRC grading criteria.

Box 174 Evidence matrix for comparison of lyophilised collagen for the treatment of diabetic foot ulcers

Component	Rating	Description
Evidence base	D	One level II study with high risk of bias
Consistency	N/A	Only one study.
Clinical impact	D	The results indicate that there is a significant clinical impact on time to ulcer healing. There is insufficient information concerning the characteristics of the intervention and control group.
Generalisability	D	There is insufficient information given to determine the generalisablility of the population.
Applicability	C	The study took place in Italy, which is probably applicable to the Australian healthcare context with some caveats.

Evidence statement

There is insufficient evidence to suggest that either lyophilised collagen or hyaluronic acid in addition to standard care are more effective than standard wound care alone for the treatment of diabetic foot ulcers (Grade D).

Table 130 Included study which compared lyophilized collagen versus hyaluronic acid for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Dimauro et al 1991) Italy	Level II RCT Poor quality study	Patients affected by non insulin dependent DM and ulcers treated for diabetic foot ulcer. Characteristics- N = 20; age range (yrs) 60-78; male 12/20 (60%); foot ulcer 19/20 (95%), wrist ulcer 1/20 (5%).	N = not reported. Patients were treated by debridement, repeated saline solution washing and local antibiotic therapy, after adequate debridement, Lyophilized collagen (LC) was applied on the surface of the ulcer or inside fistulas. Tablets were moistened with saline or antibiotic solution when applied on the ulcer; tablets were dry, cut and suitable moulded when inserted in fistulas. Dressing was renewed every two days.	N = not reported. Patients were treated by debridement, repeated saline solution washing and local antibiotic therapy, after adequate debridement, hyaluronic acid medicated gauze was applied.	Mean time to complete wound healing (days)		
					32 ± 8.6	49 ± 11	p < 0.001

Honey versus povidone iodine solution

One poor quality randomised controlled trial conducted by Shukrimi et al (2008) evaluated the effectiveness of honey as a dressing in addition to standard care for the treatment of diabetic foot ulcer (Table 131). After debridement, the ulcer of patients from the intervention group were covered with a thin layer of honey and then with sterile gauze and bandaged. The ulcers form control group patients were covered with gauze soaked in 10% povidone iodine solution diluted in saline. The difference in the time taken for the wound to be suitable for surgical closure between the two groups was not statistically significant. The mean time taken before surgical closure of the wound was 14.4 days for the honey treatment and 15.4 days for povidone iodine-soaked gauze (both in addition to standard wound care). The results indicate that there is no evidence for the use of honey in combination with standard care when compared to povidone iodine-soaked gauze. It has to be stated that the study provided minimal information on the sample sizes in both groups and population characteristics. Furthermore, the outcome was not clearly defined and it is unknown how it was evaluated. Based on the poor quality of the study and the non significant result, no recommendation will be provided. Further research is required.

Box 175 summarises the body of evidence according to the NHMRC grading criteria.

Box 175 Evidence matrix for comparison of honey versus povidone solution

Component	Rating	Description
Evidence base	D	One level II study with high risk of bias
Consistency	N/A	Only one study.
Clinical impact	D	The results do not indicate that there is a significant clinical impact on outcomes.
Generalisability	A	The evidence directly generalisable to target population
Applicability	C	The study took place in Malaysia, which is probably applicable to the Australian healthcare context with some caveats.

Evidence statement

There is insufficient evidence to suggest that honey is more effective than povidone solution in preparing diabetic foot ulcers for surgical closure (Grade D).

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Table 131 Included study for honey versus saline solution for the treatment of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Shukrimi et al 2008) Malaysia	Level II RCT Poor quality study	Patients admitted for surgery for diabetic foot related complications in teaching hospital Inclusion criteria: N = 30, NIDDM with Wagner grade-II ulcers; age between 35-65; transcutaneous oxygen tension of more than 30 mm Hg, and serum albumin levels of more than 35g/dl.	N = not reported. After surgical debridement, the wound was dressed with honey: clean non-sterile pure honey (Honey Cooperation of Australia Pty. Ltd) (pH 6.5, glucose 321mmol/l gravity 1.003) that is used commercially for food. Wound was then covered with gauze and bandage.	N = not reported. After surgical debridement, the wound was dressed with 10% povidone iodine solution soaked gauze	Mean duration (days) to be ready for surgical closure of foot ulcer		
					14.4	15.4	p = ns

RCT= randomised controlled trial; NIDDM= non insulin dependent diabetes mellitus; Wagner Classification: Grade 1 = superficial ulcer, Grade 2 = deep ulcer to tendon, capsule or bone, Grade 3 = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade 4 = localised gangrene of forefoot or heel, Grade 5 = gangrene of entire foot

Miscellaneous interventions

Biofeedback-assisted relaxation training

A poor quality randomised controlled trial conducted at several outpatient clinics in the USA attempted to evaluate the use of biofeedback-assisted relaxation in addition to standard wound care to improve foot outcomes in people with foot ulcer (Rice et al 2001). Patients were under the care of a foot-care physician for at least 2 months prior to enrolment and had ulcers which were categorised as class 2-6 by the Seattle Wound Classification system after debridement. Exclusion criteria included bone involvement and osteomyelitis and surprisingly, patients who later required surgery (reconstructive or vascular) or who were not compliant with the experimental intervention.

The randomisation process stratified the treatment allocation according to people with or without diabetes. The study indicates that sample size calculations were performed to detect a statistically significant difference, but the level of significance (α) or the power of the study (1-β) were not described.

The intervention consisted of one training session related to biofeedback-assisted relaxation which incorporated the principles of vascular physiology and the possible physical sensations of peripheral warming. The relaxation technique used progressive muscular relaxation, focused breathing, and phrases to suggest feeling warmth and heavy. Motivation for patients was assisted by focusing on lifestyle changes, learning new skills and encouragement. The training session was supplemented by a 16 minute audiotape of the relaxation technique which was to be used at least 5 days per week. Patients were able to monitor their progress by attaching an alcohol thermometer to the great toe both before and after relaxation and recording the temperatures. This was also used to monitor compliance with the intervention.

The control group received instructions to relax for 15-20 minutes per day, using any method of their choice, while off their foot.

The authors indicated that one patient was excluded from the study due to poor compliance with the intervention. This patient was replaced with another subject. It is not reported if any subjects were excluded for the later requirement for reconstructive or vascular surgery.

A total of 32 patients were analysed in this study of which 16 had diabetes. At the end of the three month follow-up, 7/8 (88%) of diabetic patients receiving the intervention had healed compared with 3/8 (38%) in the control group (RR = 2.3 [95% CI 1.04, 3.56]). Of all the patients reported in the study, including those without diabetes, 14/16 (88%) in the intervention group had healed ulcers at the end of follow-up compared with 7/16 (44%) in the control group (RR = 2.0 [95% CI 1.18, 2.74]). The authors also reported the healing rate of ulcers as the change in ulcer area per day. There was a statistically significant increase (p = 0.002) in healing rate for the intervention group (2.84 ± 3.45 mm^2/day) compared to the control group (0.85 ± 0.56 mm^2/day)

Although the reported results suggest a moderate benefit in using biofeedback-assisted relaxation techniques in addition to standard wound care, it is highly likely that there is significant bias introduced into this study by the lack of an intention-to-treat analysis.

The evidence for biofeedback-assisted relaxation is summarised in the evidence statement matrix (Box 176).

Box 176 Evidence statement matrix for the use of biofeedback-assisted relaxation for the treatment of foot ulcer

Component	Rating	Description
Evidence base	D	One level II study with a high risk of bias.
Consistency	N/A	Only one study available
Clinical impact	D	There was moderate benefit seen for healing of foot ulcer but this is likely to be substantially biased by the lack of intention-to-treat analysis.
Generalisability	B	The study would be generalisable to patients with foot ulcer receiving care from a foot-care physician.
Applicability	B	The study was conducted in USA and is therefore applicable to Australian healthcare context with few caveats.

Evidence statement

There is limited evidence to indicate that there is a slight effect on ulcer healing for biofeedback-assisted relaxation in addition to standard wound care, in patients cared for by foot-care physicians (Grade C).

Interventions for people without diabetic foot ulcers

Drug therapy for improving nerve function to prevent ulceration

Sorbinil

Sorbinil is an aldose reductase inhibitor which acts on the enzyme involved in the synthesis of fructose and sorbitol from glucose. This is thought to be the rate-limiting step leading to elevated levels of fructose and sorbitol in the nerves of diabetic patients (O'Hare et al 1988). Inhibition of this enzyme is thought to reduce the fructose and sorbitol concentration and consequently improve nerve conductivity.

O'Hare et al (1988) conducted an average quality double-blind randomised placebo-controlled trial involving 31 diabetic patients with diffuse peripheral neuropathy attending the Bristol Royal Infirmary in the United Kingdom (Table 132). Those randomised to the intervention received 250 mg sorbinil daily p.o.[2] for 12 months. Adverse events were reported for two patients that developed a hypersensitivity reaction (febrile illness with myalgia) within two days of starting treatment with sorbinil, which resolved on cessation of treatment. During the 12 month intervention no beneficial effects were demonstrated for either neuropathic outcomes such as nerve conductivity, or clinically relevant outcomes such as prevention of ulceration (Table 132). Ulcers developed in 19% of the sorbinil group and 10% of the control group (RR = 1.91 [95%CI 0.33, 12.40], p > 0.05). Although the study is underpowered to detect a statistical difference, the direction of the treatment effect would suggest that sorbinil performed worse in preventing ulcer development compared to placebo. However, it is important to note when considering these results that the baseline tarsal vibration threshold for the sorbinil group was 23.0 ± 34 μm compared to the placebo group, 10 ± 18.9 μm.

This evidence is summarised in Box 177 according to the NHMRC grading criteria.

Box 177 Evidence statement matrix for drug therapy in addition to standard wound care

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	D	The study is underpowered to detect a statistical difference. The direction of the treatment effect suggests that the intervention is worse than placebo in preventing ulcer development however it is unclear whether this is due to the greater severity of neuropathy in the intervention group at baseline.
Generalisability	A	Generalisable to people with diabetic neuropathy in an outpatient setting.
Applicability	B	Study conducted in the UK and therefore likely to be applicable to the Australian healthcare context with few caveats.

Evidence statement

The evidence is inconclusive evidence regarding the use of sorbinil for the prevention of foot ulcers in people with diabetic neuropathy (Grade C).

[2] p.o. - per os, orally or by mouth

Table 132 Study which evaluates the effectiveness of sorbinil for the prevention of diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
(O'Hare et al 1988) United Kingdom	II RCT Good quality study	N = 31. Diabetic patients with the presence of clinically evident diffuse symmetrical peripheral somatic neuropathy of at least 6 months duration. Intervention group – n = 21, mean age (yrs) 55.6 ± 8.1; duration of diabetes (yrs) 16.5 ± 8.7; mean HbA1c (%) 11.4 ± 1.9; median sensory NCV (m/s) 43.6 ± 7.2; peroneal motor NCV (m/s) 36.9 ± 4.3; heart rate variation on single breath (beats/min) 2.7 ± 1.9; tarsal vibration threshold (μm) 23.0 ± 34; insulin therapy = 15/21 (72%); oral hypoglycaemic agents = 6/21 (28%); retinopathy = 16/21 (76%); proteinuria = 4/21 (19%). Comparator group – n = 10, mean age (yrs) 55.6 ± 11.1; duration of diabetes (yrs) 13.3± 8.9; mean HbA1c (%) 11.1 ± 2.0; median sensory NCV (m/s) 45.0 ± 6.8; peroneal motor NCV (m/s) 38.5 ± 6.6; heart rate variation on single breath (beats/min) 1.8 ± 1.3; tarsal vibration threshold (μm) 10.0 ± 18.9; insulin therapy = 6/10 (60%); oral hypoglycaemic agents = 4/10 (40%); retinopathy = 7/10 (70%); proteinuria = 1/10 (10%).	n = 21 Initial 2 month run-in period where all patients in both groups received placebo tablets. Take 250 mg sorbinil tablets p.o. daily (for 12 months) in addition to usual care	n = 10 Placebo tablets for 12 months in addition to usual care	Number of patients that developed ulcers during the 12 month study period Intervention: 4/21 (19%) Comparator: 1/10 (10%) Comparison: RR = 1.91 [95% CI 0.33, 12.40]

NCV = nerve conduction velocity; p.o. = orally

Hydroxyethylrutosides

Hydroxyethylrutosides are flavenoids that have been shown to inhibit red cell aggregation and act on the microvascular endothelium to inhibit its permeability and reduce oedema (Lund et al 1999).

Lund et al (1999) reported a historically controlled comparative study of average quality involving 70 patients (37 (53%) with diabetes) with critical limb ischaemia (CLI) (Table 133). The 42 patients (52 CLI legs) with or without ischaemic foot lesions received twice daily intravenous (IV) hydroxyethylrutoside treatment and standard wound care for any lesions, and the outcomes were compared to a historical reference group of 28 patients (34 CLI legs) that received standard care. Adverse events were reported for three patients that developed exanthema soon after starting the twice daily hydroxyethylrutoside treatment and consequently, treatment was discontinued. This study demonstrated no statistically significant difference in the mortality and amputation rates between diabetic patients receiving hydroxyethylrutosides and those that did not (RR = 0.95 [95% CI 0.38, 2.38] and 0.87 [95% CI 0.56, 1.41], respectively). It is unclear as to the impact of confounding in this study given the potential for health care delivery changes between treatment of the intervention group and that of the comparator and the different types of blood thinners used in the two study arms.

Box 178 Evidence statement matrix for hydroxyethylrutosides in addition to standard wound care

Component	Rating	Description
Evidence base	D	One level III-3 study with a moderate risk of bias
Consistency	N/A	There is only one study
Clinical impact	D	There was no statistically significant reduction in the number of amputations needed after administering hydroxyethylrutosides compared with standard care.
Generalisability	C	The population consisted of patients with critical limb ischemia, 53% of which had diabetes. Thus, would only apply to diabetic patients at the severe end of the spectrum.
Applicability	B	The study was conducted in Sweden, which has comparable healthcare for diabetic patients when compared to the Australian healthcare context.

Evidence statement

On the basis of the evidence available, hydroxyethylrutosides therapy is unlikely to provide any clinical benefit in addition to standard care when treating patients with critical limb ischaemia. (Grade D)

Table 133 Effectiveness of hydroxyethylrutosides for the treatment of critical limb ischaemia and ischaemic foot lesions

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
(Lund et al 1999) Sweden	III-3 Retrospective cohort Average quality study	Patients: N = 70 Patients fulfilled the inclusion/exclusion criteria defined in the Second European Consensus Documents on Critical Limb Ischaemia (CLI) of 1991. Patients in both groups had a similar prevalence for gender, arterial reconstruction, angina pectoris, myocardial infarction, congestive heart failure, and cerebrovascular disease. The number of more advanced ischaemic lesions was also comparable. Intervention group: N = 42; diabetics 19/42 (45%); CLI legs n = 52; ischaemic ulcers 15/52 (29%); previous leg amputation 5/42 (11.9%); smokers~25%; rest pain with ischaemic cyanotic discolouration but without trophic lesions ~6%. Diabetic patients: N = 19; CLI legs N = 23; age (yrs) 71.7 ± 6.6; toe blood pressure in CLI legs (mmHg) 7.4. Comparator group: N = 28; diabetics 18/28 (64%) CLI leg n = 34; previous leg amputation 4/28 (14.3%); smokers~25%; rest pain with ischaemic cyanotic discolouration but without trophic lesions ~9%. Diabetic patients: N = 18; CLI legs N = 20; age (yrs) 70.4 ± 8.7; mean toe blood pressure in CLI legs (mmHg) 8.0.	Patients: N = 42 (CLI legs: N = 52) Diabetic patients: N = 19 (Diabetic CLI legs: N = 23) Standard care plus treatment with two slow (30 min) daily IV hydroxyethylrutosides infusions of 1.5 g each for a mean period of 3.6 weeks in combination with oral anticoagulant warfarin, which was continued until the end of the 24 month study period.	Patients: N = 28 (CLI legs: N = 34) Diabetic patients: N = 18 (Diabetic CLI legs: N = 20) Standard wound care: This included local treatment of lesions, control of diabetes, coronary heart disease, congestive heart failure, and infection if required. 11 patients received warfarin alone, a few had low-dose aspirin, 2 received subcutaneous low-molecular-weight heparin, and 1 received an IV prostacyclin analogue. This was classified as standard treatment.	Number of patients that died during the study period at: 1 month All Diabetic 0/42 0/19 (0%) (0%) 3 months All Diabetic 2/42 2/19 (5%) (11%) 6 months All Diabetic 2/42 2/19 (5%) (11%) 12 months All Diabetic 6/42 3/19 (14%) (16%) 24 months All Diabetic 17/42 6/19 (40%) (32%)	All Diabetic 1/28 0/18 (4%) (0%) All Diabetic 5/28 4/18 (18%) (22%) All Diabetic 9/28 6/18 (32%) (33%) All Diabetic 10/28 6/18 (36%) (33%) All Diabetic 11/28 6/18 (39%) (33%)	 RR_{all} = 0.00 [95% CI 0.00, 2.54] $RR_{diabetic}$ = 1 RR_{all} = 0.27 [95% CI 0.06, 1.12] $RR_{diabetic}$ = 0.47 [95% CI 0.11, 2.00] RR_{all} = 0.15 [95% CI 0.04, 0.55] $RR_{diabetic}$ = 0.32 [95% CI 0.01, 1.18] RR_{all} = 0.40 [95% CI 0.17, 0.95] $RR_{diabetic}$ = 0.47 [95% CI 0.14, 1.49) RR_{all} = 1.03 [95% CI 0.59, 1.89] $RR_{diabetic}$ = 0.95 [95% CI 0.38, 2.38]

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention	Comparator	Comparison
					Number of CLI legs requiring amputation during the study period at: 1 month All Diabetic 3/52 1/23 (6%) (4%)	All Diabetic 4/34 2/20 (12%) (10%)	RR_{all} = 0.49 [95% CI 0.13, 1.88] $RR_{diabetic}$ = 0.44 [95% CI 0.06, 3.20]
					3 months All Diabetic 17/52 7/23 (33%) (30%)	All Diabetic 13/34 8/20 (38%) (40%)	RR_{all} = 0.86 [95% CI 0.49, 1.54] $RR_{diabetic}$ = 0.76 [95% CI 0.34, 1.71]
					6 months All Diabetic 20/52 8/23 (38%) (35%)	All Diabetic 15/34 9/20 (44%) (45%)	RR_{all} = 0.97 [95% CI 0.53, 1.47] $RR_{diabetic}$ = 0.77 [95% CI 0.37, 1.61]
					12 months All Diabetic 23/52 10/23 (44%) (44%)	All Diabetic 17/34 11/20 (50%) (55%)	RR_{all} = 0.89 [95% CI 0.58, 1.41] $RR_{diabetic}$ = 0.79 [95% CI 0.44, 1.46]
					24 months All Diabetic 27/52 13/23 (52%) (57%)	All Diabetic 20/34 13/20 (59%) (65%)	RR_{all} = 0.88 [95% CI 0.62, 1.32] $RR_{diabetic}$ = 0.87 [95% CI 0.56, 1.41]

RR = relative risk; CI = confidence interval; IV = intravenous.

Therapeutic footwear

For prevention of re-ulceration

Two average quality randomised controlled trials reported on the use of therapeutic footwear to prevent reulceration (Reiber et al 2002; Uccioli et al 1995) (Table 134). In the study by Reiber et al (2002) patients attending health care centres in the USA, who had a previous history of ulcer were randomised to receive either therapeutic footwear with cork or prefabricated insoles, or to wear their usual footwear. After appropriate fitting of intervention footwear, all patients were followed for two years. There was some cross-over between the control and the intervention groups where custom shoes were prescribed for 2.5% of the control group, and custom inserts for an additional 4.4%. Furthermore, 13% of the control group purchased therapeutic footwear and 17% purchased over the counter inserts during the study period. The authors had anticipated that 33% of controls would cross-over to the intervention group and had powered the study accordingly.

After two years, the incidence of re-ulceration in the cork and prefabricated inserts and control groups was 15%, 14% and 17% respectively. The relative risk of re-ulceration in the cork insert group was 0.88 [95%CI 0.51, 1.52] compared to the control group. For the group who received the prefabricated inserts, the relative risk was 0.85 [95%CI 0.48, 1.48] compared to the control group. As such, this study does not provide evidence of a statistically significant benefit for the use of therapeutic footwear with either cork or prefabricated inserts.

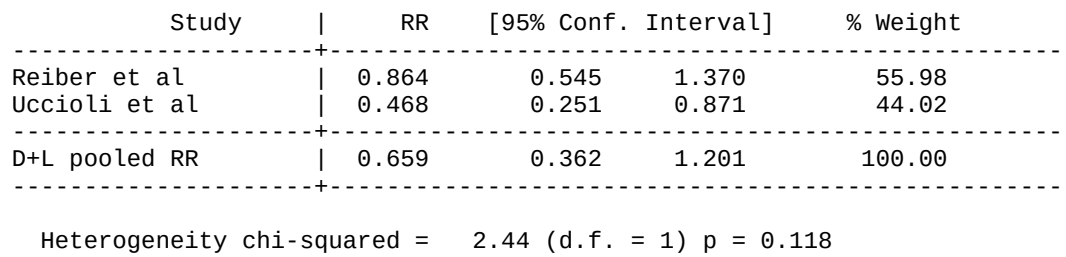
The study by Uccioli et al (1995) also considered the clinical benefit of therapeutic footwear for the prevention of re-ulceration. Patients were randomised to receive either therapeutic footwear or to wear ordinary shoes. The therapeutic shoes were designed according to Towey guidelines and their use was rated as infrequent, occasional, frequent or continuous. All patients received education on the importance of wearing appropriate footwear and footcare.

After one year, the authors reported that 28% of the intervention group had developed an ulcer compared to 58% of the control group (OR=0.25 [95%CI 0.2, 1.54]). The authors were not explicit regarding the assessment of outcome therefore there is the potential for measurement bias.

In the absence of absolute numbers in the study by Uccioli et al (1995), a meta-analysis has not been conducted.

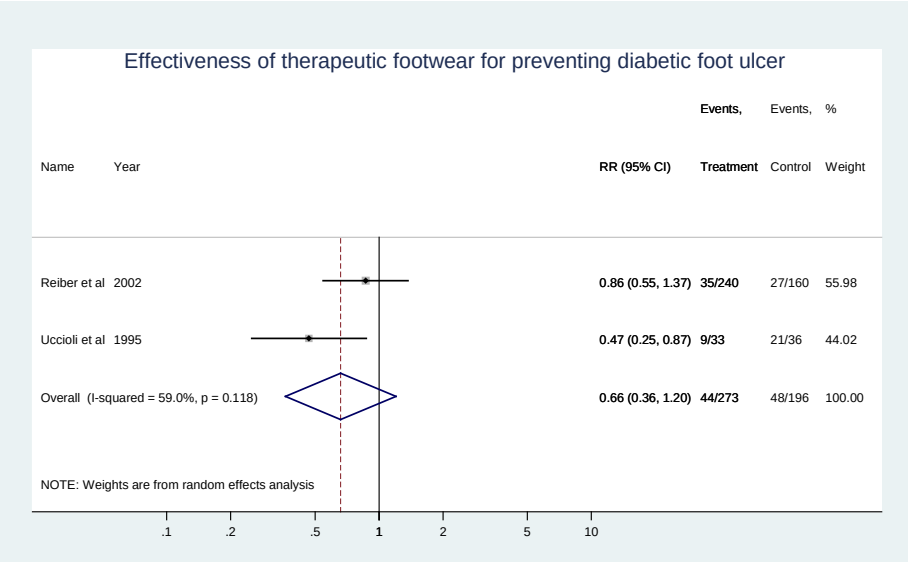
Meta-analysis of these two results highlights that there is insufficient evidence to support the use of therapeutic footwear for the prevention of recurrent foot ulcer (Figure 14). Pooling the data provided an effect size which indicates that this intervention does protect against recurrent foot ulcer however, this effect was not statistically significant (RR = 0.66 [95% CI 0.36, 1.20]). This analysis also indicated that the extent of heterogeneity was considerable which may suggest that the pooled estimate should be considered with some caution.

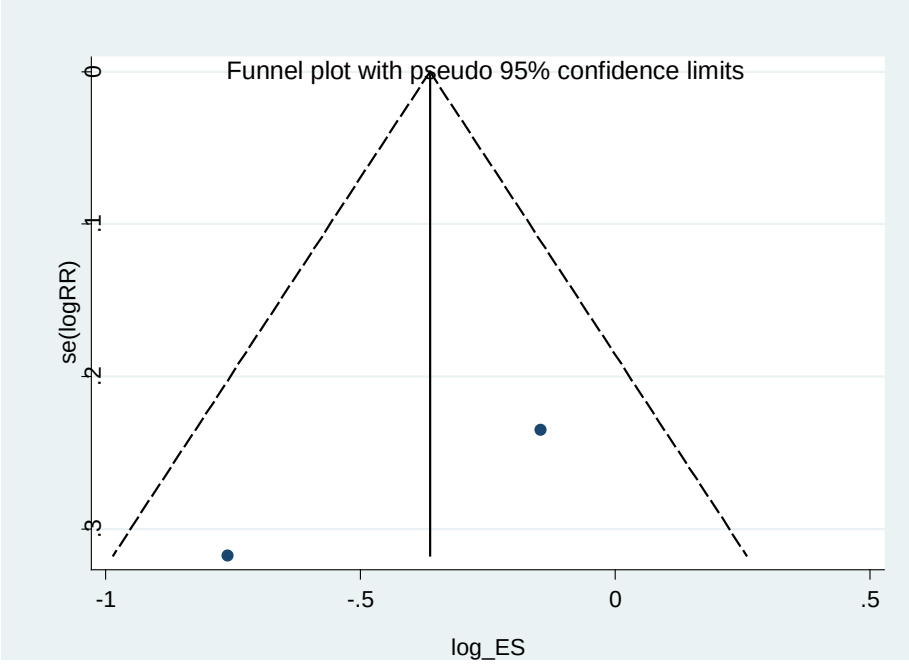
Figure 14 Meta-analysis of therapeutic footwear to prevent foot ulcer



```
I-squared (variation in RR attributable to heterogeneity) =  59.0%
Estimate of between-study variance Tau-squared =  0.1121

Test of RR=1 : z=   1.36 p = 0.174
```





The evidence for therapeutic footwear relative to usual footwear as presented here is summarised in the evidence statement matrix (Box 179).

Box 179 Evidence statement matrix for the comparison of therapeutic and usual footwear

Component	Rating	Description
Evidence base	C	Two level II studies with a moderate risk of bias.
Consistency	A	All studies are consistent
Clinical impact	D	No study provided sufficient evidence that there was a benefit of therapeutic footwear over usual footwear for preventing recurrence of foot ulcer.
Generalisability	B	The study is generalisable to people with a history of diabetic foot ulcer.
Applicability	C	The studies were conducted in the USA and Italy and therefore likely to be applicable to the Australian healthcare context with some caveats.

Evidence statement

There is insufficient evidence to support the use of therapeutic footwear over usual footwear to prevent recurrence of diabetic foot ulcers (Grade C).

To correct foot callus

An average quality randomised controlled trial conducted in Sydney, Australia considered the effect of customised rigid orthotic devices for the treatment of foot callus in a group of diabetic people with no history of foot ulcer (Colagiuri et al 1995). The population in this study was from an outpatient diabetes clinic and had plantar calluses with minimal to marked keratin thickening and after randomisation; the intervention group received a custom-made rigid orthotic device and asked to wear them for at least 7 hours per day. Patients who received the orthotic devices did not have their calluses debrided during the study and the authors did not indicate whether patients were compliant with these instructions. Patients in the control group received chiropodic care every 3 months which were timed to occur following the study assessment visit. It is not clear if the patients in the intervention group were assessed every 3 months in a similar fashion to the control group.

At the end of the 12 month study period calluses were photographed and then assessed by the three authors who were blinded to the identity and treatment of the subject (Table 134). The grade of callus (based on keratin thickness and presence of haematoma, ulcer or infected ulcer) improved in 73% of patients wearing the orthotic devices compared to 6% in the control group. None of the intervention group had calluses which deteriorated during the study whereas the control group had 22% which were of a worse grade than at baseline. These differences between intervention and controls groups were statistically significant ($p < 0.02$, Fisher's exact test).

The evidence for therapeutic footwear relative to usual footwear as presented here is summarised in the evidence statement matrix (Box 180).

Box 180 Evidence statement matrix for the comparison of therapeutic footwear and chiropody

Component	Rating	Description
Evidence base	C	One level II study with a moderate risk of bias.
Consistency	N/A	Only one study available
Clinical impact	C	The results suggest that rigid orthotic devices may improve plantar calluses.
Generalisability	B	The study would be generalisable to patients with plantar calluses and no history of foot ulcer.
Applicability	A	The study was conducted in Australia and is therefore directly applicable to Australian healthcare context

Evidence statement

There is some evidence to suggest that rigid orthotic devices may help improve plantar calluses in people with diabetes and no history of foot ulcer (Grade C).

Table 134 Included studies for therapeutic footwear in people without diabetic foot ulcers

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
(Reiber et al 2002) USA	II RCT Average quality	400 diabetic patients with a history of foot ulcer or foot infection. Patient characteristics: Age = 62 ± 10 years; female = 23%; moderate/severe foot oedema = 10%; no palpable pedal pulses = 1%; insensate to monofilament = 25%; moderate foot deformity = 32%	Therapeutic footwear with insert of either one of prefabricated (polyurethane) or custom-made (cork) material	Usual footwear	Re-ulceration during 2 year follow-up: Cork inserts: 18/121 (15%) RR = 0.88 [95%CI 0.51, 1.52] Prefabricated inserts: 17/119 (14%) RR = 0.85 [95% CI 0.48, 1.48] Usual footwear: 27/160 (17%)
(Uccioli et al 1995) Italy	II RCT Average quality	69 diabetic patients with history of foot ulcer.	Therapeutic footwear Designed according to Towey guidelines with super-depth to fit customised insoles and toe deformities, soft thermoformable leather with semi-rocker soles. Customised insoles used Alcapy (to relieve local pressures) and Alcaform (to absorb high-pressure points).	Usual footwear	Re-ulceration during 1 year follow-up: Therapeutic footwear: 27.7% OR = 0.26 [95% CI 0.2, 1.54] Usual footwear: 58.3% Correlation coefficient = -0.32 [95% CI -0.54, -0.08]
(Colagiuri et al 1995) Australia	II RCT Average quality	20 diabetic subjects with plantar callus without history of foot ulcer. Patient characteristics: Age = 66 ± 8 years; Males = 5/20 (25%); Weight = 75 ± 10kg	n = 9 (22 calluses) Custom-made rigid orthotic device. Subjects were asked to wear it for ≥ 7 hours per day.	n = 11 (32 calluses) Traditional treatment of callus by three monthly podiatry visits.	Number of calluses healed after 12 months: Intervention: 2/22 (9%) Control: $RR_{healing\ of\ callus}$ = Not calculable 0/32 (0%) Proportion improved: Intervention: Improved 16/22 (73%) Control: 2/32 (6%)

					Same 6/22 (27%) 23/32 (72%) Worse 0/22 (0%) 7/32 (22%) Fisher's Exact test: $p < 0.02$

Miscellaneous therapies

Topical antifungal nail lacquer

An average quality study evaluated the use of an antifungal nail lacquer (8% ciclopirox) applied daily in addition to instructions on daily self-inspection (Armstrong et al 2005a) to prevent foot ulceration. The study enrolled 70 people considered at high risk of diabetic foot ulceration (Category 2 and 3[3] of the International Diabetic Foot Classification system) into a preventive foot care program. Little information was provided regarding the nature of this program with the exception that instructions were provided for daily self-inspection of feet. It was also unclear if the anti-fungal lacquer was applied daily or otherwise. Patients were also provided with access to a 24 hour 'foot hotline' which would enable immediate scheduling of emergency appointments. The patients were followed in a multidisciplinary high risk diabetic foot clinic every 3 months for 12 months or until ulceration.

At the end of the study period, there was no statistically significant difference in the number of people who developed ulcers between the intervention and control groups (RR = 1.06 [95% CI 0.19, 5.87]).

The evidence for antifungal nail lacquer is summarised in the evidence statement matrix (Box 181).

Box 181 Evidence statement matrix for the addition of antifungal nail lacquer to a preventive care program

Component	Rating	Description
Evidence base	C	One level II study with a moderate risk of bias.
Consistency	N/A	Only one study available
Clinical impact	D	There was no statistically or clinically significant benefit seen for the development of foot ulcer.
Generalisability	B	The study would be generalisable to patients with at high risk of diabetic foot ulcer attending a high risk foot clinic.
Applicability	B	The study was conducted in USA and is therefore applicable to Australian healthcare context with few caveats.

Evidence statement

There is some evidence to indicate that there is no additional effect of using antifungal nail lacquer in addition to a preventive foot program to prevent the development of foot ulcer (Grade C).

Education for the prevention of foot complications

Brief education versus usual care

One good and one average quality randomised controlled trial evaluated a brief educational program in addition to general information for the prevention of diabetic foot complications relative to usual care (including general information) (Table 135). The education program involved a short one hour session, which covered causation of ulcers and amputation as well as instructions regarding the care of foot ulcers. Patients in both the intervention and control group received routine diabetic information with respect to diet, weight, exercise and medication.

[3] Category 2 consists of neuropathy/deformity; Category 3 = history of ulceration or amputation

Lincoln et al (2008) reported that there was no statistically significant difference between the intervention and control group with respect to the recurrence of foot ulcer or incidence of amputation after 12 months of follow-up (RR = 0.99 [95%CI 0.78, 1.3] and RR = 1.0 [95%CI 0.9, 1.1], respectively). In contrast, Malone et al (1989) did find a protective effect for the recurrence of foot ulcers and incidence of amputation for patients who received brief education in addition to usual care (RR = 0.29 [95% CI 0.14, 0.6] and RR = 0.0.3 [95% CI 0.14, 0.7], respectively). The estimated number needed to treat to prevent one case of foot ulceration was 9 [95% CI 7, 24] and for amputation 13 [95% CI 9, 41], indicating that the brief educational program was clinically important. The authors also evaluated the use of the brief education program to prevent diabetic foot infections, but no statistical difference was found (1.1 % in the intervention group versus 1.1% in control group). It should be noted that Malone et al (1989) used different follow-up periods for the intervention (12 months) and control group (8 months) but the impact of this on the results is uncertain. Unfortunately, the authors did not provide sufficient information concerning the study population characteristics, and given the lack of information regarding the randomisation procedure, the possibility of confounding affecting the results cannot be ruled out.

Although the study by Lincoln et al (2008) was of a higher quality than that of Malone et al (1989), the former lacked adequate power to detect any treatment effect. Due to statistically significant degree of heterogeneity (data not shown), pooling of these data has not been included in this review. The likely source of the heterogeneity could be the population considered in the study by Lincoln et al (2008) which were patients with a recently healed foot ulcer. These patients are likely to be at higher risk of recurrent ulcer and subsequent amputation than the population studied by Malone et al (1989) who had no foot infections or previous amputations.

Box 182 summarises the body of evidence according to the NHMRC grading criteria.

Box 182 Evidence matrix for comparison of brief education for the prevention of diabetic foot complications

Component	Rating	Description
Evidence base	B	One level II study with low risk of bias and one level II study with moderate risk of bias.
Consistency	B	The study by Lincoln et al (2008) was underpowered but reported a treatment effect in the same direction as Malone et al (1989).
Clinical impact	C	Given the lack of power in one study, the estimate of the benefit in regard to amputation and recurrence is still somewhat uncertain.
Generalisability	C	The studies included a sample population attending diabetes, podiatry or vascular surgery clinics, which makes them generalisable to the target population. The sample characteristics were not described by Malone et al (1989), which makes it difficult to judge the generalisability of the results.
Applicability	B	The studies took place in the UK and USA, which have similar health care for diabetes patients compared to the Australia health care context.

Evidence statement

There is some evidence to suggest that a brief education program in addition to usual care reduces the occurrence of diabetic foot infection, ulcer and amputation in the general diabetic population (Grade B).

Table 135 Studies included which compare brief education to usual care for the prevention of diabetic foot complications

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
(Lincoln et al 2008) UK	Level II RCT Good quality study	Patients with newly healed foot ulcers visiting outpatient diabetes clinics. Intervention group: N = 87, mean age , yrs (SD) 63.5 (12.1), male 71% (n=62), visit centre 1 56% (n=49), centre 2 27% (n=23), centre 3 17% (n=15), living alone 21% (n=18), partner 79% (n=69), social class 1 9% (n=8), class 2 17% (n=15), class 3 46% (n=40), class 4 21% (n=18), class 5 6% (n=5), currently working 22% (n=19), type II DM 74% (n=64), retinopathy 61% (n=32),UK white ethnicity 95% (n=83), Other 5% (n=n=5), neuropathy 29% (n=25),10g monofilament: sensitivity to all 3 22% (n=19), only 1 or 2 felt 31% (n=27), none felt 47% (n=41), neurotip felt 65% (n=57), both foot pulses palpable 35% (n=30), 1 palpable/ both diminished 45% (n=39), neither palpable 20% (n=17), previous ulcer site: forefoot 81% (n=70), mid and hindfoot 19% (n=17), previous amputation other leg minor 7% (n=6), major 3% (n=3), amputation same leg minor 20% (n=17), vibration perception >25 volt 32% (n=22), fitted foot wear 64% (n=56). Comparator group: N = 85, mean age yrs (SD) 64.9 (10.9), male 62% (n=53), visit centre 1 63% (n=54), centre 2 26% (n=22), centre 3 11% (n=9), living alone 16% (n=14), partner 84% (n=71), social class 1 5% (n=4), class 2 22% (n=19), class 3 40% (n=34), class 4 24% (n=20), class 5 9% (n=8), currently working 29% (n=25), type II DM 81% (n=69), retinopathy 59% (n=50), UK white ethnicity 96% (n=82), Other 4% (n=3), neuropathy 22% (n=19),10g monofilament: sensitivity to all 3 21% (n=18), only 1 or 2 felt 36% (n=31), none felt 42% (n=36), neurotip felt 64% (n=54), both foot pulses palpable 39% (n=33), 1 palpable/ both diminished 33% (n=28), neither palpable 28% (n=24), previous ulcer site: forefoot 80% (n=68), mid and hindfoot 20% (n=17), previous amputation other leg minor 6% (n=5), major 3% (n=3), amputation same leg minor 20% (n=17), vibration perception >25 volt 38% (n=32), fitted foot wear 64% (n=54).	N = 87, patients received a single 1 hour home education session, which involved causation of ulcers and amputation, and patient instructions for the care of foot ulcers. Education was supplemented with handouts.	N = 85, patients receiving usual care which included general information about diabetes.	Recurrence foot ulcer at 12 months Intervention 36/87 (41%) | Control 35/85 (41%) | Effect size [95% CI] RR 0.99 [0.78, 1.3] Amputation at 12 months Intervention 9/87 (10%) | Control 9/52 (11%) | Effect size [95% CI] RR 1.0 [0.9, 1.1]
(Malone et al 1989)	Level II RCT	Patients visiting podiatry and vascular surgery clinic. Intervention group: N = 203 limbs; details on other	N = 203, patients received a single 1	N = 193, patients receiving usual care.	% recurrence of foot ulcer at 12 (intervention) and 8 (control) months

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
USA	Average quality study	characteristics not given Comparator group: N = 193 limbs; details on other characteristics not given	hour home education session, which involved causation of ulcers and amputation, patient instructions for the care of foot ulcers. Education was supplemented with handouts.		Intervention 8/203 (3.9%)	Control 26/193 (13.5%)	Effect size [95% CI] RR 0.29 [0.14, 0.6] NNT 10.5 [8, 24]
					% amputation at 12 (intervention) and 8 (control) months		
					Intervention 7/203 (3.4)%	Control 21/193 (11%)	Effect size [95% CI] RR 0.3 [0.14, 0.7] NNT 13 [9, 41]
					% infection at 12 (intervention) and 8 (control) months (per protocol analysis)		
					Intervention 1.1% (n=2)	Control 1.1% (n=2)	p= ns

RCT= randomised controlled trial; RR= relative risk; ns= non significant; NNT= number needed to treat

Education program versus usual care

Two average quality studies evaluated the effectiveness of education programs in addition to usual care for the prevention of diabetic foot complications (Table 136).

Bloomgarden et al (1987) evaluated an education program that consisted of nine group sessions in a randomised controlled trial. The focus of the education sessions was to develop a general understanding of diabetes, foot care and hygiene, medication usage, risk factors for macrovascular disease, and instructions on diet and basic nutrition. All patients received usual care which involved visits to their physician and a review of medication and problem-solving with a nurse. The authors were unable to detect a statistical difference between the education program in addition to usual care and usual care alone for the prevention of diabetic foot lesions (RR=0.83 [95%CI 0.58, 1.2]). Similarly, in those patients that had a minor lesion at baseline, there was no statistically significant increase in the incidence of severe foot lesions between the intervention and control group (RR=0.57 [95% CI 0.12, 2.67], p=0.89). Furthermore, the results indicated that there was no statistically significant reduction in the rate of hospitalisation, emergency room visits or outpatient visits between the two interventions (p>0.05). The study did however, enroll mainly black and Hispanic patients with a low educational level, which makes it difficult to generalise the results to the target population in Australia.

Pieber et al (1995) evaluated an education program that consisted of four weekly teaching sessions of 90 to 120 minutes each for groups of 4 to 8 patients. In this non-randomised trial (level III-2 intervention evidence), patients received general information about diabetes, self monitoring and glycosuria, dietary measurements, weight reduction and foot care, physical activity and late complications of diabetes. Patients in the control group received routine patient care provided by their general practitioner and did not receive any education other than would normally be provided. The authors reported that those patients who received education were nearly half as likely to form a callus than those who only received usual care over a 6 month follow up period (RR=0.60 [95%CI 0.43, 0.83]). The estimated number of patients needed to be treated with the education program rather than usual care, to prevent one case of callus formation was 3 [95%CI 2, 7]. Similarly, there was a reduction in the risk of interdigit cracks or fissure or mycosis for patients that received the education program (RR=0.75 [95%CI 0.52, 1.0], p<0.05). There was no statistically significant difference found between the groups for the prevention of amputation (p=0.95). However, the lack of randomisation in the study design ensures that there is substantial uncertainty surrounding the estimate of treatment effect as a result of the potential for confounding.

The results provided above suggests that there is insufficient evidence regarding the effectiveness of an education program in addition to usual care for the prevention of diabetic foot complications compared to usual care. The inconsistency in results may depend on how much educational information was provided during ‘usual care’. Specific detail on this was not provided. Another possible confounder could be the method of delivery of the educational program i.e. didactic versus problem-based or interactive teaching. Box 183 summarises the body of evidence according to the NHMRC grading criteria.

Box 183 Evidence matrix for comparison of an education program for the prevention of diabetic foot complications

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias and one level III-2 study with moderate risk of bias.
Consistency	B	One study was inadequately powered to detect a difference although the treatment effects in both studies were in the same direction.
Clinical impact	D	The study by Bloomgarden et al (1987) did not report any statistically significant or clinically important results for the education program. Pieber's results indicated a slight to moderate effect of the intervention for secondary outcomes which may have influenced by confounding. Based on the quality of the studies, the results suggest a slight/ restricted clinical impact.
Generalisability	C	Pieber et al (1995) included a population that was generalisable to the target population. Bloomgarden et al (1987) had an over-representation of ethnic black and Hispanic patients who had a low educational level and thus, the results are not directly applicable to the Australia target population.
Applicability	C	The studies took place in the Austria and the USA, which have similar health care for diabetes patients compared to the Australia health care context

Evidence statement

There is insufficient evidence to suggest that an education program consisting of multiple teaching sessions provided to a group of patients in addition to usual care, is any more effective than usual care alone to reduce diabetic foot complications in the general diabetic population (Grade C).

Table 136 Studies included which compare education to usual care for the prevention of diabetic foot complications

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
(Bloomgarden et al 1987) USA	Level II RCT Average quality study	Patients attending diabetes clinic in a medical centre. Intervention group: N = 127, mean age (yrs) 56±12, male 39% (n=50), no education 7.8% (n=10), did not complete school 50% (n=63), high school graduate 22% (n=28), missing 22% (n=28), race: white 5.5% (n=7), black 41% (n=21), hispanic 32% (n=41), currently smoking 13% (n=17),type 2 DM 76% (n=97), hypertension 38% (n=48), duration DM (yrs) 13±8, foot lesion callus, nail dystrophy or fungal infection 24% (n=30), ulcer or amputation 5% (n=3), abnormal renal function 9.4% (n=12), cholesterol (mg/dl) 205±52, triglycerides (mg/dl) 130±77, HDL cholesterol (mg/dl) 46±14, LDL cholesterol (mg/dl) 135±45, retinopathy 17% (n=22), HbA_{1c} (%) 6.8±2.1, glucose (U/kg 223±94, insulin dose (U/kg) 0.66±0.63, BMI (kg/m^2) 31±6.2, sick days/year 11±20, emergency room visit/yr 1.1±1.7, hospitalisation/yr 0.5±0.8, history of myocardial infarction (%) 7.9 (n=10) Comparator group: N = 139, mean age (yrs) 59±13, male 52% (n=72), no education 7.2% (n=10), did not complete school 43% (n=59), high school graduate 22% (n=31), missing 28% (n=39) race: white 6.5% (n=9), black 29% (n=40), hispanic 35% (n=49), currently smoking 10% (n=14),type 2 DM 66% (n=92), hypertension 35% (n=48), duration DM (yrs) 14±9, foot lesion callus, nail dystrophy or fungal infection 32% (n=44), ulcer or amputation 6.5% (n=9), abnormal renal function 7.2% (n=10), cholesterol (mg/dl) 212±48, triglycerides (mg/dl) 132±97, HDL cholesterol (mg/dl) 45±14, LDL cholesterol (mg/dl) 139±45, retinopathy 21% (n=29), HbA_{1c} (%) 6.6±2.0, glucose (U/kg) 199±81, insulin dose (U/kg) 0.70±0.50, BMI (kg/m^2) 31±6.6, sick days/year 10±38, emergency room visit/yr 1.4±2.5, hospitalisation/yr 0.3±0.5, history of myocardial infarction (%) 5.7 (n=8)	N = 127, diabetic participants attended the diabetic clinic for medication review and discussion of problems. In addition to this, nine education sessions were offered to each participant. The completion of the educational program lasted an average of 1.6 (0.3) years.	N = 139, diabetic participants attended the diabetic clinic to discuss problems and undergo a medication review.	Incidence of foot lesion in those without lesions at baseline		
					Intervention 33/83 (40%)	Control 30/63 (48%)	Effect size [95% CI] RR 0.84 [0.58, 1.2]
					Incidence of severe lesions in those with initially minor lesion		
					Intervention 2/37 (5.4%)	Control 6/63 (4.8%)	RR 0.57 [0.12, 2.67] p=0.89
					Hospitalisation rates, emergency rates and outpatients visit rates		
					Rates were reported as not being statistically significantly different between the groups (p>0.05)		
(Pieber et al 1995) Austria	Level III-2 controlled trial	Patients attending general practices in rural areas in Austria. Intervention group: N = 45, mean age (yrs) 64±8.2, male	N = 45, participants received a structured diabetes treatment and teaching program	N = 49, patients receiving usual care.	Callus at 6 months follow up		
					Intervention 22/45	Control 40/49	Effect size [95% CI] RR 0.60 [0.43, 0.83]

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
	Average quality study	42% (n=19), duration of DM (yrs) 7.6±5.6, height (cm) 165±9, weight (kg) 82±15, BMI (kg/m²) 30±4.7, HbA_{1c} (%) 8.6±1.8, initial ulcer 2.2% (n=1), callus at baseline 78% (n=35) Comparator group: N = 49, mean age (yrs) 65±11, male 47% (n=11), duration of DM (yrs) 6.9±6.1, height (cm) 165±9, weight (kg) 82±13, BMI (kg/m²) 30±4.5, HbA_{1c} (%) 8.8±2.1, initial ulcer 4.1% (n=2), callus at baseline 82% (n=40)	for non-insulin treated type 2 diabetic patients (DTTP) + routine patient care provided by their GPs. The DTTP consisted of 4 weekly teaching sessions (90-120 min each) for groups of 4 to 8 patients. Throughout the program the patients learned the following: basic information about diabetes, self monitoring and glycosuria, about dietary measures and weight reduction, and the advantages of non-pharmacological therapy for type 2 diabetes. They also learned about foot care, physical activity, sick day rules and late complications of diabetes		(49%)	(82%)	NNT 3 [2, 7]
					Interdigital cracks/ fissure or mycosis at 6 months follow up		
					Intervention 22/45 (49%)	Control 32/49 (65%)	Effect size [95% CI] RR 0.75 [0.52, 1.0] p<0.05
					Amputation at 6 months follow up		
					Intervention 1/45 (2.2%) (n=1/45)	Control 1/49 (2.0%)	p=0.95

BMI= body mass index; DM= diabetes mellitus; GP=general practitioner; NNT= number needed to treat; RCT= randomised controlled trial; RR= relative risk

Education targeting patient and doctors versus usual care

One good quality randomised controlled trial evaluated a combined education program with the aim of decreasing the risk of lower extremity amputation in diabetic patients (Table 137).

The education program focussed on the patient and doctor. The patients received information through small groups of a maximum of 4 people instructed by a nurse, involving appropriate foot care behaviour and foot wear. Furthermore, the patients received information pamphlets and signed a behavioural contract. After 2 weeks the patients received a follow-up phone call as well as post card reminder prompts after 1 and 3 months. The intervention for doctors was focussed on making the doctors more conscious about asking the patient to remove footwear for foot examinations and to identify the patient-specific risk factors and use patient-specific practice guidelines. Colour coded patient folders were used as a prompt to remind the doctors to perform foot examinations. The control group received usual care. It is unclear from the authors description whether all patients had lesions at baseline and if so, how severe the lesions were.

Over a mean of 12 months, the authors indicated that those patients who received the intervention were less likely to develop serious foot lesions, dry or cracked skin or ingrown nails compared to the control group (OR = 0.41 [95%CI 0.16, 1.00], OR = 0.62 [95%CI 0.39, 0.98] and OR = 0.59 [95%CI 0.39, 0.92], respectively). All these outcomes are risk factors for lower extremity amputation. However, the authors did not find a statistically significant difference between the intervention and control group for the occurrence of amputation (1% in intervention versus 2% in the control group, p>0.05). Similarly, there was no statistically significant reduction in risk of foot lesions in general, fungal infection of the nail or skin or interdigit maceration. It was however noted, that the study sample had an over representation of females, patients with a lower socioeconomic status and black ethnicity, which makes the results more difficult to generalise to and Australian target population.

The results suggest that an education program that targets patient as well as doctors reduces the likelihood of diabetic foot complications that can lead to lower extremity amputations, specifically serious foot lesions, dry and cracked skin and ingrown toe nails. Box 184 summarises the body of evidence according to the NHMRC grading criteria.

Box 184 Evidence matrix for comparison of education targeted on patients and doctors for the prevention of lower extremity amputation

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study available.
Clinical impact	D	For the primary outcomes of interest, the clinical impact is likely to be slight due to a likely lack of power.
Generalisability	C	The study sample consisted of patients visiting an academic general medicine practice between 1989 and 1991 for diabetes related issues. There was an over representation of females, patients with a lower socioeconomic status and black ethnicity.
Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.

Evidence statement

An education program that focuses on the patient as well as the clinician may be effective in reducing diabetic foot complications, specifically serious foot lesions, dry or cracked skin and ingrown nails, compared to usual care in patients with diabetes (Grade C).

Table 137 Included study of education targeted at patients and doctors to usual care for the risk reduction of lower extremity amputation

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data	
(Litzelman et al 1993) USA	Level II RCT Good quality study	Patients visiting an academic general medicine practice between 1989 and 1991. Intervention group: n=191, black 75%, female 82%, mean age (yrs) 60.9 ± 9.8, annual income <$10000 (%) 77, mean education level (yrs) 9.9 ± 2.7, mean body mass index (kg/m²) 34.0 ± 7.7, mean duration of diabetes (yrs) 9.6 ± 8.0, mean HbA_{1c} (%) 10.5 ± 2.3, mean C-peptide (nmol/l) 0.55±0.50, mean plasma glucose (mmol/l) 11.48 ± 4.81, insulin use (%) 52, oral hypoglycaemic agents (%) 43, mean serum cholesterol (mmol/l) 5.88 ± 1.25, mean serum triglycerides (mmol/l) 2.72 ± 2.83, mean serum HDL (mmol/l) 1.12 ± 0.29 Comparator group: n=205, black 77%, female 80%, mean age (yrs) 59.9 ± 9.4, annual income <$10000 (%) 77, mean education level (yrs) 9.7 ± 2.8, mean body mass index (kg/m²) 33.4 ± 6.9, mean duration of diabetes (yrs) 10.1 ± 8.1, mean HbA_{1c} (%) 10.0 ± 2.6, mean C-peptide (nmol/l) 0.59 ± 0.47, mean plasma glucose (mmol/l) 11.40 ± 4.41, insulin use (%) 47, oral hypoglycaemic agents (%) 46, mean serum cholesterol (mmol/l) 5.71 ± 1.14, mean serum triglycerides (mmol/l) 2.49 ± 2.14, mean serum HDL (mmol/l) 1.12 ± 0.34	N = 191, patient: received education from a nurse in groups of 1 to 4 concerning appropriate foot care behaviour and foot wear delivered using slides and pamphlets,, behavioural contracts, phone (2wks after session) and postcard reminders (1 and 3 months). Clinician intervention: a folder was sent to remind practitioners to ask patients to remove foot wear, clinician to perform foot examination and provide foot care education at each visit.	N = 205, patients receiving usual care.	Outcome	Effect size [95% CI]
					Serious foot lesion	OR 0.41 [0.16, 1.00]
					Any foot lesion	OR 0.65 [0.36, 1.2]
					Dry or cracked skin	OR 0.62 [0.39, 0.98]
					Ingrown toe nails	OR 0.59 [0.39, 0.92]
					Fungal nail infection	OR 0.70 [0.46, 1.1]
					Fungal skin infection	OR 0.58 [0.30, 1.1]
					Interdigit maceration	OR 0.63 [0.34, 1.2]
					Amputation	Intervention 1% Control 2% difference p = ns

RCT = randomised controlled trial; HDL = high density lipoprotein; OR = odds ratio; ns = non significant

Home education versus usual care

The average quality randomised controlled trial by Rettig et al (1986) evaluated a home based teaching program to prevent foot complications and reduce hospital stay.

The home based teaching program involved a maximum of 12 sessions with a nurse who gave instructions tailored to the individual situation as indicated by a needs assessment questionnaire. The study sample was recruited from among diabetic inpatients at participating hospitals. In addition to this home-based teaching program, subjects (n =180) were allowed to participate in other diabetes education programs. Similarly, subjects in the control group (n = 193) were allowed to participate in any kind of diabetes education program, but did not receive the home education. After 6 months the subjects were followed up and assessed for foot appearance which included blisters, fissures, ulcerations, injuries, infections and abnormal colour (a high score indicated better condition of the foot). After 1 year, the rate of hospital stay and emergency room visits in the previous 6 months were assessed for both groups. There were no statistically significant differences reported between the two groups.

The authors reported that by using the foot appearance instrument, the intervention group scored a mean 70 ± 0.7 versus 69 ± 0.7 in the control group ($p > 0.05$). For hospital stays in the past 6 months for non-diabetes related, non-preventable diabetes related and preventable diabetes related issues the intervention group stayed a mean of 7, 14 and 7 days versus 7, 8 and 6 days respectively, for the control group. This indicated that there was no benefit from the intervention with regard to reducing hospitalisation. Similarly, for diabetes related emergency room visits, the authors reported no difference between the groups (0.06 ± 0.02 visits for the intervention group versus 0.08 ± 0.02 visits). The study design appeared to be vulnerable to information and recall bias. Furthermore, it was unclear how many patients in the control group participated in diabetes education.

The results suggest that there is no benefit of home education program over and above usual care and education in terms of preventing foot complications and reducing hospital and emergency room visits in a general diabetic population. Box 185 summarises the body of evidence according to the NHMRC grading criteria.

Box 185 Evidence matrix for home education

Component	Rating	Description
Evidence base	C	One level II studies with moderate risk of bias.
Consistency	N/A	Only one study.
Clinical impact	D	The study reported no significant effect as a result of the intervention.
Generalisability	B	The study sample was recruited from among diabetic inpatients identified by designated home health agency or country health department at participating hospitals.
Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.

Evidence statement

There is insufficient evidence to suggest that a home based education program is more effective than non home education for the prevention of diabetic foot complications or the reduction in hospitalisation and emergency room visits in the general diabetic population (Grade C)

Analysis of any education versus usual care

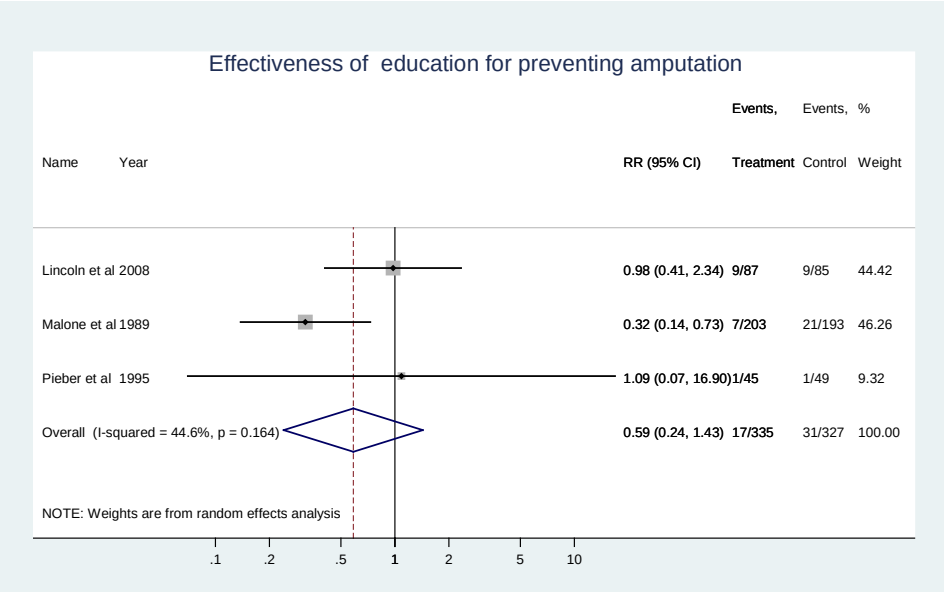
To determine whether any education intervention provides benefit over usual care with regard to clinical foot outcomes, studies were considered for meta-analysis. As discussed above, studies which reported foot ulcer recurrence had statistically significant heterogeneity and therefore should not be pooled. Two studies also reported foot lesion as an outcome however, different effect measures prevented the data being pooled (Bloomgarden et al 1987; Litzelman et al 1993). For amputation as an outcome, three studies were pooled (Lincoln et al 2008; Malone et al 1989; Pieber et al 1995). These studies reported on the effectiveness of a brief home education intervention or an education program. Despite the small differences in intervention, the heterogeneity was not statistically significant and pooling these data resulted in a 41% reduction in risk of amputation which was not statistically significant (RR = 0.59 [95% CI 0.24, 1.43]).

Figure 15 Meta-analysis of education interventions for the prevention of amputation

Study	RR	[95% Conf.	Interval]	% Weight
Lincoln et al	0.977	0.408	2.342	44.42
Malone et al	0.317	0.138	0.729	46.26
Pieber et al	1.089	0.070	16.899	9.32
D+L pooled RR	0.586	0.240	1.432	100.00

Heterogeneity chi-squared = 3.61 (d.f. = 2) p = 0.164
I-squared (variation in RR attributable to heterogeneity) = 44.6%
Estimate of between-study variance Tau-squared = 0.2682

Test of RR=1 : z= 1.17 p = 0.241



The results suggest that there is no evidence to support education programs or home education program for preventing amputation. Box 186 summarises the body of evidence according to the NHMRC grading criteria.

Box 186 Evidence matrix for education interventions versus usual care

Component	Rating	Description
Evidence base	B	Three level II studies with low to moderate risk of bias.
Consistency	C	Some inconsistency reflecting genuine uncertainty around the clinical questions
Clinical impact	D	The effect size suggested a substantial clinical impact however, the lack of statistical significance indicates that there is still some uncertainty.
Generalisability	B	Patients included those with a newly healed ulcer, attending a podiatry or vascular surgery clinic or general practice clinic in a rural setting.
Applicability	C	The studies took place in the USA, UK and Austria which have similar health care for diabetes patients compared to the Australia health care context with some caveats.

Evidence statement

There is insufficient evidence to suggest that either a home-based or structured education program is more effective than usual care for the prevention of amputation in a diabetic population (Grade C).

Intensive education versus brief education

Two average quality studies, one of which was reported by both Rönnemaa et al (1997) and Hamalainen et al (1998), evaluated the effectiveness of an intensive education program for the prevention of diabetic foot complications compared to a brief education program (Table 138).

Rönnemaa et al (1997) and Hamalainen et al (1998) both described an intensive education program, involving one-on-one teaching by a podiatrist which was tailored to the individual needs of patients. Guidance on appropriate footwear, daily hygiene, cutting of toenails, use of creams, methods of avoiding high risk situations and foot gymnastics was provided. The control group received written instructions regarding foot care. Rönnemaa et al reported that there was a statistically significant reduction in callus and diameter of the largest callus in the non-heel regions of the foot in those patients receiving intensive education, when compared to the control group ($p = 0.009$ and $p < 0.001$, respectively). Other diabetic foot complications, like callus on the heel, corns, ingrown toenail and the inability to spread out or flex toes, were not found to differ significantly between the two groups over a 12 month follow up period. Hamalainen et al (1998) reported results on the same population, but over a 7 year follow up period. The authors found only statistically significant differences for the occurrence of ingrown toe nails between the intervention and control group ($p = 0.03$). For all other diabetic foot complications, including reduced forefoot arch, hallux valgus, claw toe, fungal infections, foot callus, fissure of the calcaneous, corns verruca, hyperkeratotic changes, ulcer or amputation, there were no statistically significant differences found.

Barth et al (1991) evaluated an intensive foot care education program for the prevention of diabetic foot complications over four weekly sessions of 1.5 to 2.5 hours each (total of 9 hours). Three of the sessions were with a podiatrist, where detailed foot care recommendations and demonstrations were given and patients could practice their newly learned skills. One session was with a psychologist, where motivational techniques were discussed based on the cognitive motivation theory of Heckhausen and Kuhl. The control group received a 1 hour session with a podiatrist who highlighted the main areas of foot care. After a 6 month follow up period, the authors did not find a statistically significant difference in the number of foot problems identified between the intensive and brief education program groups ($p = 0.22$). There was a slight impact at 1 month after the program introduction ($p < 0.001$) indicating that there may be an immediate effect from the intervention but that this does not last after ceasing the program. The patients in this study were recruited partially by radio and newspaper ads, which might

have resulted in more motivated patients in the study sample than would ordinarily be the case, or people with less severe diabetic foot problems.

The result suggest that an intensive education program may reduce callus and diameter of the largest callus in non-heel regions of the foot over a 1 year follow up and prevent ingrown toe nails at 7 years follow up when compared to a brief education program. However, for these outcomes it is unclear as to the clinical importance of the effects seen and for most other diabetic foot complications intensive education was no more effective than brief education. Box 187 summarises the body of evidence according to the NHMRC grading criteria.

Box 187 Evidence matrix for comparison of intensive education for the prevention of diabetic foot complications

Component	Rating	Description
Evidence base	C	Two level II studies with moderate risk of bias.
Consistency	A	The studies were consistent.
Clinical impact	D	The studies reported on different outcomes. Barth et al did not find a statistically significant result, while the other study reported 25 outcomes but only three were statistically significant, which indicates that the education intervention had only a slight clinical impact.
Generalisability	C	The studies included a sample population attending foot clinics or podiatry clinic, which makes them generalisable to the target population. Though, the sample in one of the studies was also recruited by newspaper and radio ads, which might have lead to a more motivated and less severe population.
Applicability	A	One study took place in Australia, which is directly applicable. The other study took place in Finland, which has similar health care for diabetes patients compared to the Australia health care context.

Evidence statement

There is insufficient evidence to suggest that an intensive education program is any more effective in the prevention of diabetic foot complications than a brief education program (Grade B).

Table 138 Studies included which compared intensive education to brief education for the prevention of diabetic foot complications

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
(Rönnemaa et al 1997) & (Hamalainen et al 1998), Finland	Level II RCT Average quality study	Patients identified using the national drug imbursement register. Patient characteristics: N = 530, males 51% (n = 369), females 49% (n = 364), age range (yrs) 10-79, mean age 46.9 ± 19.1 years. Intervention group: N = 233, mean age 43.9 years Comparator group: N = 226, mean age 44.1 years	N = 233, Individual education by podiatrist over 12 months as many times as judged appropriate by podiatrist. Education was provided on use of appropriate footwear, daily hygiene, toenail cutting, use of cream, avoidance of high risk situations and foot gymnastics. Foot care was also provided.	N = 226, Written information and instructions only	% callosities in calcaneal region at 12 months		
					Intervention 12%	Control 16%	p = 0.14
					% callosities in other region at 12 months		
					Intervention 40%	Control 48%	p<0.01
					% corns at 12 months		
					Intervention 27%	Control 30%	p = 0.16
					% ingrown toenail at 12 months		
					Intervention 24%	Control 31%	p = 0.33
					% inability to spread out toes at 12 months		
					Intervention 39%	Control 47%	p = 0.23
					% inability to flex toes at 12 months		
					Intervention 18%	Control 25%	p = 0.94
					Mean ± SD diameter of greatest callosity in calcaneal region at 12 months		
					Intervention 26 ± 29	Control 28 ± 27	p = 0.065
					Mean ± SD diameter of greatest callosity in other region at 12 months		
					Intervention 11 ± 10	Control 14 ± 9.9	p<0.001

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					% reduced forefoot arch at 7 years		
					Intervention 69%	Control 72%	p = 0.61
					% Hallux valgus at 7 years		
					Intervention 34%	Control 40%	p = 0.35
					% claw toe		
					Intervention 27%	Control 26%	p = 0.96
					% mild interdigital fungal infection at 7 years		
					Intervention 2%	Control 2%	p = 1.0
					% marked interdigital fungal infection at 7 years		
					Intervention 3%	Control 1%	p = 0.45
					% fungal infection of toenail at 7 years		
					Intervention 21%	Control 27%	p = 0.28
					% ingrown toenail at 7 years		
					Intervention 29%	Control 41%	p = 0.03
					% callosity in calcaneous at 7 years		
					Intervention 12%	Control 13%	p = 1.0
					% callosity in other region at 7 years		
					Intervention 23%	Control 30%	p = 0.19
					% fissure in calcaneous at 7 years		

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention 23%	Control 30%	p = 0.19
					% corn other than interdigit at 7 years		
					Intervention 8%	Control 13%	p = 0.24
					% interdigit corn at 7 years		
					Intervention 8%	Control 13%	p = 0.24
					% verruca at 7 years		
					Intervention 11%	Control 6%	p = 0.13
					% any hyperkeratotic change at 7 years		
					Intervention 68%	Control 67%	p p = 0.91
					% ulcer at 7 years		
					Intervention 1%	Control 1%	p = 0.10
					% amputation at 7 years		
					Intervention 1%	Control 0%	p = 0.50
(Barth et al 1991), Australia	Level II RCT Average quality study	Patients recruited through radio and newspaper ads and from referrals by GP and people attending Diabetes centres in Sydney. Intervention group : n=33 age mean(yrs) 58 ± 9; male 55% (; female 45% ; mother tongue (English) 76% (n=25); other language 24% (n=8);, mean time from diagnosis DM (months) 104 ± 94; treatment with tablet 76%; treatment with insulin 24%; ; GHb (%) 12.0 ± 1.9; number of foot problems requiring treatment 4.0 ± 1.2; peripheral vascular disease 58%. Comparator group: n=29, age mean(yrs) 59 ± 5; male	N = 33, patients receiving intensive foot care intervention over 4 weekly sessions of 1.5 to 2.5 hrs after the diet intervention. Three sessions with podiatrist and one with psychologist for cognitive motivation	N = 29, a 1 hour session with a podiatrist covering areas like foot washing, drying, suitable foot wear cutting toe nails, inspecting feet etc.	Number of foot problems		
					at first follow up p < 0.001 3 months follow up p = 0.06 6 months follow up p = 0.22		

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
		59%; mother tongue (English) 86%; other language 14); mean time from diagnosis DM (months) 76 ± 72; treatment with tablet 79%; treatment with insulin 21%); GHb (%) 11.2 ± 1.8; number of foot problems requiring treatment 3.6 ± 2.2; peripheral vascular disease 21%.	(Heckhausen & Kuhl)		

RCT= randomised controlled trial; DM= diabetes mellitus;

Management programs for the prevention of foot complications

Multidisciplinary diabetes care management programs versus standard diabetes care

Two level II RCTs (one good quality and one poor quality) and one good quality level III-2 non-randomised controlled trial compared the implementation of a diabetes management program versus standard diabetic care.

McMurray et al (2002) compared standard diabetes care versus the implementation of a continuous quality improvement program of diabetes care management (Table 139). Clinical outcomes, including the rates of amputations (0% for the intervention group versus 13.1% in the control group) and hospitalisation episodes (2.2% in the intervention group versus 26.3% in the control group), showed clinically important and statistically significant benefits in favour of a diabetes care management program (RR = 0.08 [0.01, 0.5] $p<0.05$). Other identified benefits that reached statistical significance included quality of life assessments in the domains of diabetic symptoms ($p<0.001$) and health perception ($p<0.002$).

McCabe et al (1998) ran a screening and protection program over 2 years looking at the outcomes of the number of amputations required and the number of ulcers developed during the study period (Table 139). Findings suggested that less ulcers developed in the intervention group (24 versus 35) and the number of amputations required were significantly reduced in the intervention group compared to the control group ($p<0.01$ for major amputations). Patients in the control group who developed an ulcer were immediately transferred to the intervention group which is likely to reduce the treatment effect between the groups.

Birke et al (2003) in a good quality level III-2 non-randomized controlled trial compared the rates of hospitalisation and the numbers of amputations over a 2 year period between a diabetes care management program and standard diabetes care. Reduced rates of hospitalisation for foot-related problems in the intervention group (1.96 versus 2.61 per 100 person years in the control group, $p<0.001$) were observed. Similarly, the rate of amputations was lower in the intervention group than in the control group (0.72 versus 1.03 per 100 person years respectively, $p = 0.001$).

Box 188 Evidence matrix for diabetes care management programs versus standard diabetes care

Component	Rating	Description
Evidence base	B	One good quality and one poor quality level II RCTs and one good quality non-randomised controlled level III-2 study with low risk of bias
Consistency	A	All studies were consistent
Clinical impact	A	Diabetes care management programs have an excellent clinical impact on reducing the number of amputations and rates of hospitalisation for diabetic patients with foot related problems
Generalisability	B	Evidence is directly generalisable to the target population of diabetic patients
Applicability	B	Studies were from the UK and USA and while 2 of them are not similar to the Australian healthcare context they are probably applicable with few caveats

Evidence statement:

Diabetic care management programs have been shown to be substantially effective at reducing the rate of amputations and rate of hospitalisation for diabetic patients with foot-related problems when compared to standard diabetic care (Grade B).

Table 139 Diabetic management program versus standard diabetic care

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data
(McMurray et al 2002), USA	Level II RCT. Good quality study	N = 87 diabetic patients receiving haemodialysis for end stage renal disease Intervention group: n=45, age 63.0 ± 13.5 years, male 53% (n = 24), type II diabetes 84% (n = 38), duration of diabetes 20.5 ± 13.0 years, haemodialysis 82% (n = 37), duration of months on dialysis 32.4 ± 22.8, previous amputations 17.8% (n = 8) Control group: n = 38, age 60.9 ± 11.7 years, male 55% (n = 21), type II diabetes 90% (n = 34), duration of diabetes 22.0 ± 11.7 years, haemodialysis 87% (n = 33), duration of months on dialysis 33.2 ± 24.2, previous amputations 26.3% (n = 10)	N = 45 Continuous quality improvement including self-management education, diabetes care monitoring, motivational coaching, eye examinations and nutritional counselling. Assessments included skin condition, structural deformity, pulses and plantar sensation as well as blood tests. Further assessments for self-management knowledge and quality of life were also conducted (adapted questionnaire detailed below))	N = 38 After baseline observations patients received standard diabetes care including monitoring blood glucose levels	**Amputations** Intervention: 0% — Control: 13.1% (n=5) **Hospital admissions** Intervention: 2.2% (n = 1) — Control: 26.3% (n = 10) — Effect size [95% CI]: RR = 0.08 [0.01, 0.5], p < 0.05 **Quality of life (5 domains listed at end of table, scoring not stated)** Diabetes symptoms p<0.001 (details not specified) Health perception p<0.002 (details not specified) No statistically significant improvements in the other 3 domains of social functioning, role limitations and mental health
(McCabe et al 1998a), UK	Level II RCT. Poor quality study	N = 2001 diabetic patients found to have a significant deficit on examination (Semmes-Weinstein monofilaments, the biothesiometer and palpation of pedal pulses) Intervention group: n = 1001, no details specified Control group: n = 1000, no details specified	N = 1001 Diabetes protection program including chiropody and hygiene maintenance, support hosiery and protective shoes. Patients were advised to inspect and wash their feet daily, avoid constrictive clothing and footwear and to contact clinic if concerned	N = 1000 Standard diabetic foot care with no special additional care	**Amputations (major and minor)** Intervention: 0.7% (n = 7) (1 major, 6 minor) — Control: 2.3% (n = 23) (12 major, 13 minor) — p<0.04 (p<0.01 for major amputations alone) **Ulcers developing during study period (12 months)** Intervention: 0.02% (n = 24) — Control: 0.04% (n = 35) **Ulcers developed during study progressing to amputation**

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
					Intervention 29% (n=7/24)	Control 66% (n=23/35)	
(Birke et al 2003), USA	Level III-2 non randomised controlled trial. Good quality study	N = 26,342 diabetic patients with at least one outpatient visit Intervention group: n = 14,097 no details specified but participated in the Disease Management Initiative and the Diabetes Foot Program DMI including goals of HbA_{1c} <8%, nephropathy assessment 1 per year, lipid profile 1 per year, blood pressure every visit, foot exam 1 per year, self-management education 1 per year, nutrition counselling 1 per year, eye exam 1 per year, DFP provides a multidisciplinary approach to foot care including physician, nurse practitioner, physical therapist, registered nurse, pedorthist, cast technician and other support staff. Provides treatment and management of neuropathic foot problems within 24 hours of referral Control group: n = 12,245 no details specified	N = 14,097 Patients hospitalised in 1999 in Louisiana, after the implementation of a Disease Management Initiative (DMI) consisting of targeted goals of diabetes management, plus a Diabetes Foot Program (DFP) utilising a staged management approach to foot problems	N = 12,245 Patients hospitalised in 1998 in Louisiana, before the implementation of a DMI or DFP	Diabetes foot-related hospitalisation rates (per 100 person years)		
					Intervention 1.96	Control 2.61	p<0.001
					Diabetes related lower extremity amputation rates (per 100 person years)		
					Intervention 0.72	Control 1.03	p<0.001

McMurray et al (2002) Quality of Life questionnaire=Five domains, 1. Presence of diabetes symptoms, 2. Mental health concerning complications, 3. Social Functioning, 4. Role limitations caused by physical health, 5. Health perceptions, - Scoring not stated;

Diabetes care management alone versus diabetic care management plus weight bearing activity

In a good quality level II RCT, LeMaster et al (2008) compared foot care education, regular foot care and 8 sessions with a physical therapist against the same managed care plus weight bearing activity (Table 140). After 12 months of treatment there were no clinically relevant or statistically significant differences between groups in relation to presence of full thickness diabetic foot ulcers (RR = 0.93 [0.42, 2.07]). Findings suggest that, while there was no significant benefit of weight bearing activity for preventing chronic foot ulcers, there was also no increased risk associated with weight bearing activity.

Box 189 Evidence matrix for diabetes care management versus weight bearing activity

Component	Rating	Description
Evidence base	B	One good quality level II RCT with low risk of bias
Consistency	N/A	Only one study
Clinical impact	D	No significant clinical impact in relation to number of full-thickness ulcers developed during the study period of 12 months
Generalisability	B	Evidence directly generalisable to target population of patients with diabetic neuropathy
Applicability	C	The study is from the USA which while not similar to the Australian healthcare context, can probably be applicable with some caveats

Evidence statement:

Evidence suggests that diabetic care management plus weight bearing activity has no clinical benefit or disadvantage compared to diabetic care management alone (Grade C).

Table 140 Included study for diabetes care management versus diabetes care management plus weight bearing activity

Author Country	Level and quality of study	Population	Intervention	Comparator	Outcome data		
(Lemaster et al 2008),USA	Level II RCT. Good quality study	N = 79 diabetic patients aged ≥50 with diabetic neuropathy Intervention group: n = 41, mean age 66.6 ± 10.4 years, male 53% (n = 22), smoking 5% (n = 2), type II diabetes 95% (n = 39), duration of diabetes (yrs) 10.8 ± 8.3, number of comorbidities 1.8 ± 1.5, cardiovascular disease 32% (n = 13), BMI 35.9 ± 8.2, foot ulcers in past year 0.37±1.3, ankle brachial index 1.05 ± 0.1, foot related disability score (range 0-81) 25.3 ± 20 Control group: n = 38, age 64.8 ± 9.4, male 47% (n = 18), smoking 87% (n = 33), type II diabetes 92% (n = 35), duration of diabetes (yrs) 11.2 ± 8.5), number of comorbidities 2.3 ± 1.6, cardiovascular disease 26% (n = 10), BMI 37.2 ± 8, foot ulcers in past year 0.6 ± 1.5, ankle brachial index 1.01 ± 0.1, foot related disability score (range 0 - 81) 25.6 ± 18	N = 41 Foot care education, regular foot care and 8 sessions with a physical therapist plus leg strengthening and balance exercise that included a graduated, self-monitored walking program (part 1) and motivational telephone calls every 2 weeks (part 2)	N = 38 Foot care education, regular foot care and 8 sessions with a physical therapist	Full thickness ulcer		
					Intervention 21.9% (n = 9)	Control 23.7% (n = 9)	Effect size [95% CI] RR = 0.93 [0.42, 2.07]

Research question 7: Under what circumstances are antibiotics effective in the treatment of foot ulceration?

Box 190 Inclusion criteria for the evaluation of antibiotics in the treatment of foot ulcer

Parameter	Inclusion criteria
Population	Adults with type 1 or type 2 diabetes with a foot ulcer
Intervention	Antibiotic treatment or treatment strategies which include antibiotic treatment.
Comparator	Treatment strategies which do not include antibiotics.
Outcomes	*Primary outcomes:* time to healing; recurrence rates; local or major amputation; quality of life; independence; mobility restriction; harms; side effects *Secondary outcomes:* Percentage healing; and general functioning. *Cost-effectiveness outcomes:* Cost per event avoided; cost per life year gained; cost per quality adjusted life year or disability adjusted life year; incremental cost-effectiveness ratio
Study design	Randomised, pseudo-randomised or non-randomised controlled trials; cohort studies; case-control studies; interrupted time-series with or without a control group; registers; before-and-after case series; or systematic reviews of these study designs.
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified.
Publication date	1966 – 11/2009
Limitations	Human

Antibiotic therapy v standard wound care

Two small studies (one level II evidence of good quality and one level III-3 evidence of average quality) investigated the effectiveness of antibiotics in addition to standard wound care treatments for treating diabetic foot ulcers (Table 141). Both studies were conducted in outpatient clinics, a diabetic foot clinic in Germany (Chantelau et al 1996) and a vascular outpatient clinic in Austria (Hirschl & Hirschl 1992).

Chantelau et al (1996) conducted a small double blind randomised placebo-controlled trial involving 44 diabetic patients who attended a diabetic foot clinic in Germany. Patients had Wagner's grade 1A (superficial, with or without cellulitis) or 2A (deeper, reaching to joints or tendons) diabetic foot ulcers and were randomly assigned to the intervention (oral amoxicillin/clavulanic acid) or control (placebo) group using computer-generated allocation. In addition, both groups received standard wound care consisting of debridement, cleansing, sterile dressing and pressure relief. The outcomes reported were complete healing and the rate of wound healing as determined by planimetry of the ulcer surface area after 20 days of treatment, or until the ulcer had healed.

A small historically controlled study was undertaken by Hirschl and Hirschl (1992) to determine if intravenous ceftriaxone treatment of diabetic foot ulcers (with or without infection, necrosis and/or macroangiopathy) improved clinical outcomes. Although the ulcers were not classified according to Wagner's grading system, they were described as mal perforant (a deep trophic ulcer) with or without lymphangitis and/or necrosis, and are likely to be of similar severity to those treated by Chantelau et al (1996). The 25 patients enrolled in the study were treated with antibiotic plus standard wound care, which included the care described in Chantelau et al (1996) as well as treatment with the vasodilators alprostadil and prostaglandin E1. The reported outcomes were complete healing within 6 weeks, >50% improvement and <50% improvement (assessed by planimetry of weekly photographs to determine ulcer area). The

outcomes for these patients were compared to those from a historical control group of 25 consecutive patients who received standard wound care before the start of the study. Both groups had similar characteristics at baseline including age, duration and control of diabetes, and severity of the foot ulcer. Treatment for both groups continued for 6 weeks, or until the ulcer was healed.

Healing

Both studies reported healing at the end of the treatment period (see Table 141). Chantelau et al (1996) reported that 27% of the patients who received the intervention had healed compared to 45% of the control group (RR = 0.6, 95% CI 0.26, 1.37). In contrast, Hirschl and Hirschl (1992) reported that 44% of patients who received the intervention healed compared to 24% in the control group (RR = 1.83, 95% CI 0.80, 4.19). It is important to note that due to small sample sizes it is unlikely that these studies were adequately powered to detect a statistically significant result.

Hirschl and Hirschl (1992) also reported that the proportion of patients that showed >50% improvement (but were not completely healed) was the same in both the intervention and control groups (20%). In addition, it was also reported that 16% of the patients in the intervention group compared to 40% of the control group showed some improvement (up to 50%). The ulcer did not improve for 12% of patients receiving ceftriaxone compared to 16% of patients receiving standard wound care.

Chantelau et al (1996) reported the mean reduction in ulcer radius over the 20-day treatment period and found that patients with diabetic foot ulcers who received oral amoxicillin/clavulanic acid had a mean reduction of 0.27 mm/day [95% CI 0.15, 0.39] compared with the control group with a mean reduction of 0.41 mm/day [95% CI 0.21, 0.61]. This was a difference of 0.14 mm/day.

Harms/Side-effects of treatment

Few adverse events were reported in either study as a consequence of antibiotic therapy. Following amoxicillin/clavulanic acid treatment, one patient suffered from minor self-limiting diarrhoea but continued to participate in the trial (Chantelau et al 1996). Conversely, two patients discontinued ceftriaxone treatment after 3 and 5 days due to severe diarrhoea (Hirschl & Hirschl 1992).

Effectiveness of antibiotic therapy

The data evaluating the effectiveness of antibiotic therapy compared to standard wound care is inconsistent and inconclusive. The two studies described above showed no statistically significant benefits for using antibiotics, and point estimates were in the opposite direction. Whereas Hirschl and Hirschl (1992) showed a trend suggesting that antibiotic therapy was beneficial, Chantelau et al (1996) found the opposite. It is unclear whether the results differed because of the unequal distribution of confounding factors within the studies, or the different mode of antibiotic administration, antibiotic type. Either way, due to the lack of evidence, no recommendations about the use of antibiotic therapy can be made at this stage (Box 191).

Table 141 Studies included which compare antibiotic treatment to standard care

Author Country	Level and quality of study	Population	Intervention	comparator	Outcome data		
					Intervention	Comparator	Comparison
(Chantelau et al 1996) Germany	II RCT Good quality study	N = 44. Diabetic patients with skin and soft tissue lesions of the forefoot that attended a diabetic foot clinic. Intervention group – N = 22, Age (yrs) 58 [54, 62], Gender: male 16/22 (72.7%), female 6/22 (27.3%), Duration of diabetes (yrs) 22 [17, 27], Insulin therapy 11/22 (50%), Current smokers 2/22 (9.1%), HbA_{1c} < 8% 9/22 (40.9%), Diabetic retinopathy 13/22 (59.1%), Proteinuria > 500 mg/L 4/22 (18.2%), Ulcer size (mm^2) 214 [154, 274]. Comparator group – N = 22, Age (yrs) 59 [55, 63], Gender: male 12/22 (54.5%), female 10/22 (45.5%), Duration of diabetes (yrs) 19 [14, 24], insulin therapy 12/22 (54.5%), Current smokers 5/22 (22.7%), HbA_{1c} < 8% 10/22 (45.5%), Diabetic retinopathy 12/22 (54.5%), Proteinuria > 500 mg/L 2/22 (9.1%), Ulcer size (mm^2) 220 [162, 422].	N = 22 500 mg amoxicillin plus 125 mg clavulanic acid tablets, three times a day in addition to same standard wound treatment as comparator group.	N = 22 Given placebo tablets and standard wound treatment of debridement, cleansing and sterile dressings, pressure relief.	Healing within 20 days: 6/22 (27.3%)	10/22 (45.6%)	RR = 0.6 [95% CI 0.26, 1.37]
					Mean reduction in ulcer radius (mm/day) : 0.27 [95% CI 0.15, 0.39]	0.41 [95% CI 0.21, 0.61]	0.14
(Hirschl & Hirschl 1992) Austria	III-3 retrospective cohort Average quality study	N = 50. Diabetic patients with neurotrophic ulcer that Intervention group – N = 25, Age (yrs) 70 ± 11, Gender: male 15/25 (60%), female 10/25 (40%), Duration of diabetes (yrs) 13 ± 8, Insulin therapy 12/25 (48%), blood sugar before treatment 191 ± 84, % HbA_{1c} 8.0 ± 2.3, Mal perforant 14/25 (56%), Mal perforant + lymphangitis 7/25 (28%), Mal perforant + necrosis 4/25 (16%), Additional macroangiopathy 7/25 (28%). Comparator group – N = 25, Age (yrs) 67 ± 9, Gender: male 13/25 (52%), female 12/25	N = 25 2 g ceftriaxone/day i.v. Plus same standard treatment as comparator group.	N = 25 Standard treatment with alprostadil, prostaglandin, daily cleaning of ulcer with saline, application of sterile dressing, provision of orthopaedic shoe to reduce pressure	Completely healed: 11/25 (44%)	6/25 (24%)	RR = 1.83 [95% CI 0.80,4.19]
					>50% improved: 5/25 (20%)	5/25 (20%)	RR = 1.00 [95 %CI 0.34, 2.95]

		(48%), Duration of diabetes (yrs) 11 ± 6, Insulin therapy 14/25 (56%), blood sugar before treatment 176 ± 92, % HbA_{1c} 7.7 ± 2.0, Mal perforant 16/25 (64%), Mal perforant + lymphangitis 6/25 (24%), Mal perforant + necrosis 3/25 (12%), Additional macroangiopathy 8/25 (32%).			<50% improved:		
					4/25 (16%)	10/25 (40%)	RR = 0.40 [95% CI 0.14, 1.03]

Wagner Classification Grade I = superficial ulcer, Grade II = deep ulcer to tendon, capsule or bone, Grade III = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade IV = localized gangrene of forefoot or heel, Grade V = gangrene of entire foot; RR = Relative Risk.

Box 191 Evidence statement matrix for antibiotics in addition to standard wound care

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias and one level III-3 study with moderate risk of bias.
Consistency	D	The point estimates were in the opposite directions and it is unclear as to the reason for this.
Clinical impact	D	Studies were unlikely to be adequately powered to detect a statistically significant result.
Generalisability	B	The study populations consisted of diabetic patients with infected foot ulcers.
Applicability	B	The studies were conducted in Austria and Germany

Evidence statement

There was insufficient and inconsistent evidence supporting the supplementation of standard wound care with antibiotic therapy in order to treat diabetic foot ulcers. (Grade D)

In Indigenous populations with Type I or Type II diabetes

Antibiotic v other treatment

No studies comparing antibiotic treatment with other treatments for diabetic foot ulcers were identified in Indigenous populations.

Appendix A Methodology
Literature search and selection criteria

Search strategy

A systematic search of medical, psychological and educational literature was conducted to identify relevant studies to answer the research questions posed previously on the assessment and management of foot-related problems in people with diabetes.

Literature sources

As this guideline will update and expand on the previous NHMRC guideline, studies published since 1966 (or inception of the database) were identified through searching bibliographic databases, consulting content experts in the relevant fields for additional studies, and hand-searching the reference lists of included studies for any other potentially relevant articles. Bibliographic database search alerts were also used throughout the systematic review process in case key new evidence was published. The details of the literature sources are listed in Table 142.

Table 142 Bibliographic databases

Bibliographic database	Time period
CINAHL	1983-11/2009
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	1966-11/2009
EconLit (for cost-effectiveness analysis only)	1969-11/2009
Education resources information center (ERIC)	1966-11/2009
Embase.com (includes Embase and Medline)	1974-11/2009
Pre-Medline	2009
PsycInfo	1983-11/2009
Web of Science – Science Citation Index Expanded	1995-11/2009

Additional sources of literature – peer-reviewed or grey literature[4] – were sought from the sources outlined in Table 143, and from the health technology assessment agency websites provided in Table 143.

[4] Grey literature is literature that is not easily accessed or indexed on bibliographic databases, such as reports of other health technology agencies or government bodies, or research reports that are too new to have been indexed yet in the bibliographic databases.

Table 143 Additional sources of literature

Source	Location
Internet	
Australian Clinical Trials Registry	http://www.actr.org.au
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/grey.shtml
Trip database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
National guidelines clearinghouse	http://www.guideline.gov/
NICE	http://www.nice.org.uk/
SIGN	http://www.sign.ac.uk/
Google Scholar	http://scholar.google.com.au/
National Institute of Clinical Studies	http://www.nhmrc.gov.au/nics/index.htm
Hand Searching (2008-2009)	
Diabetes Care	Library or electronic access
Diabetic Medicine	Library or electronic access
Diabetes Research & Clinical Practice	Library or electronic access
Diabetes & Metabolism	Library or electronic access
Journal of Internal Medicine	Library or electronic access
Archives of Internal Medicine	Library or electronic access
Diabetes	Library or electronic access
The Diabetes Educator	Library or electronic access
Journal of Diabetes and It's Complications	Library or electronic access
Advanced Wound Care	Library or electronic access
Journal of the American Podiatric Medical Association	Library or electronic access
Journal of Foot and Ankle Surgery	Library or electronic access
Diabetes Technology & Therapeutics	Library or electronic access
Journal of Infectious Disease	Library or electronic access
Osteomy & Wound Care	Library or electronic access
The Foot	Library or electronic access
Journal of Wound Care	Library or electronic access
Value in Health	Library or electronic access
Journal of Foot and Ankle Research	Library or electronic access
Content Experts	
Studies other than those found in regular searches	Working Committee
Pearling	
All included articles will have their reference lists searched for additional relevant source material	

Search terms

A series of literature searches were conducted to revise and add to the previous NHMRC guidelines on foot problems in diabetes mellitus. The search terms used for identifying studies are listed in Table 144 to Table 152. The key words and Medical Subject Headings (MeSH) were developed on a Medline/PubMed platform. The same text words and the relevant alternatives to MeSH indexing terms, ie. EmTree headings, were used for the other bibliographic databases, where applicable.

Table 144 Search terms for the evaluation of clinical assessments which improve foot-related clinical outcomes (including type and frequency of assessment).

Element of clinical question	Suggested search terms
Population	((Diabetes Mellitus, Type 1 [MeSH] OR Diabetes Mellitus, Type 2 [MeSH] OR "NIDDM" OR (("type1" OR "type 2") AND diabet*) AND foot) OR diabetic foot OR Arthropathy, Neurogenic [MeSH] OR ((Diabet* OR Charcot*) AND (neuroarthropath* OR arthropath* OR neuroosteoarthropath*)) OR (Charcot* AND (joint OR foot))) AND
Intervention	(exam* OR assess* OR tool* OR risk assessment [MeSH] OR evaluat* OR imag* OR Diabetic Foot/diagnosis [MeSH] OR Diabetic Foot/classification [MeSH] OR "SWF" OR "Semmes-Weinstein monofilaments" OR (plantar AND foot AND pressure) OR (toe AND pressure) OR Ankle Brachial Index [Mesh] OR (ankle AND brachial AND index) OR Skin Temperature [Mesh] OR ((derma* OR skin) AND (thermomet* OR temperature*)) OR (peripheral AND vascular AND (angiogra* OR ultrasound)) OR "peripheral vascular angiography" OR "peripheral vascular ultrasound" OR "abdominal aortic ultrasound" OR (abdom* AND aort* AND ultrasound) OR Diagnostic Imaging [Mesh] OR (vibrat* AND percept* AND threshold) OR (joint AND mobil*) OR "Wagner" OR "Texas" OR ((peripheral OR pedal OR dorsalis pedis OR tibialis posterior) AND pulse) OR Arthropathy, Neurogenic/diagnosis [MeSH] OR Foot Deformities/diagnosis [MeSH] OR Diabetic Neuropathies/diagnosis [MeSH] OR Diabetic Neuropathies/radiography [MeSH]) AND
Study design	((control* OR clinical [Title/Abstract] AND trial [Title/Abstract]) OR clinical trials [MeSH] OR clinical trial [Publication Type] OR random* [title/abstract] OR random allocation [MeSH] OR meta-analysis [pt] OR Cohort Studies [Mesh] OR cohort OR meta-anal* [tw] OR systematic review [tw] OR cost-benefit analysis [MeSH] OR ((cost* OR economic*) AND (effectiveness OR benefit OR analys* OR evaluat* OR model*)))
Limits	Human; 1966 - 2009

Table 145 Search terms for the evaluation of clinical assessments which improve foot-related clinical outcomes (including type and frequency of assessment) in indigenous populations.

Element of clinical question	Suggested search terms
Population	((Diabetes Mellitus, Type 1 [MeSH] OR Diabetes Mellitus, Type 2 [MeSH] OR "NIDDM" OR (("type1" OR "type 2") AND diabet*) AND foot) OR diabetic foot OR Arthropathy, Neurogenic [MeSH] OR ((Diabet* OR Charcot*) AND (neuroarthropath* OR arthropath* OR neuroosteoarthropath*)) OR (Charcot* AND (joint OR foot))) AND (Ethnic Groups [Mesh] OR Population Groups [Mesh] OR "first nation" OR (native AND american) OR ethnic OR aborgin* OR indigenous) AND
Intervention	(exam* OR assess* OR tool* OR risk assessment [MeSH] OR evaluat* OR imag* OR Diabetic Foot/diagnosis [MeSH] OR Diabetic Foot/classification [MeSH] OR "SWF" OR "Semmes-Weinstein monofilaments" OR (plantar AND foot AND pressure) OR (toe AND pressure) OR Ankle Brachial Index [Mesh] OR (ankle AND brachial AND index) OR Skin Temperature [Mesh] OR ((derma* OR skin) AND (thermomet* OR temperature*)) OR (peripheral AND vascular AND (angiogra* OR ultrasound)) OR "peripheral vascular angiography" OR "peripheral vascular ultrasound" OR "abdominal aortic ultrasound" OR (abdom* AND aort* AND ultrasound) OR Diagnostic Imaging [Mesh] OR (vibrat* AND percept* AND threshold) OR (joint AND mobil*) OR "Wagner" OR "Texas" OR ((peripheral OR pedal OR dorsalis pedis OR tibialis posterior) AND pulse) OR Arthropathy, Neurogenic/diagnosis [MeSH] OR Foot Deformities/diagnosis [MeSH] OR Diabetic Neuropathies/diagnosis [MeSH] OR Diabetic Neuropathies/radiography [MeSH])
Limits	Human; 1966 - 2009

Table 146 Search terms for evaluation of clinical assessments which predict foot ulcer and amputation in people with diabetes.

Element of clinical question	Suggested search terms
Population	((Diabetes Mellitus, Type 1 [MeSH] OR Diabetes Mellitus, Type 2 [MeSH] OR "NIDDM" OR (("type1" OR "type 2") AND diabet*) AND foot) OR diabetic foot OR Arthropathy, Neurogenic [MeSH] OR ((Diabet* OR Charcot*) AND (neuroarthropath* OR arthropath* OR neuroosteoarthropath*)) OR (Charcot* AND (joint OR foot))) AND
Intervention	(exam* OR assess* OR tool* OR risk assessment [MeSH] OR evaluat* OR imag* OR predict* OR prognos* OR prognosis [MeSH] OR Diabetic Foot/diagnosis [MeSH] OR "SWF" OR "Semmes-Weinstein monofilaments" OR (plantar AND foot AND pressure) OR (toe AND pressure) OR Ankle Brachial Index [Mesh] OR (ankle AND brachial AND index) OR Skin Temperature [Mesh] OR ((derma* OR skin) AND (thermomet* OR temperature*)) OR "peripheral vascular angiography" OR "peripheral vascular ultrasound" OR "abdominal aortic ultrasound" OR Diagnostic Imaging [Mesh] OR (vibrat* AND percept* AND threshold) OR (joint AND mobil*)) OR ((peripheral OR pedal OR dorsalis pedis OR tibialis posterior) AND pulse) OR Arthropathy, Neurogenic/diagnosis [MeSH] OR Foot Deformities/diagnosis [MeSH] OR Diabetic Neuropathies/diagnosis [MeSH] OR Diabetic Neuropathies/radiography [MeSH] AND
Outcomes	(Sensitivity and Specificity [MeSH] OR Predictive Value of Tests [MeSH] OR ROC Curve [MeSH] "receiver operator characteristic" OR Area Under Curve [MeSH] OR AUC OR sensitiv* OR specific* OR "positive predictive value" OR "negative predictive value" OR PPV OR NPV OR accura* OR "likelihood ratio" OR LR OR Odds Ratio [MeSH] OR odds ratio*)
Limits	Human; 1966 - 2009

These search terms capture indigenous populations without the requirement for specific search terms

Table 147 Search terms to evaluate when a people should be referred to a high risk foot clinic.

Element of clinical question	Suggested search terms
Population	((Diabetes Mellitus, Type 1 [MeSH] OR Diabetes Mellitus, Type 2 [MeSH] OR "NIDDM" OR (("type1" OR "type 2") AND diabet*)) AND
Intervention	(Risk Factors [MeSH] OR risk factor* OR Precipitating Factors [MeSH]) AND
Outcomes	(Diabetic Foot/complications [Mesh] OR Diabetic Foot/diagnosis [Mesh] OR Arthropathy, Neurogenic [MeSH] OR ((Diabet* OR Charcot*) AND (neuroarthropath* OR arthropath* OR neuroosteoarthropath*)) OR (Charcot* AND (joint OR foot)) OR Foot Deformities/diagnosis [MeSH] OR Foot Deformities/complications [MeSH] OR foot deform* OR Diabetic Neuropathies/diagnosis [MeSH] OR Diabetic Neuropathies/complications [MeSH] OR ((diabet* OR peripher*) AND neuropath*) OR Peripheral Vascular Diseases/complications [Mesh] OR Peripheral Vascular Diseases/diagnosis [Mesh] OR ((diabet* OR peripheral) AND (angiopath* OR vascular dis*)) OR Osteomyelitis [Mesh] OR osteomyelit* OR Amputation [Mesh] OR amputat* OR Foot Ulcer [Mesh] OR ulcer* OR lesion* OR Soft Tissue Injuries [MeSH] OR Soft Tissue Infections [MeSH] OR infect* OR Mortality [MeSH] OR Mobility Limitation [MeSH] OR (restrict* AND mobil*) OR independ* OR (general AND function*) OR quality of life [MeSH])
Limits	Human; 1966 - 2009

These search terms capture indigenous populations without the requirement for specific search terms

Table 148 Search terms for evaluation of clinical assessments which predict foot ulcer severity and outcomes in people with foot ulcer

Element of clinical question	Suggested search terms
Population	(((Diabetes Mellitus, Type 1 [MeSH] OR Diabetes Mellitus, Type 2 [MeSH] OR "NIDDM" OR (("type1" OR "type 2") AND diabet*) AND foot) OR diabetic foot) AND (ulcer* OR lesion* OR Soft Tissue Injuries [MeSH] OR Soft Tissue Infections [MeSH] OR Diabetic Foot/complications [MeSH])) AND
Intervention	(exam* OR examination OR assess* OR tool* OR risk assessment [MeSH] OR evaluat* OR prognos* OR Prognosis [MeSH] OR grad* OR classif* OR sever* OR "Wagner" OR "Texas" OR "PEDIS" OR "SAD(AD)SAD" OR "Size (Area and Depth), Sepsis, Arteriopathy, and Denervation" OR Diabetic Foot/diagnosis [MeSH] OR Diabetic Foot/classification [MeSH])
Limits	Human; 1966 - 2009

These search terms capture indigenous populations without the requirement for specific search terms

Table 149 Search terms to identify which interventions improve clinical outcomes

Element of clinical question	Suggested search terms
Population	((Diabetes Mellitus, Type 1 [MeSH] OR Diabetes Mellitus, Type 2 [MeSH] OR "NIDDM" OR (("type1" OR "type 2") AND diabet*) AND foot) OR diabetic foot OR Arthropathy, Neurogenic [MeSH] OR ((Diabet* OR Charcot*) AND (neuroarthropath* OR arthropath* OR neuroosteoarthropath*)) OR (Charcot* AND (joint OR foot))) AND
Intervention	(Diabetic Foot/prevention and control [MeSH] OR Self Care [MeSH] OR (("patient" OR "self") AND ("care" OR manag*)) OR Diabetic Neuropathies/diet therapy [MeSH] OR Diabetic Neuropathies/drug therapy [MeSH] OR Diabetic Neuropathies/surgery [MeSH] OR Diabetic Neuropathies/therapy [MeSH] OR Diabetic Neuropathies/prevention and control [MeSH] OR (((diabet* OR peripher*) AND neuropath*) AND control OR manag* OR therap* OR prevent*) OR Hypertension/diet therapy [MeSH:NoExp] OR Hypertension/drug therapy [MeSH:NoExp] OR Hypertension/prevention and control [MeSH:NoExp] OR Hypertension/therapy [MeSH:NoExp] OR (("blood pressure" OR hypertens*) AND (control OR manag* OR therap* OR prevent*)) OR Blood Glucose Self-Monitoring [MeSH] OR Telemedicine [MeSH] OR ("remote" AND consult*) OR Diabetic Foot/prevention and control [MeSH] OR (("glucose" OR glycaem* OR glycem*) AND ("control" OR manag* OR therap* OR prevent*)) OR Hyperglycemia/drug therapy [MeSH] OR Hyperglycemia/therapy [MeSH] OR Hyperglycemia/prevention and control [MeSH] OR (lipid* AND (manag* OR control OR therap* OR prevent*)) OR Hyperlipidemias/diet therapy [MeSH] OR Hyperlipidemias/drug therapy [MeSH] OR Hyperlipidemias/therapy [MeSH] OR Hyperlipidemias/prevention and control [MeSH] OR Peripheral Vascular Diseases/diet therapy [MeSH] OR Peripheral Vascular Diseases/drug therapy [MeSH] OR Peripheral Vascular Diseases/surgery [MeSH] OR Peripheral Vascular Diseases/therapy [MeSH] OR Cardiovascular Diseases/prevention and control [MeSH] OR Peripheral Vascular Diseases/prevention and control [MeSH] OR Platelet Aggregation Inhibitors/*therapeutic use OR Anticoagulants/therapeutic use [Mesh] OR ("anti" AND (platelet OR thrombocyte) AND therap*) OR aspirin OR clopidogrel OR Diabetic Angiopathies/diet therapy [MeSH] OR Diabetic Angiopathies/drug therapy [MeSH] OR Diabetic Angiopathies/surgery[MeSH] OR Diabetic Angiopathies/prevention and control [MeSH] OR Patient Education as Topic [MeSH] OR (patient AND educat*) OR Patient Care Team [MeSH] OR (multidisciplinary AND (team OR care)) OR Pressure [MeSH] OR pressure* OR "off loading" OR Shoes [MeSH] OR shoe* OR "footwear" OR Weight-Bearing [MeSH] OR Orthotic Devices [MeSH] OR Stockings, Compression [MeSH] OR Diabetic Foot/diet therapy [MeSH] OR Diabetic Foot/drug therapy [MeSH] OR Diabetic Foot/surgery [MeSH] OR Diabetic Foot/therapy [MeSH] OR Hyperbaric Oxygenation [MeSH] OR (surg* AND debrid*) OR Debridement [MeSH] OR revasculari* OR "bypass surgery" OR ("vascular" AND surg*) OR Vascular Surgical Procedures [Mesh] OR wound care OR Wound Healing [MeSH] OR Bandages [MeSH] OR dress* OR Negative-Pressure Wound Therapy [MeSH] OR "VAC-assisted closure" OR vacuum assisted closure* OR assisted wound closure* OR larval therap* OR ((larvae OR maggot) AND therap*) OR Casts, Surgical [MeSH] OR "total contact casting" OR Skin, Artificial [MeSH] OR skin substitutes OR Honey/therapeutic use [MeSH] OR "honey" OR Diphosphonates/therapeutic use [MeSH] OR bisphosphon* OR Calcitonin/therapeutic use [MeSH] OR "calcitonin" OR Arthropathy, Neurogenic/drug therapy [MeSH] OR Arthropathy, Neurogenic/prevention and control [MeSH] OR Arthropathy, Neurogenic/surgery [MeSH] OR Arthropathy, Neurogenic/therapy [MeSH] OR Foot Ulcer/diet therapy [Mesh] OR Foot Ulcer/drug therapy [Mesh] OR Foot Ulcer/prevention and control [Mesh] OR Foot Ulcer/surgery [Mesh] OR (periperhal AND vascular AND stent*) OR sympathectomy OR ((abdom* aort* OR iliac OR femoral OR popliteal OR tibial) AND surg*) OR Foot Ulcer/therapy [Mesh] OR Epidermal Growth Factor/therapeutic use [Mesh] OR Platelet-Derived Growth Factor/therapeutic use [Mesh] OR "EGF" OR "PDGF") AND
Study design	((control* OR clinical [Title/Abstract] AND trial [Title/Abstract]) OR clinical trials [MeSH] OR clinical trial [Publication Type] OR random* [title/abstract] OR random allocation [MeSH] OR meta-analysis [pt] OR Cohort Studies [Mesh] OR cohort OR meta-anal* [tw] OR systematic review [tw] OR cost-benefit analysis [MeSH] OR ((cost* OR economic*) AND (effectiveness OR benefit OR analys* OR evaluat* OR model*)))
Limits	Human, 1966-2009

Table 150 Search terms to identify which interventions improve clinical outcomes in indigenous populations

Element of clinical question	Suggested search terms
Population	((Diabetes Mellitus, Type 1 [MeSH] OR Diabetes Mellitus, Type 2 [MeSH] OR "NIDDM" OR (("type1" OR "type 2") AND diabet*) AND foot) OR diabetic foot OR Arthropathy, Neurogenic [MeSH] OR ((Diabet* OR Charcot*) AND (neuroarthropath* OR arthropath* OR neuroosteoarthropath*)) OR (Charcot* AND (joint OR foot))) AND (Ethnic Groups [Mesh] OR Population Groups [Mesh] OR "first nation" OR (native AND american) OR ethnic OR aborgin* OR indigenous) AND
Intervention	(Diabetic Foot/prevention and control [MeSH] OR Self Care [MeSH] OR (("patient" OR "self") AND ("care" OR manag*)) OR Diabetic Neuropathies/diet therapy [MeSH] OR Diabetic Neuropathies/drug therapy [MeSH] OR Diabetic Neuropathies/surgery [MeSH] OR Diabetic Neuropathies/therapy [MeSH] OR Diabetic Neuropathies/prevention and control [MeSH] OR (((diabet* OR peripher*) AND neuropath*) AND control OR manag* OR therap* OR prevent*) OR Hypertension/diet therapy [MeSH:NoExp] OR Hypertension/drug therapy [MeSH:NoExp] OR Hypertension/prevention and control [MeSH:NoExp] OR Hypertension/therapy [MeSH:NoExp] OR (("blood pressure" OR hypertens*) AND (control OR manag* OR therap* OR prevent*)) OR Blood Glucose Self-Monitoring [MeSH] OR Telemedicine [MeSH] OR ("remote" AND consult*) OR Diabetic Foot/prevention and control [MeSH] OR (("glucose" OR glycaem* OR glycem*) AND ("control" OR manag* OR therap* OR prevent*)) OR Hyperglycemia/drug therapy [MeSH] OR Hyperglycemia/therapy [MeSH] OR Hyperglycemia/prevention and control [MeSH] OR (lipid* AND (manag* OR control OR therap* OR prevent*)) OR Hyperlipidemias/diet therapy [MeSH] OR Hyperlipidemias/drug therapy [MeSH] OR Hyperlipidemias/therapy [MeSH] OR Hyperlipidemias/prevention and control [MeSH] OR Peripheral Vascular Diseases/diet therapy [MeSH] OR Peripheral Vascular Diseases/drug therapy [MeSH] OR Peripheral Vascular Diseases/surgery [MeSH] OR Peripheral Vascular Diseases/therapy [MeSH] OR Cardiovascular Diseases/prevention and control [MeSH] OR Peripheral Vascular Diseases/prevention and control [MeSH] OR Platelet Aggregation Inhibitors/*therapeutic use OR Anticoagulants/therapeutic use [Mesh] OR ("anti" AND (platelet OR thrombocyte) AND therap*) OR Diabetic Angiopathies/diet therapy [MeSH] OR Diabetic Angiopathies/drug therapy [MeSH] OR Diabetic Angiopathies/surgery[MeSH] OR Diabetic Angiopathies/prevention and control [MeSH] OR Patient Education as Topic [MeSH] OR (patient AND educat*) OR Patient Care Team [MeSH] OR (multidisciplinary AND (team OR care)) OR Pressure [MeSH] OR pressure* OR "off loading" OR Shoes [MeSH] OR shoe* OR "footwear" OR Weight-Bearing [MeSH] OR Orthotic Devices [MeSH] OR Stockings, Compression [MeSH] OR Diabetic Foot/diet therapy [MeSH] OR Diabetic Foot/drug therapy [MeSH] OR Diabetic Foot/surgery [MeSH] OR Diabetic Foot/therapy [MeSH] OR Hyperbaric Oxygenation [MeSH] OR (surg* AND debrid*) OR Debridement [MeSH] OR revasculari* OR "bypass surgery" OR ("vascular" AND surg*) OR Vascular Surgical Procedures [Mesh] OR wound care OR Wound Healing [MeSH] OR Bandages [MeSH] OR dress* OR Negative-Pressure Wound Therapy [MeSH] OR "VAC-assisted closure" OR vacuum assisted closure* OR assisted wound closure* OR larval therap* OR ((larvae OR maggot) AND therap*) OR Casts, Surgical [MeSH] OR "total contact casting" OR Skin, Artificial [MeSH] OR skin substitutes OR Honey/therapeutic use [MeSH] OR "honey" OR Diphosphonates/therapeutic use [MeSH] OR bisphosphon* OR Calcitonin/therapeutic use [MeSH] OR "calcitonin" OR Arthropathy, Neurogenic/drug therapy [MeSH] OR Arthropathy, Neurogenic/prevention and control [MeSH] OR Arthropathy, Neurogenic/surgery [MeSH] OR Arthropathy, Neurogenic/therapy [MeSH] OR Foot Ulcer/diet therapy [Mesh] OR Foot Ulcer/drug therapy [Mesh] OR Foot Ulcer/prevention and control [Mesh] OR Foot Ulcer/surgery [Mesh] OR Foot Ulcer/therapy [Mesh] OR Epidermal Growth Factor/therapeutic use [Mesh] OR Platelet-Derived Growth Factor/therapeutic use [Mesh] OR "EGF" OR "PDGF") AND
Limits	Human, 1966-2009

Table 151 Search terms for the identification of studies using antibiotic therapy for the treatment of foot ulcer

Element of clinical question	Suggested search terms
Population	(((Diabetes Mellitus, Type 1 [MeSH] OR Diabetes Mellitus, Type 2 [MeSH] OR "NIDDM" OR (("type1" OR "type 2") AND diabet*) AND foot) OR diabetic foot) AND (ulcer* OR lesion* OR Soft Tissue Injuries [MeSH]) OR Soft Tissue Infections [MeSH])) OR Diabetic Foot/complications [MeSH] OR Diabetic Foot/microbiology [MeSH] OR Osteomyelitis [MeSH] OR "osteomyelitis") AND
Intervention	(Wound Infection/drug therapy [MeSH] OR Osteomyelitis/drug therapy [MeSH] OR Anti-Bacterial Agents/therapeutic use [MeSH] OR Anti-Bacterial Agents/therapy [MeSH] OR Anti-Infective Agents [MeSH] OR ((antibio* OR anti-bio* OR anti-bact* OR antibact* OR antimicrob* OR anti-microb* OR anti-infect*) AND (thera* OR treat* OR manage*)) OR (osteomyelit* AND (thera* OR treat* OR manage*)) OR ((ulcer* OR infect*) AND (thera* OR treat* OR manage*)))
Limits	Human, 1966-2009

Table 152 Search terms for the identification of studies using antibiotic therapy for the treatment of foot ulcer in indigenous populations

Element of clinical question	Suggested search terms
Population	(((Diabetes Mellitus, Type 1 [MeSH] OR Diabetes Mellitus, Type 2 [MeSH] OR "NIDDM" OR (("type1" OR "type 2") AND diabet*) AND foot) OR diabetic foot) AND (ulcer* OR lesion* OR Soft Tissue Injuries [MeSH]) OR Soft Tissue Infections [MeSH])) OR Diabetic Foot/complications [MeSH] OR Diabetic Foot/microbiology [MeSH] OR Osteomyelitis [MeSH] OR "osteomyelitis") AND (Ethnic Groups [Mesh] OR Population Groups [Mesh] OR "first nation" OR (native AND american) OR ethnic OR aborgin* OR indigenous) AND
Intervention	(Wound Infection/drug therapy [MeSH] OR Osteomyelitis/drug therapy [MeSH] OR Anti-Bacterial Agents/therapeutic use [MeSH] OR Anti-Bacterial Agents/therapy [MeSH] OR Anti-Infective Agents [MeSH] OR ((antibio* OR anti-bio* OR anti-bact* OR antibact* OR antimicrob* OR anti-microb* OR anti-infect*) AND (thera* OR treat* OR manage*)) OR (osteomyelit* AND (thera* OR treat* OR manage*)) OR ((ulcer* OR infect*) AND (thera* OR treat* OR manage*)))
Limits	Human, 1966-2009

All potentially relevant studies that were identified were imported into Endnote version X1.0.1 for reference management (Thomson ISI ResearchSoft 2007).

Study selection criteria

Criteria for including studies in this systematic review are based on the PICO structure – Population, Intervention (treatment or risk factors), Comparator (against which an intervention's effectiveness is measured), and Outcomes of interest. These are presented in Table 153 to Table 160 for the different clinical questions. Additional limits to the literature search are also made clear ie restricting the search to studies of a certain research design(s) (eg likely to provide unbiased or more reliable results), to a certain search period or language. In order to ensure that the selection of studies was not biased, these criteria were delineated prior to collating the literature.

Studies were excluded if they:

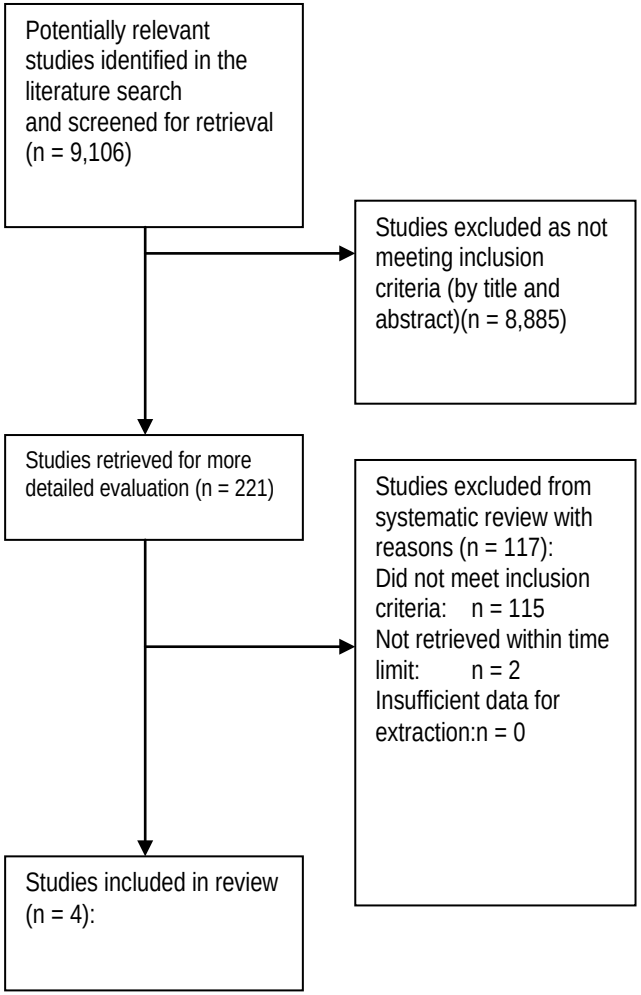
- did not meet the inclusion criteria listed;
- did not focus primarily on type 1 or type 2 diabetes mellitus
- were a lower level of evidence than is available on the same intervention or risk factor, provided that the higher level of evidence reports on the primary outcome(s). If the higher level of evidence only reported secondary outcomes, then the lower level evidence was also included if it reported primary outcomes;

- did not provide adequate data on the outcomes eg in graphical format, missing information, format or type of data are unable to be used;
- were updated by the same research group on the same research question for the same subjects, with no different information provided; or
- could not be retrieved within the timeframe of the project.

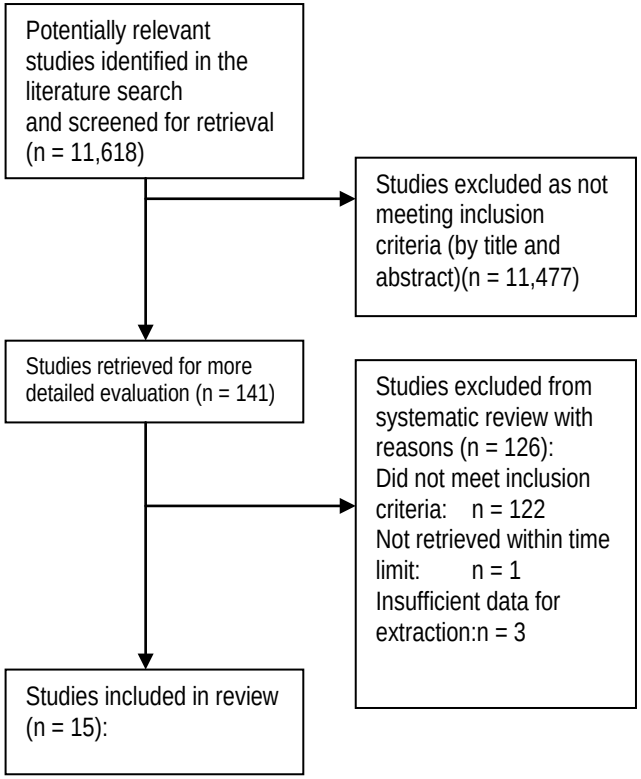
All studies that met the inclusion criteria as specified but were later excluded are documented in Appendix F, along with the reason for exclusion. The selection process of all the included studies is described using modified Quality of Reporting of Meta-analyses (QUOROM) flowchart in Figure 16 (Moher et al 1999).

Figure 16 Modified QUOROM flowchart

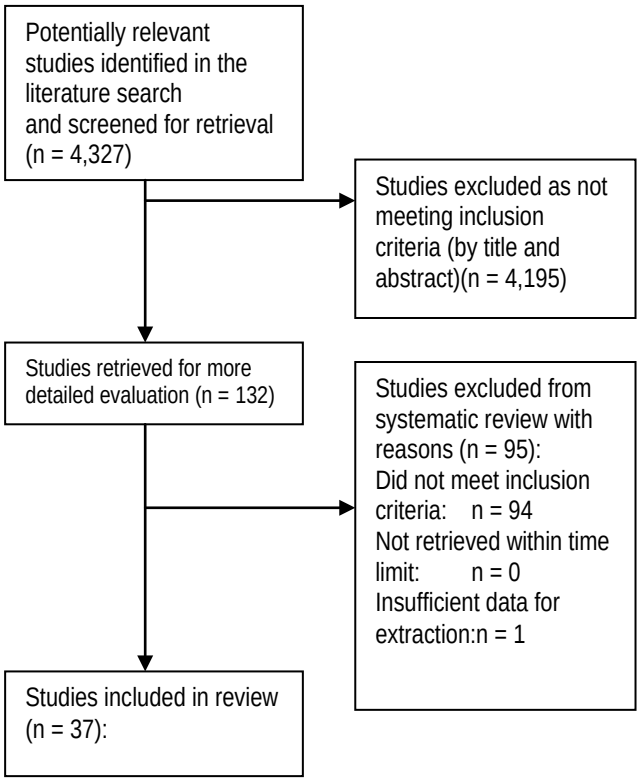
Question 1



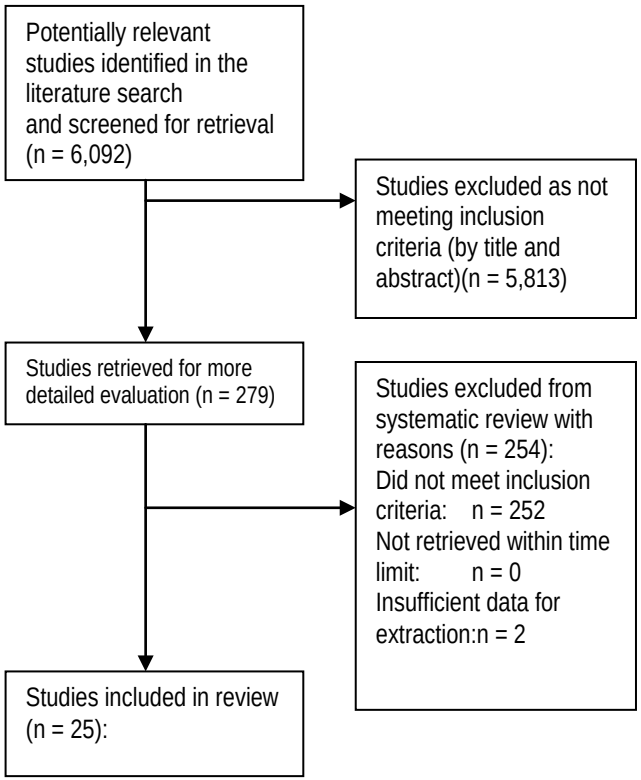
Question 2



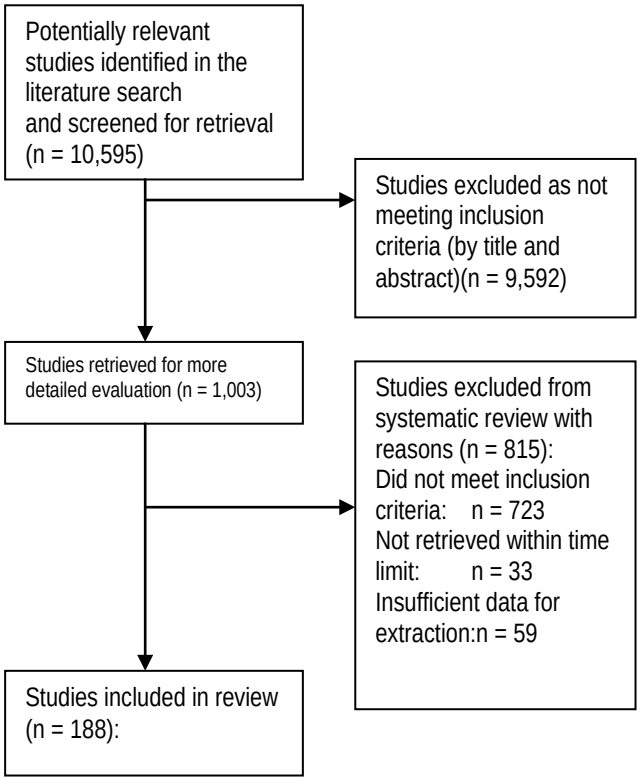
Question 3



Question 5



Question 6



Question 7

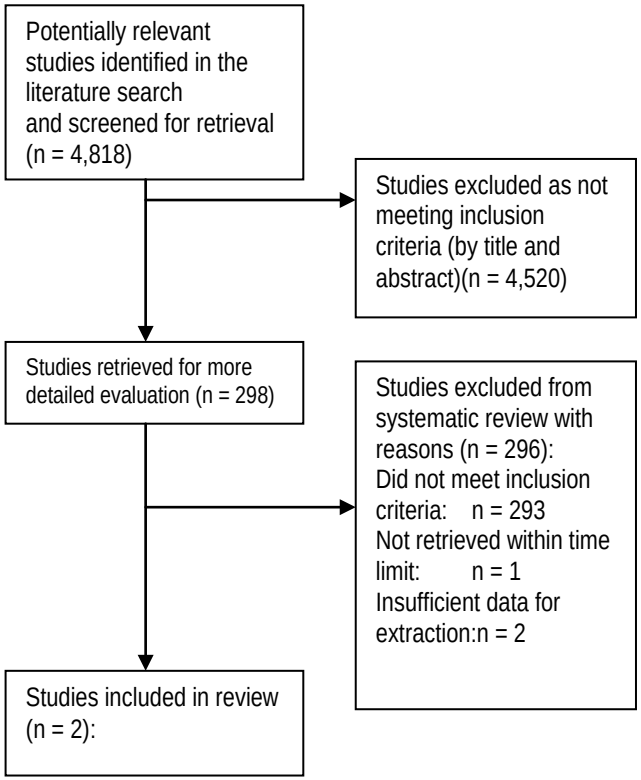


Table 153 Inclusion criteria for the evaluation of clinical assessments for foot problems

Research Question	
Which assessments lead to improved foot-related clinical outcomes in people with diabetes?	
Parameter	Inclusion criteria
Population	Adults with type 1 or type 2 diabetes mellitus Subgroups- g) who have a potentially elevated risk of ulceration (eg long duration of disease, injury, smoking, uncontrolled glucose levels for extended periods, age); or h) with the presence of a risk factor (eg PVD, peripheral neuropathy or foot deformity); or i) people with a history of foot ulcer; or j) people with a foot ulcer; or k) people with Charcot's neuroarthropathy; or l) in indigenous populations[a]
Intervention	Examinations or assessments to detect or evaluate risk factors such as neuropathy, PVD, callus or foot deformity eg clinical history, Semmes-Weinstein monofilaments; plantar foot pressure measurements, vibration perception threshold, joint mobility, toe pressures, ankle/brachial index, dermal thermometry/skin temperature. In people with foot ulcer, clinical assessments may include ulcer grading classification systems such as the Wagner and Texas scores. In people with Charcot's neuroarthropathy this may include diagnostic imaging.
Comparator	No assessment or other assessments.
Outcomes	*Primary outcomes:* Clinical outcomes such as mortality/survival; pre-ulcer lesions; time to foot ulcer; foot ulceration; amputation (major, transmetatarsal, transtibial, ray or toe); time to amputation; mobility restriction; long-term mobility; general functioning; quality of life; independence; healing; deformity. *Cost-effectiveness outcomes:* cost per event avoided; cost per life year gained; cost per quality adjusted life year or disability adjusted life year; incremental cost-effectiveness ratio
Study design	Randomised, pseudo-randomised or non-randomised controlled trials, cohort studies, or systematic reviews of these study designs.
Language	Non-English language articles were excluded unless they appeared to provide a higher level of evidence than the English language articles identified.
Publication date	1966 – 11/2009
Limitations	Human

These criteria will be applied to studies identified in the searches outlined in Table 144 and Table 145; PVD = peripheral vascular disease; [a] For this population group, case series will also be included.

Table 154 Inclusion criteria for the evaluation of clinical assessments for the prediction of foot ulcer and / or amputation

Research Question 2

Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? *(This question will only be answered in the absence of evidence for question 1 (Table 153).*

Parameter	Inclusion criteria
Population	Adults with type 1 or type 2 diabetes mellitus without foot ulcer including people f) who have a potentially elevated risk of ulceration (eg long duration of disease, injury, smoking, uncontrolled glucose levels for extended periods, age); or g) with the presence of a risk factor (eg PVD, peripheral neuropathy or foot deformity); or h) people with a history of foot ulcer; or i) with Charcot's neuroarthropathy; or j) in indigenous populations
Intervention	Clinical examinations or assessments to detect or evaluate risk factors such as neuropathy, PVD, callus or foot deformity eg clinical history, Semmes-Weinstein monofilaments; plantar foot pressure measurements, vibration perception threshold, joint mobility, toe pressures, ankle/brachial index, dermal thermometry/skin temperature.
Comparator (if available)	Observed risk of foot ulcer and amputation
Outcomes	Prognostic outcomes: Observed risk of foot ulcer and amputation Diagnostic outcomes: Sensitivity and specificity (and therefore rates of false positives and negatives), positive and negative likelihood ratios, positive and negative predictive values, diagnostic odds ratios, receiver operator characteristic curves, area under the curve, accuracy.
Study design	Prognostic studies: Prospective cohort studies [a]; all or none study; analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial; retrospective cohort study; case series or cohort study of persons at different stages of disease; or systematic reviews of these study designs. Diagnostic studies: Cross-classification studies where subjects are cross-classified on the test and comparator; or systematic reviews of cross-classification studies. Case-control diagnostic studies, or uncontrolled studies are only acceptable if cross-sectional studies are not available.
Language	Non-English language articles were excluded unless they appeared to provide a higher level of evidence than the English language articles identified.
Publication date	1966 – 11/2009
Limitations	Human

These criteria will be applied to studies identified in the search outlined in Table 146; PVD = peripheral vascular disease.

Table 155 Inclusion criteria for the evaluation of clinical assessments which predict foot ulcer severity and outcomes in people with foot ulcer

Research Question	
Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer? *(This question will only be answered in the absence of evidence for question 1 (Table 153).*	
Parameter	Inclusion criteria
Population	Adults with type 1 or type 2 diabetes mellitus with foot ulcer, including c) people with Charcot's neuroarthropathy; or d) indigenous populations
Intervention	Clinical examinations or assessments to grade the severity of foot ulcer, such as the Wagner and Texas grading systems.
Comparator (if available)	Other types of clinical examinations or assessment tools to grade the severity of foot ulcer, including more invasive methods
Outcomes	*Prognostic outcomes:* Observed risk of clinical outcomes (eg mortality/survival; ulcer healing; time to healing; amputation (major, transmetatarsal, transtibial, ray or toe); time to amputation; mobility restriction; general functioning; quality of life; independence). *Diagnostic outcomes:* Sensitivity and specificity (and therefore rates of false positives and negatives), positive and negative likelihood ratios, positive and negative predictive values, diagnostic odds ratios, receiver operator characteristic curves, area under the curve, accuracy.
Study design	For prognosis: Prospective cohort studies; all or none; analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial; a retrospective cohort study; case series or cohort study of persons at different stages of disease. For diagnosis: Cross-classification studies where subjects are cross-classified on the test and comparator; or systematic reviews of cross-classification studies. Case-control diagnostic studies, or uncontrolled studies are only acceptable if cross-sectional studies are not available
Language	Non-English language articles were excluded unless they appeared to provide a higher level of evidence than the English language articles identified.
Publication date	1966 – 11/2009
Limitations	Human

These criteria were applied to studies identified in the search outlined in Table 148.

Table 156 Inclusion criteria for the evaluation of foot assessment frequency

Research Question	
How often, and by whom, should foot assessments be carried out in people with or without foot ulcer?	
Parameter	Inclusion criteria
Population	Adults with type 1 or type 2 diabetes with or without a foot ulcer Subgroups- e) who have potentially elevated risk of ulceration (eg long duration of diseae, injury, smoking, uncontrolled glucose levels for extended periods, age); or f) with the presence of a risk factor eg PVD, peripheral neuropathy or foot deformity; or g) people with a history of foot ulcer; or h) In indigenous populations
Intervention	*This will depend on the assessments identified in question 1(Table 153)* (eg Semmes-Weinstein monofilaments; plantar foot pressure measurements; vibration perception threshold; joint mobility; or pedal pulse)
Outcomes	Clinical outcomes including mortality/survival; pre-ulcer lesions; time to foot ulcer; foot ulceration; amputation (major, transmetatarsal, transtibial, ray or toe); time to amputation; mobility restriction; general functioning; quality of life; independence; frequency of assessment.
Study design	Randomised, pseudo-randomised or non-randomised controlled trials, cohort studies, or systematic reviews of these study designs. For studies reporting diagnostic accuracy outcomes, cross-sectional studies where subjects are cross-classified on the test and comparator(s)and/or reference standard; or systematic reviews of cross-sectional studies. *In the absence of evidence regarding foot assessment as an intervention (Table 153) then frequency of assessment as a predictor of foot ulcer will be considered using the study design criteria below:* Prospective cohort studies [a]; all or none study; analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial; retrospective cohort study; case series or cohort study of persons at different stages of disease; or systematic reviews of these study designs.
Language	Non-English language articles were excluded unless they appeared to provide a higher level of evidence than the English language articles identified.
Publication date	1966 – 11/2009
Limitations	Human

These criteria were applied to studies identified in the search outlined in Table 144; [a] At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in both arms of the trial would also meet this criterion; PVD = peripheral vascular disease

Table 157 Inclusion criteria for the evaluation of When should a patient be referred to a high risk foot clinic? *(What are the risk factors for a poor foot-related outcome for people in a primary care setting?)*

Research Question	
What are the risk factors for a poor foot-related outcome for people in a primary care setting?	
Parameter	Inclusion criteria
Population	Adults with type 1 or type 2 diabetes managed in a primary care setting, including a) In indigenous populations
Intervention [a]	For people without foot ulcer: Risk factors for foot ulcer and amputation which may include severity of peripheral neuropathy; peripheral vascular disease; or previous history of ulcer. For people with foot ulcer: Risk factors for poor outcomes may include size or severity of foot ulcer; or infection.
Outcomes	Poor clinical outcomes including mortality; foot morbidity (which may include ulceration or worsening foot ulceration; amputation (major, transmetatarsal, transtibial, ray or toe) osteomyelitis; Charcot's neuroarthropathy); mobility restriction; poor general functioning; poor quality of life; lack of independence.
Study design	Prospective cohort studies [b]; all or none study; analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial; retrospective cohort study; case series or cohort study of persons at different stages of disease; or systematic reviews of these study designs.
Language	Non-English language articles were excluded unless they appeared to provide a higher level of evidence than the English language articles identified.
Publication date	1966 – 11/2009
Limitations	Human

These criteria were applied to studies identified in the search outlined in Table 147; [a] These risk factors are not an exhaustive list but rather an indication of what may be identified; [b] At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in both arms of the trial would also meet this criterion

Table 158 Inclusion criteria for the evaluation of interventions to improve foot-related clinical outcomes for people without foot ulcer

Research Question	
Which interventions improve foot-related clinical outcomes for people without foot ulcer?	
Parameter	Inclusion criteria
Population	Adults with type 1 or type 2 diabetes Subgroups- g) who have potentially elevated risk of ulceration (eg long duration of disease, injury, smoking, uncontrolled glucose levels for extended periods, age); or h) with the presence of a risk factor eg PVD, peripheral neuropathy or foot deformity; or i) people with a history of foot ulcer; or j) in people with Charcot's neuroarthropathy; or k) in Indigenous populations[a]
Intervention	Management strategies which may include blood pressure control; glucose control; lipid management; anti-platelet therapy; education; footwear; attendance at podiatry/foot care appointments; telemedicine; models of care; patient self-care / self-management; multidisciplinary approach; drug therapy or any combination of these or other strategies.
Comparator	No treatment; sham treatment; usual care; other therapies; or other means of service delivery
Outcomes	*Primary outcomes:* Mortality/survival; ulceration; local or major amputation; recurrence rates; quality of life; independence; mobility restriction; long-term mobility; healing; harms; side effects. *Secondary outcomes:* Percentage healing; general functioning; deformity and pre-ulcer lesions; hospitalisation; average length of stay. *Cost-effectiveness outcomes:* Cost per event avoided; cost per life year gained; cost per quality adjusted life year or disability adjusted life year; incremental cost-effectiveness ratio
Study design	Randomised, pseudo-randomised or non-randomised controlled trials; cohort studies, or systematic reviews of these study designs.
Language	Non-English language articles were excluded unless they appeared to provide a higher level of evidence than the English language articles identified.
Publication date	1966 – 11/2009
Limitations	Human

These criteria were applied to studies identified in the search outlined inTable 149 and Table 150. ; [a] For this population group, case series will also be included.

Table 159 Inclusion criteria for the evaluation of interventions to improve clinical outcomes for people with foot ulcer

Research Question	
Which interventions improve foot-related clinical outcomes for people with foot ulceration?	
Parameter	Inclusion criteria
Population	Adults with type 1 or type 2 diabetes with a foot ulcer , including a) In indigenous populations[a]
Intervention	Management strategies including pressure off-loading footwear; assisted wound closure; topical negative pressure therapy (assisted wound closure); biological agents; casting; skin substitutes; revascularisation; topical dressings; telemedicine; patient self-care / self-management; models of care; multidisciplinary approach; 'other' strategies or any combination of these.
Comparator	No treatment; sham treatment; usual care; other therapies; or other means of service delivery
Outcomes	*Primary outcomes*: Mortality/survival; time to healing; recurrence rates; local or major amputation; quality of life; independence; mobility restriction; harms; side effects *Secondary outcomes*: Percentage healing; hospitalisation; average length of stay; general functioning. *Cost-effectiveness outcomes*: Cost per event avoided; cost per life year gained; cost per quality adjusted life year or disability adjusted life year; incremental cost-effectiveness ratio
Study design	Randomised, pseudo-randomised or non-randomised controlled trials; cohort studies, or systematic reviews of these study designs.
Language	Non-English language articles were excluded unless they appeared to provide a higher level of evidence than the English language articles identified.
Publication date	1966 – 11/2009
Limitations	Human

These criteria were applied to studies identified in the search outlined in Table 149 and Table 150; [a] For this population group, case series were also included.

Table 160 Inclusion criteria for the evaluation of antibiotics in the treatment of foot ulcer

Research Question	
Under what circumstances are antibiotics effective in the treatment of foot ulceration?	
Parameter	Inclusion criteria
Population	Adults with type 1 or type 2 diabetes with a foot ulcer, including a) In indigenous populations[a]
Intervention	Antibiotic treatment or treatment strategies which include antibiotic treatment.
Comparator	Treatment strategies which do not include antibiotics.
Outcomes	*Primary outcomes:* time to healing; recurrence rates; local or major amputation; quality of life; independence; mobility restriction; harms; side effects *Secondary outcomes:* Percentage healing; and general functioning. *Cost-effectiveness outcomes:* Cost per event avoided; cost per life year gained; cost per quality adjusted life year or disability adjusted life year; incremental cost-effectiveness ratio
Study design	Randomised, pseudo-randomised or non-randomised controlled trials, cohort studies, or systematic reviews of these study designs.
Language	Non-English language articles were excluded unless they appeared to provide a higher level of evidence than the English language articles identified.
Publication date	1966 – 11/2009
Limitations	Human

These criteria were applied to studies identified in the search outlined in Table 151 and Table 152; [a] For this population group, case series were also included.

Validity assessment

Studies that are included were critically appraised – in terms of internal and external validity - and the statistical and clinical relevance and applicability of results was determined using the NHMRC dimensions of evidence (NHMRC 2000a; NHMRC 2000b). The evidence dimensions consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence (see Table 161). The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 161 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.[a]
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

[a] See Table 162 for designation of "level of evidence".

Strength of evidence

The strength of the evidence was collectively measured by the three sub-domains: level, quality and statistical precision.

Level of evidence

The research design of each study included in the systematic review was assessed according to its place in a hierarchy. The hierarchy reflects the effectiveness of the study design to answer a particular research question. Effectiveness was based on the probability that the design of the study has reduced or eliminated the impact of bias on the results (NHMRC 2000b).

The designations of the levels of evidence are shown in Table 162. The new NHMRC levels of evidence for intervention studies, diagnostic accuracy and prognostic studies are provided (Merlin et al 2009; NHMRC 2009). Only the highest level of evidence was reported for each intervention/risk factor assessed in the clinical research questions.

Table 162 Interim NHMRC levels of evidence (Merlin et al 2009; NHMRC 2009)

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis
I [3]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[4] among consecutive persons with a defined clinical presentation[6]	A prospective cohort study[6]
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[4] among non-consecutive persons with a defined clinical presentation[5]	All or none[7]
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial[8] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm [9] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[5]	A retrospective cohort study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[10]	Case series, or cohort study of persons at different stages of disease

Explanatory notes

1 Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

2 The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (MSAC 2005; Sackett & Haynes 2002).

3 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

4 The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

5 Well-designed population based case-control studies (eg. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin & Miller 2002).

6 At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

7 All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus;

and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

[8] This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

[9] Comparing single arm studies ie. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

[10] Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: Part-reproduced from (NHMRC 2009)

Quality of evidence

Critical appraisal of the studies included in this systematic review were performed to evaluate their methodological quality, according to the likelihood that bias, confounding and/or chance have influenced the results. The NHMRC toolkit publication *How to review the evidence: systematic identification and review of the scientific literature (2000)* provides examples of critical appraisal checklists that may be used. Similar checklists were used for this systematic review, which were adapted and evaluated by the Scottish Intercollegiate Guidelines Network (SIGN) for the assessment of systematic reviews, randomised controlled trials, cohort studies, and case-control studies (Appendix C). These checklists have been subjected to wide consultation and evaluation, and are accompanied by detailed notes on their use (SIGN 2008). Economic evaluation studies were evaluated using the Drummond checklist (Drummond & Jefferson 1996), which is recommended for Cochrane systematic reviews (Higgins & Green 2008).

Statistical precision

Statistical precision was determined using standard statistical principles. Small confidence intervals and p-values give an indication as to the probability that the reported effect is real (NHMRC 2000b). However, should there be multiple statistical comparisons, the results are at risk of type 1 error (incorrectly rejecting the null hypothesis) if there has not been a correction to the p-value (Cook et al 2004). Post hoc subgroup analyses may not have adequate statistical power and may also result in a breaking of randomisation (selection bias) and were therefore treated as hypothesis generating, and requiring further formal evaluation.

Assessing size of effect and relevance of evidence

For intervention studies it was important to assess whether statistically significant differences were also clinically important. The size of the effect was determined, as well as whether the 95% confidence interval included only clinically important effects. Similarly, the outcome being measured should be appropriate and clinically relevant. Clinical and patient relevant outcomes should be used instead of surrogate outcomes, whenever possible. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome were avoided (NHMRC 2000a). Checklists assessing the clinical importance and relevance of results from each study were used and are provided in Appendix C.

Data extraction and analysis

Standardised protocols and outcome definitions were used by the assessor to extract the data.

Data extraction forms or tables were developed prior to conducting the review to ensure the standardised extraction of outcome data for all study types. Evidence tables, as described in Appendix D, were used as a guide to summarise the extraction of data.

Meta-analyses of randomised and pseudo-randomised controlled trials were conducted, where appropriate, and tested for heterogeneity and publication bias. Data were stratified by risk of foot ulcer. Where meta-analysis could not be conducted, a narrative meta-synthesis of the data was undertaken.

All statistical calculations and testing were undertaken using the biostatistical computer package, Stata version 11 (Stata Corp LP 2009).

Assessing the body of evidence and formulating recommendations

Once each included study was assessed according to the three dimensions of evidence and relevant data extracted and summarised, this information assisted in the formulation of the evidence-based recommendations, and in determining the overall grade for the included studies (the "body of evidence") that underpin that recommendation. Recommendations were based on the highest level of evidence available. A process developed by the NHMRC for assessing the body of evidence and formulating recommendations was used to ensure consistency in the development of these recommendations. The NHMRC Evidence Statement Form for assessing the body of evidence was used to assist with the formulation of these guideline recommendations (NHMRC 2009).

Components of the evidence statement

The application of a grade to a recommendation was based on a rating of the body of evidence. The five components that were considered in rating the body of evidence are:

- *Evidence base*, which includes the number of studies sorted by their methodological quality and relevance to patients
- *consistency* of the study results
- the potential *clinical impact* of the proposed recommendation (including the balance of benefits and risks, the relevance of the evidence to the clinical question, the size of the patient population and resource issues)
- the *generalisability* of the body of evidence to the target population for the guideline
- the *applicability* of the body of evidence to the Australian healthcare context.

Each of these components was initially rated according to the matrix in Table 163.

Table 163 Body of evidence matrix

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base[1]	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency[2]	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

[1] level of evidence determined from the NHMRC evidence hierarchy (Table 162)
[2] if there is only one study, rank this component as "not applicable"

[3] e.g. Results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer

How to use the Evidence Statement Form

The Evidence Statement Form was intended to be used for each clinical question addressed in the guideline. Prior to completing the form, each individual study relevant to the clinical question was critically appraised and the relevant data synthesised. The form was used as the basis of discussion regarding the five key components important in grading the recommendations.

Rating each of the five components

Applying evidence in real clinical situations is not usually straightforward and thus the body of evidence supporting a recommendation is rarely entirely one grade for all important components. The grading process is designed to allow for this mixture of components while still reflecting the overall strength of the body of evidence supporting a recommendation.

The components described previously were rated according to the matrix shown in Table 163. Any further notes relevant to developing the recommendation were also recorded in the space provided in the form.

Preparing an evidence statement matrix

In the evidence statement matrix section of the form, the grades for each of the components and the accompanying descriptor (excellent, good, satisfactory, poor) were written in the relevant boxes. Each recommendation was accompanied by this form as well as the overall grade given to the recommendation. Any dissenting opinions or other relevant issues were recorded in the space provided in the form.

Formulating a recommendation

The recommendation addressed the original clinical question and ideally was written as an action statement. The wording of the recommendation reflected the strength of the body of evidence.

Determining the grade for the recommendation

Once the wording for the recommendation had been developed, the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence was determined.

NHMRC grades of recommendation were used to indicate the strength of the recommendation and to assist users of the clinical practice guideline in making clinical judgments (see Table 164). Grade A and B recommendations are generally based on a body of evidence which can be trusted to guide clinical practice, whereas Grade C and D recommendations must be applied carefully to individual clinical and organisational circumstances and should be followed with care.

Table 164 Definition of NHMRC grade of recommendations

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken

	in its application
D	Body of evidence is weak and recommendation must be applied with caution

In situations where there was no evidence available in areas where recommendations were made, the consensus of the experts from the Working Committee was required and a consensus statement (Expert opinion, EO) developed.

Implementing guideline recommendations

The guideline implementation strategy was considered at the time that recommendations were being formulated to identify the supports required for successful guideline uptake. The questions in the implementation of recommendation section of the Evidence Statement Form were used to achieve this purpose.

Appendix B Health Technology Assessment agencies

AUSTRALIA	
Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm
Centre for Clinical Effectiveness, Monash University	http://www.mihsr.monash.org/cce
Centre for Health Economics, Monash University	http://www.buseco.monash.edu.au/centres/che/
AUSTRIA	
Ludwig Boltzmann Institute HealthTechnology Assessment	http://hta.lbg.ac.at/en/index.php
CANADA	
Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS)	http://www.aetmis.gouv.qc.ca/site/home.phtml
The Canadian Agency for Drugs And Technologies in Health (CADTH)	http://www.cadth.ca/index.php/en/
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca
Health Utilities Index (HUI)	http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca
Institute of Health Economics	http://www.ihe.ca
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca
DENMARK	
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	http://www.sst.dk/Planlaegning_og_behandling/Medicinsk_teknologivurdering.aspx?lang=en
Danish Institute for Health Services Research (DSI)	http://www.dsi.dk/engelsk.html
FINLAND	
Finnish Office for Health Technology Assessment (FINOHTA)	http://www.stakes.fi/EN/index.htm
FRANCE	
L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)	http://www.anaes.fr/
GERMANY	
German Institute for Medical Documentation and Information (DIMDI) / HTA	http://www.dimdi.de/static/en
THE NETHERLANDS	
Health Council of the Netherlands Gezondheidsraad	http://www.gezondheidsraad.nl/
Institute for Medical Technology Assessment (Netherlands)	http://www.imta.nl/
NEW ZEALAND	
New Zealand Health Technology Assessment (NZHTA)	http://nzhta.chmeds.ac.nz/
NORWAY	
Norwegian Knowledge Centre for Health Services	http://kunnskapssenteret.no
SPAIN	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"l/Health Technology Assessment Agency (AETS)	http://www.isciii.es/htdocs/en/investigacion/Agencia_quees.jsp
Andalusian Agency for Health Technology Assessment (Spain)	http://www.juntadeandalucia.es/salud/orgdep/AETSA/default.asp?V=EN
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.gencat.cat/salut/depsan/units/aatrm/html/en/dir394/index.html
SWEDEN	
Center for Medical Health Technology Assessment	http://www.cmt.liu.se/
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/sv/

SWITZERLAND	
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/
UNITED KINGDOM	
National Institute for Health Research (NIHR) HTA programme	http://www.ncchta.org/
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
The European Information Network on New and Changing Health Technologies	http://www.euroscan.bham.ac.uk/
University of York NHS Centre for Reviews and Dissemination (NHS CRD)	http://www.york.ac.uk/inst/crd/
UNITED STATES	
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov/clinic/techix.htm
Harvard School of Public Health – Cost-Utility Analysis Registry	http://www.tufts-nemc.org/cearegistry/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Minnesota Department of Health (US)	http://www.health.state.mn.us/
National Information Centre of Health Services Research and Health Care Technology (US)	http://www.nlm.nih.gov/hsrph.html
Oregon Health Resources Commission (US)	http://egov.oregon.gov/DAS/OHPPR/HRC/about_us.shtml
U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (Tec)	http://www.bcbs.com/consumertec/index.html

Appendix C Study quality critical appraisal checklists

Methodology checklist 1: systematic reviews and meta-analyses Source: (SIGN 2008)	
Reference:	In this study this criterion is:
Internal validity	
The study addresses an appropriate and clearly focused question	++, +, -, U
A description of the methodology used is included	++, +, -, U
The literature search is sufficiently rigorous to identify all the relevant studies	++, +, -, U
Study quality is assessed and taken into account	++, +, -, U
There are enough similarities between the studies selected to make combining them reasonable	++, +, -, U, N/A
Overall assessment of the study	
How well was the study done to minimise bias?	++, +, -
If coded as +, or – what is the likely direction in which bias might affect the study results?	

++: well covered; +: adequately addressed; -: poorly addressed; U: unclear; N/A: not applicable
The overall quality each study will be classified as good (≥3 ++ and no more than 1 -); average; and poor (≥3 -- and no more than 1 ++).

Methodology checklist 2: randomised controlled trials Source: (SIGN 2008)	
Reference:	In this study this criterion is:
Internal validity	
The study addresses an appropriate and clearly focused question	++, +, -, U
The assignment of subjects to treatment groups is randomized	++, +, -, U
An adequate concealment method is used	++, +, -, U
Subjects and investigators are kept 'blind' about treatment allocation	++, +, -, U
The treatment and control groups are similar at the start of the trial	++, +, -, U
The only difference between groups is the treatment under investigation	++, +, -, U
All relevant outcomes are measured in a standard, valid and reliable way	++, +, -, U
What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	
All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat)	++, +, -, U
Where the study is carried out at more than one site, results are comparable for all sites	++, +, -, U, N/A
Overall assessment of the study	
How well was the study done to minimise bias?	++, +, -
If coded as +, or – what is the likely direction in which bias might affect the study results?	
Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
Are the results of this study directly applicable to the patient group targeted by this guideline?	

++: well covered; +: adequately addressed; -: poorly addressed; U: unclear; N/A: not applicable
The overall quality of each study will be classified as good (≥4 ++ and no more than 1 -); average; and poor (≥4 -- and no more than 1 ++).

Methodology checklist 3: cohort studies Source: (SIGN 2008)	
Reference:	In this study this criterion is:
Internal validity	
The study addresses an appropriate and clearly focused question	++, +, -, U
The two groups being studied are selected from the source populations that are comparable in respects other than the factor under investigation	++, +, -, U
The study indicates how many of the people asked to take part did so, in each of the groups being studied	++, +, -, U
The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis	++, +, -, U
What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?	
Comparison is made between full participants and those lost to follow up, by exposure status	++, +, -, U
The outcomes are clearly defined	++, +, -, U
The assessment of outcome is made blind to exposure status	++, +, -, U, N/A
Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome	++, +, -, U, N/A
The measure of assessment of exposure is reliable	++, +, -, U
Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable	++, +, -, U, N/A
Exposure level or prognostic factor is assessed more than once	++, +, -, U, N/A
The main potential confounders are identified and taken into account in the design and analysis	++, +, -, U, N/A
Confidence intervals are provided	++, +, -, U, N/A
Overall assessment of the study	
How well was the study done to minimise the risk of bias or confounding, and to establish a causal relationship between exposure and effect?	++, +, -
If coded as +, or – what is the likely direction in which bias might affect the study results?	
Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
Are the results of this study directly applicable to the patient group targeted by this guideline?	

++: well covered; +: adequately addressed; -: poorly addressed; U: unclear; N/A: not applicable
The overall quality each study will be classified as good (≥5 ++ and no more than 1 -); average; and poor (≥5 -- and no more than 1 ++).

Methodology checklist 4: case-control studies Source: (SIGN 2008)	
Reference:	In this study this criterion is:
Internal validity	
The study addresses an appropriate and clearly focused question	++, +, -, U
The cases and controls are taken from comparable populations	++, +, -, U
The same exclusion criteria are used for both cases and controls	++, +, -, U
What percentage of each group (cases and controls) participated in the study?	
Comparison is made between participants and non-participants to establish their similarities or differences	++, +, -, U
Cases are clearly defined and differentiated from controls	++, +, -, U
It is clearly established that controls are non-cases	++, +, -, U
Measures will have been taken to prevent knowledge of primary exposure influencing case ascertainment	++, +, -, U, N/A
Exposure status is measured in a standard, valid and reliable way	++, +, -, U, N/A
The main potential confounders are identified and taken into account in the design and analysis	++, +, -, U, N/A
Confidence intervals are provided	++, +, -, U, N/A
Overall assessment of the study	
How well was the study done to minimise the risk of bias or confounding?	++, +, -
If coded as +, or – what is the likely direction in which bias might affect the study results?	
Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
Are the results of this study directly applicable to the patient group targeted by this guideline?	

++: well covered; +: adequately addressed; -: poorly addressed or reported; U: unclear; N/A: not applicable
The overall quality each study will be classified as good (≥5 ++ and no more than 1 -); average; and poor (≥5 -- and no more than 1 ++).

Methodology checklist 7: economic evaluations Source: (Drummond & Jefferson 1996)	
Reference:	Yes, No, U, N/A
1. The research question is stated.	
2. The economic importance of the research question is stated.	
3. The viewpoint(s) of the analysis are clearly stated and justified.	
4. The rationale for choosing alternative programmes or interventions compared is stated.	
5. The alternatives being compared are clearly described.	
6. The form of economic evaluation used is stated.	
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	
Data collection	
8. The source(s) of effectiveness estimates used are stated.	
9. Details of the design and results of effectiveness study are given (if based on a single study).	
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	
12. Methods to value benefits are stated.	
13. Details of the subjects from whom valuations were obtained were given.	
14. Productivity changes (if included) are reported separately.	
15. The relevance of productivity changes to the study question is discussed.	
16. Quantities of resource use are reported separately from their unit costs.	
17. Methods for the estimation of quantities and unit costs are described.	
18. Currency and price data are recorded.	
19. Details of currency of price adjustments for inflation or currency conversion are given.	
20. Details of any model used are given.	
21. The choice of model used and the key parameters on which it is based are justified.	
Analysis and interpretation of results	
22. Time horizon of costs and benefits is stated.	
23. The discount rate(s) is stated.	
24. The choice of discount rate(s) is justified.	
25. An explanation is given if costs and benefits are not discounted.	
26. Details of statistical tests and confidence intervals are given for stochastic data.	
27. The approach to sensitivity analysis is given.	
28. The choice of variables for sensitivity analysis is justified.	
29. The ranges over which the variables are varied are justified.	
30. Relevant alternatives are compared.	
31. Incremental analysis is reported.	
32. Major outcomes are presented in a disaggregated as well as aggregated form.	
33. The answer to the study question is given.	
34. Conclusions follow from the data reported.	
35. Conclusions are accompanied by the appropriate caveats.	

U: unclear; N/A: not applicable

Checklist for assessing clinical importance of benefit and harm

(relates only to intervention studies)

Source: (NHMRC 2000b)

Rank scoring for assessing the clinical importance of benefit and harm

Title of review:

Title of study:

Author(s):

Year:

Comparators:

Clinically important effect:

Rank Score : /4

Ranking	Clinical importance of benefit/harm
1	A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.
2	The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.
3	The confidence interval does not include any clinically important effects.
4	The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.

Checklist for assessing the relevance of outcomes

(relates only to intervention studies)

Source: (NHMRC 2000b)

Rank scoring for classifying the relevance of evidence

Title of review:

Title of study:

Author(s):

Year:

Comparators:

Rank Score : /5

Ranking	Relevance of the evidence
1	Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
2	Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

Appendix D Evidence statement forms

Question 1

Key question: Which assessments lead to improved foot-related clinical outcomes in people with diabetes? Home-based foot temperature monitoring		Evidence table ref: (Armstrong et al 2007; Lavery et al 2004; Lavery et al 2007)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The study provided consistent results.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results reflect a rather large clinical impact. The odds ratios ranged between 3.0 to 10.3. This major difference could be ascribed to a smaller sample size used in the study of Lavery et al, 2004, which resulted in odds of10.3. The other results were less varied. The absolute reduction in risk of foot ulcer varied from 7-22%.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included diabetic patients at high risk of foot complications. In the study the majority of patients were Caucasians, but there were also a large proportion of Mexican Americans included.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

		apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
This study concerns patients already receiving care in a high risk diabetic foot clinic, therefore it is likely to be applicable to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*		
Expert working group felt there was insufficient evidence (due to small sample sizes) and concerns regarding feasibility to make a recommendation for home-based temperature monitoring.		

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.

Component	Rating	Description
Evidence base	B	Two level II studies with a low risk of bias.
Consistency	A	The studies provided consistent results.
Clinical impact	B	The results reflect a rather large clinical impact for patient-relevant primary outcomes (foot ulcer and charcot fractures). The odds ratios ranged between 3.0 and 10.3. This major difference could be ascribed to a smaller sample size used in the pilot study by Lavery et al (2004), which resulted in higher odds. The other results were less varied. The absolute reduction in risk of foot ulcer varied from 7-22%.
Generalisability	B	The study included diabetic patients at high risk of foot complications. In the study the majority of patients were Caucasians, but there were also a large proportion of Mexican Americans included.
Applicability	B	This study concerns patients already receiving care in a high risk diabetic foot clinic, therefore it is likely to be applicable to the Australian healthcare context.

EVIDENCE STATEMENT

The evidence provided indicates that twice daily home-based infrared foot temperature monitoring in addition to standard care when used by diabetic patients at high risk of lower extremity ulceration is effective in preventing foot ulcer (Grade B).

RECOMMENDATION *What recommendation (s) does the guideline development group draw from this evidence?*	GRADE OF RECOMMENDATION *(A recommendation cannot be graded A or B unless the evidence base and consistency of evidence are both either A or B).*	

UNRESOLVED ISSUES

If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation? Due to change in usual practice, there are likely to be substantial cost implications.	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which assessments lead to improved foot-related clinical outcomes in people with diabetes? Diabetic foot screening program		Evidence table ref: (McCabe et al 1998a)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a low risk of bias due to the likely to result in a conservative estimate of the treatment effect as a result of the breach of randomisation.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Although the study did not show a statistically significant reduction in the risk of foot ulcer compared to the control group, a substantial reduction in the relative risk of major amputation and consequently total amputation was apparent, both of which were statistically significant.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included diabetic patients who visit a general diabetes clinic in the UK. There are no patient characteristics presented.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was performed in the UK which has a similar healthcare context to the Australian	A	Evidence directly applicable to Australian healthcare context

health care; therefore it's directly applicable.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The population who receive the foot protection programme in this study equates to an intermediate risk population in the guideline therefore, the generalisability should be upgraded.

EVIDENCE STATEMENT

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.

Component	Rating	Description
Evidence base	C	One level II study with moderate risk of bias.
Consistency	N/A	Only one study.
Clinical impact		The study did not provide any effect size except for significant differences indicated by p values; therefore no clinical impact of the intervention can be determined.
Generalisability	B	The study included diabetic patients who visit a general diabetes clinic in the UK. There are no patient characteristics presented.
Applicability	A	The study was performed in the UK which has a similar healthcare context to the Australian health care; therefore it's directly applicable.

EVIDENCE STATEMENT

The evidence suggests that a two-stage foot screening program, followed by a protection program for those patients identified with a high risk foot for patients visiting a general diabetes clinic may reduce the incidence of major amputation. (Grade C)

RECOMMENDATION *What recommendation (s) does the guideline development group draw from this evidence?*	GRADE OF RECOMMENDATION *(A recommendation cannot be graded A or B unless the evidence base and consistency of evidence are both either A or B).*	C

- Assess all people with diabetes and stratify their risk of developing foot complications. (EBR 1)
- Assess risk stratification by inquiring about previous foot ulceration and amputation, visually inspecting the feet for structural abnormalities and ulceration, assessing for neuropathy using either the Neuropathy Disability Score or a 10 g monofilament and palpating foot pulses. (EBR 2)
- Stratify foot risk in the following manner:
  - "low risk"- people with no risk factors and no previous history of foot ulcer/amputation
  - "intermediate risk"- people with one risk factor (neuropathy, peripheral vascular disease or foot deformity) and no previous history of foot ulcer/amputation

1. "high risk" - people with two or more risk factors (neuropathy, peripheral vascular disease or foot deformity) and/or a previous history of foot ulcer/amputation (EBR 3)

- People assessed as having **"intermediate risk"** or **"high risk" feet** should be offered a **foot protection program**. A **foot protection program** includes foot education, podiatry review and appropriate footwear. (EBR 4)

UNRESOLVED ISSUES

If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?

Yes in Indigenous communities. Monofiliaments are not routinely used by FPs. Some people do some of these elements but not necessarily all of them.

Are there any resource implications associated with implementing this recommendation? Yes. Not all practices have a practice nurse.

Due to change in usual practice, there are likely to be substantial cost implications.

Monofilaments not available, particularly in ATSI communities. Also in rural environments there are limited podiatrists available.

Will the implementation of this recommendation require changes in the way care is currently organised?

Communication to be improved between GP – patient – allied health professionals

Are the guideline development group aware of any barriers to the implementation of this recommendation?

Recommendation 1:

1. Poor communication between providers
2. Length of GP consultation doesn't allow it unless the patient specifically asks for a foot check or if there is a practice nurse on site to help.
3. Lack of patient education
4. A monofilament can only be used 10 times in a day so in busy areas may need more than 1.
5. Onus is on patient to request the check and it is not a high priority for the patient
6. Resources needed (time etc to ensure assessment is done).

Enablers to implementation

7. Patient requests for foot check
8. GP Management plan
9. Patient record with assessment date clearly recorded in it and the next due date recorded.

10. Multi-pronged approach
11. GPs to give information to patients

Recommendation 2:

12. Communication
13. GP Practice Nurse required
14. Consultation time/ no time/ resources to put care plans together
15. Relevance of doing foot examination to be explained to patient
16. Communication back from podiatrists re results of foot check
17. A monofilament can only be used 10 times in a day so in busy areas may need more than 1.
18. Different Podiatrists in her area have different levels of expertise, some would be able to conduct the assessment using all of the elements in the recommendation others would not and would require more training before they could follow this recommendation.

Enablers to implementation

19. People (GPs, podiatrist, patients) need to understand why it is important to do each of the assessment elements, the relevance of each of the elements and what the assessment element is trying to achieve.
20. Communication between Podiatry council, GPs, patient and RACGP
21. Training for GPs regarding relevance of assessment elements through RACGP
22. Longer GP consult time required
23. Precedence health pilot (CDM-NET – funded by DoHA for rollout). This system generates a care plan treatment program with review dates. Sends the data to secure site and allows allied health professionals to view the care plans. Currently in Victoria and expanding to Queensland.
24. Provide monofilaments to communities
25. If no additional resources (practice nurses/rural),large GPs could run a diabetes clinic every 1-6 months
26. A Medicare claim item needs to be available (if it is not already) for Annual Foot inspection.

Recommendation 3:

1. Communication – documenting risk and updating risk status. Need to ensure updated risk is communicated to other health care professionals. GP Management Plan – 3 monthly recall could be included and risk status communicated and updated.
2. Podiatrists may be hesitant to modify the care plan created by the GP..

Enablers to implementation

3. CDMP – each care plan can be updated by the allied health professional.

Recommendation 4:

4. Patient compliance:
    a. Money is a factor as currently no funding for orthotics – NT and amputation are the exception. Deformity is not even included in funding. The patient needs health insurance to

receive any rebate on the cost of the orthotic and often patients with diabetes are of low income so cannot fund orthotics easily.

b. Orthotics are made for one pair of shoes and so when different shoes are worn, no orthotic is worn

c. Sometimes pain is experienced when first given orthotics, which stops the person from wearing them if they are not brought back for follow up review.

5. Training, supervision and workforce needs currently not being met. Need to encourage more health professionals to work in this area.
6. Communication between professionals and between podiatrist and patients
7. No national program for appropriate footwear for high risk feet. Only available program is for people with amputation.

Enablers to implementation

8. Clear descriptors / education
9. Patient record/ information disseminated widely to all healthy professional involved in the care. Patient record is used to indicate that patient is in a foot protection program.
10. Location of the Diabetic Foot Network to be added as an appendix to the guideline.
11. General information to be included in foot education materials for all health professionals – add to guideline appendix (Traffic light system etc)

Question 2

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy of neuropathy disability score assessment		Evidence table ref: (Pham et al. 2000)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicate good test sensitivity with the use of NDS score, but relatively poor specificity. This tool would be associated with substantial false positives but is likely to capture all those at high risk. The results were not reported with confidence intervals and so there is uncertainty regarding the precision of these test characteristics.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability (*How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

One study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt there was insufficient evidence, based on one study, to make a recommendation

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	NA	Only one study available.
3. Clinical impact	B	The results indicate good test sensitivity with the use of NDS score, but relatively poor specificity. This tool would be associated with substantial false positives but is likely to capture all those at high risk. The results were not reported with confidence intervals and so there is uncertainty regarding the precision of these test characteristics.
4. Generalisability	B	The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population.
5. Applicability	C	One study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The results suggest that the neuropathy disability score is a good screening tool for identifying those at high risk of foot ulceration in a general diabetes population, although it is likely to be associated with a considerable proportion of false positives. Further research is required (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of neuropathy disability score		Evidence table ref: (Abbott et al. 2002; Pham et al. 2000)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Both studies reported consistent results even though the studies used slightly different cut-off points.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The studies reported an odds ratio of 3.1 and relative risk of 2.3. Although the results should be interpreted with some caution as Pham et al included patients with a history of foot ulcers, which may have influenced the numbers of foot ulcers observed.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Abbott et al had a large proportion of patients of low socio economic status, which might have influenced the incidence of foot ulcer. The sample in Pham et al included patients with a history of ulcer. Both these samples make the results reasonably generalisable to the target population, with some caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
One study took place in the USA and one in the UK, both of which have similar health care for diabetes patients compared to the Australian health care context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account*

Component	Rating	Description
1. Evidence base	B	Two level II studies with low risk of bias.
2. Consistency	A	Both studies reported consistent results even though the studies used slightly different cut-off points.
3. Clinical impact	B	The studies reported an odds ratio of 3.1 and relative risk of 2.3. Although the results should be interpreted with some caution as Pham et al included patients with a history of foot ulcers, which may have influenced the numbers of foot ulcers observed.
4. Generalisability	B	Abbott et al had a large proportion of patients of low socio economic status, which might have influenced the incidence of foot ulcer. The sample in Pham et al included patients with a history of ulcer. Both these samples make the results reasonably generalisable to the target population, with some caveats.
5. Applicability	B	One study took place in the USA and one in the UK, both of which have similar health care for diabetes patients compared to the Australian health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Neuropathy disability is a good predictor of foot ulcer in the general diabetes population (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	

Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy of neuropathy disability assessment combined with other assessments (SWF, VPT or foot pressure assessment)		Evidence table ref: (Pham et al. 2000)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results of Pham et al indicate that while the combinations of NDS with VPT and SWF would identify those truly at high risk, and therefore rule out high risk in those with a negative result, there would also be a substantial proportion of false positives. The NDS and foot pressure assessment provided moderate specificity, but low sensitivity indicating that it would not be useful in identifying those at high or low risk of foot ulcer. Furthermore, the confidence intervals associated with these estimates are unknown and therefore significant error cannot be ruled out.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included a sample of patients attending foot or diabetes clinics, making them reasonably generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The study took place in the USA, which has similar health care for diabetes patients compared to the Australian health care context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt there was insufficient evidence to make a recommendation regarding the diagnostic accuracy of this intervention, further research is required.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study.
3. Clinical impact	C	The results of Pham et al indicate that while the combinations of NDS with VPT and SWF would identify those truly at high risk, and therefore rule out high risk in those with a negative result, there would also be a substantial proportion of false positives. The NDS and foot pressure assessment provided moderate specificity, but low sensitivity indicating that it would not be useful in identifying those at high or low risk of foot ulcer. Furthermore, the confidence intervals associated with these estimates are unknown and therefore significant error cannot be ruled out.
4. Generalisability	B	The study included a sample of patients attending foot or diabetes clinics, making them reasonably generalisable to the target population.
5. Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australian health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Neuropathy disability score combined with either vibration perception threshold; Semmes-Weinstein monofilament or foot pressure assessments may be poor screening tools to determine those patients at high risk of foot ulcer in the general diabetes population. The NDS combined with Semmes-Weinstein monofilament assessment or vibration perception threshold may be useful to rule out the high risk of foot ulcer (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action*	GRADE OF RECOMMENDATION	

statements where possible.		
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?		
Are there any resource implications associated with implementing this recommendation?		
Will the implementation of this recommendation require changes in the way care is currently organised?		
Are the guideline development group aware of any barriers to the implementation of this recommendation?		

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy of risk assessment tool		Evidence table ref: (Leese et al. 2006)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicated that the risk assessment tool is fairly accurate at identifying all those at high risk of foot ulcer, and the number of false positive is small.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included a large sample from foot or diabetes clinics in hospital and general practice, which makes them generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the UK, which has similar health care for diabetes patients compared to the Australia health care context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt that further research was required to confirm the diagnostic accuracy of this intervention consequently, no recommendation was developed.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	B	One level II study with low risk of bias.
2. Consistency	N/A	Only one study.
3. Clinical impact	A	The results indicated that the risk assessment tool is fairly accurate at identifying all those at high risk of foot ulcer, and the number of false positive is small.
4. Generalisability	B	The study included a large sample from foot or diabetes clinics in hospital and general practice, which makes them generalisable to the target population.
5. Applicability	B	The study took place in the UK, which has similar health care for diabetes patients compared to the Australia health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The risk assessment tool is a good tool for determining those at risk of foot ulcer in the general diabetes population. Further research would be required (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	

Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of risk assessment tool		Evidence table ref: (Leese et al. 2006)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicated that there is a very large odds for those patients with a risk assessment result of high and moderate to develop foot ulcer.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included a sample from foot or diabetes clinics in hospital and general practice, which makes them fairly generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the UK, which has similar health care for diabetes patients compared to the Australian health care context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	B	One level II study with low risk of bias.
2. Consistency	N/A	Only one study
3. Clinical impact	A	The results indicated that there is a very large odds for those patients with a risk assessment result of high and moderate to develop foot ulcer.
4. Generalisability	B	The study included a sample from foot or diabetes clinics in hospital and general practice, which makes them fairly generalisable to the target population.
5. Applicability	B	The study took place in the UK, which has similar health care for diabetes patients compared to the Australian health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Risk assessment using a combination of patient history, foot pulses, neuropathy and foot deformity is a strong predictor of foot ulcer in the general diabetes population. Further research would be required (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy of Hansen Disease Centre (HDC) risk assessment		Evidence table ref: (Ahroni et al.1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The (revised) HDC assessment is good for predicting amputation, the high sensitivity can rule out risk of amputation in those testing negatively, which considering the severity of the outcome is important	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included patients attending foot or diabetes clinics, which makes the results fairly generalisable to the target population. However, the sample mainly included male which may make it difficult to generalise to the results to females.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt that further research was required to confirm the diagnostic accuracy of this intervention consequently, no recommendation was developed.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study.
3. Clinical impact	B	The (revised) HDC assessment is good for predicting amputation, the high sensitivity can rule out risk of amputation in those testing negatively, which considering the severity of the outcome is important
4. Generalisability	B	The study included patients attending foot or diabetes clinics, which makes the results fairly generalisable to the target population. However, the sample mainly included male which may make it difficult to generalise to the results to females.
5. Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

HDC risk assessment may be an accurate test for ruling out risk of foot ulcer and amputation in the general diabetes population. Further research would be required (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy of Seattle risk assessment tool		Evidence table ref: (Ahroni et al. 1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The assessment had moderate sensitivity and specificity for foot ulcer. For amputation, the results indicated a good sensitivity and NPV of 100%, which indicates a substantial impact at ruling out those not at risk. Though, the results were not supported by confidence intervals, which makes it hard to interpret the uncertainty in the estimate.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included patients attending foot or diabetes clinics, which makes them generalisable to the target population. Though the sample included mainly males if may be difficult to generalise to the target population as sex might be an effect modifier.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt that further research was required to confirm the diagnostic accuracy of this intervention consequently, no recommendation was developed.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	NA	Only one study.
3. Clinical impact	C (foot) B (amputation)	The assessment had moderate sensitivity and specificity for foot ulcer. For amputation, the results indicated a good sensitivity and NPV of 100%, which indicates a substantial impact at ruling out those not at risk. Though, the results were not supported by confidence intervals, which makes it hard to interpret the uncertainty in the estimate.
4. Generalisability	B	The study included patients attending foot or diabetes clinics, which makes them generalisable to the target population. Though the sample included mainly males if may be difficult to generalise to the target population as sex might be an effect modifier.
5. Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The Seattle risk assessment may have moderate performance at accurately identifying those at risk of foot ulcer. It has better performance at accurately ruling out those who are at low risk of subsequent amputation. Further research would be required (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy of foot pressure assessment (diabetes general population)		Evidence table ref: (Pham et al. 2000; Veves et al.1992)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The studies were inconsistent. Pham et al indicated that more patients would be treated unnecessarily and that patients at risk would be missed. In contrast, Veves et al indicated that patients who were not at risk would be identified but that many patients would receive unnecessary treatment.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Veves et al presented results that suggest a 100% sensitivity and negative predictive value, indicating that patients not at risk of ulcer could be accurately identified and thus not need follow up treatment. However, Pham et al's results were less clear cut and in the opposite direction so it is unclear whether the different intervention types have different clinical impact.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Both studies included diabetic patients (type I and II), with neuropathy and or history of ulceration, visiting foot or diabetes clinics, which makes them generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
One study took place in the USA and one in the UK, which both have similar health care for	A	Evidence directly applicable to Australian healthcare context

diabetes patients compared to the Australia health care context.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Given the inconsistency of the results with regard to the diagnostic accuracy of this intervention, no recommendation was developed.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	Two level II studies with moderate risk of bias.
2. Consistency	D	The studies were inconsistent. Pham et al indicated that more patients would be treated unnecessarily and that patients at risk would be missed. In contrast, Veves et al indicated that patients who were not at risk would be identified but that many patients would receive unnecessary treatment.
3. Clinical impact	C	Veves et al presented results that suggest a 100% sensitivity and negative predictive value, indicating that patients not at risk of ulcer could be accurately identified and thus not need follow up treatment. However, Pham et al's results were less clear cut and in the opposite direction so it is unclear whether the different intervention types have different clinical impact.
4. Generalisability	A	Both studies included diabetic patients (type I and II), with neuropathy and or history of ulceration, visiting foot or diabetes clinics, which makes them generalisable to the target population.
5. Applicability	B	One study took place in the USA and one in the UK, which both have similar health care for diabetes patients compared to the Australia health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The results suggest that foot pressure assessment has variable accuracy at identifying diabetic individuals at high risk of foot ulcer. Further research is required (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of foot pressure assessment (general population)		Evidence table ref: (Crawford et al. 2007; Kastenbauer et al. 2001)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level I study with low risk of bias and one level II study with a low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The studies were consistent.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results reflect a moderate to substantial clinical impact on the patient. The confidence intervals suggest predominately clinically important effects.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Both studies assessed a general diabetic population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
One study took place in the UK, one in Austria. The UK systematic review included studies mainly undertaken in the USA. The health system in these countries is broadly similar to the	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

Australian situation.	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.

Component	Rating	Description
1. Evidence base	A	One level I study with low risk of bias and one level II study with a low risk of bias.
2. Consistency	A	The studies were consistent.
3. Clinical impact	B	The results reflect a moderate to substantial clinical impact on the patient. The confidence intervals suggest predominately clinically important effects.
4. Generalisability	A	Both studies assessed a general diabetic population.
5. Applicability	B	One study took place in the UK, one in Austria. The UK systematic review included studies mainly undertaken in the USA. The health system in these countries is broadly similar to the Australian situation.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Diabetic patients with elevated foot pressure, as assessed using peak or mean plantar pressure measurement, have a moderate to substantial increased risk of developing foot ulcer compared to diabetic patients with normal foot pressure (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy for vibration sensation perception testing (diabetes general population)		Evidence table ref: (Ahroni et al. 1997; Pham et al. 2000; Young et al. 1994)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Three level II studies with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The studies provided consistent evidence, reporting that vibration sensation perception testing has moderate accuracy at diagnosing patients at risk of foot ulcers and amputation. The sensitivity was reasonable in identifying those at risk in all three studies (range 76%- 89%). The rate of correctly classified true negatives was low in one study, giving a high false positive rate, while the other study reported a low false positive rate.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Some of the results did not provide confidence intervals or had a wide 95% confidence interval, which increased the uncertainty of the result. All studies had a time difference of 2.5 to 4 years between measurement and ulceration/amputation, which could have influenced the outcome as subjects assessed as 'at risk' received treatment. The results have therefore been assessed as having moderate clinical impact. Although this is likely to be a conservative estimate, should the confounding effect of treatment be considered.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The studies all included diabetes patients without ulcers. Ahroni's results are mainly based on male patients as the study was undertaken at a veterans' affair hospital. Pham et al had a population that included those with a history of ulceration. These populations are generalisable to the target population of this guideline	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Two studies took place in the US and one in the UK. Both have a similar health care system	A	Evidence directly applicable to Australian healthcare context

for diabetes care to the Australian system and are therefore likely applicable for the Australian context.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt there was insufficient evidence to make a recommendation

EVIDENCE STATEMENT

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.

Component	Rating	Description
1. Evidence base	C	Three level II studies with moderate risk of bias.
2. Consistency	B	The studies provided consistent evidence, reporting that vibration sensation perception testing has moderate accuracy at diagnosing patients at risk of foot ulcers and amputation. The sensitivity was reasonable in identifying those at risk in all three studies (range 76%- 89%). The rate of correctly classified true negatives was low in one study, giving a high false positive rate, while the other study reported a low false positive rate.
3. Clinical impact	C	Some of the results did not provide confidence intervals or had a wide 95% confidence interval, which increased the uncertainty of the result. All studies had a time difference of 2.5 to 4 years between measurement and ulceration/amputation, which could have influenced the outcome as subjects assessed as 'at risk' received treatment. The results have therefore been assessed as having moderate clinical impact. Although this is likely to be a conservative estimate, should the confounding effect of treatment be considered.
4. Generalisability	B	The studies all included diabetes patients without ulcers. Ahroni's results are mainly based on male patients as the study was undertaken at a veterans' affair hospital. Pham et al had a population that included those with a history of ulceration. These populations are generalisable to the target population of this guideline
5. Applicability	B	Two studies took place in the US and one in the UK. Both have a similar health care system for diabetes care to the Australian system and are therefore likely applicable for the Australian context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The assessment of vibration sensation perception in the diabetes population, with or without a history of foot ulcer, has moderate accuracy at detecting those patients at risk of a subsequent foot ulcer (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value for vibration sensation perception testing (general population)		Evidence table ref: (Ahroni et al. 1997; Crawford et al. 2007; Kastenbauer et al. 2001; Lehto et al. 1996; Pham et al. 2000; Young et al 1994)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level I study with a low risk of bias, four level II studies with low risk of bias and one level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The studies provided inconsistent results for lower extremity amputation, although not enough data was provided to ascertain the likely reason. For the primary outcome of foot ulceration, the majority of studies reported an increase in risk with absence of perception at a vibration threshold >25 Volts.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results suggest substantial impact with 2 to 25 times the risk of foot ulceration. The impact of vibration perception assessment is unclear. Crawford's systematic review found a difference in vibration perception of 17 Hz in those who did or did not subsequently develop foot ulcer.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included diabetic patients (type I and II) visiting foot or diabetes clinics. The studies by Boyko et al and Ahroni included mainly makes, due to the veterans' affairs setting, which makes the results less directly applicable.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Two studies took place in the US (one SR), two in the UK, one from Austria and one from	A	Evidence directly applicable to Australian healthcare context

Finland. All these countries have a similar health care setting to the system in Australia.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.

Component	Rating	Description
1. Evidence base	A	One level I study with a low risk of bias, four level II studies with low risk of bias and one level II study with moderate risk of bias.
2. Consistency	B	The studies provided inconsistent results for lower extremity amputation, although not enough data was provided to ascertain the likely reason. For the primary outcome of foot ulceration, the majority of studies reported an increase in risk with absence of perception at a vibration threshold >25 Volts.
3. Clinical impact	B	The results suggest substantial impact with 2 to 25 times the risk of foot ulceration. The impact of vibration perception assessment is unclear. Crawford's systematic review found a difference in vibration perception of 17 Hz in those who did or did not subsequently develop foot ulcer.
4. Generalisability	B	The study included diabetic patients (type I and II) visiting foot or diabetes clinics. The studies by Boyko et al and Ahroni included mainly makes, due to the veterans' affairs setting, which makes the results less directly applicable.
5. Applicability	B	Two studies took place in the US (one SR), two in the UK, one from Austria and one from Finland. All these countries have a similar health care setting to the system in Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Vibration sensation perception is a substantial predictor of foot ulceration in the general diabetes population. Absence of vibration perception at a threshold of >25 Volts significantly increases the risk of subsequent foot ulcer development (Grade B).

There was insufficient evidence to determine whether vibration sensation assessment as is a predictor for lower extremity amputation in the diabetes general population.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy of Semmes-Weinstein monofilament testing		Evidence table ref: (Adler et al 1999) (Pham et al 2000)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The low specificity of SWF (34-51%) means that a large proportion of patients would have incorrectly positive tests for being at risk of foot ulcer or amputation. The test is therefore better used a diagnostic tool in patients with symptoms of peripheral neuropathy, rather than as a	A	Very large
	B	Substantial

screening tool in the general diabetic population.	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The studies all include diabetes patients without ulcers. Ahroni's results were mainly based on male patients as the study was undertaken at a veteran's affair hospital. Furthermore, Pham et al had a population that included those with a history of ulceration.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Two studies took place in the US which has a similar health care system for diabetes to the Australian system.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*		
Expert working group felt the diagnostic accuracy of Semmes-Weinstein monofilaments was too poor to make a recommendation		

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	A	The odds ratio showed a large clinical effect for the prediction of foot ulcer and an even larger odds ratio for amputation. The precision of the results could not be ascertained.
4. Generalisability	B	The population included only residence of a Native American reservation, who visited a Hospital Service. The population is generalisable to the indigenous target population in Australia with some caveats.

5. Applicability	C	The study came from the US, which has a similar health care system for diabetes patients to the Australian context and is therefore applicable with some caveats..

Indicate any dissenting opinions

EVIDENCE STATEMENT

The use of Semmes-Weinstein monofilament testing to determine patients at risk of foot ulcers or lower extremity amputation in the general diabetes population is not advised, as it's diagnostic accuracy is poor (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of peripheral sensory neuropathy		Evidence table ref: (Abbott et al. 2002; Adler et al. 1999; Litzelman et al. 1997; Pham et al. 2000)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Three level II studies with low risk of bias and one level II study with moderate risk of bias	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
All studies are consistent.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results ranged between a relative risk of 1.8 and 5.4 and odds ratios of 2.7 and 5.4, although some of the estimates also had wide confidence intervals. Taking this in to account the results would indicate a substantial clinical impact.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study by Adler et al included mainly males; Litzelman et al had a large proportion of African Americans and socioeconomically disadvantaged patients. Similarly, Abbott et al had a large proportion of patients from a low socio economic class. These groups might be more vulnerable to poor health outcomes.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Three studies came from the USA and one from the UK, which have a similar health care system for diabetes patients compared to the Australian system.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	B	Three level II studies with low risk of bias and one level II study with moderate risk of bias
2. Consistency	A	All studies are consistent.
3. Clinical impact	B	The results ranged between a relative risk of 1.8 and 5.4 and odds ratios of 2.7 and 5.4, although some of the estimates also had wide confidence intervals. Taking this in to account the results would indicate a substantial clinical impact.
4. Generalisability	B	The study by Adler et al included mainly males; Litzelman et al had a large proportion of African Americans and socioeconomically disadvantaged patients. Similarly, Abbott et al had a large proportion of patients from a low socio economic class. These groups might be more vulnerable to poor health outcomes.
5. Applicability	B	Three studies came from the USA and one from the UK, which have a similar health care system for diabetes patients compared to the Australian system.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Peripheral sensory neuropathy and insensitivity to Semmes-Weinstein monofilament testing is a good predictor of risk of foot ulcer, foot injury and amputation in a general diabetes population (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
re the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy of ankle reflex assessment		Evidence table ref: (Ahroni et al 1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Not applicable as there is only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Ahroni et al's results of sensitivity, specificity and PPV of the assessment for risk of foot ulcers and amputation are very poor. Only the NPV seems reasonable for this assessment, indicating that there is a reasonable confidence in a negative result, presumably because the risk of foot ulcer and particularly amputation is low. The clinical impact of the assessment would be slight or restricted as it is a poor tool for screening those who are at high risk.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample included mainly male subjects which might restrict generalisation to females or the diabetes population in general.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA, which has a similar health care system for diabetes patients to the Australian context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Fiven the poor diagnostic performance (poor clinical impact), no recommendation was developed.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias
2. Consistency	N/A	.Not applicable as there is only one study.
3. Clinical impact	D	Ahroni et al's results of sensitivity, specificity and PPV of the assessment for risk of foot ulcers and amputation are very poor. Only the NPV seems reasonable for this assessment, indicating that there is a reasonable confidence in a negative result, presumably because the risk of foot ulcer and particularly amputation is low. The clinical impact of the assessment would be slight or restricted as it is a poor tool for screening those who are at high risk.
4. Generalisability	C	The study sample included mainly male subjects which might restrict generalisation to females or the diabetes population in general.
5. Applicability	B	The study was conducted in the USA, which has a similar health care system for diabetes patients to the Australian context

Indicate any dissenting opinions

EVIDENCE STATEMENT

In the general diabetes population, the assessment of ankle reflexes is a poor screening technique for identifying those at high risk of foot ulceration and lower extremity amputation (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of ankle reflex assessment		Evidence table ref: (Abbott et al. 2002; Boyko et al. 1999; Lehto et al. 1996)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Three level II studies with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Of the two studies that reported results for ulceration in the diabetic foot, one indicated a significant increased risk with absence of ankle reflex, while the other did not find a significant difference in ulceration between those with or without an ankle reflex. This inconsistency might be explained by the different variables that were included in the uni and multivariate analysis of both studies. There was only one study that reported on amputation as an outcome.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The significant result for ulceration suggested a moderate clinical impact (odds between 1.4 and 1.9), given bilateral absence of the reflex as the cut off (similar to other studies). The result from Boyko et al (1999) indicated no significant effect. For amputation as an outcome, the result indicates a substantial clinical impact.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Boyko et al (1999) included mainly males, which makes it difficult to generalise to females. Abbott et al (2002) included a sample with a large group of patients with lower socioeconomic status. Overall the samples studied are likely similar to the target group.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
One study came from the USA, one from Finland and one from the UK, which all have a similar health care system for diabetes patients to the Australian context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	B	Three level II studies with low risk of bias.
2. Consistency	C	Of the two studies that reported results for ulceration in the diabetic foot, one indicated a significant increased risk with absence of ankle reflex, while the other did not find a significant difference in ulceration between those with or without an ankle reflex. This inconsistency might be explained by the different variables that were included in the uni and multivariate analysis of both studies. There was only one study that reported on amputation as an outcome.
3. Clinical impact	C	The significant result for ulceration suggested a moderate clinical impact (odds between 1.4 and 1.9), given bilateral absence of the reflex as the cut off (similar to other studies). The result from Boyko et al (1999) indicated no significant effect. For amputation as an outcome, the result indicates a substantial clinical impact.
4. Generalisability	B	Boyko et al (1999) included mainly males, which makes it difficult to generalise to females. Abbott et al (2002) included a sample with a large group of patients with lower socioeconomic status. Overall the samples studied are likely similar to the target group.
5. Applicability	B	One study came from the USA, one from Finland and one from the UK, which all have a similar health care system for diabetes patients to the Australian context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is inconsistent and inconclusive evidence regarding the role of ankle reflex assessment in predicting foot ulcers in the general diabetes population (Grade C).

Ankle reflex assessment may have a role in predicting risk of amputation in a general diabetes population (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of foot deformity		Evidence table ref: (Abbott et al. 2002; Boyko et al 1999)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Both studies found significant results for foot deformity with increased odds of developing foot ulcer of between 1.5 and 3.5.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The result indicate moderate to substantial clinical impact (odds ratios between 1.5 and 3.5 for the development of foot ulcer in those with foot deformities, though the results were very dependent on the included variables in the univariate and multivariate analysis.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Boyko et al predominately studied males, which makes it difficult to generalise to females. Abbott et al included a sample with a large group of patients of lower socioeconomic status.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
One study came from the USA and one from the UK, both having a similar approach to treating diabetes patients as in the Australian context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	A	Two level II studies with low risk of bias.
2. Consistency	B	Both studies found significant results for foot deformity with increased odds of developing foot ulcer of between 1.5 and 3.5.
3. Clinical impact	C	The result indicate moderate to substantial clinical impact (odds ratios between 1.5 and 3.5 for the development of foot ulcer in those with foot deformities., though the results were very dependent on the included variables in the univariate and multivariate analysis,
4. Generalisability	B	Boyko et al predominately studied males, which makes it difficult to generalise to females. Abbott et al included a sample with a large group of patients of lower socioeconomic status.
5. Applicability	B	One study came from the USA and one from the UK, both having a similar approach to treating diabetes patients as in the Australian context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence indicates that the presence of foot deformity is a moderate predictor of foot ulcer in the general diabetes population (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	

Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy of gait assessment		Evidence table ref: (Ahroni et al. 1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study provided evidence.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The sensitivity of the test is extremely poor (17%), meaning that an unacceptable proportion of 'at risk' patients would be missed. In contrast the specificity and NPV was moderate to high, indicating that the assessment is better at detecting those not at high risk.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample included mainly male subjects therefore there may be some limitations in generalising to the female or general diabetes population	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study came from the USA, which has a similar health care system for diabetes care as the Australian system.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt there was insufficient evidence (only one study and poor clinical impact) to make a recommendation

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study provided evidence.
3. Clinical impact	D	The sensitivity of the test is extremely poor (17%), meaning that an unacceptable proportion of 'at risk' patients would be missed. In contrast the specificity and NPV was moderate to high, indicating that the assessment is better at detecting those not at high risk.
4. Generalisability	C	The study sample included mainly male subjects therefore there may be some limitations in generalising to the female or general diabetes population
5. Applicability	B	The study came from the USA, which has a similar health care system for diabetes care as the Australian system.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Based on a single study, the assessment of gait in the general diabetes population is a poor screening technique for identifying those patients at high risk of foot ulcer and amputation (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy of peripheral artery pulse assessment		Evidence table ref: (Adler et al. 1999)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study provided evidence.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
This study provides evidence that peripheral arterial pulse assessment is useful in ruling out risk of amputation as indicated by the low level of false negatives. However, this is primarily because the risk of amputation is uncommon. Test sensitivity was low to moderate.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample included predominantly male subjects. Therefore it may be hard to generalise to females or the general diabetes population	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study came from the USA, which has a similar health system for diabetes care as the Australian system.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt that as a result of the poor clinical impact in this assessment, no recommendation was developed.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study provided evidence.
3. Clinical impact	D	This study provides evidence that peripheral arterial pulse assessment is useful in ruling out risk of amputation as indicated by the low level of false negatives. However, this is primarily because the risk of amputation is uncommon. Test sensitivity was low to moderate.
4. Generalisability	C	The study sample included predominantly male subjects. Therefore it may be hard to generalise to females or the general diabetes population
5. Applicability	B	The study came from the USA, which has a similar health system for diabetes care as the Australian system.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Evidence suggests that peripheral arterial pulse assessment alone is a poor screening technique to identify those patients in the general diabetes population at high risk of amputation (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	

Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of peripheral artery pulse		Evidence table ref: (Abbott et al. 2002; Lehto et al. 1996)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Both studies found significant results for peripheral arterial pulse as a predictor of foot ulcer and amputation.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The significant result for ulceration indicates a moderate clinical impact with an odds ratio of 1.80. For amputation as an outcome, the result indicated a substantial clinical impact, although this result was likely confounded.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Abbott et al included a sample with a large group of patients of low socioeconomic status, while Lehto et al had a population that was generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
One study came from the USA and one from the Finland and both have similar health care for diabetes patients as in Australian.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
• Evidence base	A	Two level II studies with low risk of bias.
• Consistency	B	Both studies found significant results for peripheral arterial pulse as a predictor of foot ulcer and amputation.
• Clinical impact	C	The significant result for ulceration indicates a moderate clinical impact with an odds ratio of 1.80. For amputation as an outcome, the result indicated a substantial clinical impact, although this result was likely confounded.
• Generalisability	B	Abbott et al included a sample with a large group of patients of low socioeconomic status, while Lehto et al had a population that was generalisable to the target population.
• Applicability	B	One study came from the USA and one from the Finland and both have similar health care for diabetes patients as in Australian .

Indicate any dissenting opinions

EVIDENCE STATEMENT

Peripheral arterial pulse is a moderate predictor of subsequent foot ulcer or amputation in the general diabetes population (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	

Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy of ankle arm index assessment		Evidence table ref: (Adler et al. 1999)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study provided evidence.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
This study shows that AAI has low sensitivity and moderate specificity at identifying those patients at high risk.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample included mainly male subjects. Therefore there may be limited generalisability to females with diabetes .	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA, which has similar health care for diabetes patients as in Australian.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt there was insufficient evidence (only one study and poor clinical impact) to make a recommendation

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study provided evidence.
3. Clinical impact	D	This study shows that AAI has low sensitivity and moderate specificity at identifying those patients at high risk.
4. Generalisability	C	The study sample included mainly male subjects. Therefore there may be limited generalisability to females with diabetes .
5. Applicability	C	The study was conducted in the USA, which has similar health care for diabetes patients as in Australian.

Indicate any dissenting opinions

EVIDENCE STATEMENT

On the bases of limited evidence, Ankle Arm Index assessment would appear to be a poor screening technique to predict lower extremity amputation in the general diabetes population (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of ankle arm index assessment		Evidence table ref: (Adler et al. 1999; Boyko et al. 1999)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results presented by Boyko et al indicate that the ankle arm index may have a moderate clinical impact as the adjusted odds ratios were between 1.4 and 1.9. Adler et al presented a rather large relative risk, which had a wide confidence interval for major amputation. Both studies used data from the Seattle Diabetes Foot study.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Both studies used data from the same sample that included mainly male. Therefore it will be hard to generalise to females or the general diabetes population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study came from the USA, which has similar health care for diabetes patients as in Australian.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation was developed as this is prognostic evidence

EVIDENCE STATEMENT

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.

Component	Rating	Description
1. Evidence base	B	One level II study with low risk of bias and one level II study with moderate risk of bias.
2. Consistency	N/A	Only one study.
3. Clinical impact	B	The results presented by Boyko et al indicate that the ankle arm index may have a moderate clinical impact as the adjusted odds ratios were between 1.4 and 1.9. Adler et al presented a rather large relative risk, which had a wide confidence interval for major amputation. Both studies used data from the Seattle Diabetes Foot study.
4. Generalisability	C	Both studies used data from the same sample that included mainly male. Therefore it will be hard to generalise to females or the general diabetes population.
5. Applicability	C	The study came from the USA, which has similar health care for diabetes patients as in Australian.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The Ankle Arm Index may be a moderate predictor of foot ulceration and substantial predictor of major amputation in the male diabetes population (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of ankle blood pressure assessment		Evidence table ref: (Boyko et al. 1999)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study provided evidence.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results presented by Boyko et al indicate that ankle blood pressure assessment may have a moderate clinical impact with a relative risk of 2.0.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample included mainly male subjects. Therefore it may be difficult to generalise to females or the general diabetes population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study came from the USA, which has similar health care for diabetes patients as in Australian.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study provided evidence.
3. Clinical impact	C	The results presented by Boyko et al indicate that ankle blood pressure assessment may have a moderate clinical impact with a relative risk of 2.0.
4. Generalisability	C	The study sample included mainly male subjects. Therefore it may be difficult to generalise to females or the general diabetes population.
5. Applicability	C	The study came from the USA, which has similar health care for diabetes patients as in Australian.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Ankle blood pressure may be a moderate predictor of foot ulceration in male diabetes patients. However, further research is required to confirm this association (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of orthostatic blood pressure drop		Evidence table ref: (Boyko et al. 1999)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study provided evidence.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicate that orthostatic blood pressure has a likely slight to restricted clinical impact with a relative risk of 1.23. More importantly, the study did not describe the level of orthostatic blood pressure which would indicate a high risk of foot ulcer.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample included mainly male subjects. Therefore it could be difficult to generalise to females or the general diabetes population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study came from the USA, which has similar health for diabetes patients as in Australian.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	NA	Only one study provided evidence.
3. Clinical impact	D	The results indicate that orthostatic blood pressure has a likely slight to restricted clinical impact with a relative risk of 1.23. More importantly, the study did not describe the level of orthostatic blood pressure which would indicate a high risk of foot ulcer.
4. Generalisability	C	The study sample included mainly male subjects. Therefore it could be difficult to generalise to females or the general diabetes population.
5. Applicability	C	The study came from the USA, which has similar health for diabetes patients as in Australian.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is limited evidence suggesting that orthostatic blood pressure is a poor predictor for the development of subsequent foot ulcer in male diabetes patients (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	

Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy of transcutaneous oxygen tension assessment		Evidence table ref: (Adler et al. 1999)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study provided evidence.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results presented by Adler et al indicate that $TcPO_2$ assessment had low specificity and therefore had a high proportion of false positives receiving unnecessary treatment. The sensitivity was reasonable at identifying true positives, but had a rather wide confidence interval. Overall this results in a poor screening tool of a moderate clinical impact.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample included mainly male subjects. Therefore it may be difficult to generalise the results to females or the general diabetes population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA, which has a similar health care for diabetes patients as in Australian.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt there was insufficient evidence (only one study and limited clinical impact) to make a recommendation, further research is required.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study provided evidence.
3. Clinical impact	C	The results presented by Adler et al indicate that $TcPO_2$ assessment had low specificity and therefore had a high proportion of false positives receiving unnecessary treatment. The sensitivity was reasonable at identifying true positives, but had a rather wide confidence interval. Overall this results in a poor screening tool of a moderate clinical impact.
4. Generalisability	C	The study sample included mainly male subjects. Therefore it may be difficult to generalise the results to females or the general diabetes population.
5. Applicability	C	The study was conducted in the USA, which has a similar health care for diabetes patients as in Australian.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Transcutaneous oxygen tension assessment is of limited value as a screening tool for identifying those at high risk of lower extremity amputation in a general diabetic population. However, it has moderate value as a diagnostic tool. Further research is required to confirm this association (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of transcutaneous oxygen tension		Evidence table ref: (Adler et al. 1999; Boyko et al. 1999)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II sub-study with low risk of bias and one level II sub- study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Adler et al's reported relative risk of 3 with a confidence interval that generally included clinically important effects. The results presented by Boyko et al suggested that those with an increased $TcPO_2$ of 15 mmHg did not develop foot ulcer.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample included mainly male subjects and thus it is difficult to females or the general diabetes population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA, which has similar health care for diabetic patients as in Australian.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	B	One level II sub-study with low risk of bias and one level II sub- study with moderate risk of bias.
2. Consistency	N/A	Only one study.
3. Clinical impact	C	Adler et al's reported relative risk of 3 with a confidence interval that generally included clinically important effects. The results presented by Boyko et al suggested that those with an increased $TcPO_2$ of 15 mmHg did not develop foot ulcer.
4. Generalisability	C	The study sample included mainly male subjects and thus it is difficult to females or the general diabetes population.
5. Applicability	C	The study was conducted in the USA, which has similar health care for diabetic patients as in Australian.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Transcutaneous oxygen tension may be a moderate predictor for the development of foot ulcer and the occurrence of amputation in male diabetic patients (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	

Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy of glycaemic control assessment		Evidence table ref: (Adler et al. 1999; Ahroni et al. 1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results suggest that the assessment of HbA1c has little clinical use in predicting either foot ulcer or amputation. Therefore, the overall clinical impact of the assessment can be stated as slight to restricted.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study samples included mainly male subjects , thus making it difficult to generalise to females or the general diabetes population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study came from the USA, which has a similar health care system for diabetes patients to the Australian context and is therefore applicable with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt there was insufficient evidence to make a recommendation given the poor clinical impact and evidence available from only one study.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study.
3. Clinical impact	D	The results suggest that the assessment of HbA1c has little clinical use in predicting either foot ulcer or amputation. Therefore, the overall clinical impact of the assessment can be stated as slight to restricted.
4. Generalisability	C	The study samples included mainly male subjects , thus making it difficult to generalise to females or the general diabetes population.
5. Applicability	C	The study came from the USA, which has a similar health care system for diabetes patients to the Australian context and is therefore applicable with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Limited evidence suggests that the assessment of glycaemic control has poor accuracy at identifying those at risk of foot ulcer or lower extremity amputation (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of glycaemic control		Evidence table ref: (Lehto et al. 1996)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study provided evidence.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Lehto et al reported a 2.4 RR for the assessment of HbA1 and 2.2 for fasting plasma glucose, which can be seen as potentially having substantial impact. However, the study did include patients with other risk factors for lower extremity amputation, which were not controlled for.. Therefore, the clinical impact is stated as moderate.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample was a good representation of the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study came from Finland, which has a similar health care system for diabetes patients to the Australian context and is therefore applicable with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	B	One level II study with low risk of bias.
2. Consistency	N/A	Only one study provided evidence.
3. Clinical impact	C	Lehto et al reported a 2.4 RR for the assessment of HbA1 and 2.2 for fasting plasma glucose, which can be seen as potentially having substantial impact. However, the study did include patients with other risk factors for lower extremity amputation, which were not controlled for.. Therefore, the clinical impact is stated as moderate.
4. Generalisability	B	The study sample was a good representation of the target population.
5. Applicability	B	The study came from Finland, which has a similar health care system for diabetes patients to the Australian context and is therefore applicable with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Limited evidence suggests that glycaemic control may be a moderate predictor of lower extremity amputation as a consequence of arteriosclerotic vascular disease in a general diabetes population (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy of laboratory creatinine assessment		Evidence table ref: (Adler et al. 1999)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
This study shows that the creatinine test has low sensitivity and moderate specificity at identifying those patients at high risk of amputation.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample included mainly male subjects. Therefore there may be limited generalisability to females with diabetes.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA, which has similar health care for diabetes patients as in Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt there was insufficient evidence to make a recommendation given that the evidence was available from only one study and the poor clinical impact.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study provided evidence.
3. Clinical impact	D	This study shows that the creatinine test has low sensitivity and moderate specificity at identifying those patients at high risk of amputation.
4. Generalisability	C	The study sample included mainly male subjects. Therefore there may be limited generalisability to females with diabetes.
5. Applicability	C	The study was conducted in the USA, which has similar health care for diabetes patients as in Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

On the basis of limited evidence, creatinine testing would appear to be a poor test for predicting amputation in a general diabetes population (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of laboratory HDL assessment		Evidence table ref: (Lehto et al. 1996; Litzelman et al. 1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The evidence provided by both studies was contradictory.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Both results presented, suggest a slight to moderate clinical impact.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Litzelman et al's study samples included a large proportion of females and patients with a low socio economic status. Therefore it may be hard to generalise to males or the general diabetes population. Lehto et al had a population that was generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
One study came from the USA and one from Finland, which have similar health care diabetes patients as to Australian.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	B	Two level II studies with low risk of bias.
2. Consistency	C	The evidence provided by both studies was contradictory.
3. Clinical impact	D	Both results presented, suggest a slight to moderate clinical impact.
4. Generalisability	B	Litzelman et al's study samples included a large proportion of females and patients with a low socio economic status. Therefore it may be hard to generalise to males or the general diabetes population. Lehto et al had a population that was generalisable to the target population.
5. Applicability	B	One study came from the USA and one from Finland, which have similar health care diabetes patients as to Australian.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence regarding HDL cholesterol as a predictor of lower extremity amputation and major foot injury (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	

Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Diagnostic accuracy of foot pressure assessment in the neuropathic diabetes population		Evidence table ref: (Lavery et al. 2003; Veves et al. 1992)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The evidence provided by both studies was inconsistent, which might be explained by or the small sample size of Veves et al.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The moderate to poor performance of foot pressure assessment would suggest that it would have little clinical impact for predicting foot ulcer in neuropathic diabetic patients, with the exception of potentially ruling out those at low risk.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Veves et al (1992) included patients visiting a Manchester diabetes centre, while Lavery et al (2003) included patients from an urban managed care outpatient clinic. The samples were only diabetes patients with peripheral neuropathy.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

Both studies came from the USA, which has a similar health care system for diabetes patients to the Australian context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt there was insufficient evidence to make a recommendation given the limited clinical impact of this intervention.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	Two level II studies with moderate risk of bias.
2. Consistency	B	The evidence provided by both studies was inconsistent, which might be explained by or the small sample size of Veves et al.
3. Clinical impact	C	The moderate to poor performance of foot pressure assessment would suggest that it would have little clinical impact for predicting foot ulcer in neuropathic diabetic patients, with the exception of potentially ruling out those at low risk.
4. Generalisability	B	Veves et al (1992) included patients visiting a Manchester diabetes centre, while Lavery et al (2003) included patients from an urban managed care outpatient clinic. The samples were only diabetes patients with peripheral neuropathy.
5. Applicability	C	Both studies came from the USA, which has a similar health care system for diabetes patients to the Australian context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Despite some inconsistencies, the evidence suggests that foot pressure assessment in a neuropathic diabetes population is not accurate at predicting foot ulcer. However, optical pedobarography may only be of value at ruling out those at risk of foot ulcer. (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of foot pressure assessment in the neuropathic diabetes population		Evidence table ref: (Lavery et al. 2003)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The odds ratio shows a moderate clinical effect for predicting foot ulcer.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Lavery et al included patients from an urban managed care outpatient clinic. The sample included only diabetes patients with neuropathy.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The study came from the USA, which has a similar health care system for diabetes patients to the Australian context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with low risk of bias
2. Consistency	NA	Only one study.
3. Clinical impact	C	The odds ratio shows a moderate clinical effect for predicting foot ulcer.
4. Generalisability	B	Lavery et al included patients from an urban managed care outpatient clinic. The sample included only diabetes patients with neuropathy.
5. Applicability	C	The study came from the USA, which has a similar health care system for diabetes patients to the Australian context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggests that foot pressure assessment in a diabetes population with neuropathy is a moderate predictor for the development of foot ulcer (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of risk categorisation assessment in the indigenous diabetes population		Evidence table ref: (Rith-Najarian et al. 1992)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The odds ratio showed a large clinical effect for the prediction of foot ulcer.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The population included only residence of an Indian reservation, who visited a Indian Hospital Service. The population is generalisable to the indigenous target population in Australia with some caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study came from the US, which has a similar health care system for diabetes patients to	A	Evidence directly applicable to Australian healthcare context

the Australian context.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with low risk of bias.
2. Consistency	NA	Only one study.
3. Clinical impact	A	The odds ratio showed a large clinical effect for the prediction of foot ulcer.
4. Generalisability	B	The population included only residents of a Native American reservation, who visited a Hospital Service. The population is generalisable to the indigenous target population in Australia with some caveats.
5. Applicability	C	The study came from the US, which has a similar health care system for diabetes patients to the Australian context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Limited evidence suggests that indigenous diabetes patients with a risk categorisation indicating insensitivity to Semmes-Weinstein monofilaments (SWF) or SWF combined with foot deformity or a history of a lower extremity event may be more likely to develop foot ulcers than those with normal sensation (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive value of risk categorisation assessment in the indigenous diabetes population		Evidence table ref: (Rith-Najarian et al. 1992)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The odds ratio showed a large clinical effect for the prediction of foot ulcer and an even larger odds ratio for amputation. The precision of the results could not be ascertained.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The population included only residence of an Indian reservation, who visited a Indian Hospital Service. The population is generalisable to the indigenous target population in Australia with some caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study came from the US, which has a similar health care system for diabetes patients to	A	Evidence directly applicable to Australian healthcare context

the Australian context and is therefore applicable with some caveats.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with low risk of bias.
2. Consistency	NA	Only one study.
3. Clinical impact	A	The odds ratio showed a large clinical effect for the prediction of foot ulcer and an even larger odds ratio for amputation. The precision of the results could not be ascertained.
4. Generalisability	B	The population included only residence of an Indian reservation, who visited a Indian Hospital Service. The population is generalisable to the indigenous target population in Australia with some caveats.
5. Applicability	B	The study came from the US, which has a similar health care system for diabetes patients to the Australian context and is therefore applicable with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Limited evidence suggests that indigenous diabetes patients with a risk categorisation indicating insensitivity to Semmes-Weinstein monofilaments (SWF) or SWF combined with foot deformity or a history of a lower extremity event may be more likely to develop foot ulcers than those with normal sensation (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which clinical assessments best predict foot ulcer and / or amputation in people with diabetes? Predictive accuracy of Semmes-Weinstein monofilament testing in an Indigenous diabetes population		Evidence table ref: (Rith-Najarian et al 1992)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The odds ratio showed a large clinical effect for the prediction of foot ulcer and an even larger odds ratio for amputation. The precision of the results could not be ascertained.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The population included only residence of a Native American reservation, who visited a Hospital Service. The population is generalisable to the indigenous target population in Australia with some caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The study came from the US, which has a similar health care system for diabetes patients to the Australian context and is therefore applicable with some caveats..	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt there was insufficient evidence to make a recommendation

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	A	The odds ratio showed a large clinical effect for the prediction of foot ulcer and an even larger odds ratio for amputation. The precision of the results could not be ascertained.
4. Generalisability	B	The population included only residence of a Native American reservation, who visited a Hospital Service. The population is generalisable to the indigenous target population in Australia with some caveats.
5. Applicability	C	The study came from the US, which has a similar health care system for diabetes patients to the Australian context and is therefore applicable with some caveats..

Indicate any dissenting opinions

EVIDENCE STATEMENT

Limited evidence suggests that indigenous diabetes patients who are insensate to the Semmes-Weinstein monofilament assessment are more likely to develop foot ulcers and undergo amputation compared to those patients with normal sensation (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Question 3

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer? Diagnostic accuracy of bone scans for osteomyelitis		Evidence table ref: (Balsells et al 1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a high risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results are difficult to interpret as the diagnostic accuracy of the combined use of plain x-ray and combined bone and leukocyte scans are not reported.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to diabetic people with severe foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The study was conducted in Spain.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation was developed due to the poor clinical impact and evidence base.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
• Evidence base	D	One level II study with a high risk of bias.
• Consistency	N/A	One study only
• Clinical impact	D	The results are difficult to interpret as the diagnostic accuracy of the combined use of plain x-ray and combined bone and leukocyte scans are not reported.
• Generalisability	B	The study would be generalisable to diabetic people with severe foot ulcers.
• Applicability	C	The study was conducted in Spain.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is weak evidence to support the use of bone scans to identify higher risk of amputation in patients with severe diabetic foot ulcers (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer? Predictive ability of bone scans for osteomyelitis		Evidence table ref: (Balsells et al 1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a high risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results suggest that osteomyelitis is a strong predictor of amputation however there is considerable uncertainty in the point estimate.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to diabetic people with severe foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The study was conducted in Spain which is probably applicable to the Australian healthcare context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level II study with a high risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	C	The results suggest that osteomyelitis is a strong predictor of amputation however there is considerable uncertainty in the point estimate.
4. Generalisability	B	The study would be generalisable to diabetic people with severe foot ulcers.
5. Applicability	C	The study was conducted in Spain which is probably applicable to the Australian healthcare context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to suggest that osteomyelitis is a strong predictor of amputation in patients with severe diabetic foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer? Diagnostic accuracy of ankle peak systolic velocity.		Evidence table ref: (Bishara et al 2009)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a high risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results suggest that measurement of APSV has high discriminatory ability for identifying those at risk of non-healing. However, these results are likely to be unreliable given the questionable methods regarding patient entry into the study.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to diabetic people with foot ulcers and absence of pedal pulses. Furthermore, it may also be generalisable to people who have undergone revascularisation.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
It is likely that the study was conducted in a teaching hospital in Egypt which may restrict the applicability of these results to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation was developed due to the poor clinical impact, applicability to the Australian healthcare context and evidence base.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level II study with a high risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	D	The results suggest that measurement of APSV has high discriminatory ability for identifying those at risk of non-healing. However, these results are likely to be unreliable given the questionable methods regarding patient entry into the study.
4. Generalisability	B	The study would be generalisable to diabetic people with foot ulcers and absence of pedal pulses. Furthermore, it may also be generalisable to people who have undergone revascularisation.
5. Applicability	D	It is likely that the study was conducted in a teaching hospital in Egypt which may restrict the applicability of these results to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

APSV measurements may be useful in identifying diabetic patients with foot lesions or gangrene, who are at risk of not healing. (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer? Predictive ability of ankle peak systolic velocity for non-healing foot lesions.		Evidence table ref: (Bishara et al 2009)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a high risk of bias	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results suggest that APSV measurement is an independent predictor of non-healing however, it is unlikely that these results can be relied upon.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to diabetic people with foot ulcers and absence of pedal pulses. Furthermore, it may also be generalisable to people who have undergone revascularisation.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
It is probable that the study was conducted in a teaching hospital in Egypt which may restrict the applicability of these results to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level II study with a high risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	D	The results suggest that APSV measurement is an independent predictor of non-healing however, it is unlikely that these results can be relied upon.
4. Generalisability	B	The study would be generalisable to diabetic people with foot ulcers and absence of pedal pulses. Furthermore, it may also be generalisable to people who have undergone revascularisation.
5. Applicability	D	It is probable that the study was conducted in a teaching hospital in Egypt which may restrict the applicability of these results to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

It is possible that APSV is an independent predictor of non-healing in diabetic patients with foot lesions or gangrene (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	

Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer? Diagnostic ability of skin perfusion pressure for foot ulcer healing.		Evidence table ref: (Faris & Duncan 1985)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results suggest that skin perfusion pressure is a good diagnostic tool to predict healing (including local surgery or amputation) and in particular, to rule out the likelihood of healing in patients with low skin perfusion pressure. However, the potential for introduced biases ensures that the evidence for this is weak.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to diabetic people with foot ulcers or gangrene.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
This study is directly applicable to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation was developed due to the poor clinical impact and evidence base.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level II study with a high risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	D	The results suggest that skin perfusion pressure is a good diagnostic tool to predict healing (including local surgery or amputation) and in particular, to rule out the likelihood of healing in patients with low skin perfusion pressure. However, the potential for introduced biases ensures that the evidence for this is weak.
4. Generalisability	A	The study would be generalisable to diabetic people with foot ulcers or gangrene.
5. Applicability	A	This study is directly applicable to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

It is possible that skin perfusion pressure is able to predict healing in diabetic patients with foot lesions or gangrene. In particular, it is possible that skin perfusion pressure may rule out the likelihood of healing in patients with low skin perfusion pressure (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer? Predictive ability of capillary circulation with macro-aggregated albumin for healing of foot lesions.		Evidence table ref: (Moriarty et al 1994)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a high risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The impact of this evidence is likely to be restricted as the grades and outcome of healing were poorly defined and furthermore, the association between capillary circulation and healing was not adjusted for treatments received by patients.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to diabetic people with ischaemic foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the United Kingdom and is applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level II study with a high risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	D	The impact of this evidence is likely to be restricted as the outcome of healing was poorly defined and the association between capillary circulation and healing was not adjusted for treatments received by patients.
4. Generalisability	A	The study would be generalisable to diabetic people with ischaemic foot ulcers.
5. Applicability	B	This study is directly applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is likely to be an association between poor capillary circulation and non-healing, as well as between increased perfusion and healing of foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer? Predictive ability of $TcPO_2$ and TBP for healing of chronic foot lesions.		Evidence table ref: (Kalani et al 1999)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a high risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The impact of this evidence is likely to be restricted as the outcome of healing was poorly defined and is likely to have included patients with improved rather than complete healing. $TcPO_2$ appears to have greater ability to identify those with healing compared to TBP but given the uncertainty regarding the definitions of outcomes, it would be more appropriate to suggest that it identifies improvement rather than ulcer healing.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to diabetic people with chronic foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
This study was conducted in Sweden and would be applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level II study with a high risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	C	The impact of this evidence is likely to be restricted as the outcome of healing was poorly defined and is likely to have included patients with improved rather than complete healing. $TcPO_2$ appears to have greater ability to identify those with healing compared to TBP but given the uncertainty regarding the definitions of outcomes, it would be more appropriate to suggest that it identifies improvement rather than ulcer healing.
4. Generalisability	A	The study would be generalisable to diabetic people with chronic foot ulcers.
5. Applicability	B	This study was conducted in Sweden and would be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

It is possible that $TcPO_2$ measurement can better identify those ulcers which will improve compared with TBP (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer? Predictive ability of systolic ankle and toe blood pressure.		Evidence table ref: : (Apelqvist et al 1989a)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II studies with a high risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There is likely to be restricted use of this evidence in the prediction of ulcer healing.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
This study was conducted in Sweden and is applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level II studies with a high risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	D	There is likely to be restricted use of this evidence in the prediction of ulcer healing.
4. Generalisability	A	The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.
5. Applicability	B	This study was conducted in Sweden and is applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to indicate that the toe and ankle systolic pressure indices are likely to be higher in patients who achieve primary healing than those who are amputated (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer? Predictive ability of hyperspectral imaging of ocyhaemoglobin and deoxyhaemoglobin for healing of foot lesions.		Evidence table ref: (Khaodhiar et al 2007; Nouvong et al 2009)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The differences in diagnostic accuracy are likely to be attributable to the greater statistical power of the larger study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results of this study provide evidence that tissue oxygenation as measured by hyperspectral imaging could identify both healing and to a lesser extent, non-healing ulcers. However, some caution should be used with these results as they ought to be validated in an external data set to confirm the accuracy of the model in identifying ulcer healing.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to people with diabetic foot ulcers attending diabetic foot clinics.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
This study is applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Two level II studies with a moderate risk of bias.
2. Consistency	B	The differences in diagnostic accuracy are likely to be attributable to the greater statistical power of the larger study.
3. Clinical impact	C	The results of this study provide evidence that tissue oxygenation as measured by hyperspectral imaging could identify both healing and to a lesser extent, non-healing ulcers. However, some caution should be used with these results as they ought to be validated in an external data set to confirm the accuracy of the model in identifying ulcer healing.
4. Generalisability	A	The study would be generalisable to people with diabetic foot ulcers attending diabetic foot clinics.
5. Applicability	B	This study is applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to suggest that hyperspectral imaging of tissue oxygenation can identify healing of diabetic foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer? Predictive ability of plasma fibrinogen for predicting amputation.		Evidence table ref: (Rattan & Nayak 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II studies with a high risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results of this study suggest that plasma fibrinogen levels are a good discriminator of those at high and low risk of amputation in people with diabetic foot ulcers. However, due to the potential confounding by treatment and possible lack of blinding by treating physician, it is difficult to determine whether these results would be useful in a clinical setting.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to people with Wagner grade 1 and 2 diabetic foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Conducted in India, this study is probably applicable to the Australian healthcare context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level II studies with a high risk of bias.
2. Consistency	N/A	Only one study available.
3. Clinical impact	C	The results of this study suggest that plasma fibrinogen levels are a good discriminator of those at high and low risk of amputation in people with diabetic foot ulcers. However, due to the potential confounding by treatment and possible lack of blinding by treating physician, it is difficult to determine whether these results would be useful in a clinical setting.
4. Generalisability	A	The study would be generalisable to people with Wagner grade 1 and 2 diabetic foot ulcers.
5. Applicability	C	Conducted in India, this study is probably applicable to the Australian healthcare context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to suggest that plasma fibrinogen levels may identify those at risk of amputation in people with Wagner grade 1 or 2 diabetic foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer? Predictive ability of DEPA score for healing of foot ulcers.		Evidence table ref: (Younes & Albsoul 2004)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II studies with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results of the study indicate a strong linear association between DEPA score and ulcer outcome however, no measures are provided of its diagnostic or predictive performance.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to people with diabetic foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Conducted in Jordan, this study is probably applicable to the Australian healthcare context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II studies with a moderate risk of bias.
2. Consistency	N/A	Only one study available.
3. Clinical impact	D	The results of the study indicate a strong linear association between DEPA score and ulcer outcome however, no measures are provided of its diagnostic or predictive performance.
4. Generalisability	A	The study would be generalisable to people with diabetic foot ulcers.
5. Applicability	C	Conducted in Jordan, this study is probably applicable to the Australian healthcare context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to suggest that there is a strong linear relationship between DEPA score and foot ulcer outcome. (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with foot ulcer? Predictive ability of University of Texas classification for healing of foot lesions.		Evidence table ref: (Armstrong et al 1998)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level III-3 study with moderate risk of bias	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The evidence provided suggests that there is a strong association between grade 3 and/or stage D foot ulcers and midfoot or higher amputations.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care. It should be noted that the majority of patients were Mexican Americans.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Conducted in the USA, this study is probably applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Level III-3 study with moderate risk of bias
2. Consistency	N/A	Only one study available
3. Clinical impact	C	The evidence provided suggests that there is a strong association between grade 3 and/or stage D foot ulcers and midfoot or higher amputations.
4. Generalisability	B	The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care. It should be noted that the majority of patients were Mexican Americans.
5. Applicability	B	Conducted in the USA, this study is probably applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence that there may be a strong association between stage and grade of ulcer, and midfoot or higher amputation in the short term (6 months) (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*
Will this recommendation result in changes in usual care?
Are there any resource implications associated with implementing this recommendation?
Will the implementation of this recommendation require changes in the way care is currently organised?
Are the guideline development group aware of any barriers to the implementation of this recommendation?

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with diabetes? Predictive ability of Wagner classification to predict foot ulcer outcomes.			Evidence table ref:(Apelqvist et al 1989b)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Level II study with moderate risk of bias	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	N/A	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
The evidence provides relative measures of risk and indicates that the risk of not achieving primary healing increases with increasing Wagner grade.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Conducted in Sweden, this study is probably applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as its prognostic evidence.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Level II study with moderate risk of bias
2. Consistency	N/A	Only one study available
3. Clinical impact	C	The evidence provides relative measures of risk and indicates that the risk of not achieving primary healing increases with increasing Wagner grade.
4. Generalisability	A	The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.
5. Applicability	B	Conducted in Sweden, this study is probably applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

With regard to non-primary healing, there is evidence that there is an increase in relative risk with increasing Wagner grade (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with diabetes? Predictive ability of baseline characteristics to predict ulcer lesions.		Evidence table ref: (Ince et al 2007; Oyibo et al 2001a)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II and III-3 study with moderate risk of bias	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There are some inconsistencies which may be explained by the smaller sample size in the study by Obiyo et al (2001).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The evidence provided is likely to have a moderate clinical impact as the studies do not provide sufficient information to estimate risk, nor do they provide adequate information regarding its ability to discriminate between those who are likely to heal and those who are not. However, they do show a relationship between these baseline characteristics and time to healing.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The studies would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Conducted in the United Kingdom and the USA, these studies are probably applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Level II and III-3 study with moderate risk of bias
2. Consistency	B	There are some inconsistencies which may be explained by the smaller sample size in the study by Obiyo et al (2001).
3. Clinical impact	C	The evidence provided is likely to have a moderate clinical impact as the studies do not provide sufficient information to estimate risk, nor do they provide adequate information regarding its ability to discriminate between those who are likely to heal and those who are not. However, they do show a relationship between these baseline characteristics and time to healing.
4. Generalisability	A	The studies would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.
5. Applicability	B	Conducted in the United Kingdom and the USA, these studies are probably applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence that ulcer area, arteriopathy, ulcer site and duration of diabetes are strong independent predictors of time to healing (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with diabetes? Comparison of Wagner, University of Texas and S(AD)SAD classification to predict foot ulcer outcomes.		Evidence table ref: (Oyibo et al 2000; Parisi et al 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Both studies provide evidence that the UT classification is likely to be superior in predicting amputation and healing of foot ulcers.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
This evidence would likely have a substantial impact on clinical practice.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Conducted in Brazil, UK and USA, these studies are probably applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Two level II studies with a moderate risk of bias.
2. Consistency	C	Both studies provide evidence that the UT classification is likely to be superior in predicting amputation and healing of foot ulcers
3. Clinical impact	B	This evidence would likely have a substantial impact on clinical practice.
4. Generalisability	A	The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.
5. Applicability	B	Conducted in Brazil, UK and USA, these studies are probably applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence provided suggests that the UT classification would better predict the outcome of ulcers and healing compared to Wagner grading (Grade C).

There is reasonable evidence to suggest that the UT classification of diabetic foot ulcer is better able to predict the likelihood of healing or amputation than the Wagner and S(AD)SAD classification systems (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	C

Foot ulcer severity can be graded on the basis of wound depth, presence of infection (local, systemic or bone) and presence of peripheral arterial disease. Ulcer grading helps determine the degree of risk to the person and limb (Oyibo et al 2001b; Parisi et al 2008). The University of Texas (UT) wound classification system is the most useful tool for grading foot ulcers. (EBR 5)
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*
Will this recommendation result in changes in usual care?
Are there any resource implications associated with implementing this recommendation?
Will the implementation of this recommendation require changes in the way care is currently organised?
Are the guideline development group aware of any barriers to the implementation of this recommendation? 12. Knowledge/education in wound care for GPs required. 13. Access to grading tools 14. Access to dressings **Enablers to implementation** 15. Provide a range of tools for grading ulcer severity in the Guideline. Easier method required for GPs to manage ulcers ie. Clear instructions on when to refer on, if the ulcer is taking too long (specify how long) to heal or not progressing.

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with diabetes? Predictive ability of capillary circulation for healing of foot lesions.		Evidence table ref:
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II studies with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
This study suggests that all three classifications are likely to predict the outcome of healing although with regard to discriminatory ability, the UT system is superior (no measure of discrimination was provided for S(AD)SAD)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Conducted in Brazil, UK and USA, these studies are probably applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II studies with a moderate risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	B	This study suggests that all three classifications are likely to predict the outcome of healing although with regard to discriminatory ability, the UT system is superior (no measure of discrimination was provided for S(AD)SAD)
4. Generalisability	A	The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.
5. Applicability	B	Conducted in Brazil, UK and USA, these studies are probably applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with diabetes? Comparison of Wagner and Van Acker/Peter classification for predicting healing of foot lesions.		Evidence table ref:(Van Acker et al 2002)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level III-3 studies with a high risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study provides evidence that there is an association between VA/P classification and amputation, and that the grading of patients is significantly correlated between the two systems.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to people with diabetic foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Conducted in Belgium the study is probably applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt there was insufficient evidence to make a recommendation

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level III-3 studies with a high risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	C	The study provides evidence that there is an association between VA/P classification and amputation, and that the grading of patients is significantly correlated between the two systems.
4. Generalisability	A	The study would be generalisable to people with diabetic foot ulcers.
5. Applicability	B	Conducted in Belgium the study is probably applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence that the VA/P classification is moderately correlated with the Wagner grading of foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with diabetes? Predictive ability of DUSS and MAID for healing of foot lesions.		Evidence table ref: (Beckert et al 2009; Beckert et al 2006)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Inconsistencies are likely to be explained by the additional population in the later study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The evidence provided suggests that there is a decreasing likelihood of healing with an increase in DUSS or M.A.I.D. however no information was provided regarding the accuracy of the scores to predict healing in people with foot ulcer	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The studies should be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Conducted in Germany, the studies is probably applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Two level II studies with a moderate risk of bias.
2. Consistency	B	Inconsistencies are likely to be explained by the additional population in the later study.
3. Clinical impact	C	The evidence provided suggests that there is a decreasing likelihood of healing with an increase in DUSS or M.A.I.D. however no information was provided regarding the accuracy of the scores to predict healing in people with foot ulcer
4. Generalisability	B	The studies should be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.
5. Applicability	B	Conducted in Germany, the studies is probably applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence provided suggests that an increase in DUSS or M.A.I.D score is associated with a decreased probability of foot ulcer healing (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	C

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with diabetes? Predictive ability of the Scottish foot ulcer risk score for healing of foot lesions.		Evidence table ref: (Leese et al 2007)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II studies with a high risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
This poor quality evidence and lack of information regarding the predictive ability of the foot risk score prevent the evaluation of the potential clinical impact.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care. There is likely to be substantial selection bias which would decrease the generalisability.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Conducted in Scotland, the study is probably applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level II studies with a high risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	D	This poor quality evidence and lack of information regarding the predictive ability of the foot risk score prevent the evaluation of the potential clinical impact.
4. Generalisability	B	The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care. There is likely to be substantial selection bias which would decrease the generalisability.
5. Applicability	B	Conducted in Scotland, the study is probably applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence for the association between foot risk score and outcomes is poor (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with diabetes? Predictive ability of CHS model for non-healing of foot lesions.		Evidence table ref: (Margolis et al 2002; Margolis et al 2003; Margolis et al 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level III studies with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available which reported outcomes of predictive ability	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study provided evidence that the models were able to discriminate and satisfactorily identify those patients who were unlikely to heal. Greater discrimination was seen in the model with the most predictor variables. Basic evaluation of the calibration of the models indicated that the predicted risk was similar to the observed risk of non-healing.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

Conducted in the USA, the study is probably applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level III studies with a moderate risk of bias.
2. Consistency	N/A	Only one study available which reported outcomes of predictive ability
3. Clinical impact	B	The study provided evidence that the models were able to discriminate and satisfactorily identify those patients who were unlikely to heal. Greater discrimination was seen in the model with the most predictor variables. Basic evaluation of the calibration of the models indicated that the predicted risk was similar to the observed risk of non-healing.
4. Generalisability	B	The study would be generalisable to people with diabetic foot ulcers receiving multidisciplinary care.
5. Applicability	B	Conducted in the USA, the study is probably applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to suggest that the predictive model developed by the Curative Health Services is able to discriminate and accurately predict the risk of non-healing in people with diabetic foot ulcers attending specialist wound care centres (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with diabetes? Predictive ability of clinical history, physical examination and MRI for non-healing of foot lesions.		Evidence table ref: (Edelman et al 1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II studies with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study provided evidence that the absence of an audible posterior tibial pulse on Doppler examination and the presence of pain at the site of the ulcer were strong predictors of non-healing. However, the ability of model to accurately predict the risk of this outcome was not assessed.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to people with diabetic foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Conducted in the USA, the study is probably applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II studies with a moderate risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	C	The study provided evidence that the absence of an audible posterior tibial pulse on Doppler examination and the presence of pain at the site of the ulcer were strong predictors of non-healing. However, the ability of model to accurately predict the risk of this outcome was not assessed.
4. Generalisability	A	The study would be generalisable to people with diabetic foot ulcers.
5. Applicability	B	Conducted in the USA, the study is probably applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to suggest that audible posterior tibial pulse on Doppler examination and the presence of pain at the site of the ulcer are strong predictors of non-healing in people with diabetic foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which assessments best predict foot ulcer severity and outcomes in people with diabetes? Predictive ability of the International consensus on the diabetic foot wound classification for amputation.		Evidence table ref: (Widatalla et al 2009)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II studies with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
This study only provides evidence that the criteria are predictors of amputation. It remains unclear whether the results were crude or adjusted estimates of association.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study may be generalisable to people with diabetic foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Conducted in the Sudan, the study is probably applicable to the Australian healthcare context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II studies with a moderate risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	C	This study only provides evidence that the criteria are predictors of amputation. It remains unclear whether the results were crude or adjusted estimates of association.
4. Generalisability	B	The study may be generalisable to people with diabetic foot ulcers.
5. Applicability	C	Conducted in the Sudan, the study is probably applicable to the Australian healthcare context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

This study provides evidence that neuropathy, end stage renal disease, ischaemia and infection are strong predictors of amputation (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Question 4

Key question: How often, and by whom, should foot assessments be carried out in people with or without foot ulcer? Home based temperature monitoring versus standard care		Evidence table ref: Lavery et al 2004, lavery et al 2007, Armstrong et al 2007
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with a low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The studies provided consistent results.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results on the prevention of foot ulceration or lower extremity amputation reflect a substantial clinical impact The absolute reduction in risk of foot ulcer varied from 7-22% when patients complied to the screening program accordingly.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included diabetic patients at high risk of foot complications, able to apply the intervention by themselves in their home situation.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation has been made to use home based foot temperature monitoring to prevent foot complications (see Question 1)

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
6. Evidence base	B	Two level II studies with a low risk of bias.
7. Consistency	A	The studies provided consistent results.
8. Clinical impact	B	The results on the prevention of foot ulceration or lower extremity amputation reflect a substantial clinical impact The absolute reduction in risk of foot ulcer varied from 7-22% when patients complied to the screening program accordingly.
9. Generalisability	B	The study included diabetic patients at high risk of foot complications, able to apply the intervention by themselves in their home situation.
10. Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence indicates that home based foot temperature monitoring in addition to standard care should be applied twice daily by the patient to prevent diabetic foot ulceration and lower extremity amputation (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: How often, and by whom, should foot assessments be carried out in people with or without foot ulcer? Foot screening and protection program		Evidence table ref: McCabe et al 1998
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Although the study did not show a statistically significant reduction in the risk of foot ulcer compared to the control group, a substantial reduction in the relative risk of major amputation and consequently total amputation was apparent, both of which were statistically significant.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included patients from a general diabetes clinic in the UK. There are no patient characteristics presented.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was performed in the UK which has a similar healthcare context to the Australian health care system.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt there was insufficient information regarding the frequency of screening to make an evidence-based recommendation regarding how often it should be performed.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study.
3. Clinical impact	B	Although the study did not show a statistically significant reduction in the risk of foot ulcer compared to the control group, a substantial reduction in the relative risk of major amputation and consequently total amputation was apparent, both of which were statistically significant.
4. Generalisability	B	The study included patients from a general diabetes clinic in the UK. There are no patient characteristics presented.
5. Applicability	B	The study was performed in the UK which has a similar healthcare context to the Australian health care system.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggests that foot screening, performed by a registrar, should take place in two direct sequential stages to identify those patients at high risk of lower extremity amputation, followed by a protection program to prevent amputation. (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Question 5

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Sensory neuropathy as a risk factor for poor foot outcomes		Evidence table ref: (Abbott et al 1998; Boyko et al 1996; Bruce et al 2005; Davis et al 2006; Hamalainen et al 1999; Ledoux et al 2005; Lehto et al 1996; Litzelman et al 1997; Nelson et al 1988; Pham et al 2000; Wallace et al 2002; Winkley et al 2007)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
• Evidence base	B	Ten level II study with low to moderate risk of bias.
• Consistency	B	Most studies consistently showed that neuropathy is a risk factor for poor foot outcomes in people with and without foot ulcer. Any inconsistencies can be explained.
• Clinical impact	C	The evidence suggests that neuropathy is a weak to moderate risk factor for poor foot outcomes. Although some studies show a moderate strength of relationship, the confidence intervals around the estimate would suggest a lesser clinical impact.
• Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
• Applicability	B	Studies were undertaken in Australia, UK, Finland and the USA therefore, overall the evidence is likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is good evidence to show that sensory neuropathy, as measured by VPT, SWF and the Michigan Neuropathy Screening Instrument, is an independent risk factor for amputation, foot ulceration and general functioning (mobility/falls) in people with diabetes managed in a primary care setting (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?		
Are there any resource implications associated with implementing this recommendation?		
Will the implementation of this recommendation require changes in the way care is currently organised?		
Are the guideline development group aware of any barriers to the implementation of this recommendation?		

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Abnormal neuropathic symptom score/ neuropathic disability score as a risk factor for poor foot outcomes		Evidence table ref: Pham et al (2000)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study by Pham et al indicates that an abnormal NDS score is a moderate risk factor for the development of foot ulcer.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Patients from tertiary care facilities were included in this study which may overestimate the relationship between abnormal NDS score and foot ulcer.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was undertaken in the USA therefore likely to be applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study available.
3. Clinical impact	C	The study by Pham et al indicates that an abnormal NDS score is a moderate risk factor for the development of foot ulcer.
4. Generalisability	C	Patients from tertiary care facilities were included in this study which may overestimate the relationship between abnormal NDS score and foot ulcer.
5. Applicability	B	The study was undertaken in the USA therefore likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to show that an abnormal NDS score may be a risk factor for the development of foot ulcer in people with diabetes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Foot pressure		Evidence table ref: (Pham et al 2000)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study by Pham et al indicates that an abnormal high foot pressure is a moderate risk factor for the development of foot ulcer.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Patients from tertiary care facilities were included in this study which may overestimate the relationship between high foot pressures and foot ulcer.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The study was undertaken in the USA therefore likely to be applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study available.
3. Clinical impact	C	The study by Pham et al indicates that an abnormal high foot pressure is a moderate risk factor for the development of foot ulcer.
4. Generalisability	C	Patients from tertiary care facilities were included in this study which may overestimate the relationship between high foot pressures and foot ulcer.
5. Applicability	B	The study was undertaken in the USA therefore likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to show that an abnormal high foot pressure (≥ 6 kg/cm^2) may be a moderate risk factor for the development of foot ulcer in people with diabetes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Reflexes		Evidence table ref: (Nelson et al 1988), (Lehto et al 1996)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Although the measures of association are all in the same direction, the likely effects of confounding in these two studies results in difficulty in assessing the consistency o f the results. Potential confounding ensures that there is considerable uncertainty around these estimates of association.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Although the studies report that the absence of Achilles and patellar tendon reflexes are moderate to strong risk factors for amputation, the uncertainty surrounding these results limits the likely clinical impact.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results are likely to be generalisable to people with diabetes in community settings including indigenous populations. Given the community based setting, it is possible that not all subjects were receiving primary care.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The studies were undertaken in the USA and Finland therefore likely to be applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Two level II studies with moderate risk of bias.
2. Consistency	C	Although the measures of association are all in the same direction, the likely effects of confounding in these two studies results in difficulty in assessing the consistency o f the results. Potential confounding ensures that there is considerable uncertainty around these estimates of association.
3. Clinical impact	C	Although the studies report that the absence of Achilles and patellar tendon reflexes are moderate to strong risk factors for amputation, the uncertainty surrounding these results limits the likely clinical impact.
4. Generalisability	C	The results are likely to be generalisable to people with diabetes in community settings including indigenous populations. Given the community based setting, it is possible that not all subjects were receiving primary care.
5. Applicability	B	The studies were undertaken in the USA and Finland therefore likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence to conclude that absent Achilles and patellar tendon reflexes are risk factors for amputation in people with diabetes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible*	GRADE OF RECOMMENDATION	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?		
Are there any resource implications associated with implementing this recommendation?		
Will the implementation of this recommendation require changes in the way care is currently organised?		
Are the guideline development group aware of any barriers to the implementation of this recommendation?		

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Systolic and diastolic blood pressure		Evidence table ref: (Lee et al 1993; Moss et al 1992; Moss et al 1996; Moss et al 1999; Resnick et al 2004; Roy & Peng 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Most studies consistently showed that systolic and diastolic blood pressure are risk factors for poor foot outcomes in people with and without foot ulcer.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The evidence suggests that blood pressure is a weak to moderate risk factor for poor foot outcomes. Although some studies show a moderate strength of relationship, the confidence intervals around the estimate may suggest a lesser clinical impact.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting. Two studies were in American indigenous populations.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

All four studies were conducted in the USA therefore, the evidence is likely to be applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Five level II studies with a moderate risk of bias.
2. Consistency	B	Most studies consistently showed that systolic and diastolic blood pressure are risk factors for poor foot outcomes in people with and without foot ulcer.
3. Clinical impact	C	The evidence suggests that blood pressure is a weak to moderate risk factor for poor foot outcomes. Although some studies show a moderate strength of relationship, the confidence intervals around the estimate may suggest a lesser clinical impact.
4. Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting. Two studies were in American indigenous populations.
5. Applicability	B	All four studies were conducted in the USA therefore, the evidence is likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to indicate that increasing systolic and diastolic blood pressure are risk factors lower extremity amputation particularly in American Indians. Less evidence is available for blood pressure as a risk factor for foot ulcer (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Hypertension		Evidence table ref: (Hypertension in Diabetes Study 1993; Nelson et al 1988)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Two level II studies with a moderate risk of bias.
2. Consistency	C	Both studies reported measures of association in the same direction. It is likely that the HDS reported a statistically significant relationship as a result of the composite nature of the outcome.
3. Clinical impact	D	Given the uncertainty surrounding the evidence, it is unclear what the clinical impact would be.
4. Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting. One study was in an American indigenous population.
5. Applicability	B	The studies were conducted in the USA and UK therefore, the evidence is likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence regarding the relationship between hypertension and poor foot outcomes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Glycosylated haemoglobin		Evidence table ref: (Winkley et al 2007); (Resnick et al 2004); (Lehto et al 1996); (Davis et al 2006); (Moss et al 1992; Moss et al 1996; Moss et al 1999)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Five level II studies with a low to moderate risk of bias.
2. Consistency	B	Most studies consistently showed that glycosylated haemoglobin is a risk factor for poor foot outcomes in people with and without foot ulcer. Any inconsistencies are likely explained by the short follow-up period.
3. Clinical impact	C	The evidence suggests that glycosylated haemoglobin is a moderate risk factor for poor foot outcomes.
4. Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
5. Applicability	B	The studies were conducted in Australia, Finland, UK and the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is reasonable evidence to indicate that increasing levels of glycosylated haemoglobin (> 6.5%) is a risk factor for lower extremity amputation in people with diabetes. Further evidence is required with regard to foot ulcer development (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Plasma glucose		Evidence table ref: (Nelson et al 1988); (Lehto et al 1996); (Lee et al 1993)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Three level II studies with a moderate risk of bias.
2. Consistency	C	All studies reported estimates of association in the same direction however given the limitations of two studies, genuine uncertainty still remains.
3. Clinical impact	C	Given the uncertainty surrounding plasma glucose as a risk factor it is difficult to assess the likely clinical impact.
4. Generalisability	B	The evidence is likely to be generalisable to the target population, including indigenous populations, although it is possible that some subjects were receiving care other than in a primary care setting.
5. Applicability	B	The studies were conducted in Finland and the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is limited evidence to indicate that increasing levels of plasma glucose is a risk factor for lower extremity amputation in people with diabetes. (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?		
Are there any resource implications associated with implementing this recommendation?		
Will the implementation of this recommendation require changes in the way care is currently organised?		
Are the guideline development group aware of any barriers to the implementation of this recommendation?		

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Retinopathy		Evidence table ref: (Boyko et al 1996); (Otiniano et al 2003); (Davis et al 2006); (Lee et al 1993); (Lehto et al 1996); (Hamalainen et al 1999); (Nelson et al 1988); (Roy & Peng 2008); (Klein et al 2007); (Moss et al 1992; Moss et al 1996; Moss et al 1999);(Winkley et al 2007)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Nine level II studies with a low to moderate risk of bias.
2. Consistency	B	Most studies consistently showed that retinopathy is a risk factor for poor foot outcomes in people with and without foot ulcer.
3. Clinical impact	B	The evidence suggests that retinopathy is a moderate to strong risk factor for poor foot outcomes.
4. Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
5. Applicability	B	The studies were conducted in Australia, Finland, UK and the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is reasonable evidence to indicate that increasing severity of retinopathy (including self-reported retinopathy) is a risk factor for lower extremity amputation in people with diabetes. There is also some evidence to suggest that retinopathy is a risk factor for foot ulcer and ulcer recurrence (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Nephropathy / proteinuria		Evidence table ref: (Boyko et al 1996); (Otiniano et al 2003); (Davis et al 2006); (Resnick et al 2004); (Lehto et al 1996); (Nelson et al 1988); (Moss et al 1992; Moss et al 1996; Moss et al 1999);(Winkley et al 2007); (Bruce et al 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Seven level II studies (9 articles) with a moderate risk of bias.
2. Consistency	B	Most studies consistently showed that nephropathy or proteinuria is a moderate risk factor for poor foot outcomes.
3. Clinical impact	C	The evidence suggests that nephropathy/proteinuria is a moderate risk factor for poor foot outcomes.
4. Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
5. Applicability	B	The studies were conducted in Australia, Finland, UK and the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to indicate that the presence of nephropathy or proteinuria is a risk factor for lower extremity amputation in people with diabetes. There is also some evidence to suggest that nephropathy or proteinuria is a risk factor for foot ulcer, ulcer recurrence and mobility impairment (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Duration of diabetes		Evidence table ref: (Boyko et al 1996); (Resnick et al 2004); (Lee et al 1993); (Lehto et al 1996); (Roy & Peng 2008); (Moss et al 1992; Moss et al 1996; Moss et al 1999);(Ledoux et al 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Six level II studies (8 articles) with a low to moderate risk of bias.
2. Consistency	B	Most studies consistently showed that diabetes duration is a weak risk factor for poor foot outcomes.
3. Clinical impact	D	The evidence suggests that diabetes duration is a weak risk factor for poor foot outcomes.
4. Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
5. Applicability	B	The studies were conducted in Finland and the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is reasonable evidence to indicate that the diabetes duration is a weak risk factor for lower extremity amputation in people with diabetes (Grade B).

There is also some evidence to suggest that diabetes duration is a weak risk factor for foot ulcer (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Age		Evidence table ref: (Winkley et al 2007); (Boyko et al 1996); (Moss et al 1992; Moss et al 1996; Moss et al 1999); (Resnick et al 2004); (Ledoux et al 2005); (Abbott et al 1998); (Bruce et al 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
For mortality, the effect sizes are in the same direction although one study was underpowered. For amputation, there is some genuine inconsistency in the results with one study showing age groups as moderate risk factors for amputation but one study showing that mean age is protective against amputation. For foot ulcer, there is some inconsistency in the direction of the effect sizes although only one study showed a statistically significant (protective) relationship between age and foot ulcer.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The evidence suggests that age has a weak relationship with poor foot outcomes.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Six level II studies (7articles) with a low to moderate risk of bias.
2. Consistency	D	For mortality, the effect sizes are in the same direction although one study was underpowered. For amputation, there is some genuine inconsistency in the results with one study showing age groups as moderate risk factors for amputation but one study showing that mean age is protective against amputation. For foot ulcer, there is some inconsistency in the direction of the effect sizes although only one study showed a statistically significant (protective) relationship between age and foot ulcer.
3. Clinical impact	D	The evidence suggests that age has a weak relationship with poor foot outcomes.
4. Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
5. Applicability	B	The studies were conducted in Australia, the UK and USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence to indicate that age is a (weak) risk factor for lower extremity amputation and foot ulcer in people with diabetes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Sex		Evidence table ref: (Winkley et al 2007); (Moss et al 1992; Moss et al 1996; Moss et al 1999); (Resnick et al 2004); (Hamalainen et al 1999); (Roy & Peng 2008); (Ledoux et al 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Six level II studies (8 articles) with a low to moderate risk of bias.
2. Consistency	B	Most studies consistent and inconsistencies may be explained.
3. Clinical impact	C	The evidence suggests that age has a moderate relationship with poor foot outcomes.
4. Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
5. Applicability	B	The studies were conducted in Australia, the UK and USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to indicate that male sex is a moderate risk factor for lower extremity amputation in people with diabetes (Grade B).

There is insufficient evidence to indicate that male sex is a risk factor for new foot ulcer (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Ankle-brachial index (ABI)		Evidence table ref: (Winkley et al 2007); (Boyko et al 1996); (Resnick et al 2004); (Hamalainen et al 1999); (Davis et al 2006)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Three level II studies with a low to moderate risk of bias.
2. Consistency	B	Most studies consistent and inconsistencies may be explained.
3. Clinical impact	B	The evidence suggests that ABI has a moderately strong relationship with mortality and lower extremity amputation.
4. Generalisability	B	The evidence is likely to be generalisable to the target population, including indigenous populations, although it is possible that some subjects were receiving care other than in a primary care setting.
5. Applicability	B	The studies were conducted in Australia, the UK, Finland and USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to indicate that an ABI less than 0.9 is a moderate risk factor for lower extremity amputation in people with diabetes (Grade B).

There is also evidence that an ABI greater than 1.3 is a moderate risk factor for lower extremity amputation (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Claudication		Evidence table ref: (Bruce et al 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study available.
3. Clinical impact	C	The strength of the relationship between claudication and impaired mobility is moderate.
4. Generalisability	B	The evidence is likely to be generalisable to the target population although it is possible that some subjects were receiving care other than in a primary care setting.
5. Applicability	A	This study was undertaken in Western Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is limited evidence to suggest that self-reported claudication may be a risk factor for impaired mobility in a population with type II diabetes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Peripheral pulses		Evidence table ref: (Lehto et al 1996)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study available.
3. Clinical impact	B	The strength of the relationship between absent pulses and amputation is substantial however, insufficient information regarding the measurement of peripheral arterial pulses was provided.
4. Generalisability	C	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting. Furthermore, it may only be generalisable to people with peripheral arterial disease.
5. Applicability	B	This study was undertaken in Finland and is likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence to indicate that the absence of two or more peripheral arterial pulses may be a risk factor for amputation due to atherosclerotic disease in a population with type II diabetes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Arterial calcification		Evidence table ref: (Everhart et al 1988)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study (reported in two articles) with moderate risk of bias.
2. Consistency	N/A	Only one study available.
3. Clinical impact	B	The strength of the relationship between MAC and first amputation is substantial.
4. Generalisability	C	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting. Furthermore, it may only be generalisable to American Indians.
5. Applicability	B	This study was undertaken in the USA and is likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to indicate that the presence of medial arterial calcification is a strong risk factor for first lower extremity amputation in a diabetic indigenous population (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Cardiovascular disease		Evidence table ref: (Winkley et al 2007); (Boyko et al 1996); (Davis et al 2006); (Volpato et al 2005); (Bruce et al 2005); (Wallace et al 2002)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Four level II studies with low to moderate risk of bias.
2. Consistency	B	Most studies consistent and inconsistency may be explained.
3. Clinical impact	B	The strength of the relationship between CVD and mortality and falls or mobility impairment is moderate. The strength of the relationship between CVD and first lower extremity amputation is strong however only one study reports on this outcome.
4. Generalisability	C	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting.
5. Applicability	B	These studies were undertaken in Australia, the UK and the USA and are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to indicate that a history of cerebrovascular disease is a strong risk factor for lower extremity amputation in people with diabetes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Lipids		Evidence table ref: (Nelson et al 1988); (Lehto et al 1996); (Lee et al 1993); (Litzelman et al 1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Most studies consistent and inconsistency may be explained. For foot lesion as the outcome, only one study was available (rating = C).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Four level II studies with low to moderate risk of bias.
2. Consistency	B C	Most studies consistent and inconsistency may be explained. For foot lesion as the outcome, only one study was available.
3. Clinical impact	C	The strength of the relationship between total cholesterol and amputation i s likely to be moderate particularly with cholesterol levels > 6.2mmol/l for atherosclerotic amputation. The strength of the relationship between increasing HDL levels and foot ulcer is moderate.
4. Generalisability	C	The studies covered a broad range of populations including socioeconomically disadvantaged and indigenous populations.
5. Applicability	B	These studies were undertaken in Finland and the USA and are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to indicate that increasing total cholesterol concentration, higher than 6.2mmol/l, may be a moderate risk factor for lower extremity amputation, in particular as a result of atherosclerotic vascular disease, in people with diabetes (Grade B).

There is some evidence to indicate that an increasing HDL concentration is a moderate risk factor for foot lesions with a Seattle Classification ≥ 1.3, in people with diabetes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?		
Are there any resource implications associated with implementing this recommendation?		
Will the implementation of this recommendation require changes in the way care is currently organised?		
Are the guideline development group aware of any barriers to the implementation of this recommendation?		

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? BMI		Evidence table ref: (Resnick et al 2004); (Ledoux et al 2005); (Volpato et al 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Three level II studies with low to moderate risk of bias.
2. Consistency	C	Some inconsistency reflecting genuine uncertainty around the clinical question.
3. Clinical impact	D	Given the uncertainty around the point estimates it is unclear what the clinical impact would be.
4. Generalisability	C	The studies covered a broad range of populations including indigenous populations, people with a history of ulcer and elderly women in the community.
5. Applicability	B	These studies were undertaken in the USA and are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence to indicate that increasing BMI is a risk factor for poor foot outcomes in people with diabetes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Smoking		Evidence table ref: (Nelson et al 1988); (Bruce et al 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Three level II studies with low to moderate risk of bias.
2. Consistency	C	Some inconsistency reflecting genuine uncertainty around the clinical question.
3. Clinical impact	D	Given the lack of power in most of the studies it is difficult to assess the likely clinical impact.
4. Generalisability	C	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting.
5. Applicability	B	These studies were undertaken in the USA and Australia and are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Based on the evidence identified, there is insufficient evidence to indicate that smoking is a risk factor for amputation in people with diabetes (Grade C).

For mobility impairment and poor activities of daily living, there is some evidence to suggest that smoking is a moderate risk factor (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Foot ulcer		Evidence table ref: (Winkley et al 2007); (Boyko et al 1996); (Davis et al 2006) (Roy & Peng 2008); (Litzelman et al 1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Three level II studies with low to moderate risk of bias.
2. Consistency	B	Most studies consistent and inconsistency may be explained.
3. Clinical impact	B	The presence or development of a foot ulcer appears to be a moderate or strong risk factor for lower extremity amputation or arterial disease.
4. Generalisability	C	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting.
5. Applicability	B	These studies were undertaken in the UK, USA and Australia and are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to indicate that the presence of a foot ulcer is a moderate risk factor for lower extremity amputation or arterial disease (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Foot deformity / shape		Evidence table ref: (Cowley et al 2008); (Ledoux et al 2005); (Wallace et al 2002)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Three level II studies with low to moderate risk of bias.
2. Consistency	B	For the risk factors which were statistically significant, most studies were consistent and the inconsistency may be explained.
3. Clinical impact	C	The presence of a hammer/claw toe or hallux limitus are moderate risk factors first new foot ulcer and ulcer recurrence.
4. Generalisability	C	The evidence may be generalisable to the target population.
5. Applicability	B	These studies were undertaken in the USA and are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to indicate that hallux limitus and hammer/claw toe is a moderate risk factor for new foot ulcer and ulcer recurrence (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Foot ulcer history		Evidence table ref: (Boyko et al 1996); (Moss et al 1992; Moss et al 1999)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
History of foot ulcer appears to be a moderate risk factor for amputation after 14 years of follow-up.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II studies with moderate risk of bias.
2. Consistency	N/A	Only one study available.
3. Clinical impact	B	History of foot ulcer appears to be a moderate risk factor for amputation after 14 years of follow-up.
4. Generalisability	A	The evidence is generalisable to the target population.
5. Applicability	B	These studies were undertaken in the USA and are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence that history of sores or ulcers is a moderate risk factor for amputation in people with diabetes managed in a primary care setting (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Insulin treatment		Evidence table ref: (Boyko et al 1996); (Winkley et al 2007); (Volpato et al 2005); (Bruce et al 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Three level II studies with low to moderate risk of bias.
2. Consistency	C	Given the different outcomes reported it is difficult to determine whether these results are consistent. There appears to be consistency for the secondary outcomes however this is not so for ulcer recurrences.
3. Clinical impact	C	It would appear that insulin use is a moderate risk factor for falls and mobility impairment. There is insufficient evidence to determine the clinical impact for ulcer recurrence.
4. Generalisability	A	The evidence is generalisable to the target population.
5. Applicability	B	These studies were undertaken in Australia, the UK and the USA and are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to indicate that insulin use is a moderate risk factor for falls and mobility impairment in people with diabetes (Grade C).

There is insufficient evidence for insulin use as a risk factor for foot ulcer recurrence in people with diabetes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Depression		Evidence table ref: (Winkley et al 2007);(Bruce et al 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Two level II studies with low to moderate risk of bias.
2. Consistency	B	Most studies are consistent and the inconsistency may be explained.
3. Clinical impact	C	It would appear that depressive symptoms are a moderate risk factor for difficulties in Activities of Daily Living
4. Generalisability	B	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting.
5. Applicability	B	These studies were undertaken in Australia and the UK and are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence that depressive symptoms are a moderate risk factor for difficulties in Activities of Daily Living in people with diabetes (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Type I or type II diabetes		Evidence table ref: (Boyko et al 1996); (Winkley et al 2007)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	One level II studies with low to moderate risk of bias.
2. Consistency	N/A	Only one study available.
3. Clinical impact	D	It is unclear what the clinical impact of this evidence would be given the uncertainty around the association between type of diabetes and poor foot outcomes
4. Generalisability	B	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting.
5. Applicability	B	These studies were undertaken in the USA and UK and are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence to suggest that the type of diabetes is a risk factor for foot ulcer recurrence (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Physical activity		Evidence table ref: (LeMaster et al 2003); (Bruce et al 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Two level II studies with low to moderate risk of bias.
2. Consistency	B	Most studies consistent and inconsistency may be explained.
3. Clinical impact	C	Physical activity is a moderate protective factor against foot ulcer recurrence and mobility impairement.
4. Generalisability	B	The evidence may be generalisable to the target population and it is possible that some subjects were receiving care other than in a primary care setting.
5. Applicability	B	These studies were undertaken in the USA and Australia and are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence to suggest that the type of diabetes is a risk factor for foot ulcer recurrence (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Education		Evidence table ref: Resnick et al (2004)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	B	The evidence does not suggest that high school education or higher is a risk factor for first lower extremity amputation.
4. Generalisability	B	The evidence is likely to be generalisable to a community-based indigenous population. Given the community setting, it can't be ruled out that some subjects were not receiving primary care.
5. Applicability	B	The studies was conducted in the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to indicate that high school education level or higher is not a risk factor for first lower extremity amputation in indigenous populations with diabetes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Risk score		Evidence table ref: Rith-Najarian et al (1992)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	D	The unadjusted nature of the results prevents an assessment of the clinical impact.
4. Generalisability	B	The evidence is likely to be generalisable to a community-based indigenous population. Given the community setting, it can't be ruled out that some subjects were not receiving primary care.
5. Applicability	B	The study was conducted in the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to indicate that high school education level or higher is not a risk factor for first lower extremity amputation in indigenous populations with diabetes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): What are the risk factors for a poor foot-related outcome for people in a primary care setting? Other potential risk factors		Evidence table ref: (Volpato et al 2005); (Bruce et al 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation as it is prognostic evidence

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Two level II studies with a moderate risk of bias.
2. Consistency	N/A	For the one common risk factor assessed by the two studies, the effect sizes were in the same direction although the result of Volpato et al (2005) did not reach statistical significance.
3. Clinical impact	B-C	Arthritis and fluency in English were both moderate risk factors for poor outcomes, while lower extremity pain, indigenous status and poor physical performance were strong risk factors for poor outcomes.
4. Generalisability	B	The evidence is likely to be generalisable to a community-based population. Given the community setting, it can't be ruled out that some subjects were not receiving primary care.
5. Applicability	B	The studies was conducted in Australia and the USA which indicates that the results are likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence to indicate that risk score is a risk factor for amputation or ulceration in an American indigenous population (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Question 6

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Systemic therapeutic drug interventions - ANGIPARS		Evidence table ref: (Bahrami et al 2008; Larijani et al 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Comparisons between these two studies are limited due to the potential for some overlap in populations and also differences in ulcer size at baseline.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Clinically and statistically significant benefits were reported for complete ulcer healing in one study, and the percent reduction in ulcer size in both studies.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of diabetic patients with chronic foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

One study was conducted in Iran, and the other in Iran and United Arab Emirates, , which may have a different context for the delivery of healthcare to diabetic patients with foot disease when compared to the Australian system.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation was developed due to the small sample sizes and poor applicability of the evidence.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
• Evidence base	C	Two level II studies with a moderate risk of bias.
• Consistency	C	Comparisons between these two studies are limited due to the potential for some overlap in populations and also differences in ulcer size at baseline.
• Clinical impact	A	Clinically and statistically significant benefits were reported for complete ulcer healing in one study, and the percent reduction in ulcer size in both studies.
• Generalisability	B	Population consisted of diabetic patients with chronic foot ulcers.
• Applicability	D	One study was conducted in Iran, and the other in Iran and United Arab Emirates, which has different healthcare for diabetes patients compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to suggest that systemic administration of ANGIPARS may decrease ulcer size for people with chronic diabetic foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Systemic therapeutic drug interventions - low-molecular-weight heparins		Evidence table ref: (Kalani et al 2003; Rullan et al 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with a low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
It is unclear if the results of the studies are directly comparable. The diabetic patients differed in the comorbidities present between the two studies; the patients in one study had peripheral arterial occlusive disease (PAOD) in addition to chronic foot ulcers. However, results were in the same direction for both studies.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
A clinically significant benefit for amputation was observed with dalteparin in a population with PAOD. A clinically significant benefit for ulcer improvement was observed with bemiparin in a general diabetic population with Wagner grade 2 ulcers.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Dalteparin was used in a comorbid diabetic population with PAOD and foot ulcers. Whereas bemiparin was used in a general diabetic population with foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The two studies were conducted in Spain and Sweden, which have comparable healthcare for diabetic patients when compared to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not wish to make a recommendation based on evidence from that consists of two trials with small subject numbers.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Two level II studies with a low risk of bias.
2. Consistency	B	It is unclear if the results of the studies are directly comparable. The diabetic patients differed in the comorbidities present between the two studies; the patients in one study had peripheral arterial occlusive disease (PAOD) in addition to chronic foot ulcers. However, results were in the same direction for both studies.
3. Clinical impact	B	A clinically significant benefit for amputation was observed with dalteparin in a population with PAOD. A clinically significant benefit for ulcer improvement was observed with bemiparin in a general diabetic population with Wagner grade 2 ulcers.
4. Generalisability	C	Dalteparin was used in a comorbid diabetic population with PAOD and foot ulcers. Whereas bemiparin was used in a general diabetic population with foot ulcers.
5. Applicability	B	The two studies were conducted in Spain and Sweden, which have comparable healthcare for diabetic patients when compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Systemic low-molecular-weight heparins in addition to standard wound care provided a significant benefit in Wagner grade 2 ulcers only over a 3 month period in patients with diabetes when compared with placebo and standard wound care. The risk of amputation is similarly reduced in diabetic patients with comorbid peripheral arterial occlusive disease (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?		
Are there any resource implications associated with implementing this recommendation?		
Will the implementation of this recommendation require changes in the way care is currently organised?		
Are the guideline development group aware of any barriers to the implementation of this recommendation?		

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Systemic therapeutic drug interventions - iloprost		Evidence table ref: (Sert et al 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There is only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There was no statistically significant difference in the number of ulcers that healed or needed amputations after administering iloprost in addition to standard wound care relative to standard wound care alone.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The population consisted of diabetic patients with a severe peripheral ischemic foot ulcer unsuitable for revascularisation, and thus, the study results would apply to diabetic patients at the severe end of the disease spectrum.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Turkey, which may have a different context for the delivery of	A	Evidence directly applicable to Australian healthcare context

healthcare to diabetic patients with foot disease when compared to the Australian system.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the limitations of the evidence in regard to evidence base and clinical impact, no recommendation was developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level III study with a moderate risk of bias
2. Consistency	N/A	There is only one study
3. Clinical impact	D	There was no statistically significant difference in the number of ulcers that healed or needed amputations after administering iloprost in addition to standard wound care relative to standard wound care alone.
4. Generalisability	B	The population consisted of diabetic patients with a severe peripheral ischemic foot ulcer unsuitable for revascularisation, and thus, the study results would apply to diabetic patients at the severe end of the disease spectrum.
5. Applicability	C	The study was conducted in Turkey, which have different healthcare for diabetic patients when compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

It is unclear whether iloprost therapy is likely to provide any clinical benefit in addition to standard wound care when treating patients for diabetic foot ulcers. Further large trials are required to determine the impact on wound healing and major amputation rates (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Systemic therapeutic drug interventions - Ketanserin		Evidence table ref: (Apelqvist et al 1990a)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There is only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There was no statistically significant difference in the number of ulcers that healed or patients requiring amputation after administration of ketanserin in addition to standard wound care. The trial was small and likely underpowered for these outcomes.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
These results are generalisable to diabetic patients with a foot ulcer and severe peripheral vascular disease.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The study was conducted in Sweden, where the care of diabetic foot ulcers is likely to be similar to Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the lack of power and consequently evidence of a clinical impact, no recommendation has been developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	One level II study with a low risk of bias
2. Consistency	N/A	There is only one study
3. Clinical impact	D	There was no statistically significant difference in the number of ulcers that healed or patients requiring amputation after administration of ketanserin in addition to standard wound care. The trial was small and likely underpowered for these outcomes.
4. Generalisability	C	These results are generalisable to diabetic patients with a foot ulcer and severe peripheral vascular disease
5. Applicability	B	The study was conducted in Sweden, where the care of diabetic foot ulcers is likely to be similar to Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

It is unclear whether ketanserin therapy is likely to provide any clinical benefit in addition to standard wound care when treating patients for diabetic foot ulcers, relative to standard wound care alone (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Systemic therapeutic drug interventions - pentoxifylline		Evidence table ref: (Ramani et al 1993)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level III-1 study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There was only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The clinical importance of the statistically significant difference in the number of ulcers that 'responded' to treatment is unknown, given the lack of definition of response. No differences in amputation rate or the length of hospital stay was observed after administering pentoxifyllinein addition to standard wound care compared with standard wound care alone.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consists of diabetic patients with ischaemic foot ulcers of Wagner grade 2 or more.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

This study was conducted in India, where health care is likely to be provided differently to patients with diabetic foot ulcers than in Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the poor evidence base and applicability to the Australian healthcare context, no recommendation has been developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level III-1 study with a moderate risk of bias
2. Consistency	N/A	There was only one study
3. Clinical impact	C	The clinical importance of the statistically significant difference in the number of ulcers that 'responded' to treatment is unknown, given the lack of definition of response. No differences in amputation rate or the length of hospital stay was observed after administering pentoxifyllinein addition to standard wound care compared with standard wound care alone.
4. Generalisability	C	Population consists of diabetic patients with ischemic foot ulcers of Wagner grade 2 or more
5. Applicability	D	This study was conducted in India, where health care is likely to be provided differently to patients with diabetic foot ulcers than in Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Pentoxifylline therapy is unlikely to provide further benefit in addition to standard wound care when treating diabetic patients with ischaemic foot ulcers of Wagner grade 2 or more (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Systemic therapeutic drug interventions - pycnogenol		Evidence table ref: (Belcaro et al 2006)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There was only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There was a statistically significant difference in the % reduction of ulcer area after topical or oral application of pycnogenol compared to standard wound care alone. The application of both topical and oral pycnogenol together offers an additional benefit.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of diabetic patients being treated with insulin, with severe microangiopathy causing chronic foot ulceration. Given the small sample size caution would be needed in generalising these results to a larger diabetic foot ulcer population group.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
This study was conducted in Italy, which is likely to provide similar health care to diabetic foot	A	Evidence directly applicable to Australian healthcare context

patients as in Australia.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation was developed given the evidence is from a single study with very small subject numbers.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias
2. Consistency	N/A	There was only one study
3. Clinical impact	B	There was a statistically significant difference in the % reduction of ulcer area after topical or oral application of pycnogenol compared to standard wound care alone. The application of both topical and oral pycnogenol together offers an additional benefit.
4. Generalisability	C	Population consisted of diabetic patients being treated with insulin, with severe microangiopathy causing chronic foot ulceration. Given the small sample size caution would be needed in generalising these results to a larger diabetic foot ulcer population group
5. Applicability	B	This study was conducted in Italy, which is likely to provide similar health care to diabetic foot patients as in Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Pycnogenol therapy may reduce ulcer size when used in addition to standard wound care compared to standard wound care alone, in diabetic patients with ischaemic foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Drugs that improve immune function

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? *Tinospora cordifolia*		Evidence table ref: (Purandare & Supe 2007)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There was only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There were no statistically significant clinical benefits after the additional administration of *Tinospora cordifolia* to standard wound care.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of diabetic patients admitted to hospital with Wagner grade 1 or 2 diabetic foot ulcers of not less than 4 cm in diameter or non-healing ulcers on foot with digital, ray or forefoot amputation.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied

	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

This study was conducted in India, where health care is likely to be provided differently to patients with diabetic foot ulcers than in Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the poor clinical impact and applicability, no recommendation has been developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias
2. Consistency	N/A	There was only one study
3. Clinical impact	D	There were no statistically significant clinical benefits after the additional administration of *Tinospora cordifolia* to standard wound care.
4. Generalisability	C	Population consisted of diabetic patients admitted to hospital with Wagner grade 1 or 2 diabetic foot ulcers of not less than 4 cm in diameter or non-healing ulcers on foot with digital, ray or forefoot amputation.
5. Applicability	D	This study was conducted in India, where health care is likely to be provided differently to patients with diabetic foot ulcers than in Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Tinospora cordifolia therapy is unlikely to provide additional clinical benefit to standard wound care when treating patients for diabetic foot ulcer (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

There is insufficient evidence to make a recommendation for the use of *tinospora cordifolia* extract in people with diabetic foot ulcers.	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Other drugs

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Does fenofibrate improve clinical outcomes for people with of diabetic foot ulcers?		Evidence table ref: (Rajamani et al 2009)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There was only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There would be a moderate clinical impact for all amputation ie minor and major but, there is likely to be a substantial impact for minor amputations and in particular those without associated peripheral vascular disease.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Populations consisted of people with type II diabetes who did not require lipid modifying therapy.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

This study was conducted in Australia, New Zealand and Finland which would make it directly applicable to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group felt that this study provided promising results but confirmatory studies are needed. Particularly studies that identify which patients should be treated as the effect is not observed across all types of amputation..

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
6. Evidence base	B	One level II study with a low risk of bias.
7. Consistency	N/A	Only one study available.
8. Clinical impact	C	There would be a moderate clinical impact for all amputation ie minor and major but, there is likely to be a substantial impact for minor amputations and in particular those without associated peripheral vascular disease.
9. Generalisability	A	Populations consisted of people with type II diabetes who did not require lipid modifying therapy.
10. Applicability	A	This study was conducted in Australia, New Zealand and Finland which would make it directly applicable to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to suggest that treatment with fenofibrate may reduce the risk of amputation, and in particular minor amputation, in people with type II diabetes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Surgical interventions

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Achilles tendon lengthening surgery compared to total contact cast + standard wound care		Evidence table ref: (Mueller et al. 2003; Mueller et al. 2004)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level III study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study indicated a low clinical impact for ulcer healing although a moderate to substantial preventative clinical impact for ulcer recurrence (RR of 0.25 and RR of 0.47 over 6 months and 2 years respectively). In contrast, ATL surgery had a slight negative clinical impact on the physical well being of the diabetes subjects, although not to a clinically important degree. No effect was found on the mental wellbeing.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population. The sample did have an overrepresentation of males.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Given the limited clinical impact and and small numbers studied, no recommendation has been developed.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
11. Evidence base	C	One level III study with moderate risk of bias.
12. Consistency	N/A	Only one study available
13. Clinical impact	D- ulcer healing C- recurrence	The study indicated a low clinical impact for ulcer healing although a moderate to substantial preventative clinical impact for ulcer recurrence (RR of 0.25 and RR of 0.47 over 6 months and 2 years respectively). In contrast, ATL surgery had a slight negative clinical impact on the physical well being of the diabetes subjects, although not to a clinically important degree. No effect was found on the mental wellbeing.
14. Generalisability	B	The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population. The sample did have an overrepresentation of males.
15. Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The results suggest that in addition to immobilisation with a total contact cast and standard wound care, surgical Achilles tendon lengthening is effective at preventing foot ulcer recurrence in diabetic patients, although it does not appear to improve ulcer healing (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

Expert working group felt there was insufficient evidence to make a recommendation	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Resection arthroplasty compared to standard wound care		Evidence table ref: (Armstrong et al. 2003; Armstrong et al. 2005a)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level III study with low risk of bias and on level III study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The studies are consistent.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The studies suggest substantial clinical impact with respect to the healing time of foot ulcer and a large preventative clinical impact for ulcer recurrence (RR of 0.14 and RR of 0.16).	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population. The sample did have an over representation of males.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the USA, which has similar health care for diabetes patients compared	A	Evidence directly applicable to Australian healthcare context

to the Australia health care context.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Given the small number of subjects studied across both studies, no recommendation has been developed.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
6. Evidence base	C	One level III study with low risk of bias and on level III study with moderate risk of bias.
7. Consistency	A	Studies are consistent.
8. Clinical impact	B	The studies suggest substantial clinical impact with respect to the healing time of foot ulcer and a large preventative clinical impact for ulcer recurrence (RR of 0.14 and RR of 0.16).
9. Generalisability	B	The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population. The sample did have an over representation of males.
10. Applicability	C	The studies took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The results suggest that in addition to standard off loading and wound care, surgical arthroplasty is effective at preventing foot ulcer recurrence in diabetes subjects and reduces the healing time of foot ulcer (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Conservative orthopaedic surgery compared to standard medical treatment		Evidence table ref: (Ha Van et al. 1996)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level III-2 study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study indicated a substantial clinical impact of the intervention on time for foot ulcer healing compared to standard medical care. No significant clinical impact was found in terms of the proportion of healed foot lesions, by treatment group.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population. The sample did have an overrepresentation of males.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in France, which has similar health care for diabetes patients compared to the Australia health care context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

Given the limitations of the body of evidence ie evidence base and only one small study available, no recommendation has been developed.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level III-2 study with moderate risk of bias.
2. Consistency	NA	Only one study available
3. Clinical impact	C	The study indicated a substantial clinical impact of the intervention on time for foot ulcer healing compared to standard medical care. No significant clinical impact was found in terms of the proportion of healed foot lesions, by treatment group.
4. Generalisability	C	The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population. The sample did have an overrepresentation of males.
5. Applicability	C	The study took place in France, which has similar health care for diabetes patients compared to the Australia health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The results suggest that in addition to standard medical care involving antibiotics, off loading and wound care, conventional orthopaedic surgery accelerates time to foot ulcer healing in diabetes patients with foot osteomyelitis (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Recombinant Human Epidermal Growth Factor – topical application		**Evidence table ref:** (Afshari et al. 2005; Tsang et al. 2003)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II RCTs with low and moderate risk of bias .	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Most studies were consistent and any inconsistencies can be explained.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Topical application of rhEGF is likely to have a moderate clinical impact in regard to ulcer healing.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Participants were diabetic patients with existing Wagner Grade I or II foot ulcers and are therefore generalisable to target population	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Although the studies were carried out in Iran and Hong Kong which have different health care systems to Australia, the evidence is probably applicable to the Australian healthcare context with	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

some caveats.	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Human growth factors

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group felt that more research was required given the small sample sizes within these studies.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	A	Three good quality level II studies with low risk of bias
2. Consistency	B	Most studies were consistent and any inconsistencies can be explained
3. Clinical impact	D	Slight clinical impact in relation to number of ulcers healed or partially healed. In general, the studies were under-powered to detect clinically important effects
4. Generalisability	B	Participants were diabetic patients with existing Wagner Grade I, II, III or IV foot ulcers and are therefore generalisable to target population
5. Applicability	C	Although the studies were carried out in Cuba, Iran and Hong Kong which have different health care systems to Australia, the evidence is probably applicable to the Australian healthcare context

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to suggest that topical application of recombinant human epidermal growth factor may have some effect at increasing the number of foot ulcers healed or partially healed, relative to standard wound care plus or minus placebo, in patients with Wagner grade I or II diabetic foot ulcers with adequate perfusion (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Recombinant Human Epidermal Growth Factor – intralesion application			Evidence table ref: (Fernández Montequín et al 2007)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
One level II RCT with low risk of bias	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	N/A	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Due to the lack of statistical power no statistically significant benefit was seen following the intralesion application of rhEGF.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
Participants were diabetic patients with existing Wagner Grade III or IV foot ulcers at risk of amputation.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Although the study was carried out in Cuba the evidence is probably applicable to the Australian	A	Evidence directly applicable to Australian healthcare context	

healthcare context with some caveats.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the poor clinical impact and lack of statistical power, no recommendation has been developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
Evidence base	B	One level II RCT with low risk of bias
Consistency	N/A	Only one study available.
Clinical impact	D	Due to the lack of statistical power no statistically significant benefit was seen following the intralesion application of rhEGF.
Generalisability	B	Participants were diabetic patients with existing Wagner Grade III or IV foot ulcers at risk of amputation.
Applicability	C	Although the study was carried out in Cuba the evidence is probably applicable to the Australian healthcare context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence to suggest that higher dose intralesion application of recombinant human epidermal growth factor has any beneficial effect at increasing the number of foot ulcers healed or partially healed, relative to low dose intralesion application of recombinant human epidermal growth factor and standard wound care, in patients with Wagner grade III or IV diabetic foot ulcers at high risk of amputation (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Recombinant Human Platelet-Derived Growth Factor (rhPDGF)		**Evidence table ref:** (d'Hemecourt et al. 1998; Hardikar et al. 2005; Smiell et al. 1999; Steed 1995; Steed 2006; Wieman et al. 1998)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Four level II studies with low risk of bias. One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Most studies were consistent and any inconsistencies can be explained.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Substantial clinical impact in relation to number of ulcers healed, reduced healing time and decreased ulcer area for non-healed ulcers.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Evidence directly generalisable to the target population of diabetic patients with existing chronic foot ulcers with adequate perfusion.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were from the USA and India which although not similar to the Australian healthcare system	A	Evidence directly applicable to Australian healthcare context

it is probably applicable with few caveats.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	A	Four level II studies with low risk of bias. One level II study with moderate risk of bias
2. Consistency	B	Most studies were consistent and any inconsistencies can be explained
3. Clinical impact	B	Substantial clinical impact in relation to number of ulcers healed, reduced healing time and decreased ulcer area for non-healed ulcers
4. Generalisability	B	Evidence directly generalisable to the target population of diabetic patients with existing chronic foot ulcers with adequate perfusion.
5. Applicability	C	Studies were from the USA and India which although not similar to the Australian healthcare system , is probably applicable with few caveats

Indicate any dissenting opinions

EVIDENCE STATEMENT

In patients with full thickness chronic foot ulcers and adequate perfusion, recombinant human platelet-derived growth factor 100µg/g gel is effective in substantially increasing the number of completely healed ulcers, reducing healing time and reducing the surface area of ulcers not completely healed compared to placebo (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Recombinant Human Platelet-Derived Growth Factor (rhPDGF) versus standard wound care with saline dressings		Evidence table ref: (d'Hemecourt et al. 1998)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One good quality level II RCT.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Substantial clinical impact regarding number of ulcers completely healed, reduction in ulcer area and time to healing of diabetic foot ulcers.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Generalisable to population of diabetic patients with chronic foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

Probably applicable to the Australian healthcare context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not wish to develop a recommendation based on one trial with relatively small numbers of subjects.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	One good quality level II RCT
2. Consistency	N/A	Only one study
3. Clinical impact	B	Substantial clinical impact regarding number of ulcers completely healed, reduction in ulcer area and time to healing of diabetic foot ulcers
4. Generalisability	B	Generalisable to population of diabetic patients with chronic foot ulcers
5. Applicability	C	Probably applicable to the Australian healthcare context with some caveats

Indicate any dissenting opinions

EVIDENCE STATEMENT

In patients with full thickness chronic ulcers with adequate perfusion, recombinant human platelet-derived growth factor 100µg/g gel is effective in substantially increasing the number of completely healed ulcers, reducing healing time and reducing the surface area of ulcers not completely healed compared to standard wound care with saline dressings (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Autologous/homologous platelet-rich plasma gel or releasate		Evidence table ref: (Driver et al. 2006; Holloway et al. 1993; Krupski et al. 1991; Saldalamacchia et al. 2004; Steed et al. 1992; Steed et al. 1996)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Four good quality level II RCTs with low risk of bias, one average and one poor quality level II RCTs with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Most studies consistent and any inconsistencies can be explained.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Moderate clinical impact.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Evidence directly generalisable to target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were from Italy and the USA which although not the same as the Australian healthcare	A	Evidence directly applicable to Australian healthcare context

system are probably applicable to the Australian healthcare context with some caveats.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not wish to develop a recommendation without evidence of effectiveness in increasing the number of ulcers.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Four good quality level II RCTs with low risk of bias, and one average and one poor quality level II RCTs with moderate risk of bias
2. Consistency	B	Most studies consistent and any inconsistencies can be explained
3. Clinical impact	C	Moderate clinical impact
4. Generalisability	B	Evidence directly generalisable to target population
5. Applicability	C	Studies were from Italy and the USA which although not the same as the Australian healthcare system are probably applicable to the Australian healthcare context with some caveats

Indicate any dissenting opinions

EVIDENCE STATEMENT

Autologous/homologous platelet-rich plasma gel or releasate is moderately effective in reducing healing time, ulcer volume and surface area of chronic diabetic foot ulcers when compared to standard wound care/placebo (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

Expert working group felt there was insufficient evidence to make a recommendation	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Recombinant Human Granulocyte-Colony Stimulating Factor (rhG-CSF)		Evidence table ref: (de Lalla et al. 2001; Gough et al. 1997; Huang et al. 2005; Kästenbauer et al. 2003; Yonem et al. 2001)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Five level II studies: three good quality with low risk of bias and two average quality with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Clinical impact varied from slight/restricted to substantial depending on the outcome measured and the quality of the study.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Evidence directly generalisable to the target population of diabetics with foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in Italy, China, Austria, England and Turkey, with the majority being	A	Evidence directly applicable to Australian healthcare context

different from the Australian healthcare system however probably applicable to the Australian healthcare context with some caveats.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the small sample sizes in these trials, the expert working group felt that these provided insufficient evidence to develop a recommendation.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Five level II studies: three good quality with low risk of bias and two average quality with a moderate risk of bias
2. Consistency	C	Most studies are consistent and any inconsistencies can be explained
3. Clinical impact	B-D	Clinical impact varied from slight/restricted to substantial depending on the outcome measured and the quality of the study.
4. Generalisability	B	Evidence directly generalisable to the target population of diabetics with foot ulcers
5. Applicability	B	Studies were conducted in Italy, China, Austria, England and Turkey, with the majority being different from the Australian healthcare system however probably applicable to the Australian healthcare context with some caveats

Indicate any dissenting opinions

EVIDENCE STATEMENT

Recombinant human granulocyte-colony stimulating factor (rhG-CSF) may reduce the number of amputations and improve ulcer healing in people with severe limb-threatening diabetic foot ulcers and infection when compared to standard wound care/placebo (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? **Transforming Growth Factor β2**		Evidence table ref: (Robson et al. 2002)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One good quality level II study.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Not applicable, only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Moderate clinical impact in relation to numbers of ulcers healed and reducing ulcer area for wounds not completely healed in intervention group versus placebo. However the standard wound care alone group performed similarly. The level of standard wound care was particularly intense.	A	Very large
	B	Substantial
	C	Moderate (versus placebo)
	D	Slight/Restricted (versus standard wound care)
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Evidence directly generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Evidence applicable to that Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given only one study was available with small numbers, no recommendation has been developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	One good quality level II study
2. Consistency	N/A	Not applicable, only one study
3. Clinical impact	C vs placebo D vs standard wound care	Moderate clinical impact in relation to numbers of ulcers healed and reducing ulcer area for wounds not completely healed in intervention group versus placebo. However the standard wound care alone group performed similarly. The level of standard wound care was particularly intense
4. Generalisability	B	Evidence directly generalisable to the target population
5. Applicability	B	Evidence applicable to that Australian healthcare context with few caveats

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence is inconclusive regarding whether transforming growth factor β2 is superior to standard wound care. In addition to standard wound care, increasing doses of TGF-β2 provided increased the clinical benefit compared to placebo with regard to number of ulcers healed and reducing ulcer area. However, these findings were not statistically significantly better than standard wound care alone (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Vascular endothelial growth factor		Evidence table ref: (Hanft et al. 2008; Kusumanto et al. 2006)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II good quality studies.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Most studies consistent and inconsistencies can be explained.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Slight clinical benefit however the benefits that achieved statistical significance were not the focus of this study. Study was underpowered for amputation outcome where point estimate indicated a clear clinical benefit.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Evidence directly generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were from the Netherlands and USA which are different to the Australian healthcare	A	Evidence directly applicable to Australian healthcare context

context however probably applicable with some caveats.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the poor clinical impact, no recommendation has been developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Two level II good quality studies
2. Consistency	B	Most studies consistent and inconsistencies can be explained
3. Clinical impact	D	Slight clinical benefit however the benefits that achieved statistical significance were not the focus of this study. Study was underpowered for amputation outcome where point estimate indicated a clear clinical benefit.
4. Generalisability	B	Evidence directly generalisable to the target population
5. Applicability	C	Studies were from the Netherlands and USA which are different to the Australian healthcare context however probably applicable with some caveats

Indicate any dissenting opinions

EVIDENCE STATEMENT

Vascular endothelial growth factor versus standard wound care/placebo is superior in reducing time to amputation and facilitating clinical improvements in ulcers. However, positive trends for other clinical outcomes did not reach statistical significance in these small studies (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Topical Basic Fibroblast Growth Factor		Evidence table ref: (Richard et al. 1995)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study of good quality.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No statistically or clinically significant benefits of the intervention were observed.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Evidence is directly generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in France which is not similar to the Australian healthcare context	A	Evidence directly applicable to Australian healthcare context

however it is probably applicable with some caveats.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the poor clinical impact, no recommendation has been developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	One level II study of good quality
2. Consistency	NA	Only one study
3. Clinical impact	D	No statistically or clinically significant benefits of the intervention were observed
4. Generalisability	B	Evidence is directly generalisable to the target population
5. Applicability	C	The study was conducted in France which is not similar to the Australian healthcare context however it is probably applicable with some caveats

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to suggest that topical basic fibroblast growth factor used as a spray and used daily for six weeks and twice weekly for 12 weeks does not provide any clinical benefits in the treatment of diabetic foot ulcers over standard wound care/placebo (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Hyperbaric oxygen therapy

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Hyperbaric Oxygen Therapy (HBOT)		Evidence table ref: (Abidia et al. 2003; Doctor et al. 1992; Duzgun et al. 2008; Faglia et al. 1996; Heng et al. 2000; Kessler et al. 2003; Leslie et al. 1988; Roeckl-Wiedmann et al. 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One good quality systematic review, one good quality and five average quality level II RCTs with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Most studies were consistent and any inconsistencies can be explained.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Clinically significant benefits were identified for reduction in amputations, reduction in surface area of ulcers, reduction in number of ulcers and time to heal.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
All but one study exclusively included patients with diabetic foot ulcers and the other study had a cohort of participants with diabetic foot ulcers which are directly generalisable to the target population. Patients had severe chronic foot lesions often requiring admission to hospital.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

Studies were conducted in the USA, UK, Italy, France, Germany, Turkey and India which, while not all have similarities to the Australian healthcare system, are probably applicable to the Australian healthcare context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	One good quality systematic review, one good quality and five average quality level II RCTs with low risk of bias
2. Consistency	B	Most studies were consistent and any inconsistencies can be explained
3. Clinical impact	B	Clinically significant benefits were identified for reduction in amputations, reduction in surface area of ulcers, reduction in number of ulcers and time to heal
4. Generalisability	B	All but one study exclusively included patients with diabetic foot ulcers and the other study had a cohort of participants with diabetic foot ulcers which are directly generalisable to the target population. Patients had severe chronic foot lesions often requiring admission to hospital.
5. Applicability	C	Studies were conducted in the USA, UK, Italy, France, Germany, Turkey and India which, while not all have similarities to the Australian healthcare system, are probably applicable to the Australian healthcare context with some caveats

Indicate any dissenting opinions

EVIDENCE STATEMENT

Hyperbaric oxygen therapy is superior to standard wound care/placebo in reducing the number of amputations, reducing the surface area of ulcers, reducing healing time and increasing the number of ulcers healed in patients with severe diabetic foot ulcers (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	B

Hyperbaric oxygen therapy may be considered for the management of foot ulcers in specialist centres, as part of a comprehensive wound managment program. (EBR 12)
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*
Will this recommendation result in changes in usual care? Rural aboriginal health services don't have access.
Are there any resource implications associated with implementing this recommendation? Need more sites to have them but there are not a big waiting lists.
Will the implementation of this recommendation require changes in the way care is currently organised? Currently available in all states but under-utilised (used by divers and football players).
Are the guideline development group aware of any barriers to the implementation of this recommendation? 16. Patient preference – extended treatment, 40 sessions at 4 hours a day 17. Patients medically unstable can't use it.

Negative pressure wound therapy

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? For treating diabetic foot ulcers and amputation wounds		Evidence table ref: (Akbari et al 2007; Blume et al 2008; Eginton et al 2003; Etoz et al 2004; Etoz & Kahveci 2007; McCallon et al 2000; Mody et al 2008)Akbari et al. 2007; Blume et al. 2008; Eginton et al. 2003; Etoz et al. 2004; Etoz & Kahveci 2007; McCallon et al. 2000; Mody et al. 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Six level II studies (2 with a low risk of bias, and 4 with a moderate risk of bias).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
All 4 studies reporting % reduction in ulcer size were consistent. The 3 studies reporting number of ulcers healed showed some inconsistent trends, but this was probably due to the small size of two of the studies.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Moderate clinical impact. Four studies showed statistically significant % reductions in wound size, the large multicentre study showed a statistically significant difference in the number of ulcers that healed by secondary intention and the number of amputations.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The population consisted of diabetic patients who had undergone debridement (generally surgical) for non-healing foot ulcers (plus a few leg ulcers), with and without infections, with varied degrees of severity.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Three studies were conducted in USA, which has similar healthcare for diabetes patients compared to the Australian healthcare context. The other three studies took place in Turkey, Iran, and India, which have different healthcare for diabetes patients compared to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Six level II studies (2 with a low risk of bias, and 4 with a moderate risk of bias)
2. Consistency	B	All 4 studies reporting % reduction in ulcer size were consistent. The 3 studies reporting number of ulcers healed showed some inconsistent trends, but this was probably due to the small size of two of the studies.
3. Clinical impact	C	Moderate clinical impact. Four studies showed statistically significant % reductions in wound size, the large multicentre study showed a statistically significant difference in the number of ulcers that healed by secondary intention and the number of amputations.
4. Generalisability	B	The population consisted of diabetic patients who had undergone debridement (generally surgical) for non-healing foot ulcers (plus a few leg ulcers), with and without infections, with varied degrees of severity.
5. Applicability	C	Three studies were conducted in USA, which has similar healthcare for diabetes patients compared to the Australian healthcare context. The other three studies took place in Turkey, Iran, and India, which have different healthcare for diabetes patients compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Negative pressure therapy after surgical debridement may improve wound healing and reduce the need for minor amputations when compared to standard wound care for the treatment of non-healing diabetic foot ulcers (Grade B).

There is some evidence to suggest that treatment with NPWT may increase the number of patients who achieve complete healing of amputation wounds in people with diabetes and evidence of adequate perfusion. There is also evidence that the time taken to achieve complete healing is reduced in patients receiving NPWT

compared to standard wound care (Grade C)		
RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	B
Negative pressure therapy may be considered for the management of foot ulcers in specialist centres, as part of a comprehensive wound managment program. (EBR 11)		
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care? yes		
Are there any resource implications associated with implementing this recommendation? Up skill / training of post-op care providers/nurses. Vac dressings are available / applied in hospital currently for all types of wounds so if not available may have to purchase or lease them – cost offset is the saved bed stay.		
Will the implementation of this recommendation require changes in the way care is currently organised? May change who provides post-op care. Need stepped down models of care / transitional care or rehab. Currently only done in major centres. Although in Victoria RDNS are managing this as they have been trained.		
Are the guideline development group aware of any barriers to the implementation of this recommendation? 18. Major education/training for post-op carers to use vacuum dressings eg. When and when not to use them. There are implications (eg. Amputation) if left on too long. **Enablers to implementation** 19. Identify which hospitals provide Vac dressings 20. Transitional care units / or rehab to be used to provide short term post-op care – must be capable of Vac dressing changing. Hospitals to train post-op wound care nurse for vac dressing.		

Nutritional supplements

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Nutritional supplements		Evidence table ref: (Eneroth et al. 2004; Leung et al. 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two good quality level II RCTs with a low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Some inconsistency reflecting genuine uncertainty around question.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Slight and uncertain clinical impact regarding number of amputations and time to healing.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Generalisable to target population of diabetic patients with chronic foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Evidence applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the poor clinical impact no recommendation has been developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Two good quality level II RCTs with a low risk of bias
2. Consistency	C	Some inconsistency reflecting genuine uncertainty around question
3. Clinical impact	D	Slight and uncertain clinical impact regarding number of amputations and time to healing
4. Generalisability	B	Generalisable to target population of diabetic patients with chronic foot ulcers
5. Applicability	B	Evidence applicable to the Australian healthcare context with few caveats

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggests that nutritional supplements show a positive trend towards improving outcomes for people with diabetic foot ulcers however the differences did not reach statistical significance. Further research is required to confirm any such effect, as well as determine which type of nutritional supplement is associated with the potential benefit (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

Expert working group felt there was insufficient evidence to make a recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Debridement interventions

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Surgical debridement		Evidence table ref: (Piaggesi et al 1998)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There was only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Slight clinical impact. Ulcers in the conventional therapy group took longer to heal compared to surgical debridement group, but there was no statistically significant difference between groups regarding the number of ulcers that healed completely, although it was trending that way.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of diabetic patients with neuropathic foot ulcer of Wagner grade 1 or 2.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

This study was conducted in Italy, which has comparable healthcare for diabetic patients when compared to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the uncertainty surrounding the effect on overall ulcer healing, no recommendation was developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias.
2. Consistency	NA	There was only one study.
3. Clinical impact	D	Slight clinical impact. Ulcers in the conventional therapy group took longer to heal compared to surgical debridement group, but there was no statistically significant difference between groups regarding the number of ulcers that healed completely, although it was trending that way.
4. Generalisability	B	Population consisted of diabetic patients with neuropathic foot ulcer of Wagner grade 1 or 2.
5. Applicability	B	This study was conducted in Italy, which has similar healthcare for diabetic patients when compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Surgical debridement using conic ulcerectomy reduces the time for ulcer healing when compared to standard wound care using conventional sharp debridement for patients with diabetic foot ulcers. However, it is uncertain if it has any benefit for overall ulcer healing. (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

Expert working group felt there was insufficient evidence to make a recommendation	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Wound debridement using larval therapy		Evidence table ref: (Armstrong et al 2005d; Paul et al 2009; Sherman 2003)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Three level III-2 studies with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
All three studies showed consistent trends.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Moderate clinical impact. All three studies reported shortened times to healing or hospital stays, but only two were statistically significant. Both studies that reported amputation rates showed a reduction in number of amputations after maggot therapy compared to conventional surgical debridement, but only one was statistically significant.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The population consisted of diabetic patients with non-healing foot and leg ulcers, with and without infections, with and without ischaemia.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Two studies were conducted in USA, which has similar healthcare for diabetic patients when compared to the Australian healthcare context. The third study took place in	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

Malaysia, which has less similar healthcare for diabetic patients when compared to the Australian healthcare context. In Australia, sterile maggots are currently available from the Department of Medical Entomology, Westmead Hospital, NSW.	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	Three level III-2 studies with a moderate risk of bias.
2. Consistency	A	All three studies showed consistent trends.
3. Clinical impact	C	Moderate clinical impact. All three studies reported shortened times to healing or hospital stays, but only two were statistically significant. Both studies that reported amputation rates showed a reduction in number of amputations after maggot therapy compared to conventional surgical debridement, but only one was statistically significant.
4. Generalisability	C	The population consisted of diabetic patients with non-healing foot and leg ulcers, with and without infections, with and without ischaemia.
5. Applicability	C	Two studies were conducted in USA, which has similar healthcare for diabetic patients when compared to the Australian healthcare context. The third study took place in Malaysia, which has less similar healthcare for diabetic patients when compared to the Australian healthcare context. In Australia, sterile maggots are currently available from the Department of Medical Entomology, Westmead Hospital, NSW.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Larval debridement therapy may improve foot ulcer healing time and prevent amputation when used in addition to standard wound care over standard wound care with surgical debridement alone in patients with severe diabetic foot ulcers. More research outside this setting is required. (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	C

Larval therapy may be considered for the management of foot ulcers in specialist centres, as part of a comprehensive wound managment program. (EBR 13)
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*
Will this recommendation result in changes in usual care? No
Are there any resource implications associated with implementing this recommendation? Yes. Low cost but can only get maggots from certain centres. Expertise and close follow-up required. Must remove after 3 days.
Will the implementation of this recommendation require changes in the way care is currently organised? No
Are the guideline development group aware of any barriers to the implementation of this recommendation? 21. Education 22. Patients' attitude to being able to feel the wriggling larvae. 23. Staff attitudes to putti 24. 25. 26. 27. ng the larvae on the wound.

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Wound debridement using hydrogels		Evidence table ref: (d'Hemecourt et al 1998; Edwards & Stapley 2010; Jensen et al 1998; Vandeputte & Gryson 1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One study of level I evidence with a moderate risk of bias, 3 level II evidence studies (one each with a low, moderate and high risk of bias).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
All studies consistently showed either trends or statistically significant benefits for the number of ulcers healed, time to healing and/or reduction of ulcer size for hydrogels compared to standard wound care.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Substantial clinical impact. There was a clinically significant increase in the number of ulcers that healed in the hydrogel treatment groups compared to those that received standard care only. The number of amputations and harms such as infections that occurred were less frequent in the hydrogel groups compared to standard care.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of diabetic patients with foot ulcers, mostly with full-thickness ulcers with or without infection.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Two studies, including the level I evidence study, were conducted in Europe (UK and Belgium), which has comparable healthcare for diabetic patients when compared to the Australian	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

healthcare context. Two studies were conducted in USA, which has similar healthcare for diabetic patients when compared to the Australian healthcare context.	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	One study of level I evidence with a moderate risk of bias, 3 level II evidence studies (one each with a low, moderate and high risk of bias).
2. Consistency	A	All studies consistently showed either trends or statistically significant benefits for the number of ulcers healed, time to healing and/or reduction of ulcer size for hydrogels compared to standard wound care.
3. Clinical impact	B	Substantial clinical impact. There was a clinically significant increase in the number of ulcers that healed in the hydrogel treatment groups compared to those that received standard care only. The number of amputations and harms such as infections that occurred were less frequent in the hydrogel groups compared to standard care.
4. Generalisability	A	Population consisted of diabetic patients with foot ulcers, mostly with full-thickness ulcers with or without infection.
5. Applicability	B	Two studies, including the level I evidence study, were conducted in Europe (UK and Belgium), which has comparable healthcare for diabetic patients when compared to the Australian healthcare context. Two studies were conducted in USA, which has similar healthcare for diabetic patients when compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Treatment of diabetic foot ulcers with hydrogels produces a substantial increase in the number of ulcers healed and reduced harms over treatment with standard care alone. (Grade B)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	B

Topical hydrogel dressings may be considered for autolytic debridement to assist the management of non-ischaemic, non-healing ulcers with dry, non-viable tissue. (EBR 6)	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? NO	
Are there any resource implications associated with implementing this recommendation? No	
Will the implementation of this recommendation require changes in the way care is currently organised? No	
Are the guideline development group aware of any barriers to the implementation of this recommendation? Yes. Education – hydrogels expire/limited shelf life and can be overused.	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Wound debridement using advanced moist wound dressings		Evidence table ref: (Ahroni et al 1993; Blackman et al 1994; Donaghue et al 1998; Jeffcoate et al 2009; Lalau et al 2002; Piaggesi et al 2001)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Six level II studies (3 with a low risk of bias, 3 with a moderate risk of bias).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The three highest quality studies did not find statistically significant differences, with the exception of time to ulcer healing in one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Slight/restricted clinical impact. Only one of the three highest quality studies found a statistically significant difference (time to healing) favouring advanced moist wound dressings.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of diabetic patients with foot ulcers, mostly with full-thickness ulcers not penetrating to the bone or tendons.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Four studies were conducted in Europe (one in the UK, one in Italy, and two in France), which has comparable healthcare for diabetic patients when compared to the	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

Australian healthcare context. The other two studies were conducted in the USA, which has similar healthcare for diabetic patients when compared to the Australian healthcare context.	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the poor clinical impact, no recommendation has been developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	A	Six level II studies (3 with a low risk of bias, 3 with a moderate risk of bias).
2. Consistency	B	The three highest quality studies did not find statistically significant differences, with the exception of time to ulcer healing in one study.
3. Clinical impact	D	Slight/restricted clinical impact. Only one of the three highest quality studies found a statistically significant difference (time to healing) favouring advanced moist wound dressings.
4. Generalisability	A	Population consisted of diabetic patients with foot ulcers, mostly with full-thickness ulcers not penetrating to the bone or tendons.
5. Applicability	B	Four studies were conducted in Europe (one in the UK, one in Italy, and two in France), which has comparable healthcare for diabetic patients when compared to the Australian healthcare context. The other two studies were conducted in the USA, which has similar healthcare for diabetic patients when compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is little evidence to suggest that the use of advanced moist wound therapy dressings offer better clinical outcomes for treating diabetic foot ulcers compared to wet, dry or greasy gauze as a primary dressing for standard wound care. (Grade B)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

Expert working group felt there was insufficient evidence to make a recommendation	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Wound debridement comparing two different advanced moist wound debridement therapies		Evidence table ref: (Foster et al 1994; Jude et al 2007; Varma et al 2006)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Three level II studies (1 with a low risk of bias and 2 with a high risk of bias).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Some inconsistency, reflecting genuine uncertainty around question. All three of the studies found a statistically significant difference for at least one clinical outcome, but failed to show that any one dressing could consistently outperform another.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Slight clinical impact. The best quality study showed a statistically significant reduction in ulcer depth, although the clinical significance of the difference is uncertain. One found a statistically significant shortened time to healing and the third showed a statistically significant increase in adverse events for one treatment compared to another. However, given the quality of the latter two studies, it is uncertain whether these results were due to confounding from an unbalanced distribution of baseline characteristics between trail arms.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Two studies, including the better quality study, recruited diabetic patients with neuropathic or ischaemic foot ulcer, but the third study also allowed diabetic patients with leg and thigh ulcers to participate.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

Two studies were conducted in Europe (one in the UK, and one in the UK, France, Germany and Sweden), which has comparable healthcare for diabetic patients when compared to the Australian healthcare context. The other study was conducted in India, which has different healthcare for diabetic patients when compared to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the poor clinical impact, no recommendation has been developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Three level II studies (1 with a low risk of bias and 2 with a high risk of bias).
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question. All three of the studies found a statistically significant difference for at least one clinical outcome, but failed to show that any one dressing could consistently outperform another.
3. Clinical impact	D	Slight clinical impact. One study showed a statistically significant reduction in ulcer depth, one found a statistically significant shortened time to healing and the third showed a statistically significant increase in adverse events for one treatment compared to another.
4. Generalisability	C	Two studies used diabetic patients with neuropathic or ischaemic foot ulcer, but the third study also allowed diabetic patients with leg and thigh ulcers to participate.
5. Applicability	C	Two studies were conducted in Europe (one in the UK, and one in the UK, France, Germany and Sweden), which has comparable healthcare for diabetic patients when compared to the Australian healthcare context. The other study were conducted in India, which has different healthcare for diabetic patients when compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is little evidence to suggest that one advanced moist wound debridement therapy can consistently outperform another when used in conjunction with standard wound care. (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

Expert working group felt there was insufficient evidence to make a recommendation	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Promogran		Evidence table ref: (Kakagia et al 2007; Lobmann et al 2006; Veves et al 2002)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Three level II studies (1 with a low risk of bias, 2 with a moderate risk of bias).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Two studies showed a statistically significant difference in the % reduction of ulcer size and the third study showed a statistically significant difference in the time needed to heal.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Moderate clinical impact. Although no study showed a statistically significant difference in the number of ulcers healed, all three studies showed statistically significant clinical outcomes for either time to healing or % reduction in ulcer size. However, only the outcome of reduction in ulcer size showed a clinically important difference as a consequence of Promogran use.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of diabetic patients with chronic diabetic foot lesions mostly superficial, but some involving tendon, capsule or bone.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Two studies were conducted in Europe (one in Germany and one in Greece), which	A	Evidence directly applicable to Australian healthcare context

has comparable healthcare for diabetic patients when compared to the Australian healthcare context. The other study was conducted in the USA, which has similar healthcare for diabetic patients when compared to the Australian healthcare context.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the treatment effect was seen for time to healing and reduction in ulcer size, no significant effect was seen in terms number of ulcers healed. Consequently, the expert working group did not wish to develop a recommendation.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Three level II studies (1 with a low risk of bias, 2 with a moderate risk of bias).
2. Consistency	A	Two studies showed a statistically significant difference in the % reduction of ulcer size and the third study showed a statistically significant difference in the time needed to heal.
3. Clinical impact	C	Moderate clinical impact. Although no study showed a statistically significant difference in the number of ulcers healed, all three studies showed statistically significant clinical outcomes for either time to healing or % reduction in ulcer size. However, only the outcome of reduction in ulcer size showed a clinically important difference as a consequence of Promogran use.
4. Generalisability	B	Population consisted of diabetic patients with chronic diabetic foot lesions mostly superficial, but some involving tendon, capsule or bone
5. Applicability	B	Two studies were conducted in Europe (one in Germany and one in Greece), which has comparable healthcare for diabetic patients when compared to the Australian healthcare context. The other study was conducted in the USA, which has similar healthcare for diabetic patients when compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The use of Promogran wound dressing with or without the use of autologous platelet derived growth factors offers better clinical outcomes in terms of reduction in ulcer size and time to healing when treating diabetic foot ulcers compared to standard wound care. (Grade B)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

In Indigenous populations

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Professional foot care interventions		Evidence table ref: (Rith-Najarian et al. 1998; Schraer et al. 2004)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level III-3 studies with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Both studies showed a statistically significant difference in the incidence of amputations per 1000 diabetic person-years between specialist foot care management programs and standard care at the discretion of the primary care provider.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There is a statistically significant decrease in the incidence of amputations per 1000 diabetic person-years when patients are treated by a specialist foot care management program compared with standard care treatment at the discretion of the primary care provider.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The population consisted of Native Alaskans with diabetes in one study and Chippewa Indians with diabetes in the other.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

Both of these studies were conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation was produced due to the poor evidence base and low rating regarding the applicability of the evidence to the Australian healthcare context.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	Two level III-3 studies with a moderate risk of bias
2. Consistency	A	Both studies showed a statistically significant difference in the incidence of amputations per 1000 diabetic person-years between specialist foot care management programs and standard care at the discretion of the primary care provider.
3. Clinical impact	B	There is a statistically significant decrease in the incidence of amputations per 1000 diabetic person-years when patients are treated by a specialist foot care management program compared with standard care treatment at the discretion of the primary care provider.
4. Generalisability	A	The population consisted of Native Alaskans with diabetes in one study and Chippewa Indians with diabetes in the other.
5. Applicability	C	Both of these studies were conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Treatment of diabetic foot ulcers according to the protocols of professional management programs, instead of standard care at the discretion of the primary care provider, reduces the likelihood that the Native Alaskan and Chippewa Indians with diabetes will require an amputation. (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

Expert working group felt there was insufficient evidence to make a recommendation	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Surgical treatment of hallux limitus		Evidence table ref: (Daniels 1989)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level IV study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Although the effect of surgery was substantial, without a comparator group it is not possible to determine whether these patients would have healed without surgical intervention.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
These results are likely to be generalisable to all ethnic groups with foot deformities and foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
This study was conducted in the USA (Phoenix Medical Center) and is likely to be applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation was produced due to the poor evidence base and clinical impact.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level IV study with moderate risk of bias.
2. Consistency	NA	Only one study available.
3. Clinical impact	D	Although the effect of surgery was substantial, without a comparator group it is not possible to determine whether these patients would have healed without surgical intervention.
4. Generalisability	B	These results are likely to be generalisable to all ethnic groups with foot deformities and foot ulcers.
5. Applicability	B	This study was conducted in the USA (Phoenix Medical Center) and is likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to suggest that surgical correction of foot deformity may increase healing of foot ulcer and prevent recurrence however, it is not known whether this intervention is more effective than others in this population for these outcomes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

Expert working group felt there was insufficient evidence to make a recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Skin replacement therapies

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Split-skin grafting		Evidence table ref: (Mahmoud et al. 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level III-2 study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Moderate clinical impact. The study showed a statistically significant difference in time to healing of ulcer and the length of hospital stay.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The population consisted of diabetic patients with foot ulcers greater than 2 cm diameter.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The study was conducted in Sudan, which has different healthcare for diabetes patients compared to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group developed a recommendation for this intervention on the basis that it was unlikely to be further studied by RCTs because it is considered "standard care" and could be offered broadly across most general surgical settings without the need for expensive and specialised technologies.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level III-2 study with a moderate risk of bias.
2. Consistency	N/A	Only one study.
3. Clinical impact	C	Moderate clinical impact. The study showed a statistically significant difference in time to healing of ulcer and the length of hospital stay.
4. Generalisability	B	The population consisted of diabetic patients with foot ulcers greater than 2 cm diameter.
5. Applicability	D	The study was conducted in Sudan, which has different healthcare for diabetes patients compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Split-skin grafting is likely to reduce the time for ulcer healing and length of hospital stay when compared to standard wound care for patients with diabetic foot ulcers. (Grade D)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	D

Skin grafting may be considered for the management of foot ulcers in specialist centres, as part of a comprehensive wound managment program. (EBR 14)	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?No	
Are there any resource implications associated with implementing this recommendation? Cost unknown	
Will the implementation of this recommendation require changes in the way care is currently organised? No	
Are the guideline development group aware of any barriers to the implementation of this recommendation? 1. Not readily available in Australia / access. 2. Living cells, which die so time factor. 3. Could be utilised more frequently.	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Meshed skin grafting		Evidence table ref: (Puttirutvong 2004)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Slight clinical impact. The study showed no statistically significant differences between the two skin grafting methods.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The population consisted of diabetic patients with infected foot ulcers of any severity.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Thailand, which has different healthcare for diabetes patients compared to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group developed a recommendation for this intervention on the basis that it was unlikely to be further studied by RCTs because it is considered "standard care" and could be offered broadly across most general surgical settings without the need for expensive and specialised technologies.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias.
2. Consistency	N/A	Only one study.
3. Clinical impact	D	Slight clinical impact. The study showed no statistically significant differences between the two skin grafting methods.
4. Generalisability	C	The population consisted of diabetic patients with infected foot ulcers of any severity.
5. Applicability	D	The study was conducted in Thailand, which has different healthcare for diabetes patients compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is no evidence to suggest that there is any difference in clinical outcomes after meshed skin grafting compared to split-skin grafting for people with chronic diabetic foot ulcers. (Grade D)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	D

Skin grafting may be considered for the management of foot ulcers in specialist centres, as part of a comprehensive wound managment program. (EBR 14)	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? No	
Are there any resource implications associated with implementing this recommendation? Cost unknown	
Will the implementation of this recommendation require changes in the way care is currently organised? No	
Are the guideline development group aware of any barriers to the implementation of this recommendation? 4. Not readily available in Australia / access. 5. Living cells, which die so time factor. 6. Could be utilised more frequently.	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Epidermal grafting		Evidence table ref: (Yamaguchi et al. 2004)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level III-2 study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There was only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Moderate clinical impact. There was a statistically significant difference in time to healing for ulcer without exposed bone, and for the number of amputations required by patients with ulcers where the bone is exposed.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Asian patients with diabetic foot ulcers that have not responded to conservative treatments for more than 2 months.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Japan, which has similar healthcare for diabetes patients compared to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence as they felt that due to the small, non-randomised nature of the study, there was still significant uncertainty in this area. As a consequence the group felt that the evidence statement should be downgraded to a D.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level III-2 study with a moderate risk of bias.
2. Consistency	N/A	There was only one study.
3. Clinical impact	C	Moderate clinical impact. There was a statistically significant difference in time to healing for ulcer without exposed bone, and for the number of amputations required by patients with ulcers where the bone is exposed.
4. Generalisability	B	Asian patients with diabetic foot ulcers that have not responded to conservative treatments for more than 2 months.
5. Applicability	C	The study was conducted in Japan, which has similar healthcare for diabetes patients compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to suggest that epidermal grafts improve the time to healing for people with chronic diabetic foot ulcers without exposed bone, and that bone scraping plus epidermal grafts reduces the risk of amputation for people with chronic diabetic foot ulcers that are exposed to the bone (Grade D)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Cultured keratinocytes or fibroblasts		Evidence table ref: (Bayram et al. 2005; Han et al. 2009; Moustafa et al. 2007)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with a moderate risk of bias and one level III-2 study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Two studies found statistically significant differences in ulcer area, time to healing and/or number of ulcers healed. The third study was very small and showed similar trends.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Moderate clinical impact. One study reported a reduction in ulcer area, two studies reported a reduction in time to healing, and one study reported an increased number of healed ulcers that were all statistically significant.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of patients with chronic diabetic foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
One study was conducted in the UK, where the care of diabetic foot ulcers is likely to be similar to Australia. The other two studies were conducted in Turkey and Korea, where health care is	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

likely to be provided differently to patients with diabetic foot ulcers than in Australia.	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt that small study numbers, the likely limited reproducibility and availability of the technique suggests that the grade of the evidence statement should be downgraded. Additionally, there is uncertainty regarding which component of the intervention is causing the treatment effect if any. As this area is an evolving field the intervention may soon be obsolete. As a consequence, no recommendation was be made.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Two level II studies with a moderate risk of bias and one level III-2 study with a moderate risk of bias
2. Consistency	B	Two studies found statistically significant differences in ulcer area, time to healing and/or number of ulcers healed. The third study was very small and showed similar trends.
3. Clinical impact	C	Moderate clinical impact. One study reported a reduction in ulcer area, two studies reported a reduction in time to healing, and one study reported an increased number of healed ulcers that were all statistically significant.
4. Generalisability	B	Population consisted of patients with chronic diabetic foot ulcers
5. Applicability	C	One study was conducted in the UK, where the care of diabetic foot ulcers is likely to be similar to Australia. The other two studies were conducted in Turkey and Korea, where health care is likely to be provided differently to patients with diabetic foot ulcers than in Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Treatment with cultured keratinocytes or fibroblasts, when compared with placebo or control, was found to reduce the ulcer size, decrease the time required to heal, and increase the number of ulcers that healed completely for people with chronic diabetic foot ulcers. (Grade D)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Cultured skin equivalents		Evidence table ref: (Blozik & Scherer 2008; Caravaggi et al. 2003; Edmonds et al. 2009; Gentzkow et al. 1996; Hanft & Suprenant 2002; Lipkin et al. 2003; Marston et al. 2003; Pollak et al. 1997; Sabolinski & Veves 2000; Veves et al. 2001)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level I study with a moderate risk of bias and nine level II studies (3 with a low risk of bias, 5 with a moderate risk of bias, and 1 with a high risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
All studies showed either trends towards or statistically significant differences between the two groups for all outcomes reported.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Substantial clinical impact. Meta-analysis showed a statistically significant increase in the number of ulcers that healed after treatment with cultured cell equivalents compared to standard wound care alone. All studies showed either trends towards or statistically significant differences between the two groups for all outcomes reported in favour of using cultures skin equivalents.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of diabetic patients with chronic, non-healing, full-thickness, foot ulcers with adequate perfusion.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Three studies were conducted in Europe (one multicentre trial also in Australia), where the care	A	Evidence directly applicable to Australian healthcare context

of diabetic foot ulcers is likely to be comparable to Australia. Seven studies were conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	One level I study with a moderate risk of bias and nine level II studies (3 with a low risk of bias, 5 with a moderate risk of bias, and 1 with a high risk of bias.
2. Consistency	A	All studies showed either trends towards or statistically significant differences between the two groups for all outcomes reported
3. Clinical impact	B	Substantial clinical impact. Meta-analysis showed a statistically significant increase in the number of ulcers that healed after treatment with cultured cell equivalents compared to standard wound care alone. All studies showed either trends towards or statistically significant differences between the two groups for all outcomes reported in favour of using cultures skin equivalents.
4. Generalisability	A	Population consisted of diabetic patients with chronic, non-healing, full-thickness, foot ulcers with adequate perfusion.
5. Applicability	B	Three studies were conducted in Europe (one multicentre trial also in Australia), where the care of diabetic foot ulcers is likely to be comparable to Australia. Seven studies were conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is substantial evidence to suggest that clinical outcomes are significantly improved for people with chronic diabetic foot ulcers treated with cultures skin equivalents and standard wound care compared to standard wound care alone. (Grade B)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	B

Cultured skin equivalents may be considered for the management of foot ulcers in specialist centres, as part of a comprehensive wound managment program. (EBR 14)	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? NO	
Are there any resource implications associated with implementing this recommendation? Not readily available in Australia. Cost unknown	
Will the implementation of this recommendation require changes in the way care is currently organised? No	
Are the guideline development group aware of any barriers to the implementation of this recommendation? 7. Not readily available in Australia / access. 8. Living cells, which die so time factor. 9. Could be utilised more frequently.	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Cultured skin equivalent versus acellular wound matrix		Evidence table ref: (Landsman et al. 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There was only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Slight clinical impact. There were no statistically significant differences for either the number of healed ulcers or the time to healing.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of diabetic patients with a full-thickness ulcer of at least 4 weeks duration that does not extend to bone or tendons, and with a viable wound bed with granulation tissue.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA, where the care of diabetic foot ulcers is likely to be similar	A	Evidence directly applicable to Australian healthcare context

to Australia.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt that the rating of the evidence statement should be downgraded as it is difficult to separate the treatment effect from baseline healing in this study. As a consequence, no recommendation has been produced from this evidence.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II studies with a moderate risk of bias.
2. Consistency	N/A	There was only one study
3. Clinical impact	D	Slight clinical impact. There were no statistically significant differences for either the number of healed ulcers or the time to healing.
4. Generalisability	C	Population consisted of diabetic patients with a full-thickness ulcer of at least 4 weeks duration that does not extend to bone or tendons, and with a viable wound bed with granulation tissue
5. Applicability	C	The study was conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence presented in this study suggests that there is no statistical or clinical advantage when using either Dermagraft or OASIS wound matrix in addition to standard wound care for people with chronic diabetic foot ulcers. (Grade D)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

Expert working group felt there was insufficient evidence to make a recommendation	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Acellular wound matrix versus moist wound therapy		Evidence table ref: (Reyzelman et al.2009)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Moderate clinical impact. One study reported a reduction in ulcer area, and one study reported an increased number of healed ulcers that were statistically significant.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of diabetic patients with a non-healing full-thickness ulcer of at least 6 weeks duration for one study and diabetic patients with a University of Texas grade 1 or 2 diabetic foot ulcer with no signs of infection, and with adequate perfusion to affected limb, for the other.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Both studies were conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt that the one study include, with small patient numbers, was insufficient to make a recommendation.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias.
2. Consistency	N/A	Only one study available.
3. Clinical impact	C	Moderate clinical impact. Reyzelman et al (2009) reported an increased number of healed ulcers that was statistically significant.
4. Generalisability	B	Population consisted of diabetic patients with a University of Texas grade 1 or 2 diabetic foot ulcer with no signs of infection, and with adequate perfusion to affected limb.
5. Applicability	C	The study was conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The use of GraftJacket wound matrix with Silverlon may increase the likelihood of ulcers healing when used in addition to moist wound therapy in diabetic patients with surgically debrided chronic foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer Acellular wound matrix versus moist wound therapy plus sharp debridement?		Evidence table ref: (Brigido et al 2004)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Moderate clinical impact. Brigido et al (2004) reported a greater reduction in ulcer size with the intervention compared to the control. This difference was reported to be statistically significant.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of diabetic patients with a chronic, non-healing, full-thickness ulcer of the lower extremity (leg or foot) least 6 weeks duration.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Expert working group felt that the one study include, with small patient numbers, was insufficient to make a recommendation.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component		Rating	Description
1.	Evidence base	C	One level II study with a moderate risk of bias.
2.	Consistency	N/A	Only one study available.
3.	Clinical impact	D	Moderate clinical impact. Brigido et al (2004) reported a greater reduction in ulcer size with the intervention compared to the control. This difference was reported to be statistically significant.
4.	Generalisability	B	Population consisted of diabetic patients with a chronic, non-healing, full-thickness ulcer of the lower extremity (leg or foot) least 6 weeks duration.
5.	Applicability	C	The study was conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The use of GraftJacket wound matrix may aid in reducing the size of ulcers when used in addition to moist wound therapy in diabetic patients with surgically debrided chronic foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	
Expert working group felt there was insufficient evidence to make a recommendation		
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?		
Are there any resource implications associated with implementing this recommendation?		
Will the implementation of this recommendation require changes in the way care is currently organised?		
Are the guideline development group aware of any barriers to the implementation of this recommendation?		

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Acellular wound matrix versus Regranex gel with recombinant human platelet derived growth factor		Evidence table ref: (Niezgoda et al. 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There was only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Slight clinical impact. The difference in the number of ulcers that healed did not reach statistical significance for all patients, only for subgroups of patients with either type 2 diabetes or plantar ulcers.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of diabetic patients with chronic, non-healing, full-thickness, University of Texas grade 1A ulcers of more than 1 month duration, and with a viable wound bed with granulation tissue. However, given the per protocol analysis it is uncertain whether the results are generalisable to other populations with similar characteristics.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA and Canada, where the care of diabetic foot ulcers is likely	A	Evidence directly applicable to Australian healthcare context

to be similar to Australia.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation was produced due to the poor generalisability and lack of evidence of a clinical impact.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias.
2. Consistency	N/A	There was only one study.
3. Clinical impact	D	Slight clinical impact. The difference in the number of ulcers that healed did not reach statistical significance for all patients, only for subgroups of patients with either type 2 diabetes or plantar ulcers.
4. Generalisability	D	Population consisted of diabetic patients with chronic, non-healing, full-thickness, University of Texas grade 1A ulcers of more than 1 month duration, and with a viable wound bed with granulation tissue. However, given the per protocol analysis it is uncertain whether the results are generalisable to other populations with similar characteristics.
5. Applicability	B	The study was conducted in the USA and Canada, where the care of diabetic foot ulcers is likely to be similar to Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

OASIS acellular wound matrix, used in conjunction with a dressing to protect the healing environment and standard wound care may improve healing in patients with type 2 diabetes and/or plantar ulcers when compared to Regranex Gel, a sodium carboxymethyl cellulose gel with 0.01% recombinant human platelet derived growth factor (rhPDGF), in addition to standard wound care. (Grade D)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Radiowave or electric therapy

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Electric stimulation versus standard wound care		Evidence table ref: (Baker et al. 1997; Lundeberg et al. 1992; Peters et al. 2001)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias and two level II studies with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Although all studies were underpowered to detect a significant difference, the direction of the treatment effect differed in the study by Baker et al (1997).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There was no statistically significant clinical impact of the intervention on ulcer healing.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The studies were mostly homogenic, patients were recruited from an outpatient clinic or a department of an university hospital, where they were treated for diabetic foot ulceration. Two studies included more males than females and one study had a high proportion of Hispanic patients.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The studies took place in the USA and Sweden, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

This is an emerging field however, the studies in this review are small and underpowered. The expert working group felt that these reasons should result in downgrading the evidence statement from a C to a D. As a consequence no recommendation was developed.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with low risk of bias and two level II studies with moderate risk of bias.
2. Consistency	C	Although all studies were underpowered to detect a significant difference, the direction of the treatment effect differed in the study by Baker et al (1997).
3. Clinical impact	D	There was no statistically significant clinical impact of the intervention on ulcer healing.
4. Generalisability	B	The studies were mostly homogenic, patients were recruited from an outpatient clinic or a department of an university hospital, where they were treated for diabetic foot ulceration. Two studies included more males than females and one study had a high proportion of Hispanic patients.
5. Applicability	C	The studies took place in the USA and Sweden, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is no evidence to suggest that electric stimulation provides any additional benefit with regard to healing compared to standard wound care alone for diabetic foot ulceration (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Non contact normothermic wound therapy versus standard wound care		Evidence table ref: (Alvarez et al. 2003; McCulloch et al. 2002)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Three level II studies with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Although one study was underpowered, the direction of the treatment effects was consistent for healing of ulcers.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The meta analysis indicates a moderate clinical impact with a relative risk of 2.2 [95% CI 1.2, 3.9].	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The studies were homogenic, Patients were recruited from an outpatient clinic, where they were treated for chronic diabetic foot ulceration.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The studies took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

This is an emerging field however, the studies in this review are small and underpowered. The expert working group felt that these reasons should result in downgrading the evidence statement from a C to a D. As a consequence, no recommendation was developed.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
16. Evidence base	C	Three level II studies with moderate risk of bias.
17. Consistency	B	Although one study was underpowered, the direction of the treatment effects was consistent for healing of ulcers.
18. Clinical impact	C	The meta analysis indicates a moderate clinical impact with a relative risk of 2.2 [95% CI 1.2, 3.9].
19. Generalisability	C	The studies were homogenic, Patients were recruited from an outpatient clinic, where they were treated for chronic diabetic foot ulceration.
20. Applicability	C	The studies took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggests that non contact normothermic wound therapy in addition to standard wound care is more effective at healing foot ulcers than standard wound care by itself (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	
Expert working group felt there was insufficient evidence to make a recommendation		

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Local heat versus global heat		Evidence table ref: (Petrofsky et al. 2007)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results presented a significant clinical impact of the intervention.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample consisted of patients attending a wound care centre for chronic diabetic foot ulceration.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group felt that this study was small and underpowered and therefore the evidence statement should be downgraded to reflect the uncertainty surrounding these results. Consequently, no recommendation was developed.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	C	The results presented a significant clinical impact of the intervention.
4. Generalisability	B	The study sample consisted of patients attending a wound care centre for chronic diabetic foot ulceration.
5. Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggests that global heat in addition to electric stimulation and standard wound care is more effective than additional local heat or standard wound care alone (Grade D).

Application of heat, either global or local, in addition to electric stimulation and standard wound care is more effective at reducing wound area than standard wound care alone (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

Expert working group felt there was insufficient evidence to make a recommendation	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? High Voltage pulsed current versus placebo/standard wound care		Evidence table ref: (Houghton et al. 2003)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No statistically significant effect was seen between the two groups.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The studies included patients attending a hospital division of vascular surgery and outpatient foot clinics, which is generalisable to the target population with some caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in Canada, which has a similar health care for diabetes patients compared to the Australia health care context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence due to the poor clinical impact and small study numbers.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study available.
3. Clinical impact	D	No statistically significant effect was seen between the two groups.
4. Generalisability	C	The studies included patients attending a hospital division of vascular surgery and outpatient foot clinics, which is generalisable to the target population with some caveats.
5. Applicability	B	The study took place in Canada, which has a similar health care for diabetes patients compared to the Australia health care context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is no evidence to support high voltage pulsed current in addition to standard wound care for ulcer healing in patients with chronic leg ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	
Expert working group felt there was insufficient evidence to make a recommendation		

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Shock wave therapy versus standard wound care		Evidence table ref: (Moretti et al. 2009)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicated that there was no clinical impact of the additional intervention on the ulcer healing rate, but did show an increase in re-epithelisation and acceleration of healing for the intervention group compared to standard wound care.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included a sample population recruited from a diabetic ambulatory of endocrinology unit of a university for neuropathic foot ulcers, which makes the sample generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the Italy, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence due to the evidence coming from one study with small study numbers.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	C	The results indicated that there was no clinical impact of the additional intervention on the ulcer healing rate, but did show an increase in re-epithelisation and acceleration of healing for the intervention group compared to standard wound care.
4. Generalisability	B	The study included a sample population recruited from a diabetic ambulatory of endocrinology unit of a university for neuropathic foot ulcers, which makes the sample generalisable to the target population.
5. Applicability	C	The study took place in the Italy, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence that shock wave therapy in addition to standard wound care is more effective than standard care alone for the healing of neuropathic foot ulcers in diabetic patients. However, the therapy may accelerate the healing process and increase the re-epithelisation of the neuropathic foot ulcer compared to standard wound care alone in diabetic patients (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	
Expert working group felt there was insufficient evidence to make a recommendation		

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Shock wave therapy versus hyperbaric oxygen therapy		Evidence table ref: (Wang et al. 2009)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicated that there were no statistically significant effects in the intervention group relative to the comparator.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included a sample of outpatients attending a hospital for chronic diabetic foot ulcers, which makes the sample generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the Taiwan, which has different health care for diabetes patients compared to the Australia health care context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence due to the poor clinical impact and applicability to the Australian healthcare context.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
11. Evidence base	C	One level II study with moderate risk of bias
12. Consistency	N/A	Only one study available
13. Clinical impact	D	The results indicated that there were no statistically significant effects in the intervention group relative to the comparator.
14. Generalisability	C	The study included a sample of outpatients attending a hospital for chronic diabetic foot ulcers, which makes the sample generalisable to the target population.
15. Applicability	D	The study took place in the Taiwan, which has different health care for diabetes patients compared to the Australia health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is no evidence to support the use of shock wave therapy over hyperbaric oxygen therapy in addition to standard wound care for ulcer improvement or healing (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	
Expert working group felt there was insufficient evidence to make a recommendation		

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Ultrasound versus placebo		Evidence table ref: (Ennis et al. 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicate that there is statistically significant clinical effect on the healing of ulcers for the intervention compared to the control group.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included patients attending hospital clinics and private wound clinics. A third of the population consisted of black or Hispanic ethnicity which makes the study sample generalisable to the target population with some caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the USA and Canada, which has a health care for diabetes patients compared to the Australia health care context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence and felt that the evidence statement should be downgraded as a result of the large losses to follow-up.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with low risk of bias.
2. Consistency	N/A	Only one study available
3. Clinical impact	B	The results indicate that there is statistically significant clinical effect on the healing of ulcers for the intervention compared to the control group.
4. Generalisability	C	The study included patients attending hospital clinics and private wound clinics. A third of the population consisted of black or Hispanic ethnicity which makes the study sample generalisable to the target population with some caveats.
5. Applicability	C	The study took place in the USA and Canada, which has a health care for diabetes patients compared to the Australia health care context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggests that ultrasound in addition to standard care is more effective at healing diabetic foot ulcer than standard care by itself. However, it should be taken in account that there is an increased risk for mild adverse events with the additional ultrasound treatment (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Foot compression versus standard care		Evidence table ref: (Armstrong et al. 2000)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The result indicates that there is a statistically significant clinical impact for the treatment.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample consisted of patients with chronic diabetic foot wounds and consisted of mainly Mexican Americans. This makes the sample generalisable to the target population with some caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The studies took place in USA, which have similar health care for diabetes patients compared to the Australia health care context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence as it is based on one study with relatively small study numbers.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	B	One level II study with low risk of bias.
2. Consistency	N/A	Only one study
3. Clinical impact	B	The result indicates that there is a statistically significant clinical impact for the treatment.
4. Generalisability	C	The study sample consisted of patients with chronic diabetic foot wounds and consisted of mainly Mexican Americans. This makes the sample generalisable to the target population with some caveats.
5. Applicability	C	The studies took place in USA, which have similar health care for diabetes patients compared to the Australia health care context

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggests that foot compression in addition to standard wound care is more effective for healing of infected diabetic foot ulcers than standard care alone (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Radiotherapy versus placebo		Evidence table ref: (Chantelau et al. 1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The result indicates that there is no statistically significant difference.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample consisted for patients with severe diabetic foot complications. This makes the sample generalisable to the target population with some caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The studies took place in Germany, which have similar health care for diabetes patients compared to the Australia health care context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence due to the poor clinical impact and very small study numbers.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	N/A	Only one study
3. Clinical impact	D	The result indicates that there is no statistically significant difference.
4. Generalisability	C	The study sample consisted for patients with severe diabetic foot complications. This makes the sample generalisable to the target population with some caveats.
5. Applicability	C	The studies took place in Germany, which have similar health care for diabetes patients compared to the Australia health care context

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence to suggest that radiotherapy in addition to standard care is better than standard care by itself for the treatment of diabetic foot osteoarthropathy (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Interventions to improve the clinical management of diabetic foot ulcers

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Staged multidisciplinary management		Evidence table ref: (Horswell et al. 2003; Rerkasem et al. 2007; Rerkasem et al. 2009; Yesil et al. 2009)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level III-2 study and two level III-3 studies with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The studies were mostly consistent in finding a statistically significant reduction in the amputation rate.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Overall, the studies have shown a statistically significant reduction in the amputation rate favouring multidisciplinary, staged management care over standard care. One study also found that the length and the rate of foot-related hospital stays were shorter and less frequent, respectively, for patients treated by the multidisciplinary, staged management care than for those treated with standard care. The SF-36 scores for patients that had received multidisciplinary, staged management care were statistically significantly higher than for patients that received standard care.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of diabetic patients with foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
One study was conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia. The other two studies were conducted in Thailand and Turkey, which has different healthcare for diabetes patients compared to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level III-2 study and two level III-3 studies with a moderate risk of bias
2. Consistency	B	The studies were mostly consistent in finding a statistically significant reduction in the amputation rate.
3. Clinical impact	B	Overall, the studies have shown a statistically significant reduction in the amputation rate favouring multidisciplinary, staged management care over standard care. One study also found that the length and the rate of foot-related hospital stays were shorter and less frequent, respectively, for patients treated by the multidisciplinary, staged management care than for those treated with standard care. The SF-36 scores for patients that had received multidisciplinary, staged management care were statistically significantly higher than for patients that received standard care.
4. Generalisability	A	Population consisted of diabetic patients with foot ulcers
5. Applicability	C	One study was conducted in the USA, where the care of diabetic foot ulcers is likely to be similar to Australia. The other two studies were conducted in Thailand and Turkey, which has different healthcare for diabetes patients compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to suggest that multidisciplinary, staged management care reduces the risk of amputation rate for patients with diabetic foot ulcers compared to standard care. (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	C
People with diabetes-related foot ulceration are best managed by a **multi-disciplinary foot care team** (EBR 9)		
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care? Yes and no		
Are there any resource implications associated with implementing this recommendation? Workforce implications.		
Will the implementation of this recommendation require changes in the way care is currently organised? Yes		
Are the guideline development group aware of any barriers to the implementation of this recommendation? 10. Continuity of care 11. Not enough multidisciplinary teams available		

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? GP training program		Evidence table ref: (Benotmane et al. 2004)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level III-3 study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Slight/restricted impact. No differences were found between the two groups for either the number of patients that died or the number that required amputations.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of diabetic patients with a foot ulcer.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Algeria, which has different healthcare for diabetes patients compared to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence due to the poor evidence base, clinical impact and applicability to the Australian Healthcare context.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level III-3 study with a moderate risk of bias.
2. Consistency	N/A	Only one study
3. Clinical impact	D	Slight/restricted impact. No differences were found between the two groups for either the number of patients that died or the number that required amputations.
4. Generalisability	A	Population consisted of diabetic patients with a foot ulcer
5. Applicability	D	The study was conducted in Algeria, which has different healthcare for diabetes patients compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence that a GP training program has had any impact on the mortality and amputation rates in patients with diabetic foot ulcers. (Grade D)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	
Expert working group felt there was insufficient evidence to make a recommendation		

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Remote expert wound consultation using digital imaging		Evidence table ref: (Santamaria et al. 2004)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Very large impact. There were statistically significant differences between the two groups for the ulcer healing rate (% size reduction per week) the number of patients that required amputations.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of patients with chronic ulcers of various aetiologies on the lower extremity.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Australia, and therefore is directly applicable.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias.
2. Consistency	N/A	Only one study
3. Clinical impact	A	Very large impact. There were statistically significant differences between the two groups for the ulcer healing rate (% size reduction per week) the number of patients that required amputations.
4. Generalisability	C	Population consisted of patients with chronic ulcers of various aetiologies on the lower extremity
5. Applicability	A	The study was conducted in Australia, and therefore is directly applicable.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Digital imaging of the wound, electronically transferring those images to a remote expert consultant and receiving treatment advice increase the ulcer healing rate and decrease the rate of amputation surgery when compared to treatment at the discretion of the local clinician for patients with lower extremity ulcers, including diabetic foot ulcers. (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	C

Remote expert consultation with digital imaging should be made available to people with diabetic foot ulceration living in remote areas who are unable to attend a multi-disciplinary foot care team/service for management (EBR 10)
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*
Will this recommendation result in changes in usual care? yes
Are there any resource implications associated with implementing this recommendation? Cost offsets ie. Don't need to have patients flown to team Digital cameras Servers (PACS) to store images received by multidisciplinary team (old files updated – changes over time?)
Will the implementation of this recommendation require changes in the way care is currently organised? Especially in states that do not have the facilities available. SA has cardiology network for ECG. WA and Queensland also have something.
Are the guideline development group aware of any barriers to the implementation of this recommendation? 12. Incentives by hospitals to take in E-health patients outside of catchment. Need a funding incentive – unless already being done. 13. No national policy exists. Policy in SA needs to be changed. 14. Each state spends money in their own way as Chronic Disease management is managed by each state. **Enablers to implementation** 15. In absence of this currently being done, systems are available for other types of health care ie. Cardiac, digital mammography, etc. 16. Some rural – urban hospital links/integrated telemedicine already. Could piggy back off of this. 17. A Sinha advised that a remote services system was developed for rural Queensland and funded by Cairns hospital. Chronic disease management done state by state. No national consistent policy.

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Providing prognostic data to improve care		Evidence table ref: (Kurd et al. 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Moderate clinical impact. There was a statistically significant difference for the number of ulcers healed between centres receiving week 4 prognostic information and those receiving none.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Population consisted of diabetic patients with a neuropathic foot ulcer.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA, which has similar healthcare for diabetes patients compared to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group felt that the evidence statement should be downgraded as these results are not reproducible without knowledge of the prognostic information used. Consequently, no recommendation was developed from this evidence.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias.
2. Consistency	N/A	Only one study
3. Clinical impact	C	Moderate clinical impact. There was a statistically significant difference for the number of ulcers healed between centres receiving week 4 prognostic information and those receiving none.
4. Generalisability	A	Population consisted of diabetic patients with a neuropathic foot ulcer.
5. Applicability	C	The study was conducted in the USA, which has similar healthcare for diabetes patients compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to suggest that supplying week 4 prognostic algorithms to treatment centres increases the rate of neuropathic foot ulcers that heal compared to supplying no prognostic algorithms (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Orthotics

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Total contact cast versus traditional dressing treatment		Evidence table ref: (Mueller et al 1989; Zimny et al 2003)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two average quality level II RCTs with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Although one study did not detect a statistically significant difference in time to healing, both studies reported that the intervention group healed quicker than the standard wound care groups.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
With a weighted mean difference of 14.5 days the reduction in time to healing with off-loading would provide a moderate clinical impact.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Evidence directly generalisable to target population of diabetic patients with chronic foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

Evidence probably applicable to Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Two average quality level II RCTs with moderate risk of bias.
2. Consistency	B	Although one study did not detect a statistically significant difference in time to healing, both studies reported that the intervention group healed quicker than the standard wound care groups.
3. Clinical impact	C	With a weighted mean difference of 14.5 days the reduction in time to healing with off-loading would provide a moderate clinical impact.
4. Generalisability	B	Evidence directly generalisable to target population of diabetic patients with chronic foot ulcers
5. Applicability	B	Evidence applicable to the Australian healthcare context with few caveats

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is evidence to suggest that off-loading interventions in addition to standard wound care will significantly reduce the time to healing relative to standard wound care alone in people with diabetic plantar foot ulcers (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	B

Pressure reduction, otherwise referred to as redistribution of pressure or offloading, is required to optimise the healing of plantar foot ulcers. (EBR 7)
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*
Will this recommendation result in changes in usual care? Yes
Are there any resource implications associated with implementing this recommendation? Yes and no. Cost to patient / hospitals to access offloading devices. For ATSI a less effective device is better than none. Home care required due to immobilisation/crutches.
Will the implementation of this recommendation require changes in the way care is currently organised? No
Are the guideline development group aware of any barriers to the implementation of this recommendation? 18. Patient adherence / education – not to remove cast 19. Patient doesn't get off loaded / have access to a device 20. Costs to patient of off loading device 21. Language re "off loading" meaning to GPs – reword recommendation 22. Education of GP regarding type of device needed. **Enablers to implementation** GP plan – incorporate it into plan / aim for allied health involvement

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Total contact cast versus removable cast walker		Evidence table ref: (Armstrong et al 2005; Armstrong et al 2001)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two average quality level II RCTs with low risk of bias	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Most studies are consistent in their findings and any inconsistency can be explained	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Slight clinical impact in relation to number of ulcers healed and time to heal however positive trends did not always reach statistical significance	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Likely generalisable to the population of diabetic patients with chronic foot ulcers	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Although studies were from the USA and Italy, evidence is probably applicable to the Australian healthcare context with some caveats	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence due to the poor clinical impact in regard to the comparison of total contact walkers and removable cast walkers.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	Two average quality level II RCTs with low risk of bias
2. Consistency	B	Most studies are consistent in their findings and any inconsistency can be explained
3. Clinical impact	D	Slight clinical impact in relation to number of ulcers healed and time to heal however positive trends did not always reach statistical significance
4. Generalisability	C	Likely generalisable to the population of diabetic patients with chronic foot ulcers
5. Applicability	B	Although studies were from the USA and Italy, evidence is probably applicable to the Australian healthcare context with some caveats

Indicate any dissenting opinions

EVIDENCE STATEMENT
Evidence suggests that use of a total contact cast versus removable cast walker shows a positive trend towards improving clinical outcomes for patients with chronic diabetic foot ulcers in relation to number of ulcers healed and time to heal. Findings however did not always reach clinical significance (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Total contact cast versus instant total contact cast		Evidence table ref: (Katz et al 2005; Piaggesi et al 2007)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two average quality level II RCTs with moderate risk of bias	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Most studies are consistent in their findings and any inconsistency can be explained	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No statistically significant difference was detected for ulcer healing and healing time.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Likely generalisable to the population of diabetic patients with chronic foot ulcers	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Although studies were from the USA and Italy, evidence is probably applicable to the Australian healthcare context with some caveats	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

The expert working group did not develop a recommendation based on this evidence due to the poor clinical impact in regard to to ulcer healing and healing time for this comparison.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
• Evidence base	C	Two average quality level II RCTs with moderate risk of bias
• Consistency	B	Most studies are consistent in their findings and any inconsistency can be explained
• Clinical impact	D	No statistically significant difference was detected for ulcer healing and healing time.
• Generalisability	B	Likely generalisable to the population of diabetic patients with chronic foot ulcers
• Applicability	B	Although studies were from the USA and Italy, evidence is probably applicable to the Australian healthcare context with some caveats

Indicate any dissenting opinions

EVIDENCE STATEMENT

There was no evidence to suggest that there were any differences in the proportion of ulcers which healed, or the healing time of ulcers between total contact casts and instant total contact casts in patients with diabetic foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Non-removable cast versus a half shoe		Evidence table ref: (Armstrong et al. 2001; Ha Van et al. 2003; Van De Weg et al. 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II RCTS and one level III-2 prospective non randomized study, all of average quality with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Most studies are consistent and any inconsistencies can be explained.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Substantial clinical impact in relation to time to healing of ulcers, number of ulcers healed and reduction in secondary infections.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Evidence directly generalisable to target population of diabetic patients with chronic foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were from the USA, Netherlands and France which although not the same as the Australian	A	Evidence directly applicable to Australian healthcare context

healthcare context are probably applicable with some caveats.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

This evidence was subsequently combined with other studies to assess whether there was benefit for non-removable devices over removable devices which enabled the development of EBR 9.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Two level II RCTS and one level III-2 prospective non randomized study all of average quality with moderate risk of bias
2. Consistency	B	Most studies are consistent and any inconsistencies can be explained
3. Clinical impact	B	Substantial clinical impact in relation to time to healing of ulcers, number of ulcers healed and reduction in secondary infections
4. Generalisability	B	Evidence directly generalisable to target population of diabetic patients with chronic foot ulcers
5. Applicability	C	Studies were from the USA, Netherlands and France which although not the same as the Australian healthcare context are probably applicable with some caveats

Indicate any dissenting opinions

EVIDENCE STATEMENT

The use of a non-removable cast is effective in increasing the likelihood that an ulcer heals, reducing the time it takes for an ulcer to heal and decreasing the risk of developing osteomyelitis compared to the use of a half shoe in patients with foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Non-removable cast versus a therapeutic shoe		Evidence table ref: (Caravaggi et al. 2000)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II RCT with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Moderate clinical impact in relation to reduction of surface area of ulcer.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Evidence generalisable to the target population of diabetic patients with chronic foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Italy which although not the same as the Australian healthcare context is	A	Evidence directly applicable to Australian healthcare context

probably applicable.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

This evidence was subsequently combined with other studies to assess whether there was benefit for non-removable devices over removable devices which enabled the development of EBR 9.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II RCT with moderate risk of bias
2. Consistency	N/A	Only one study
3. Clinical impact	C	Moderate clinical impact in relation to reduction of surface area of ulcer
4. Generalisability	B	Evidence generalisable to the target population of diabetic patients with chronic foot ulcers
5. Applicability	C	The study was conducted in Italy which although not the same as the Australian healthcare context is probably applicable

Indicate any dissenting opinions

EVIDENCE STATEMENT

Non-removable casts are moderately effective in reducing the surface area of ulcers at a faster rate compared to therapeutic shoes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

Expert working group felt there was insufficient evidence to make a recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Non-removable casts versus removable casts		Evidence table ref: (Armstrong et al 2001; Armstrong et al 2005; Caravaggi et al 2000; van De Weg et al 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context

	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Four level II RCTs with moderate risk of bias
2. Consistency	B	Most studies consistent and inconsistency may be explained.
3. Clinical impact	C	Moderate clinical impact in relation to ulcer healing.
4. Generalisability	B	Evidence generalisable to the target population of diabetic patients with chronic foot ulcers
5. Applicability	B	The studies were conducted in a number of countries in Europe and also in the USA suggesting that these results are applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Non-removable off-loading devices are more effective for ulcer healing in patients with diabetic plantar foot ulcers with regard to complete ulcer healing compared with removable off-loading devices (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	B

Offloading of the wound can be achieved with the use of a **total contact cast or other device rendered irremovable.** (EBR 8)	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? 23. Yes Podiatrists vary in their degree of knowledge some do debridement others don't. 24. EPC – funded for 5 visits to podiatrist but podiatrist sends back to GP due to limited resources but the GP also has same problem re funding. Problem exists until patient goes to hospital. 25. Resourcing /dressing of service is standard $55/hr but this can then be applied to a 15 min toe cut Vs 45 min for debridement + dressing. 26. This is in the guideline but the message is not getting through	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Topical treatments

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Zinc hyaluronic acid compared to standard wound care		Evidence table ref: Evidence table ref: (Ramos Cuevas et al. 2007; Tankova et al. 2002)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias and one level II study with high risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The direction of the treatment effect was consistent, although one study did not reach significance.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Moderate clinical impact. Tankova et al (2007) reported a substantial clinical impact of the intervention on time to healing. Though, Ramos Cuevas et al (2007) did not find a significant clinical effect. For ulcer healing no significant results were reported.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The studies included a sample population attending outpatient hospital foot or diabetes clinics, which makes them generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

One study took place in Bulgaria, and other in Mexico, where the care of diabetic foot ulcers is likely to be different for diabetes patients compared to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence due to the poor applicability to the Australian healthcare context and the likelihood that the treatment effect was due to chance given the small study numbers.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias and one level II study with high risk of bias.
2. Consistency	C	The direction of the treatment effect was consistent, although one study did not reach significance.
3. Clinical impact	C	Moderate clinical impact. Tankova et al (2007) reported a substantial clinical impact of the intervention on time to healing. Though, Ramos Cuevas et al (2007) did not find a significant clinical effect. For ulcer healing no significant results were reported.
4. Generalisability	A	The studies included a sample population attending outpatient hospital foot or diabetes clinics, which makes them generalisable to the target population.
5. Applicability	D	One study took place in Bulgaria, and other in Mexico, where the care of diabetic foot ulcers is likely to be different for diabetes patients compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The use of zinc hyaluronic acid may provide some benefit in reducing ulcer healing time when used in conjunction with standard wound care to treat diabetic foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Topical phenytoin compared to standard care		Evidence table ref: (Muthukumarasamy et al. 1991; Pai et al 2001)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias and on level III-2 study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Both studies were underpowered to detect a difference. Uncertainty regarding the effect of phenytoin powder remains.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Both studies reported non-significant results for ulcer healing. Muthukumarasamy et al (1991) also reported non-significant results for ulcer improvement (granulation), but did find a moderate effect when two outcomes were combined (healing and improvement). There was no significant clinical impact of the intervention for wound size reduction.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The studies included a sample population that were inpatients in hospital for foot ulcers, which makes them generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
One study took place in India, and one study in the USA, which might be applicable to the Australian context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence due to the likelihood that the studies lacked statistical power, resulting in poor clinical impact and uncertainty regarding the effect of phenytoin powder.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias and on level III-2 study with moderate risk of bias.
2. Consistency	C	Both studies were underpowered to detect a difference. Uncertainty regarding the effect of phenytoin powder remains.
3. Clinical impact	D	Both studies reported non-significant results for ulcer healing. Muthukumarasamy et al (1991) also reported non-significant results for ulcer improvement (granulation), but did find a moderate effect when two outcomes were combined (healing and improvement). There was no significant clinical impact of the intervention for wound size reduction.
4. Generalisability	B	The studies included a sample population that were inpatients in hospital for foot ulcers, which makes them generalisable to the target population.
5. Applicability	C	One study took place in India, and one study in the USA, which might be applicable to the Australian context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The use of phenytoin powder in addition to standard wound care for patients hospitalised with diabetic foot ulcers is not effective for ulcer healing, ulcer improvement or wound size reduction (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

Expert working group felt there was insufficient evidence to make a recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Total immersion in pH neutral superoxidised solution compared to saline solution		Evidence table ref: (Martínez De Jesús et al. 2007)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results are substantial and show statistically significant differences in cellulitis and the condition of the wound. However, these are secondary outcomes and the relevance to primary ulcer healing outcomes is uncertain.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population. Though the study only included patient with severe diabetic foot infections.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study came from Mexico, which might be applicable to the Australian context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence base as it relies on one study with small subject numbers. The group had concerns that the treatment effect may be due to chance and that uncertainty remained regarding the primary outcomes for this guideline.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	One level II studies with low risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	C	The results are substantial and show statistically significant differences in cellulitis and the condition of the wound. However, these are secondary outcomes and the relevance to primary ulcer healing outcomes is uncertain.
4. Generalisability	B	The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population. Though the study only included patient with severe diabetic foot infections.
5. Applicability	C	The study came from Mexico, which might be applicable to the Australian context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Evidence suggests that immersion in pH neural superoxidised solution followed by the same spray is more effective at improving infection parameters e.g. increase granulating tissue, reduce cellulitis and improving the surrounding skin than immersion in saline followed by povidone iodine spray of severely infected diabetic foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

Expert working group felt there was insufficient evidence to make a recommendation	
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Povidone iodine dressing versus non-adherent viscose filament gauze dressing or Aquacel moist wound dressing		Evidence table ref: (Jeffcoate et al. 2009)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study did not report any clinically or statistically significant results.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included a sample population that attended clinic outpatient settings for foot ulcers, which makes them generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the UK, which might be applicable to the Australian context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence due to the lack of clinically or statistically significant results ie poor clinical impact.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	One level II study with low risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	D	The study did not report any clinically or statistically significant results.
4. Generalisability	B	The study included a sample population that attended clinic outpatient settings for foot ulcers, which makes them generalisable to the target population.
5. Applicability	B	The study took place in the UK, which might be applicable to the Australian context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The results suggest that the use of povidone iodine dressing is as effective as a non-adherent viscose gauze dressing or the Aquacel moist wound dressing for the healing and time to healing in chronic diabetic foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Cadexomer iodine ointment versus gentamicin solution		Evidence table ref: (Apelqvist et al. 1996)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II studies with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study did not report significant results, therefore the clinical impact would be slight.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included a sample population that attended a clinic outpatient setting for foot ulcers, which makes them generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the Sweden, which might be applicable to the Australian context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence due to the lack of clinically or statistically significant results ie poor clinical impact.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II studies with moderate risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	D	The study did not report significant results, therefore the clinical impact would be slight.
4. Generalisability	B	The study included a sample population that attended a clinic outpatient setting for foot ulcers, which makes them generalisable to the target population.
5. Applicability	B	The study took place in the Sweden, which might be applicable to the Australian context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggests that the use of cadexomer iodine ointment is as effective as gentamicin solution for the healing or reduction of wound area of diabetic foot ulcer (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Zinc oxide tape versus hydrocolloid dressing		Evidence table ref: (Apelqvist et al. 1990)
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study did not report significant results for the separate outcomes. Though for the combined outcome the intervention has a moderate clinical impact, as there are also risks involved in the use of zinc oxide tape.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included a sample population that attended a clinic outpatient setting for foot ulcers. Though the subjects all had necrotic diabetic foot ulcers which makes them generalisable to the target population with some caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the Sweden, which might be applicable to the Australian context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence due to the lack of clinically or statistically significant results ie poor clinical impact.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	One level II study with low risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	D	The study did not report significant results for the separate outcomes. Though for the combined outcome the intervention has a moderate clinical impact, as there are also risks involved in the use of zinc oxide tape.
4. Generalisability	C	The study included a sample population that attended a clinic outpatient setting for foot ulcers. Though the subjects all had necrotic diabetic foot ulcers which makes them generalisable to the target population with some caveats.
5. Applicability	B	The study took place in the Sweden, which might be applicable to the Australian context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The use of adhesive zinc oxide tape in the treatment of necrotic diabetes foot ulcer might be beneficial for the reduction of initial necrosis, though this treatment still involves risks. Further research would be necessary (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Tretinoin versus saline solution		Evidence table ref: (Tom et al. 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study reported significant results for wound area and depth, indicating with p values <0.02 a moderate clinical impact of the treatment with tretinoin solution. Still some mild adverse events are involved. The study might be underpowered due to the small sample size.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included a sample population that attended a clinic outpatient Veteran setting for foot ulcers. Though the subjects were mainly males, they are likely to be generalisable to the target population with some caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the USA, which might be applicable to the Australian context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence as it is from only one study with relatively small subject numbers.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	One level II study with low risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	C	The study reported significant results for wound area and depth, indicating with p values <0.02 a moderate clinical impact of the treatment with tretinoin solution. Still some mild adverse events are involved. The study might be underpowered due to the small sample size.
4. Generalisability	C	The study included a sample population that attended a clinic outpatient Veteran setting for foot ulcers. Though the subjects were mainly males, they are likely to be generalisable to the target population with some caveats.
5. Applicability	C	The study took place in the USA, which might be applicable to the Australian context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggests that the use of 0.05% tretinoin solution therapy for 10 minutes in addition to standard care is beneficial for reduction in wound area and depth. Though some mild to moderate adverse effects are involved (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Argidene gel versus standard care		Evidence table ref: (Steed et al. 1995)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicate a moderate to substantial clinical impact as the relative risk are 1.6 and 4.4 for complete healing and ulcer improvement, respectively. Furthermore, the NNT indicated that the treatment is very effective.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included a sample population that attended outpatient clinics for their foot ulcers. There was a slight overrepresentation of males in the sample, which makes the sample generalisable to the target group with some caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the USA, which might be applicable to the Australian context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence as it is from only one study with relatively small subject numbers.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	B	One level II study with low risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	B	The results indicate a moderate to substantial clinical impact as the relative risk are 1.6 and 4.4 for complete healing and ulcer improvement, respectively. Furthermore, the NNT indicated that the treatment is very effective.
4. Generalisability	C	The study included a sample population that attended outpatient clinics for their foot ulcers. There was a slight overrepresentation of males in the sample, which makes the sample generalisable to the target group with some caveats.
5. Applicability	C	The study took place in the USA, which might be applicable to the Australian context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggests that the use of Argidene gel in addition to standard wound care results in a greater reduction in wound area, and greater healing (> 50% healing or completely healing) of diabetic foot ulcers compared to standard care alone (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Doxycycline hydrogel versus the hydrogel alone		Evidence table ref: (Chin et al. 2003)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study reported a significant difference in healing of foot ulcer. Caution should be used with these results as the two groups had significant difference at baseline.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
It is unclear where the subjects were recruited, though the patient characteristics indicate diabetic patients treated in a medical centre. Most of the subjects were male and had coronary artery disease as a comorbidity.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the USA, which might be applicable to the Australian context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence as it is from only one study with relatively small subject numbers.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	D	The study reported a significant difference in healing of foot ulcer. Caution should be used with these results as the two groups had significant difference at baseline.
4. Generalisability	C	It is unclear where the subjects were recruited, though the patient characteristics indicate diabetic patients treated in a medical centre. Most of the subjects were male and had coronary artery disease as a comorbidity.
5. Applicability	C	The study took place in the USA, which might be applicable to the Australian context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggests that the use of 1% doxycycline hydrogel on chronic foot ulcer would improve the healing of foot ulcers in diabetes patients compared to a vehicle hydrogel. Though, further research should be conducted (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	
Expert working group felt there was insufficient evidence to make a recommendation		

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Ketanserin hydrogel versus saline		Evidence table ref: (Martinez de Jesus et al. 1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicated that there is a substantial clinical impact on wound area reduction when using ketanserin ointment compared to normal saline. However, it is uncertain whether this translates into ulcer healing.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample was patient admitted to hospital for several diabetic foot related problems, which makes them generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in Mexico, which might be applicable to the Australian context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence given the uncertainty as to whether the results would translate into ulcer healing.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	B	The results indicated that there is a substantial clinical impact on wound area reduction when using ketanserin ointment compared to normal saline. However, it is uncertain whether this translates into ulcer healing.
4. Generalisability	B	The study sample was patient admitted to hospital for several diabetic foot related problems, which makes them generalisable to the target population.
5. Applicability	C	The study took place in the USA, which might be applicable to the Australian context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggests that the use of ketanserin in addition to standard wound care was more effective at reducing the area of the foot ulcer than the use of normal saline in diabetic patients hospitalised for foot problems (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Dimethylsulphoxide versus standard care		Evidence table ref: (Lishner et al. 1985)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level III-1 study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
For both outcomes the results indicate a substantial clinical impact, as the relative risks are both above 2 and the NNT's are small with a narrow confidence interval.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included patients with neuropathy and a non healing foot ulcer.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the Israel, which might be applicable to the Australian context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based as they felt that further research was required to confirm the results.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level III-1 study with moderate risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	A	For both outcomes the results indicate a substantial clinical impact, as the relative risks are both above 2 and the NNT's are small with a narrow confidence interval.
4. Generalisability	B	The study included patients with neuropathy and a non healing foot ulcer.
5. Applicability	C	The study took place in the Israel, which might be applicable to the Australian context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggests that soaking the affected foot in 25% or 50% dimethylsulphoxide solution in addition to standard care was more effective in healing and improving foot ulcer than standard care on itself in diabetic patients with chronic foot ulcers (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Iamin gel versus placebo		Evidence table ref: (Mulder et al. 1994)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicate that there is a substantial clinical impact of 2% Iamin gel in achieving diabetic foot wound closure, but only if applied immediately after sharp debridement.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample consisted of patients with different sizes of ulcers attending special clinics in several medical centres. Therefore, they are generalisable to the target population with few caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the USA, which might be applicable to the Australian context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence as it is from only one study with relatively small subject numbers.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	B	The results indicate that there is a substantial clinical impact of 2% lamin gel in achieving diabetic foot wound closure, but only if applied immediately after sharp debridement.
4. Generalisability	B	The study sample consisted of patients with different sizes of ulcers attending special clinics in several medical centres. Therefore, they are generalisable to the target population with few caveats.
5. Applicability	C	The study took place in the USA, which might be applicable to the Australian context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggests that immediate application of 2% lamin gel after sharp debridement in addition to standard wound care is more effective than standard wound care alone, particularly in large ulcers. Delayed application of either 2% or 4% lamin gel after sharp debridement provides no additional benefit to standard wound care for the treatment of diabetic foot ulcer (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Local insulin treatment in addition to standard wound care		Evidence table ref: (Razzak et al. 1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicate that there is a significant effect of local insulin used in addition to standard wound care, however it is possible the effect size has been overestimated.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample consisted of patients admitted to hospital for diabetic foot complications. There were more males included than females. Therefore, they are generalisable to the target population with some caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in Saudi-Arabia, which might be not be directly applicable to the Australian context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence as it is from only one study with relatively small subject numbers, and has poor applicability to the Australian healthcare context.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	B	The results indicate that there is a significant effect of local insulin used in addition to standard wound care, however it is possible the effect size has been overestimated.
4. Generalisability	C	The study sample consisted of patients admitted to hospital for diabetic foot complications. There were more males included than females. Therefore, they are generalisable to the target population with some caveats.
5. Applicability	D	The study took place in Saudi-Arabia, which might be not be directly applicable to the Australian context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggests that, in addition to standard wound care, local insulin therapy is effective in reducing hospital stays in complicated diabetic foot ulcer (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Talactoferrin versus placebo		Evidence table ref: (Lyons et al. 2007)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicate that there was no significant effect of talactoferrin gel in addition to standard care for ulcer healing.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample consisted of patients visiting outpatients settings and had an over representation of females. Therefore the sample is generalisable to the target population with few caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the USA, which might be applicable to the Australian context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence given it's poor clinical impact.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	D	The results indicate that there was no significant effect of talactoferrin gel in addition to standard care for ulcer healing.
4. Generalisability	B	The study sample consisted of patients visiting outpatients settings and had an over representation of females. Therefore the sample is generalisable to the target population with few caveats.
5. Applicability	C	The study took place in the USA, which might be applicable to the Australian context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence indicates that the use of talactoferrin in addition to standard wound care is no more beneficial than standard wound care alone for healing of severe diabetic foot ulcer (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	

Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Thrombin peptide Chrysalin versus saline placebo		Evidence table ref: (Fife et al. 2007)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicate that Chrysalin may be effective in the treatment of diabetic foot and heel ulcers however, further research may be required.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study population consisted of diabetic patients with a lower extremity, Wagner grade 1-3 ulcer (below the knee) of more than 8 weeks duration. Therefore the results are generalisable to the target population with some caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the USA, which might be applicable to the Australian context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence as it stems from only one study with relatively small subject numbers. Further research is required to confirm these results.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	C	The results indicate that Chrysalin may be effective in the treatment of diabetic foot and heel ulcers however, further research may be required.
4. Generalisability	C	The study population consisted of diabetic patients with a lower extremity, Wagner grade 1-3 ulcer (below the knee) of more than 8 weeks duration. Therefore the results are generalisable to the target population with some caveats.
5. Applicability	C	The study took place in the USA, which might be applicable to the Australian context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to suggest that 1 µg and 10 µg Chrysalin® in addition to standard wound care is effective in healing and accelerating the healing process of diabetic foot and heel ulcers compared to standard wound care alone. Further research may be required (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	
Expert working group felt there was insufficient evidence to make a recommendation		

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Ozone treatment in addition to standard wound care		Evidence table ref: (Martinez-Sanchez et al. 2005)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicated that there was a substantial clinical impact of the ozone treatment compared to conventional therapy. The non significant result on healing numbers can be explained by the short follow up.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample consisted of patient s hospitalised for diabetic foot complications. Furthermore, the sample included a third of black or other ethnicity in the sample and therefore are generalisable to the target population with few caveats.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in Cuba, which difference in health care for diabetic patients than in Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence as it came from only one study with relatively small subject numbers. Additionally, the evidence had poor applicability to the Australian healthcare context.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	C	The results indicated that there was a substantial clinical impact of the ozone treatment compared to conventional therapy. The non significant result on healing numbers can be explained by the short follow up.
4. Generalisability	C	The study sample consisted of patient s hospitalised for diabetic foot complications. Furthermore, the sample included a third of black or other ethnicity in the sample and therefore are generalisable to the target population with few caveats.
5. Applicability	D	The study took place in Cuba, which difference in health care for diabetic patients than in Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence suggest that the use of ozone in addition to standard care was not more effective in ulcer healing than conventional therapy, but did accelerate the time to healing and reduces the days of hospitalisation (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Bensal HP versus silver sulphadiazine		Evidence table ref: (Jacobs et al. 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with high risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicate that there is a significant clinical impact on the reduction of ulcer diameter, but no effect on ulcer healing. This can be explained by the short follow up of 6 weeks. It is unclear if the two groups were comparable.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study population consisted of diabetic patients with a Wagner grade 1 or 2 ulcer on the plantar aspect of the foot, visiting an outpatient clinic. There were no baseline characteristics given, except ulcer grade, size and location, which makes it difficult to generalise to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in Dutch Antilles, which difference in health care for diabetic patients than	A	Evidence directly applicable to Australian healthcare context

in Australia.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence as it came from only one study with relatively small subject numbers, and had poor generalisability and applicability

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	D	One level II study with moderate risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	C	The results indicate that there is a significant clinical impact on the reduction of ulcer diameter, but no effect on ulcer healing. This can be explained by the short follow up of 6 weeks. It is unclear if the two groups were comparable.
4. Generalisability	D	The study population consisted of diabetic patients with a Wagner grade 1 or 2 ulcer on the plantar aspect of the foot, visiting an outpatient clinic. There were no baseline characteristics given, except ulcer grade, size and location, which makes it difficult to generalise to the target population.
5. Applicability	D	The study took place in Dutch Antilles, which difference in health care for diabetic patients than in Australia.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence to suggest that Bensal HP in addition to standard care is more effective than silver sulphadiazine cream for the treatment of diabetic foot ulcer (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*

information will be used to develop the implementation plan for the guidelines.	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question: Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Lyophilised collagen versus hyaluronic acid		Evidence table ref: (Dimauro et al. 1991)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with high risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results indicate that there is a significant clinical impact on of time to ulcer healing. There is insufficient information concerning the characteristics of the intervention and control group.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
There is insufficient information given to determine the generalisablility of the population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in Italy, which is probably applicable to the Australian healthcare context	A	Evidence directly applicable to Australian healthcare context

with some caveats.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

6. Other factors (*Indicate here any other factors that you took into account when assessing the evidence base, eg. issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence due to the poor evidence base and generalisability.

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*

Component	Rating	Description
1. Evidence base	D	One level II study with high risk of bias
2. Consistency	N/A	Only one study.
3. Clinical impact	D	The results indicate that there is a significant clinical impact on of time to ulcer healing. There is insufficient information concerning the characteristics of the intervention and control group.
4. Generalisability	D	There is insufficient information given to determine the generalisablility of the population.
5. Applicability	C	The study took place in Italy, which is probably applicable to the Australian healthcare context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence to suggest that either lyophilised collagen or hyaluronic acid in addition to standard care are more effective than standard wound care alone for the treatment of diabetic foot ulcers (Grade D).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Honey versus povidone iodine solution		Evidence table ref: (Shukrimi et al 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Likely generalisable to the population of diabetic patients with chronic foot ulcers	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Based on the poor quality of the study and the lack of clinical impact, no recommendation was developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
o Evidence base	D	One level II study with high risk of bias
o Consistency	N/A	Only one study.
o Clinical impact	D	The results do not indicate that there is a significant clinical impact on outcomes.
o Generalisability	A	The evidence directly generalisable to target population
o Applicability	C	The study took place in Malaysia, which is probably applicable to the Australian healthcare context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT
There is insufficient evidence to suggest that honey is more effective than povidone solution in preparing diabetic foot ulcers for surgical closure (Grade D)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Miscellaneous interventions

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Biofeedback-assisted relaxation training		Evidence table ref: (Rice et al. 2001)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a high risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There was moderate benefit seen for healing of foot ulcer but this is likely to be substantially biased by lack of intention-to-treat analysis.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to patients with foot ulcer receiving care from a foot-care physician.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The study was conducted in USA and is therefore applicable to Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence due to the lack of clinical impact.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
Evidence base	D	One level II study with a high risk of bias.
Consistency	N/A	Only one study available
Clinical impact	D	There was moderate benefit seen for healing of foot ulcer but this is likely to be substantially biased by lack of intention-to-treat analysis.
Generalisability	B	The study would be generalisable to patients with foot ulcer receiving care from a foot-care physician.
Applicability	B	The study was conducted in USA and is therefore applicable to Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is limited evidence to indicate that there is a slight effect on ulcer healing for biofeedback-assisted relaxation in addition to standard wound care, in patients cared for by foot-care physicians (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Interventions for people without diabetic foot ulcers

Drug therapy for improving nerve function to prevent ulceration

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Sorbinil		Evidence table ref: (O'Hare et al. 1988)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study is underpowered to detect a statistical difference. The direction of the treatment effect suggests that the intervention is worse than placebo in preventing ulcer development however it is unclear whether this is due to the greater severity of neuropathy in the intervention group at baseline.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Generalisable to people with diabetic neuropathy in an outpatient setting.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Study conducted in the UK and therefore likely to be applicable to the Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence as it is of a limited nature (moderate risk of bias) and uncertainty remains around the clinical impact.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
. Evidence base	D	One level II study with moderate risk of bias.
. Consistency	NA	Only one study available.
. Clinical impact	D	The study is underpowered to detect a statistical difference. The direction of the treatment effect suggests that the intervention is worse than placebo in preventing ulcer development however it is unclear whether this is due to the greater severity of neuropathy in the intervention group at baseline.
. Generalisability	C	Generalisable to people with diabetic neuropathy in an outpatient setting.
. Applicability	B	Study conducted in the UK and therefore likely to be applicable to the Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

The evidence is inconclusive evidence regarding the use of sorbinil for the prevention of foot ulcers in people with diabetic neuropathy (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Hydroxyethylrutosides		Evidence table ref: (Lund et al. 1999)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level III-3 study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There is only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There was no statistically significant reduction in the number of amputations needed after administering hydroxyethylrutosides compared with standard care.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The population consisted of patients with critical limb ischemia, 53% of which had diabetes. Thus, would only apply to diabetic patients at the severe end of the spectrum.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Sweden, which has comparable healthcare for diabetic patients when compared to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence due to the poor evidence base and clinical impact.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	One level III-3 study with a moderate risk of bias
2. Consistency	N/A	There is only one study
3. Clinical impact	D	There was no statistically significant reduction in the number of amputations needed after administering hydroxyethylrutosides compared with standard care.
4. Generalisability	C	The population consisted of patients with critical limb ischemia, 53% of which had diabetes. Thus, would only apply to diabetic patients at the severe end of the spectrum.
5. Applicability	B	The study was conducted in Sweden, which has comparable healthcare for diabetic patients when compared to the Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

On the basis of the evidence available, hydroxyethylrutosides therapy is unlikely to provide any clinical benefit in addition to standard care when treating patients with critical limb ischaemia. (Grade D)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Therapeutic footwear

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Therapeutic footwear versus usual footwear		Evidence table ref: (Reiber et al. 2002; Uccioli et al. 1995)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
All studies are consistent.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No study provided sufficient evidence that there was a benefit of therapeutic footwear over usual footwear for preventing recurrence of foot ulcer.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study is generalisable to people with a history of diabetic foot ulcer.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The studies were conducted in the USA and Italy and therefore likely to be applicable to the Australian healthcare context with some caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence due to the poor clinical impact.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Two level II studies with a moderate risk of bias.
2. Consistency	A	All studies are consistent.
3. Clinical impact	D	No study provided sufficient evidence that there was a benefit of therapeutic footwear over usual footwear for preventing recurrence of foot ulcer.
4. Generalisability	B	The study is generalisable to people with a history of diabetic foot ulcer.
5. Applicability	C	The studies were conducted in the USA and Italy and therefore likely to be applicable to the Australian healthcare context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence to support the use of therapeutic footwear over usual footwear to prevent recurrence of diabetic foot ulcers (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	C

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Therapeutic footwear compared to chiropody		Evidence table ref: (Colagiuri et al. 1995)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The results suggest that rigid orthotic devices may improve plantar calluses.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to patients with plantar calluses and no history of foot ulcer.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Australia and is therefore directly applicable to Australian healthcare	A	Evidence directly applicable to Australian healthcare context

context.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Due to the small number of subjects studied, no recommendation was developed from this evidence.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias.
2. Consistency	N/A	Only one study available.
3. Clinical impact	C	The results suggest that rigid orthotic devices may improve plantar calluses.
4. Generalisability	B	The study would be generalisable to patients with plantar calluses and no history of foot ulcer.
5. Applicability	A	The study was conducted in Australia and is therefore directly applicable to Australian healthcare context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to suggest that rigid orthotic devices may help improve plantar calluses in people with diabetes and no history of foot ulcer (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Topical antifungal nail lacquer		Evidence table ref: (Armstrong et al 2005a)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with a moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There was no statistically or clinically significant benefit seen for the development of foot ulcer.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study would be generalisable to patients with at high risk of diabetic foot ulcer attending a high risk foot clinic.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in USA and is therefore applicable to Australian healthcare context with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Due to the poor clinical impact of this intervention, no recommendation has been developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias.
2. Consistency	NA	Only one study available.
3. Clinical impact	D	There was no statistically or clinically significant benefit seen for the development of foot ulcer.
4. Generalisability	B	The study would be generalisable to patients with at high risk of diabetic foot ulcer attending a high risk foot clinic.
5. Applicability	B	The study was conducted in USA and is therefore applicable to Australian healthcare context with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to indicate that there is no additional effect of using antifungal nail lacquer in addition to a preventive foot program to prevent the development of foot ulcer (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Education for the prevention of foot complications

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Brief education versus usual care		Evidence table ref: (Lincoln et al. 2008; Malone et al. 1989)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with low risk of bias and one level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The study by Lincoln et al (2008) was underpowered but reported a treatment effect in the same direction as Malone et al (1989).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Given the lack of power in one study, the estimate of the benefit in regard to amputation and recurrence is still somewhat uncertain.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The studies included a sample population attending diabetes, podiatry or vascular surgery clinics, which makes them generalisable to the target population. The sample characteristics were not described by Malone et al (1989), which makes it difficult to judge the generalisablity of the results.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The studies took place in the UK and USA, which have similar health care for diabetes patients compared to the Australia health care context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group felt that further research is required given the uncertainty in the treatment effect size. As a consequence, no recommendation has been developed. The expert working group felt that this uncertainty in effect size should downgrade the grade of the evidence statement.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	One level II study with low risk of bias and one level II study with moderate risk of bias.
2. Consistency	C	The study by Lincoln et al (2008) was underpowered but reported a treatment effect in the same direction as Malone et al (1989).
3. Clinical impact	D	Given the lack of power in one study, the estimate of the benefit in regard to amputation and recurrence is still somewhat uncertain.
4. Generalisability	C	The studies included a sample population attending diabetes, podiatry or vascular surgery clinics, which makes them generalisable to the target population. The sample characteristics were not described by Malone et al (1989), which makes it difficult to judge the generalisablity of the results.
5. Applicability	B	The studies took place in the UK and USA, which have similar health care for diabetes patients compared to the Australia health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is some evidence to suggest that a brief education program in addition to usual care reduces the occurrence of diabetic foot infection, ulcer and amputation in the general diabetic population (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Education program versus casual care		Evidence table ref: (Bloomgarden et al. 1987; Pieber et al. 1995)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias and one level III-2 study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
One study was inadequately powered to detect a difference although the treatment effects in both studies were in the same direction.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study by Bloomgarden et al (1987) did not report any statistically significant or clinically important results for the education program. Pieber's results indicated a slight to moderate effect of the intervention for secondary outcomes which may have influenced by confounding. Based on the quality of the studies, the results suggest a slight/ restricted clinical impact.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Pieber et al (1995) included a population that was generalisable to the target population. Bloomgarden et al (1987) had an over-representation of ethnic black and Hispanic patients who had a low educational level and thus, the results are not directly applicable to the Australia target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The studies took place in the Austria and the USA, which have similar health care for diabetes	A	Evidence directly applicable to Australian healthcare context

patients compared to the Australia health care context.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the poor clinical impact, no recommendation has been developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias and one level III-2 study with moderate risk of bias.
2. Consistency	B	One study was inadequately powered to detect a difference although the treatment effects in both studies were in the same direction.
3. Clinical impact	D	The study by Bloomgarden et al (1987) did not report any statistically significant or clinically important results for the education program. Pieber's results indicated a slight to moderate effect of the intervention for secondary outcomes which may have influenced by confounding. Based on the quality of the studies, the results suggest a slight/ restricted clinical impact.
4. Generalisability	C	Pieber et al (1995) included a population that was generalisable to the target population. Bloomgarden et al (1987) had an over-representation of ethnic black and Hispanic patients who had a low educational level and thus, the results are not directly applicable to the Australia target population.
5. Applicability	C	The studies took place in the Austria and the USA, which have similar health care for diabetes patients compared to the Australia health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence to suggest that an education program consisting of multiple teaching sessions provided to a group of patients in addition to usual care, is any more effective than usual care alone to reduce diabetic foot complications in the general diabetic population (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Intensive education for the prevention of diabetic foot problems		Evidence table ref: (Barth et al. 1991; Hamalainen et al. 1998; Rönnemaa et al. 1997)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level II studies with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The studies were consistent.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The studies reported on different outcomes. Barth et al did not find a statistically significant result, while the other study reported 25 outcomes but only three were statistically significant, which indicates that the education intervention had only a slight clinical impact.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The studies included a sample population attending foot clinics or podiatry clinic, which makes them generalisable to the target population. Though, the sample in one of the studies was also recruited by newspaper and radio ads, which might have lead to a more motivated and less severe population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
One study took place in Australia, which is directly applicable. The other study took place in Finland,	A	Evidence directly applicable to Australian healthcare context

which has similar health care for diabetes patients compared to the Australia health care context.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the lack of clinical impact, no recommendation has been developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	Two level II studies with moderate risk of bias.
2. Consistency	A	The studies were consistent.
3. Clinical impact	D	The studies reported on different outcomes. Barth et al did not find a statistically significant result, while the other study reported 25 outcomes but only three were statistically significant, which indicates that the education intervention had only a slight clinical impact.
4. Generalisability	C	The studies included a sample population attending foot clinics or podiatry clinic, which makes them generalisable to the target population. Though, the sample in one of the studies was also recruited by newspaper and radio ads, which might have lead to a more motivated and less severe population.
5. Applicability	A	One study took place in Australia, which is directly applicable. The other study took place in Finland, which has similar health care for diabetes patients compared to the Australia health care context.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence to suggest that an intensive education program is any more effective in the prevention of diabetic foot complications than a brief education program (Grade B)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Education targeting patients and doctors		Evidence table ref: (Litzelman et al. 1993)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
For the primary outcomes of interest, the clinical impact is likely to be slight due to a likely lack of power.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample consisted of patients visiting an academic general medicine practice between 1989 and 1991 for diabetes related issues. There was an over representation of females, patients with a lower socioeconomic status and black ethnicity.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the USA, which has similar health care for diabetes patients compared to	A	Evidence directly applicable to Australian healthcare context

the Australia health care context with some caveats.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The expert working group did not develop a recommendation based on this evidence as it of limited clinical impact particularly with regard to the primary outcomes.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	NA	Only one study available.
3. Clinical impact	D	For the primary outcomes of interest, the clinical impact is likely to be slight due to a likely lack of power.
4. Generalisability	C	The study sample consisted of patients visiting an academic general medicine practice between 1989 and 1991 for diabetes related issues. There was an over representation of females, patients with a lower socioeconomic status and black ethnicity.
5. Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

An education program that focuses on the patient as well as the clinician may be effective in reducing diabetic foot complications, specifically serious foot lesions, dry or cracked skin and ingrown nails, compared to usual care in patients with diabetes (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Home education versus usual care		Evidence table ref: (Rettig et al. 1986)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study available.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study reported no significant effect as a result of the intervention.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study sample was recruited from among diabetic inpatients identified by designated home health agency or country health department at participating hospitals.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study took place in the USA, which has similar health care for diabetes patients compared to	A	Evidence directly applicable to Australian healthcare context

the Australia health care context with some caveats.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the poor clinical impact and limitations regarding the evidence base, no recommendation has been developed.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias.
2. Consistency	NA	Only one study available.
3. Clinical impact	D	The study reported no significant effect as a result of the intervention.
4. Generalisability	B	The study sample was recruited from among diabetic inpatients identified by designated home health agency or country health department at participating hospitals.
5. Applicability	C	The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

There is insufficient evidence to suggest that a home based education program is more effective than non home education for the prevention of diabetic foot complications or the reduction in hospitalisation and emergency room visits in the general diabetic population (Grade C)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Management programs for the prevention of foot complications

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Multidisciplinary diabetes care management programs versus standard diabetes care		Evidence table ref: (Birke et al. 2003; McCabe et al. 1998; McMurray et al 2002)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One good quality and one poor quality level II RCTs and one good quality non-randomised controlled level III-2 study with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
All studies were consistent.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Diabetes care management programs have a substantial clinical impact on reducing the number of amputations and rates of hospitalisation for diabetic patients with foot related problems.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Evidence is directly generalisable to the target population of diabetic patients.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

Studies were from the UK and USA and while 2 of them are not similar to the Australian healthcare context they are probably applicable with few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Recommendation incorporating multi-discplinary management/protection programs is covered by EBR 4 (Question1). Given its use as a screening program, the recommendation was developed only from McCabe et al (1998) and consequently, the grade has been downgraded to C.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	B	One good quality and one poor quality level II RCTs and one good quality non-randomised controlled level III-2 study with low risk of bias.
2. Consistency	A	All studies were consistent.
3. Clinical impact	B	Diabetes care management programs have a substantial clinical impact on reducing the number of amputations and rates of hospitalisation for diabetic patients with foot related problems.
4. Generalisability	B	Evidence is directly generalisable to the target population of diabetic patients.
5. Applicability	B	Studies were from the UK and USA and while 2 of them are not similar to the Australian healthcare context they are probably applicable with few caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Diabetic care management programs have been shown to be substantially effective at reducing the rate of amputations and rate of hospitalisation for diabetic patients with foot-related problems when compared to standard diabetic care (Grade B).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Key question(s): Which interventions improve foot-related clinical outcomes for people with or without foot ulcer? Diabetes care management versus weight bearing activity		Evidence table ref: (Lemaster et al. 2008)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One good quality level II RCT with low risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No significant clinical impact in relation to number of full-thickness ulcers developed during the study period of 12 months.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Evidence directly generalisable to target population of patients with diabetic neuropathy.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study is from the USA which while not similar to the Australian healthcare context, can probably	A	Evidence directly applicable to Australian healthcare context

be applicable with some caveats.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation was developed given the evidence is from a single study with small subject numbers.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
6. Evidence base	B	One good quality level II RCT with low risk of bias.
7. Consistency	N/A	Only one study.
8. Clinical impact	D	No significant clinical impact in relation to number of full-thickness ulcers developed during the study period of 12 months.
9. Generalisability	B	Evidence directly generalisable to target population of patients with diabetic neuropathy.
10. Applicability	C	The study is from the USA which while not similar to the Australian healthcare context, can probably be applicable with some caveats.

Indicate any dissenting opinions

EVIDENCE STATEMENT

Evidence suggests that diabetic care management plus weight bearing activity has no clinical benefit or disadvantage compared to diabetic care management alone (Grade C).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Question 7

Key question(s): Under what circumstances are antibiotics effective in the treatment of foot ulceration? Antiobiotic therapy versus standard wound care		Evidence table ref: (Chantelau et al 1996; Hirschl & Hirschl 1992)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study with moderate risk of bias and one level III-3 study with moderate risk of bias.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The point estimates were in the opposite directions and it is unclear as to the reason for this.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	N/A	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Studies were unlikely to be adequately powered to detect a statistically significant result.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study populations consisted of diabetic patients with infected foot ulcers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		

The studies were conducted in Austria and Germany	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No recommendation was developed given the poor consistency and clinical impact of the evidence.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias and one level III-3 study with moderate risk of bias.
2. Consistency	D	The point estimates were in the opposite directions and it is unclear as to the reason for this.
3. Clinical impact	D	Studies were unlikely to be adequately powered to detect a statistically significant result.
4. Generalisability	B	The study populations consisted of diabetic patients with infected foot ulcers.
5. Applicability	B	The studies were conducted in Austria and Germany

Indicate any dissenting opinions

EVIDENCE STATEMENT

There was insufficient and inconsistent evidence supporting the supplementation of standard wound care with antibiotic therapy in order to treat diabetic foot ulcers. (Grade D)

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	
Are there any resource implications associated with implementing this recommendation?	
Will the implementation of this recommendation require changes in the way care is currently organised?	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	

Appendix E Evidence tables

Question 1

<table>
<tr><td colspan="5">STUDY DETAILS</td></tr>
<tr><td colspan="5">Reference [1] Armstrong, D. G., K. Holtz-Neiderer, et al. (2007). "Skin temperature monitoring reduces the risk for diabetic foot ulceration in high-risk patients." Am J Med 120(12): 1042-6.</td></tr>
<tr><td colspan="5">Affiliation/source of funds [2]
Supported by VA HRS&D Merit Award 20-059</td></tr>
<tr><td colspan="2">Study design [3]
Single blinded randomized clinical trial</td><td colspan="2">Level of evidence [4]
Level II</td><td>Location/setting [5]
South Arizona VA Health Care System, US</td></tr>
<tr><td colspan="3">Intervention [6]
Standard therapy (therapeutic foot wear, diabetic foot education, daily structured foot exam and regular foot care) + twice daily Infrared skin thermometer (TempTouch) on 6 sites of foot
Sample size [7]
106</td><td colspan="2">Comparator(s) [8]
Standard therapy (therapeutic foot wear, diabetic foot education, daily structure foot exam and regular foot care)
Sample size [9]
N=115</td></tr>
<tr><td colspan="5">Selection criteria
Inclusion criteria : diagnosis of diabetes, history of foot ulceration, ankle brachial indexes of ≥0.70 and ability to provide informed consent, age 18-80 ,
Exclusion criteria : patients with active or open ulcers, amputation sites, active Charcot arthropathy, severe peripheral vascular disease, non palpable foot pulse or ankle-brachial index <0.8 on either extremity, dementia, impaired cognitive function, history of drug or alcohol abuse <1 year, sight impaired or unable to walk without assistance of wheelchair or crutches.</td></tr>
<tr><td colspan="3">Patient characteristics [10] Intervention group
Age 68.2 (9.6)
Men 98.2%
Duration diabetic 13.6 (11.6)
Retinopathy 23.4%
Risk classification 2 84.7%
Risk classification 3 15.3%
VPT (volts) 42.6 (21.0)
Neuropathy with loss of protective sensation 100%</td><td colspan="2">Comparator group(s) standard
Age 69.7 (10.4)
Men 94.7%
Duration diabetic 12.6 (9.1)
Retinopathy 34.2%
Risk classification 2 82.5%
Risk classification 3 17.5%
VPT (volts) 50.1 (85.4)
Neuropathy with loss of protective sensation 100%</td></tr>
<tr><td colspan="3">Length of follow-up [11]
18 months</td><td colspan="2">Outcome(s) measured [12]
Foot ulceration</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
random</td><td>Comparison of study groups [14]
Non significant differences</td><td>Blinding [15]
Physician blinded for therapy</td><td>Treatment/ measurement bias [16]
Both groups received standard treatment.</td><td>Follow-up (ITT) [17]
Lost 4</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18]</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td rowspan="3">Outcome [19]
Foot ulceration</td><td rowspan="2">Intervention group [20]
Foot ulcer = 5</td><td rowspan="2">Control group [21]
Standard therapy
Foot ulcer = 14</td><td rowspan="2">Measure of effect/effect size [22]
OR= 3.0
95% CI [25]
1.0, 8.5</td><td>Benefits (NNT) [23]
95% CI [25]</td></tr>
<tr><td>Harms (NNH) [24]
95% CI [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26]</td><td colspan="2">Relevance (1-5) [27]</td></tr>
</table>

Any other adverse effects [28] no
EXTERNAL VALIDITY
Generalisabilty [29]
Applicability [30]
Comments [31]

STUDY DETAILS			
Reference [1] Beckert, S., M. Witte, et al. (2006). "A new wound-based severity score for diabetic foot ulcers - A prospective analysis of 1,000 patients." Diabetes Care 29(5): 988-992.			
Affiliation/source of funds [2] Departement of General and Transplant Surgery, University of Tubingen, Germany			
Study design [3] Prospective inception cohort	Level of evidence [4] II	Location/setting [5] Outpatient wound care unit	
Patient characteristics [10]	No (%) or Mean (SD from reference value)		Sample size [7] 1000
Male/ female	675 (67.5%)/ 325 (32.5%)		
Age (years)	69 (26-95)		
Number of visits	5 (2-60)		Length of follow-up [11] 365 days or until healing or amputation
Multiple ulcer	404 (40.4)		
Time follow up (days)	68 (3-365)		
Hospitalization	621 (62.1)		
Wound history (days)	31 (1-18708)		
Wound area (cm²)	0.9 (0.1-123)		
Soft tissue infection	354 (35.4)		
Probing to bone	269 (26.9)		
Ulcer location toe/ foot	356 (35.6%)/ 644 (64.4%)		
Palpable peripheral pulse	656 (65.6)		
Grade 1	29 (2.9)		
Grade 2	635 (63.5)		
Grade 3	20 (2.0)		
Grade 4	47 (4.7)		
Grade5	269 (26.9)		
Sharp debridement	1000		
Bone resection	136 (13.6)		
Selection criteria Inclusion criteria : diagnosis of diabetes by WHO, Exclusion criteria : -			
Prognostic factor(s): Diabetes Ulceration Severity Score DUSS (Followed by local wound care (debridement, pressure offloading and moist wound therapy)	Data collection method palpable pedal pulse yes=0, no=1, probing to bone yes=1, no=0, ulcer location toe=0, foot=1, multiple ulcerations yes=1, no=0)		
Potential confounders: -			
INTERNAL VALIDITY			
Outcome measurement method [12] Healing (complete epithelisation) and amputation	Comparison of study groups [14] Vs DUSS 0		Blinding [15] N/A
Measurement bias [16] No information on measurement bias	Follow-up (ITT) [17] 100%		
Overall quality assessment (descriptive) [18] .			
RESULTS			
Outcome [19] All four variables in the DUSS had a low probability for healing (p<0.01), therefore they are independent variables for healing.	Quality assessment: +		
outcome [19]	Measure of effect/effect size + 95% CI [22]		

Multivariate outcome for 4 variables: Multiple ulcers (yes) Probing to bone (yes) Location ulcer (foot) Non palpable pulses	 OR=0.65 [95%CI 0.54, 0.78] OR=0.78 [95%CI 0.62, 0.97] OR=0.48 [95%CI 0.40, 0.58] OR=0.72 [95%CI 0.60, 0.87]	 P<0.01 P=0.025 P<0.01 P<0.01
Healing Score 0 Score 4 Minor Amputation(toe and forefoot) Major amputations (below or above knee) Score 0 Score 1 Score 2 Score 3 Score 4	 93% 57% p<0.01 N=99 (9.9%) N=26 (2.6%) 0% 2.4% 7.7% 11.2% 3.8%	Correlation RR= 0.65 (95%CI 0.59, 0.71), p<0.01 No significant correlation p=0.67 No significant increase with DUSS score p=0.52 only trend
EXTERNAL VALIDITY		
Generalisabilty:		
Comments:		

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] Lavery, L. A., K. R. Higgins, et al. (2007). "Preventing diabetic foot ulcer recurrence in high-risk patients: use of temperature monitoring as a self-assessment tool." Diabetes Care 30(1): 14-20.</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2]
Funded by the National Institute of Health/National institute of Diabetes and Digestive and Kidney Diseases (NIDDK) under the Small Business Innovation Research program</td></tr>
<tr><td colspan="2">Study design [3]
Single blinded randomized clinical trial</td><td colspan="2">Level of evidence [4]
Level II</td><td colspan="2">Location/setting [5]
High risk diabetics clinic university of Texas Health Science Centre, San Antonio</td></tr>
<tr><td colspan="3">Intervention [6]
Standard care (8 week evaluation of physician, education program focussing on foot complication, self care practice, insoles and footwear) + twice daily Infrared skin thermometer
Sample size [7]
59</td><td colspan="3">Comparator(s) [8]
1. Standard therapy (therapeutic foot wear, diabetic foot education and foot evaluation by podiatrist)
2. Standard therapy + structured self foot inspection
Sample size [9]
1. N=58
2. N= 56</td></tr>
<tr><td colspan="6">Selection criteria
Inclusion criteria : diagnosis of diabetes, history of foot ulceration, ankle brachial indexes of ≥0.70 and ability to provide informed consent, age 18-80 ,
Exclusion criteria : patients with open ulcers or open amputation sites, active Charcot arthropathy, severe peripheral vascular disease, active foot infection, dementia, impaired cognitive function, history of drug or alcohol abuse <1 year, or other conditions.</td></tr>
<tr><td colspan="2">Patient characteristics [10] Intervention group
Age 65.4 ±9.3
Men 55.9%
Duration diabetic 12.7 ±9.7</td><td colspan="2">Comparator group(s) standard
Age 65.0 ±9.6
Men 53.4%
Duration diabetic 13.7 ±10.3</td><td colspan="2">Comparator standard + insp
Age 64.2.0 ±8.6
Men 51.7%
Duration diabetic 13.8 ±11.5</td></tr>
<tr><td colspan="3">Length of follow-up [11]
15 months</td><td colspan="3">Outcome(s) measured [12]
Foot ulceration</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
random</td><td>Comparison of study groups [14]
Non significant differences</td><td>Blinding [15]
Physician blinded for therapy</td><td>Treatment/ measurement bias [16]
All three groups received standard treatment.</td><td colspan="2">Follow-up (ITT) [17]
10 in enhanced group
6 in standard group
6 in standard + insp</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18]
Study takes in account the daily appliance of the foot inspection or skin temperature.</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="3">Outcome [19]
Foot ulceration</td><td>Intervention group [20]
Foot ulcer = 5</td><td>Control group [21]
Standard therapy
Foot ulcer = 17</td><td>Measure of effect/effect size [22]
OR= 4.48
95% CI [25]
1.53, 13.14</td><td colspan="2">Benefits (NNT) [23]
95% CI [25]</td></tr>
<tr><td>Intervention group
Foot ulcer = 5</td><td>Standard + inspect
Foot ulcer = 17</td><td>Measure of effect/effect size [22]
OR= 4.71
95% CI [25]
1.60, 13.85</td><td colspan="2">Harms (NNH) [24]
95% CI [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26]</td><td colspan="3">Relevance (1-5) [27]</td></tr>
<tr><td colspan="6">Any other adverse effects [28] no</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
</table>

Generalisabilty [29]
Applicability [30]
Comments [31]

<table>
<tr><td colspan="5">STUDY DETAILS</td></tr>
<tr><td colspan="5">Reference [1] Lavery, L. A., K. R. Higgins, et al. (2004). "Home monitoring of foot skin temperatures to prevent ulceration." Diabetes Care 27(11): 2642-7.</td></tr>
<tr><td colspan="5">Affiliation/source of funds [2]
Funded by the National Institute of Health/National institute of Diabetes and Digestive and Kidney Diseases (NIDDK) under the Small Business Innovation Research program</td></tr>
<tr><td colspan="2">Study design [3]
Single blinded randomized clinical trial</td><td colspan="2">Level of evidence [4]
Level II</td><td>Location/setting [5]
High risk diabetics clinic university of Texas Health Science Centre, San Antonio</td></tr>
<tr><td colspan="3">Intervention [6]
Standard care + Infrared skin thermometer
Sample size [7]
44</td><td colspan="2">Comparator(s) [8]
Standard therapy (therapeutic foot wear, diabetic foot education and foot evaluation by podiatrist)
Sample size [9] 41</td></tr>
<tr><td colspan="5">Selection criteria
Inclusion criteria : diagnosis of diabetes by WHO, ability to provide informed consent, age 18-80 and risk group 2 or 3 of the diabetic foot risk classification.
Exclusion criteria : patients with open ulcers or open amputation sites, active Charcot arthropathy, peripheral vascular disease, active foot infection, dementia, impaired cognitive function, history of drug or alcohol abuse <1 year, or other conditions.</td></tr>
<tr><td colspan="3">Patient characteristics [10] Intervention group
Age 54.8 ±9.6
Men 52.3%
Duration diabetic 12.7 ±10.0
Risk group 2 26 (59%)
Risk group 3 18 (41%)
History amputation 1(5th toe)
Risk category mean 2.41 ±0.50
VPT (left) 33.8 ±10.4
VPT (right) 35.9 ±11.3</td><td colspan="2">Comparator group(s) –
Age 55.0 ±9.3
Men 48.8%
Duration diabetic 14.8 ±11.5
Risk group 2 26 (59%)
Risk group 3 18 (41%)
History amputation 1 (2nd toe)
Risk category mean 2.41 ±0.50
VPT (left) 35.9 ±9.1
VPT (right) 36.5 ±8.6</td></tr>
<tr><td colspan="3">Length of follow-up [11]
6 months</td><td colspan="2">Outcome(s) measured [12]
Incident of foot ulcer, infections, charcot fractures and amputation</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
random</td><td>Comparison of study groups [14]
Non significant differences</td><td>Blinding [15]
Physician blinded for therapy</td><td>Treatment/ measurement bias [16]
Both groups received standard treatment.</td><td>Follow-up (ITT) [17]
Dropout
1 in enhanced group
4 in standard group</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18]</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td rowspan="2">Outcome [19]
Foot ulceration and Charcot fractures</td><td rowspan="2">Intervention group [20]
Foot ulcer = 1
Charcot fracture= 0</td><td rowspan="2">Control group [21]
Foot ulcer = 7
Charcot fracture= 2
x^2=6.63, p= 0.01</td><td rowspan="2">Measure of effect/effect size [22]
OR= 10.3
95% CI [25]
1.2-85.3</td><td>Benefits (NNT) [23]
95% CI [25]</td></tr>
<tr><td>Harms (NNH) [24]
95% CI [25]</td></tr>
<tr><td></td><td colspan="2">Clinical importance (1-4) [26]</td><td colspan="2">Relevance (1-5) [27]</td></tr>
<tr><td colspan="5">Any other adverse effects [28] no</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29]</td></tr>
</table>

Applicability [30]
Comments [31]

STUDY DETAILS		
Reference [1] Margolis, D. J., L. Allen-Taylor, et al. (2002). "Diabetic neuropathic foot ulcers - The association of wound size, wound duration, and wound grade on healing." Diabetes Care 25(10): 1835-1839.		
Affiliation/source of funds [2] Department of Dermatology, and department of biostatistics and epidemiology, university of Pennsylvania school of medicine US		
Study design [3] Prospective cohort	Level of evidence [4] II	Location/setting [5] Curative Health Centres >150 districts in 38 states in US
Patient characteristics [10] Male/ female Age (years) Grade ≤2 Mean duration of wound Median duration of wound Log mean duration wound Mean Wound size Median wound size Log mean wound size	No (%) or Mean (SD from reference value) 53.9/ 20.5% 63.8 (mean) 76.2% 5.39 months 1.0 months 0.48 months (1.39 SD) 588.6mm^2 118.0mm^2 4.86l ogmm^2 (1.68 SD)	Sample size [7] 31106 individuals, 72525 ulcers Length of follow-up [11] 20 weeks
Selection criteria Inclusion criteria : diabetic patients with foot ulceration seen in Curative Health Service (CHS) between 1988 and 2000 and at least one DNFU Exclusion criteria : individuals with significant lower limb arterial disease (absence response 10-SWF, flow abnormalities with $TcPo_2$ monitoring or arterial Doppler), subject with only one visit or documentation of surgical procedure within 6 weeks of the first visit.		
Prognostic factor(s): CHS wound grade scale Patient age, patient sex, duration of wound, size of wound, number of wounds, prior care at CHS.	Data collection method Grade 1: partial thickness involving only dermis and epidermis Grade 2: Full thickness and subcuteous tissue Grade 3: Grade 2 plus exposed tendons, ligament, and/or joint Grade 4: Grade 3 plus abscess and/or osteomyelitis Grade 5: Grade 3 plus necrotic tissue in wound Grade 6: Grade 3 plus gangrene in the wound and surrounding tissue	
Potential confounders: Mention of not included body weight, ulcer location, degree of foot deformation the use or compliance to treatments used for diabetes, fasting blood glucose etc.		
INTERNAL VALIDITY		
Outcome measurement method [12] Healed at 20th week.	Comparison of study groups [14] No assessment	Blinding [15] N/A
Measurement bias [16] For the measurement of wound size, the article does mention that there might be some bias due to under measurement of wound size.	Follow-up (ITT) [17] unclear	
Overall quality assessment (descriptive) [18] The study does not provide information about the drop outs and have not compared the4 group with source or drop out population.		
RESULTS		
Outcome [19] At 20 weeks 50.3% of wounds healed.	Quality assessment: +	
outcome [19]	Measure of effect/effect size + 95% CI [22]	

Healed wounds (not individuals)	
Grade 1	63.8% (n=46271)
Grade 2	55.3% (n= 40106)
Grade 3	39.3% (n= 28502)
Grade 4	32.9% (n= 23861)
Grade5	21.3% (n= 15448)
Grade 6	8.5% (n= 6165)
Grade ≤2	55.9% (n= 40541
Grade ≥3	32.6% (n= 23643)
EXTERNAL VALIDITY	
Generalisabilty:	
Comments: In the study there were patients included that received treatment before at the centre. These patients were more likely to be succesfull again compared to the new patients. This might give bias.	

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] McCabe, C. J., R. C. Stevenson, et al. (1998). "Evaluation of a diabetic foot screening and protection programme (Structured abstract)." Diabetic Medicine 15(1): 80-84.</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2]
Department of Health UK</td></tr>
<tr><td colspan="2">Study design [3]
Single blinded randomized clinical trial</td><td colspan="2">Level of evidence [4]
Level II</td><td colspan="2">Location/setting [5]
Department of Orthopaedic Surgery at the Royal Liverpool University Hospital, UK</td></tr>
<tr><td colspan="3">Intervention [6]
Foot screening (SWM, biothesiometer, palpation pedal pulse, ankle-brachial index, subcutaneous oxygen levels and foot pressure and x-ray) +foot protection program
Sample size [7]
1001</td><td colspan="3">Comparator(s) [8]
Normal care (Chiropody service and protection for damaged tissue)

Sample size [9] 41
1000</td></tr>
<tr><td colspan="6">Selection criteria
Inclusion criteria : Diabetes I and II patients who visit a weekly general diabetic clinic
Exclusion criteria : -</td></tr>
<tr><td colspan="3">Patient characteristics [10] Intervention group
Mentioned in other article</td><td colspan="3">Comparator group(s) –
Not elsewhere mentioned</td></tr>
<tr><td colspan="3">Length of follow-up [11]
2 years</td><td colspan="3">Outcome(s) measured [12]
Incident of foot ulcer, major and minor amputation</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Random, except for 4 patients with active foot ulcer</td><td>Comparison of study groups [14]
N/A</td><td>Blinding [15]
N/A</td><td>Treatment/ measurement bias [16]
Same basic normal care</td><td colspan="2">Follow-up (ITT) [17]
Control 469
Index 678</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18]
There is no information on blinding and differences between index and control group. The characteristics of the index group were retrieved from other article.</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="2">Outcome [19]
Foot ulceration and amputation</td><td>Intervention group [20]
Foot ulcer = 24
Minor amputation= 6
Major amputation= 1
Total amputations= 7</td><td>Control group [21]

Foot ulcer = 35
Minor amputation= 13
Major amputation= 12
Total amputation= 23</td><td>Measure of effect/effect size [22]
Foot ulcer : RR = 0.69 [95% CI 0.41, 1.14], P>0.14
Minor amputation: RR = 0.46 [95% CI 0.18, 1.21], P>0.15
Major amputation: RR = 0.08 [95% CI 0.01, 0.64], P<0.01
Total amputation: RR = 0.30 [95% CI 0.13, 0.71], P<0.04</td><td colspan="2">Benefits (NNT) [23]
Foot ulcer = 91 [95% CI -250, 38]
Minor amputation = 143 [95% CI -542, 60]
Major amputation = 91 [95% CI 244, 50]
Total amputation = 62 [95% CI 185, 36]

Harms (NNH) [24]

95% CI [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26]</td><td colspan="3">Relevance (1-5) [27]</td></tr>
<tr><td colspan="6">Any other adverse effects [28] no</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisabilty [29]</td></tr>
<tr><td colspan="6">Applicability [30]</td></tr>
</table>

Comments [31]

Question 2

STUDY DETAILS		
Reference [1] Abbott, C. A., A. L. Carrington, et al. (2002). "The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort." Diabet Med 19(5): 377-384.		
Affiliation/source of funds [2] Diabetes Foot Clinic, Disablement Services Centre, Whitington hospital, Medical Statistics Research Support Unit, University of Manchester and university department of Medicine, Manchester Royal infirmary. UK		
Study design [3] Prospective cohort study	Level of evidence [4] Level II	Location/setting [5] GP practice setting in six health districts in North west England.
Selection criteria Inclusion criteria : patients with type I or II diabetes Exclusion criteria :		
Patient characteristics [10]		Sample size [7] 9710
Age years	61.3±14.1	
Diabetes duration (years)	8.9±11.1	
Male	53.8%	
Socio economic class		Length of follow-up [11] 2 years
Professional	145 (1.6%)	
Intermediate	1086 (12.1%)	
Skilled	4588 (51.2%)	
Partly skilled	1334 (14.9%)	
Unskilled	1812 (20.2%)	
Ethnicity		
White Caucasian	8508 (87.6%)	
African-Caribbean	260 (2.7%)	
South Asia	920 (9.5%)	
Other	22 (0.2%)	
Live alone	2137/9361 (22.8%)	
Blind/ impaired vision	1324/9619 (13.8%)	
Nephopathy	254/9541 (2.7%)	
Neuropathy disability score ≥6	2171/9688 (22.4%)	
10g monofilament insensitivity	1978/9476 (20.9%)	
≤2 pedal pulses	2043/9699 (21.1%)	
Prognostic factor(s):	Data collection method	
Cutaneous pressure perception	SWF 1,10, 75gramat three valid plantar sites(1st, and 5th metatarsal heads and the heel) on each foot. With eyes closed patient confirms touché. Commencing with the 1g followed by 10 and 75 if not felt. Absence is defined as not feeling 10g.	
Peripheral neuropathy (neuropathy symptom score) Neuropathy disability score (NDS)	Vibration sensation measured with 128Hz Tuning fork dorsal temperature sensation using warm cold rods and Achilles tendon reflex	
Six Point foot deformity score	Small muscle wasting, charcot foot deformity, bony prominence, hammer or claw toes, limited joint mobility	
PVD	Palpation of the dorsal pedis and posterior tibial pulses on both feet	
Potential confounders:		
INTERNAL VALIDITY		
Outcome(s) measured [12] Foot ulceration that took > 14 days to heal.	Comparator(s) [8] Observation of foot ulcer	

Measurement bias [16] High risk patients received foot evaluations, shoes, education.	Follow-up (ITT) [17] 70%	
Overall quality assessment (descriptive) [18] Study provides very detailed information; drop outs and non responders (+reason) are compared to responders, large population, reasonable low attrition		Quality assessment: ++
RESULTS		
Results: In two years 291 out of 6613 patients developed ulceration (4.4%)		
Groups	Relative risk (univariate)	Relative risk (multivariate)
Neuropathy symptom score (5-9 vs 0-4)	1.94 [1.54, 2.43]	
Neuroppathy disability score (6-10 vs 0-5)	6.28 [4.93, 7.99]	2.32 [1.61, 3.35]
Vibration sensation Abnormal one side vs normal Abnormal two side vs normal	 2.41 [1.69, 3.43] 4.95 [3.83, 6.39]	
Ankle reflex score Present with reinforcement 1 side Present with reinforcement both sides Absent 1 side/ reinforcement 1 side Absent both sides	 0.48 [0.12, 1.98] 2.88 [1.88, 4.39] 4.86 [2.77, 8.53] 5.12 [3.75, 6.98]	 0.40 [0.10, 1.65] 1.99 [1.26, 3.12] 2.25 [1.24, 4.10] 1.55 [1.01, 2.36]
Foot deformity score (3-6 vs 0-2)	2.65 [2.04, 3.22]	1.57 [1.22, 2.02]
Monofilament insensitive 10g	4.82 [3.82, 6.07]	1.80 [1.36, 2.39]
Foot pulses (number max 4) 3 2 1 0 0-2	 1.52 [1.02, 2.26] 2.51 [1.87, 3.37] 4.03 [2.54, 6.37] 4.72 [3.28, 6.78]	 1.80 [1.40, 2.32]
EXTERNAL VALIDITY		
Generalisabilty [29] Abbott et al had a large proportion of patients of low socio economic status		
Applicability [30] study came from the UK which has similar health care for diabetes patients compared to the Australian health care context.		
Comments [31]		

STUDY DETAILS		
Reference [1] Adler, A. I., E. J. Boyko, et al. (1999). "Lower-extremity amputation in diabetes: the independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers." Diabetes Care 22(7): 1029-1035.		
Affiliation/source of funds [2] Health Service Research and Development Program, The medical service and the Seattle Epidemiologic Research and Information Centre, Veterans Affairs Puget Sound Health Care System and the Department of Medicine and Orthopaedic Surgery, University of Washington, Seattle.		
Study design [3] Prospective cohort study	Level of evidence [4] Level II	Location/setting [5] Internal medicine clinic of Veteran Affairs Puget Sound, WA
Selection criteria Inclusion criteria : patients with type I or II diabetes diagnosed by physician Exclusion criteria : patient too ill to participate, who could not walk 50 feet and who were unable or declined to consent		
Patient characteristics [10] Male White Medium age Type II DM Receive insulin treatment DM duration medium	 98.2% 78% 65 years (28-91) 93% 47% 9 years	Sample size [7] 776 Length of follow-up [11] Mean 3.3 years (0-5.8 years)
Prognostic factor(s):	Data collection method	
Peripheral sensory neuropathy	SWF 10gram at nine (eight plantar sites and one dorsal) sites on either foot	
Peripheral Vascular Disease	Absent or diminished DP and PT pulses to palpation in the same limb, AAI≤0.8 (ankle arm index) in either foot, or $TcPo_2$ ≤50mmHg in either foot at dorsum foot	
Glycosylated haemoglobin	≥12.6%	
Creatinine	>1.3 mg/dl	
AAI	AAI was calculated as the ratio of the ankle systolic pressure (defined as the higher of the posterior tibialis or the dorsalis pedis measurement) divided by the higher brachial systolic pressure.	
Duration diabetes, treatment insuline, DM type I, Lower extremity history(ulcer, previous LEA, arterial bypass, smoking, infection LE, blisters, orthopaedic shoe		
Potential confounders:		
INTERNAL VALIDITY		
Outcome(s) measured [12] Lower extremity amputation	Comparator(s) [8] Observation of foot ulcer or amputation	
Measurement bias [16]	Follow-up (ITT) [17] ±90%	
Overall quality assessment (descriptive) [18] Not for every assessment data is available of all participants.		Quality assessment: +
RESULTS		
Results: In 3.3 years 30 patient underwent LEA		

Groups	sensitivity	Specificity	Positive predictive value	Negative Predictive value
Peripheral sensory neuropathy (n=770)	83.3% (25/30) [64.5, 93.7]	50.8% (376/740) [47.1, 54.5]	6.4% (25/389) [4.28, 9.46]	98.7% (376/381) [96.8, 99.5]
AAI≤0.8 (n=690)	52% [95%CI 33, 70%]	74% [95%CI 70, 77%]	8% [95%CI 4.6, 13%]	97% [95%CI 95, 98%]
$TcPo_2$ ≤50mmHg (n=698)	76% [95%CI 56, 89%]	52% [95%CI 48, 56%]	6.4% [95%CI 4.8, 9.6%]	98% [95%CI 96, 99]
DP and PT pulse (n=690)	48% (14/29)	77% (508/661)	8% (14/167)	97% (508/523)
HbA1 9.6-12.6% (n=771)	67% [95%CI 43, 85%]	51% [95%CI 46, 55%]	5.3% [95%CI 3.0, 8.9%]	97% [95%CI 94, 99%]
HbA1 ≥12.6% (n=771)	56% [95%CI 31. 79%]	53% [95%CI 48, 57%]	3.8% [95%CI 1.8, 7.2%]	97% [95%CI 94, 99%]
Creatinine (n=774)	50% (15/30)	62% (464/744)	5% (15/295)	97% (464/479)

Groups	Amputation	Minor amputation	Major amputation
Peripheral sensory neuropathy	RR= 2.9 [1.1, 7.8]	RR= 5.4 [1.2, 24.7]	RR= 3.4 [0.7, 16.3]
AAI≤0.8	-	RR=2.6 [0.7, 9.3]	RR=5.8 [1.6, 20.4]
$TcPo_2$ ≤50mmHg	RR= 3.0 [1.3, 7.1]	-	-

EXTERNAL VALIDITY
Generalisabilty [29] only generalisable to male diabetics not female.
Applicability [30] The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.
Comments [31]

STUDY DETAILS				
Reference [1] Ahroni, J. H. (1997). The evaluation and development of diabetic foot risk stratification tools, Walden University: 206 p.				
Affiliation/source of funds [2] Veteran's affairs Merit Review Rehabilitation Research and Development Grant A318-3RA and the National Service Fellowship Grant. PhD at Walden university				
Study design [3] Prospective cohort study	Level of evidence [4] Level II	Location/setting [5] Internal medicine clinic of Veteran Affairs Puget Sound Health Care, Seattle		
Selection criteria Inclusion criteria : subject with DM Exclusion criteria : Patients with foot ulcer at baseline and or without completed baseline data				
Patient characteristics [10]	All subjects	High risk (HDC)	Low risk (HDC)	Sample size [7] 778
Age (years)	63.4±9.9	64.4±9.1	61.7±11.0	
Race				
White	567 (78%)	371 (81%)	196 (72%)	Length of follow-up [11] Mean 2.6 years ±1.4SD
African American	118 (16%)	60 (13%)	58 (21%)	
Native American	11 (2%)	8 (2%)	3 (1%)	
Asian pacific islander	17 (2%)	10 (2%)	7 (3%)	
Hispanic or Latino	10 (1%)	7 (2%)	3 (1%)	
Other	7 (1%)	3 (1%)	4 (2%)	
Male	715 (98%)	455 (99%)	260 (96%)	
IDDM	46 (6%)	26 (6%)	20 (7%)	
NIDDM	672 (92%)	428 (93%)	244 (90%)	
Other DM	12 (2%)	5 (1%)	7 (3%)	
DM duration (years)	11.4±9.7	12.3±10.1	9.7±8.7	
Treatment DM				
Diet	88 (12%)	49 (11%)	39 (14%)	
OHA	300 (41%)	165 (36%)	135 (50%)	
Insulin	342 (47%)	245 (54%)	97 (36%)	
HbA1c (%)	11.2±3.3	11.4±3.4	10.9±3.2	

Prognostic factor(s):	Data collection method
ADA clinical practice recommendations	High risk: patients with neuropathy, vascular disease, structural deformity, abnormal gait, skin or nail deformities, history of ulcer, poor understanding of casual compliance, Low risk: patient with none of the above
HDC risk assessment (loss of protective sensation, structural deformity, callus, history of ulceration, history of amputation, vascular disease)	A four level risk categorization. 0= patient without loss of protective sensation, 1= loss of protective sensation, but without weakness, deformities, callus, pre ulcer or history of ulceration, 2= loss of protective sensation and any weakness, deformities, callus, pre ulcer or history of ulceration, 3=patient with history of ulceration or ischemic index less then 0.45. Two level: low risk = 0 and 1, high risk = 2and 3.
Revised HDC risk assessment (callus and AAI were eliminated and deformities were revised)	
Seattle risk assessment (foot ulcer)	Assessment of neuropathy, history of amputation, absent toe vibration, insulin treatment and history of ulceration.
Loss of protective sensation	SWF 10gram at nine (eight plantar sites and one dorsal) sites on either foot
Peripheral Vascular Disease	Absent or diminished DP and PT pulses to palpation in the same limb, AAI≤0.8 (ankle arm index) in either foot,
Achilles tendon reflex	
Vibration sensation	at great toe
AAI	
Gender, age, race, blood sugar control, diabetes type, Dm treatment, DM duration, history of DM complications, laser photocoagulation, poor vision, symptoms of numbness, smoking history	

Potential confounders:

INTERNAL VALIDITY

Outcome(s) measured [12]	Comparator(s) [8]
Full thickness cutaneous foot ulcer below the ankle present for at least 14 daysor lower extremity amputation.	Observation of foot ulcer or amputation
Measurement bias [16]	Follow-up (ITT) [17] 94%

Overall quality assessment (descriptive) [18]	Quality assessment:
Not for every assessment data is available of all participants.	++

RESULTS

Results:

ADA clinical practice recommendations provided no information on risk of foot ulceration or amputation in this diabetes cohort., because in the all subjects would fall into the high risk category based on the ADA.

118 subjects developed ulceration and 21 subjects had a lower extremity amputation.

Outcome: ulceration

Groups	sensitivity	Specificity	PL ratio	NL ratio	Positive predictive value	Negative Predictive value
Two level HDC risk assessment	94.0%	43.1%	1.65	0.14	24.2%	97.4%
Revised HDC risk assessment	90.7%	48.5%	1.76	0.19	25.4%	96.4%

Seattle risk assessment	65.1%	75.4%	2.64	0.46	36.2%	90.9%
Vibration sensation (toe)	76.7%	54.9%	1.70	0.42	26.8%	91.6%
Absent Achilles tendon reflex	35.3%	54.3%	0.77	1.19	13.0%	81.3%
HbA1c ≥10%	31.4%	57.1%	0.73	1.20	12.4%	81.1%
Abnormal gait	17.0%	74.2%	0.66	1.12	11.2%	82.3%
Outcome: Amputation						
Assessment	sensitivity	Specificity	PL ratio	NL ratio	Positive predictive value	Negative Predictive value
Two level HDC risk assessment	100%	38.2%	1.62	0.00	4.6%	100%
Revised HDC risk assessment	100%	43.4%	1.77	0.00	5.0%	100%
Seattle risk assessment	100%	54.3%	2.19	0.00	5.9%	100%
Vibration sensation (toe)	88.9%	50.5%	1.80	0.22	5.4%	99.3%
Absent Achilles tendon reflex	40.0%	55.8%	0.91	1.07	2.5%	97.0%
HbA1c ≥10%	42.9%	59.0%	1.05	0.97	3.0%	97.2%
Abnormal gait	9.5%	75.2%	0.38	1.20	1.1%	96.6%
Assessment		Odds ratio Ulceration			Odds ratio amputation	
Neuropathy (SWF)		3.15 [1.77, 5.57]			ns	
Vibration sensation (toe)		2.01 [1.22, 3.64]			ns	
EXTERNAL VALIDITY						
Generalisabilty [29] The study included patients attending foot or diabetes clinics, which makes the results fairly generalisable to the target population. However, the sample mainly included male which may make it difficult to generalise to the results to females.						
Applicability [30] The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.						
Comments [31]						

STUDY DETAILS		
Reference [1] Boyko, E. J., J. H. Ahroni, et al. (1999). "A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study." Diabetes Care 22(7): 1036-1042.		
Affiliation/source of funds [2] Department of Medicine and Orthopaedic Surgery, University of Washington and the research and Development Service, Veterans affairs Puget Sound Health Care System, Seattle, Washington US		
Study design [3] Prospective cohort study	Level of evidence [4] Level II	Location/setting [5] Internal medicine patients at veterans Affairs Medical centre, Washington US
Selection criteria Inclusion criteria : patients with diabetes Exclusion criteria : current foot ulcer bilateral foot amputation, wheelchair bound or unable to walk, too sick to participate and psychiatric illness that prevented informed consent.		
Patient characteristics [10] Intervention group Age 63.2 years Male 98% Diabetes type II 93.6% Diabetes duration (years) 11.4		Sample size [7] 749 veterans, 1483 lower limbs Length of follow-up [11] Mean 3.7 years

Prognostic factor(s):	Data collection method
Semmes Weinstein monofilament 5.07	Testing on nine location on the foot. Inability to sens one or more sites on the foot= presents of peripheral sensory neuropathy
Vibration sensation	Measured with 128Hz Tuning fork on plantar hallux. Absence when patient could not sens vibration while examiner could.
Reflex	Achilles tendon reflex tested in seated position
$TcPo_2$	Lower limb transcutaneous O_2 tension measured with TCM-3 monitors (Radiometrer, Copenhagen) on the dorsal foot proximal of second toe and plantar hallux.
Ankle blood pressure	Measured with Doppler blood pressure. Cut off point at 200mmHg
Ankle arm index	Calculated as the ratio of ankle systolic pressure (dorsalis pedis and posterior tibialis) divided bythe higher brachialis systolic pressure.
Charcot deformity	
orthostatic blood pressure drop	Immediate systolic blood pressure response to standing from a supine position.
Two measures for cardiovascular autonomic neuropathy, blood sample for plasma glucose, serum glycosyled hemoglobulin, serum creatinine and erythrocyte sedimentation rate, weight height, duration diabetes, type II diabetes, insuline use, glucose, claudication, clinician diagnosis PVD/ neuropathy, history ulcer/amputation/ bypass, , vision	

Potential confounders: Not specified but taken in account.

INTERNAL VALIDITY	
Outcome(s) measured [12] Foot ulceration that took > 14 days to heal and first ulcer occurring on the foot.	Comparator(s) [8] Observation of foot ulcer

Measurement bias [16]			Follow-up (ITT) [17] 77%	
Overall quality assessment (descriptive) [18]				Quality assessment: ++
RESULTS				
Results: 162 ulcers developed over 5442.6 cumulative person years (3.0/100 person years)				
Groups	univariate	Multivariate without orthostatic blood pressure drop[#]	Multivariate with orthostatic blood pressure drop[†]	Non significant in multivariate*
Ankle blood pressure >200mmHg	RR 0.74 [0.62, 0.89]	RR 2.17 [1.52, 23.08]	RR 1.96 [1.36, 2.83]	
AAI <0.8 AAI ≤0.5 AAI >0.5 ≤0.8	RR 0.80 [0.68, 0.95]	 1.94 [95%CI 1.07, 3.52] 1.68 [95%CI 1.14, 2.48]		
$TcPo_2$ >15mmHg	RR 0.74 [0.64, 0.85]	RR 0.80 [0.69, 0.93]	RR 0.77 [0.66, 0.90]	
Semmes Weinstein monofilament 5.07 insensitive	RR 3.37 [2.45, 4.63]			
Vibration sensation absent	RR 2.33 [1.66, 3.28]			RR 1.28 [0.85, 1.91]
Reflex absent	RR 1.40 [1.03, 1.90]			RR 1.16 [0.84, 1.61]
Total hallux dorsal and plantar joint mobility	RR 0.77 [0.65, 0.90]			RR 0.89 [0.75, 1.05]
Charcot deformity	RR 3.62 [1.59, 8.23]	RR 3.49 [1.22, 9.92]	RR 2.74 [0.77, 9.76]	
orthostatic blood pressure drop	RR 1.36 [1.17, 1.58]		RR 1.23 [1.05, 1.45]	
[#] sensory neuropathy, history of ulcer/amputation insuline use, $TcPo_2$ >15mmHg, weight, Log (AAI), vision [†] sensory neuropathy, history of ulcer/amputation insuline use, $TcPo_2$ >15mmHg, weight, Log (AAI), vision and orthostatic blood pressure drop * Adjusted to Sensory neuropathy SWF, history foot ulcer/ amputation, insulin use, $TcPo_2$ >15mmHg, weight, charcot deformaties, vision and orthostatic pressure				
EXTERNAL VALIDITY				
Generalisabilty [29]p[opulation consisted of mainly males and was therefore slightly limited to generalise to the target population.				
Applicability [30] The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.				
Comments [31]				

STUDY DETAILS

Reference [1]

Boyko, E. J., J. H. Ahroni, et al. (2006). "Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study." Diabetes Care 29(6): 1202-1207.

Affiliation/source of funds [2]

Department of Medicine and Orthopaedic Surgery, University of Washington and the research and Development Service, Veterans affairs Puget Sound Health Care System, Seattle, Washington US

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective cohort study	Level II	Internal medicine patients at veterans Affairs Medical centre, Washington US

Selection criteria

Inclusion criteria : patients with diabetes

Exclusion criteria : current foot ulcer bilateral foot amputation, wheelchair bound or unable to walk, too sick to participate and psychiatric illness that prevented informed consent.

Patient characteristics [10]	no ulcer at follow up	Ulcer at follow up	Sample size [7]
Age (yrs) mean±SD	62.4±10.8	62.3±9.2	1285
Male (%)	98	98	
Race: white (%)	77	83	
Black	16	13	Length of follow-up [11]
Other	7	4	Mean 3.4 years
Weight (lb)	213.2±48.7	215.7±45.5	
Diabetes duration (years)	10.0±9.3	12.6±10.0	
Diabetes treatment: (%)			
Diet	11	7	
Insulin	38	60	
Oral medication	51	33	
A1C(%)	9.5±3.0	11.8±3.4	
Claudication			
None	72	60	
<1 block	14	21	
≥1 block	14	19	
Monofilament insensitivity (%)	33	60	
History foot ulcer (%)	20	51	
History of amputation (%)	3	14	
Abnormal foot shape (%)	40	50	
Callus present (%)	29	40	
Hallux limitus (%)	36	29	
Edema (%)	29	40	
Tinea pedis (%)	35	37	
Onychomycosis (%)	52	67	
Poor vision (%)	11	18	
Laser photocoagulation (%)	14	24	
Current smoker (%)	24	19	

Prognostic factor(s):	Data collection method
Semmes Weinstein monofilament 5.07	Testing on nine location on the foot. Inability to sens one or more sites on the foot= presents of peripheral sensory neuropathy
Foot deformities	Abnormal foot shape (high arch or dropped foot), hammer cloe toe, Charcor foot hallux limitus, pedal edema,callus, tinea pedis and Onychomycosis

Potential confounders:

Not specified but taken in account.

INTERNAL VALIDITY

Outcome(s) measured [12] Foot ulceration that took > 14 days to heal and first ulcer occurring on the foot.			Comparator(s) [8] Observation of foot ulcer			
Measurement bias [16] All patients measured similar			Follow-up (ITT) [17] 210 died and 277 lost at follow up. 78.4%			
Overall quality assessment (descriptive) [18] study is of good quality						Quality assessment: ++
RESULTS						
Results: 162 ulcers developed over 5442.6 cumulative person years (3.0/100 person years)						
Groups	univariate	Multivariate model*	sensitivity	specificity	PPV	NPV
Monofilament insensitivity	HR 3.1 [2.4, 4.1]	HR 2.0 [1.5, 2.7]	60% [54, 66]	67% [66, 68]	27% [24, 30]	89% [88, 91]
Abnormal foot shape	HR 1.9 [1.0, 3.5]					
Area under the curve for model*: 1 year follow up: 0.81 5 year follow up: 0.76 *Corrected for A1C, vison pore than 20/40, history of foot ulcer, history of amputation, tinea pedis and Onychomycosis						
EXTERNAL VALIDITY						
Generalisabilty [29]p[opulation consisted of mainly males and was therefore slightly limited to generalise to the target population.						
Applicability [30] The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.						
Comments [31]						

STUDY DETAILS			
Reference [1] Crawford, F., M. Inkster, et al. (2007). "Predicting foot ulcers in patients with diabetes: A systematic review and meta-analysis." QJM 100(2): 65-86.			
Affiliation/source of funds [2] Division of Community Health Science: General Practice Section, University of Edinburgh, UK			
Study design [3] Systematic review	Level of evidence [4] Level I		Location/setting [5] UK
Assessment[6] see results list Boyko et al (1999); Kastenbauer et al (2001) Litzelman et al (1997) Peters et al (2001) Pham et al (2000) Veves et al (1992) Murray et al (1996) Lavery et al (2003) Young et al (1994) Sample size [7] 5 case control (not taken into account), 11 cohort studies (only 9 with data for pooled estimate)	Sample size: 900 187 352 213 248 86 63 1666 469 Total : 4184		Comparator(s) [8] Observation of foot ulcer or amputation
Selection criteria Inclusion criteria : cohort or case control studies that evaluate the factors used to predict diabetic foot ulceration. Studie participants free of active foot ulceration at the time of study entry, all participants had diagnosis of Diabetes (type I or either type II) and outcome is foot ulceration Exclusion criteria : -			
Patient characteristics [10] NA			
Length of follow-up [11] 12 weeks to 4 years		Outcome(s) measured [12] Foot ulceration	

INTERNAL VALIDITY				
Allocation [13] N/A	Comparison of study groups [14] N/A	Blinding [15] U	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Overall quality assessment (descriptive) [18] Review did not present any patient characteristics				Quality assessment: ++

RESULTS			
Assessment	Study	Measure of effect/effect size unadjusted [95%CI]	adjusted [95%CI]
Peak plantar pressure (kg/cm² or N/cm²)	Pham et al (2000) Murray et al (1996) Kastenbauer et al (2001) Lavery et al (2003)	OR=3.2 [2.0,5.1] RR=4.7 [1.2, 18.9]	OR=2.0 [1.2, 3.3] RR=6.3 [1.2, 32.7] OR=2.0 [1.4, 2.9]
Vibration perception threshold	Pham et al (2000) Kastenbauer et al (2001) Boyko et al (1999) Young et al (1994)	OR=8.2 [7.4, 18.4] OR=2.33 [1.66, 3.28] OR=7.99 [3.65, 17.5]	OR=3.4 [1.7, 6.8] RR=25.4 [3.1, 205] OR=6.82 [2.75, 16.92]
Transcutaneous oxygen tension (≤30mmHg)	Boyko et al (1999)	RR=1.35 [1.18, 1.56	RR=1.25 [1.08, 1.45]

HbA $_{1c}$	Boyko et al (1999) Litzelman et al (1997)	RR=1.26 [1.11, 1.43] OR=1.08 [0.94, 1.24]	
Fasting blood glucose (mmol increase)	Litzelman et al (1997)	OR=1.00 [1.00, 1.00]	
Ankle Brachial Index	Boyko et al (1999)	RR=1.25 [1.05, 1.47]	RR=1.20 [1.04, 1.37]
Serum Creatine	Boyko et al (1999)	RR=1.16 [1.04, 1.29]	
Monofilament (SWF)	Boyko et al (1999) Kastenbauer et al (2001) Litzelman et al (1997) Peters et al (2001) Pham et al (2000) Veves et al (1992)	RR=3.37 [2.45, 4.63] OR=5.46 [2.39, 12.45] OR=5.4 [2.6, 11.6] OR=9.9 [4.8, 21.0]	RR=2.17 [52, 3.08] OR=5.23 [2.26, 12.13] OR=33.2 [5.6, 181.6] OR=2.4 [1.1, 5.3]
Absents reflex	Boyko et al (1999)	RR=1.40 [1.03, 1.90]	
Limited subtalar joint motion	Pham et al (2000)	OR=1.03 [1.00, 1.05]	
Limited 1st metatarsal-Phalangeal mation	Boyko et al (1999) Pham et al (2000)	RR=1.30 [1.11, 1.54] OR=1.05 [1.01, 1.03]	

Assessment	Pooled estimates WMD/SMD (95%CI)	Studies
Peak plantar pressure (kg/cm² or N/cm²)	SMD 0.47 [0.24, 0.70]	Lavery et al (2003), Pham et al (2000)
Vibration perception threshold	WMD 17.07 [13.89, 20.26]	Kastenbauer et al (2001), Pham et al (2000)
HbA $_{1c}$	1 [0.46, 1.5]	Boyko et al (1999)

Any other adverse effects [28]
EXTERNAL VALIDITY
Generalisabilty [29] assessed a general diabetic population
Applicability [30] systematic review included studies mainly undertaken in the USA. The health system in these countries is broadly similar to the Australian situation.
Comments [31] Only the results form the cohort studies are taken in account as case control studies are excluded for the review.

STUDY DETAILS			
Reference [1] Kastenbauer, T., S. Sauseng, et al. (2001). "A prospective study of predictors for foot ulceration in type 2 diabetes." J Am Podiatr Med Assoc 91(7): 343-350.			
Affiliation/source of funds [2] Institute of Metabolic diseases and Nutrition, Hospital Lainz, Austria and Third medical Department of Metabolic Disease and Nephrology, Vienna, Austria			
Study design [3] Prospective cohort study	Level of evidence [4] Level II	Location/setting [5] Yearly check-up at Outpatients Diabetes centre at Third Medical Department, Hospital Lianz, Vienna, Austria	
Selection criteria Inclusion criteria : type II diabetes (WHO criteria), age <75 years, had a normal gait pattern in which plantar pressure could be reliably measured. Exclusion criteria : no current or past foot ulceration (defined as full thickness skin lesions) or lower extremity amputations, severe pheripheral arterial disease (intermittent claudicatio), severe neurological deficits due to other diseases than diabetes; presence of any other cause of peripheral neuropathy (alcohol, drug use, malignancy and renal disease) and charcot foot			
Patient characteristics [10]	Normal VPT (n=135)	Elevated VPT (n=52)	Sample size [7] 187 consented of 236 eligible patients
Age	57.1±7.7	62.6±7.3	
Male /female	45.9/54.1	76.9/23.1	
Diabetes duration (years)	9.7±7.3	12.6±7.3	
Insulin use(%)	31.9	51.9	Length of follow-up [11] 3.6 years (yearly examination)
HbA1c (%)	9.7±1.6	9.4±1.5	
Serum creatinine (µm)	90.2±15.9	101.7±23.0	
Body weight (kg)	80.7±13.1	87.3±13.1	
BMI (kg/cm²)	29.1±4.5	29.1±4.2	
History of myocardial infarction (%)	5.9	15.4	
History of Angiography (%)	8.1	19.2	
Cigarettes smoking, current (%)	57.8	57.7	
Daily alcohol intake (%)	5.9	23.1	
Hammer/claw toe (%)	20.7	21.2	
/intrinsic muscle atrophy (%)	21.5	28.8	
Minor foot care (%)	6.7	9.6	
Hyperkeratosis at forefoot (%)\	55.6	48.1	
Limited joint mobility ankle (%)	33.3	51.9	
First foot ulceration (%)	0.7	17.3	
Mediasclerosis by x-ray (%)	14.1	40.4	
Skeletal abnormality x-ray (%)	8.1	19.2	
Nonproliferative retinopathy	30.4	48.1	
Symptomatic sensory NP (%)	31.1	55.8	
10g monofilament (%)	5.2	11.5	
AAI	1.07±0.16	1.04±0.20	
Cardiac autonomic NP	11.1	32.7	
Orthostatic BP drop (mmHg)	4.6±11.1	11.1±12.6	
Peroneal NCV	43.6±4.4	40.4±4.7	
MMP (kPa)			
Hallux	417±238	407±277	
Toe 2-5	180±80	179±91	
MTH 1	310±210	335±214	
MTH 2-5	553±247	654±299	
MPP elevated (%)	33.3	53.8	

Prognostic factor(s):	Data collection method
Vibration perception threshold	Biothesiometer (Biomedical, Newbury, Ohio), three times at the pulp of both great toes. Cut off point 25 Volt chosen based on the 90th percentile of the VPT at the great toe of 60 year old healthy subjects.
Monofilament perception	Semmes Weinstein monofilament 10g tested at eight plantar sited on each foot. Abnormal when subject could not feel at least two sites.
Plantar pressure	Means of measurement on the Novell SF platform device (Novel, Munich, Germany) For each patient one typical left and one typical right foot gait was selected out of five single steps.selection criteria were; consistency and distribution of plantar pressure at forefoot and the duration ofthe single step. The two typical steps were used to measure the Mean Plantar Pressure of the hallux, lesser toe, 1st metatarsal head and 2nd through 5th metatarsal hed. Abnormal when >2SD above the corresponding area of the foot in a healthy subject (control group)
Peripheral Vascular Disease	Non palpable foot pulse and ankle brachial index <0.8
Deformities	For both feet: Callus presence of hallux valgus, hammer or claw toes, intrinsic muscle atrophy
Peroneal neuropathy velocity, indicators of autonomic neuropathy by cardio respiratory reflexes and orthostatic drop of systolic pressure	
Potential confounders:	

INTERNAL VALIDITY		
Outcome(s) measured [12] Foot ulceration= full thickness neuropathic plantar or lateral forefoot ulcerations penetrating the Curtis and subcurtis.	Comparator(s) [8] Observation of foot ulcer	
Measurement bias [16] All patients were given instructions in foot care, those with elevated VPT and hyperkeratosis or had received minor foot care, were instructed to special attention to foot care	Follow-up (ITT) [17] 25 did not turn up at follow up (13%)	
Overall quality assessment (descriptive) [18] Study has a small sample size and even smaller ulceration number, which decreases the statistical power of the study.		Quality assessment: ++

RESULTS	
Results: in 3.6 years 10 patients developed 18 ulcers, nine of these patients had elevated VPT.	
assessment	Measure of effect/effect size [22] multivariate analysis
Vibration Perception Treshold elevated (>25 volt at hallux)	RR 25.4, [95%CI 3.1, 205]
Mean Plantar Pressure elevated (>2SD in at least one forefoot region)	RR 6.3, [95%CI 1.2, 32.7]

EXTERNAL VALIDITY
Generalisabilty [29] the study only included type II diabetes patients, while target population is type I and II.
Applicability [30]study came from Austria, which has a fairly similar diabetes care as in Asutralia.
Comments [31]

STUDY DETAILS					
Reference [1] Lavery, L. A., D. G. Armstrong, et al. (2003). "Predictive value of foot pressure assessment as part of a population-based diabetes disease management program." Diabetes Care 26(4): 1069-1073.					
Affiliation/source of funds [2]					
Study design [3] Prospective cohort study	Level of evidence [4] Level II	Location/setting [5] Large urban managed care based outpatient clinic, San Antonio USA			
Selection criteria Inclusion criteria : diagnosis of diabetes (ICD-9-CM) Exclusion criteria : -					
Patient characteristics [10] Intervention group Age 69.1±11.1 Male 50.4% Weight 83.8±19.7 kg Diabetes duration (years) 11.1±9.5 Peak plantar pressure (N/cm²) 86.6±27.4 Vibration perception threshold (V) 22.5±11.7				Sample size [7] 1666 Length of follow-up [11] 24 months (range 20-29)	
Prognostic factor(s): Peak plantar pressure (PPP)	Data collection method Novel's EMED force plate gait analysis system ((Novell, Minneapolis, MN). Two step method for each foot, measures pressure at resolution of ~4 pixels per square cm over the entire surface.				
Peripheral Sensory neuropathy	Vibration perception threshold >25V Semmes Weinstein monofilament 10g				
PVD	Non palpable foot pulse and ankle brachial index <0.8				
Deformities	Callus presence of hallux valgus, hammer or claw toes, tailors bunions, hallux rigidus and ankle equinus				
Potential confounders: Foot deformaties, Pressure time intergral, activity level, combination of shear forces on the foot and repetitive injury and callus formation					
INTERNAL VALIDITY					
Outcome(s) measured [12] Foot ulceration	Comparator(s) [8] Observation of foot ulcer				
Measurement bias [16] High risk patients received foot evaluations, shoes, education.	Follow-up (ITT) [17] Unclear				
Overall quality assessment (descriptive) [18]	Quality assessment: +				
RESULTS					
Results: in 24 months 263 patients developed foot ulcers (15.8%). PPP was higher in those with neuropathy, than those without. Peak plantar pressure was significant higher in patients who developed foot ulcerations during follow up. (95.5±26.4 vs 85.1±27.3 N/cm^2 , p<0.01) There was a significant trend (p,0.01) toward higher plantar foot pressure with increased risk category (categories = no neuropathy, 1= neuropathy, 2= neuropathy +deformity, 3=ulcer/amputation history)					
Groups	sensitivity	Specificity	Positive predictive value	Negative Predictive value	

In group with neuropathy with PPP ≥87.5 N/cm² cut point (excluded non neuropathy)	63.5%	46.3%	17.4%	90.4%	
assessment PPP ≥87.5 N/cm²	Measure of effect/effect size [22] OR 2.0 (1.4, 2.9), p<0.01				
Neuropathy	ROC= 0.57, p=0.03 (0.51, 0.62)				
EXTERNAL VALIDITY					
Generalisabilty [29] population is generalisable to the target population no caveats.					
Applicability [30] The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.					
Comments [31]					

STUDY DETAILS		
Reference [1] Leese, G. P., F. Reid, et al. (2006). "Stratification of foot ulcer risk in patients with diabetes: a population-based study." International Journal of Clinical Practice 60(5): 541-545.		
Affiliation/source of funds [2] Diabetes department , Ninewell hospital, university of Dundee, Ninewell hospital and medical school, Tayside Primary care Trust, Westgate Health Centre, Tayside Health Board, Kings Cross Hospital, Arthurstone Mill general practice, Dundee, Parth Royal infirmary, Perth UK		
Study design [3] Prospective cohort study	Level of evidence [4] Level II	Location/setting [5] Diabetes care in hospital and general practice-based diabetes clinic in Dundee and Perth, UK
Selection criteria Inclusion criteria : diagnosis of diabetes (WHO definition) Exclusion criteria : -		
Patient characteristics [10] Age (mean) Type II DM Diabetes duration (years) HbAc1	 64.7 years (range 15-101) 91% 8.8±8.1 7.5% (±1.5)	Sample size [7] 3526 Length of follow-up [11] 1.7 years (±0.9) (seen every 6 months)
Prognostic factor(s): Risk assessment tool	Data collection method Patient history: see or reach feet, history of ulcers Foot pulses: absence of both dorsalis pedis and posterior tibial pulse in either foot. Neuropathy: 10g monofilament sensation on more than one site of 10 on the plantar aspect of both feet. (1,2,3 and 5th metatarsal head and great toe) Foot deformities: change in foot shape that resulted in difficulty in fitting standard shoes, subjectively assessed by practitioner	
Risk categories	Low risk: no risk factors present Moderate risk: one risk factor High risk: those with two or more risk factors	
Potential confounders: Foot deformities, pressure time integral, activity level, combination of shear forces on the foot and repetitive injury and callus formation		
INTERNAL VALIDITY		
Outcome(s) measured [12] Foot ulceration defined by full thickness skin break below the l;evel of the malleoli	Comparator(s) [8] Observation of foot ulcer	
Measurement bias [16] Assessment was done twice by two different assessors. Results recorded in masked way and compared afterwards. Ulcers were only recorded if the patient seek help from professional for ulcer, might have caused some missed ulcers that healed within 6 months rescreening.	Follow-up (ITT) [17] Unclear	
Overall quality assessment (descriptive) [18] The study showed that there was no significant difference between the study population and general population.		Quality assessment: ++ / moderate
RESULTS		
Results: High risk developed ulcer 140 (29.4%), no ulcer 337 (70.6%) Moderate risk developed ulcer 18 (2.3%), no ulcer 778 (97.7% Low risk developed ulcer 8 (0.36%), no ulcer 2245 (99.6%) Total developed ulcer 166 (4.75), no ulcer 3360 (95.3%)		

Groups	sensitivity	Specificity	Positive predictive value	Negative Predictive value
High risk group vs moderate +low	84.3% [95%CI 77.7, 89.3]	90.0% [95%CI 89.0, 90.9]	29.4% [95%CI 25.4, 33.7]	99.1% [95%CI 98.7, 99.4]
High + moderate vs low	95.2% [95%CI 90.4, 97.7]	66.8% [95%CI 65.2, 68.4]	12.4% [95%CI 10.7, 14.4]	99.6% [95%CI 97.7, 99.4]
assessment high vs moderate and low	Measure of effect/effect size [22] OR= 48.3 [95%CI 31.3, 74.5]			
High and moderate vs low	OR= 39.8 [95%CI 19.5, 81.2]			
EXTERNAL VALIDITY				
Generalisabilty [29] population had no significant difference to the general population.				
Applicability [30] the assessment is very applicable to the foot clinic and general practice as is does not involve any complicated and expensive assessments.				
Comments [31]				

STUDY DETAILS			
Reference [1] Lehto, S., T. Rönnemaa, et al. (1996). "Risk factors predicting lower extremity amputations in patients with NIDDM." Diabetes Care 19(6): 607-612.			
Affiliation/source of funds [2] Departement of medicine , Kuopio University hospital, department of medicine, Turku university Central Hospital and the Social insurance Institution Turku, Finland			
Study design [3] Prospective cohort study	**Level of evidence** [4] Level II	**Location/setting** [5] Eats and west finland	
Selection criteria **Inclusion criteria** : patients classified as NIDDM according to WHO, born or living in district of west and east finland, aged 45-64 years **Exclusion criteria** : patient with IDDM and amputation before baseline			
Patient characteristics [10]	**Without amputation**	**With amputation**	**Sample size** [7]
N	986	58	1059
Age (years)	58.0±0.2	58.9±0.7	
Previous stroke	6.3	6.9	
Previous MI	10.6	6.9	**Length of follow-up** [11]
Retinopathy	3.6	12.2	7 years
Hypertension	62.4	74.1	
Sys/ dia blood pressure (mmHg)	152.3±0.8/ 85.7±0.4	195±3.2/ 87.2±1.6	
Urinary protein (mgl/l)	0.30±0.02	0.58±0.16	
Total cholesterol(mmol/l)	6.71±0.05	6.90±0.17	
HDL cholesterol (mmol/l)	1.22±0.01	1.14±0.04	
Triglycerides (mmol/l)	2.55±0.09	2.81±0.29	
HbA_1 (%)	9.8±0.7	11.1±0.3	
Plasma glucose (mmol/l)	11.5±0.1	14.2±0.5	
BMI (kg/m²)	29.3±0.2	28.3±0.6	
Smokling (%)	16.9	10.3	
Alcohol use (%)	37.9	29.3	
Diabetes duration (years)	7.9±0.1	9.6±0.5	
Claudication (%)	9.8	17.5	
Absence two or more peripheral artery pulses	24.7	58.6	
Gangrene of foot(%)	0.1	1.7	
Femoral artery bruit (%)	11.2	22.4	
Bilateral absence vibration perception (%)	22.6	44.8	
Bilateral absence Achilles tendon reflex (%)	27.2	62.1	
Prognostic factor(s):	**Data collection method**		
Fasting plasma glucose	Glucose oxidase method >13.4mmol/l abnormal (Boehringer Mannheim, Germany)		
HbA_1	Chromatography >10.7% abnormal		
Cholesterol	HDL (>0.9mmol/l) total (>6.2mmol/l)		
triglycerides	>2.3mmol/l		
Absence two or more peripheral artery pulses			
Achilles tendon reflex	Bilateral absence		
Vibration perception	Bilateral absence		
* All laboratory specimens were drawn after a 12h fast at 0800			
Potential confounders:			
INTERNAL VALIDITY			
Outcome(s) measured [12] Lower extremity amputation defined amputations performed due to arterosclerotic vascular disease based on diagnosis at the time of hospitalization.	**Comparator(s)** [8] Observation of LEA		

Measurement bias [16]			Follow-up (ITT) [17] 83% (west Finland group) 79% (east Finland group)	
Overall quality assessment (descriptive) [18] Study is of good quality				Quality assessment: ++
RESULTS				
Results: incidents of amputation in 7 years follow up 5.6% of men and 5.3% of females , 58 amputations; 31 toe, 17 below knee 10 above knee.				
assessment	Measure of effect/effect size [22] (age and sex adjusted)			
Total cholesterol (>6.2mmol/l)	RR 1.8 [1.1, 3.2]			
HDL cholesterol (>0.9mmol/l)	RR 1.3 [0.7, 2.5			
Triglycerides (>2.3mmol/l)	RR 1.4 [0.8, 2.4]			
Fasting plasma glucose (>13.4mmol/l)	RR 2.5 [1.5, 4.3	RR 2.5 [1.4, 4.3]*	RR 2.3 [1.3, 4.1]†	RR2.2 [1.2, 3.9]††
HbA_1 (>10.7%)	RR2.4 [1.4, 4.0]			
Absence two or more peripheral artery pulses	R+R 3.9 [2.3, 6.8]			
Femoral artery bruit on auscultation	RR 2.1 [1.1, 4.0]			
Achilles tendon reflex, bilateral absence	RR 4.3 [2.5, 7.3]			
Vibration perception bilateral absence	RR 2.7 [1.6, 4.7]			
* Adjusted for age, sex, area, previous MI, retinopathy, total cholesterol, smoking, BMI,hypertension † adjusted for * and urinary protein, HDL cholesterol, triglycerides, duration of diabetes †† adjusted for * and † and claudication, absence of two or more peripheral pulses, absence bilateral Achilles reflex, absence bilateral vibration sensation.				
EXTERNAL VALIDITY				
Generalisabilty [29] population was well described and therefore clearly generalisable to the target population.				
Applicability [30] The study took place in the finland, which has similar health care for diabetes patients compared to the Australia health care context.				
Comments [31]				

STUDY DETAILS		
Reference [1] Litzelman, D. K., D. J. Marriott, et al. (1997) Independent physiological predictors of foot lesions in patients with NIDDM. Diabetes Care 1273-1278		
Affiliation/source of funds [2] Health services research and development service, Richard L Roudebush Veterans Affairs Medical Center, The regenstief Institute for Health Care, Department of Medicine, Indiana university School of Medicine, Centers for Disease Control and prevention, Atlanta, Georgia.		
Study design [3] Prospective cohort study	**Level of evidence** [4] Level II	**Location/setting** [5] From RCT population US
Selection criteria **Inclusion criteria**: Patients with NIDDM who received primary health care from general practice that serves a municipal socioeconomic disadvantage population. >40 years, at or above ideal body weight diagnosed with NIDDM after age 30. **Exclusion criteria** : patients being pregnant, , had a major psychiatric illness, unable to provide any self care, renal failure, had a terminal illness likely to cause death within a year or were under care of the study investigator.		
Patient characteristics [10] African American Women Age (years) Annual income (<$10000 Educational level (years) BMI (kg/m²) Duration diabetes (years) Taking insulin Taking oral hypoglycaemic agents	 76% 81% 60.4±9.6 77% 9.7±2.8 33.7±7.3 9.9±8.1 49% 45%	**Sample size** [7] 395 **Length of follow-up** [11] 1 year
Prognostic factor(s):	**Data collection method**	
Monofilament	SWM touch/ pressure sensation with 10g (5.07log) using standard method. Abnormal pressure sensation was defined as absence at one or more of three sites (great toe, first and fifth metatarsal heads) tested on plantar site of each foot.	
Thermal sensitivity	Sensortek Thermal Sensitivity testing apparatus measures warm and cold sensation. Thermal sensation was defined as abnormal if the detection of temperature change was >2 SD's of the standard (healthy people) 25ºC (warm >2.04ºC above reference, cool > 1.58ºC below reference). Measured on the great toe using standard method.	
Total cholesterol		
HDL cholesterol (mmol/l)		
Triglyvcerides (mmol/l)		
Hemoglobulin A_{1c}		
Fasting blood glucose (mmol/l)		
Dermatologica	Dryness, cracks, fissures, ingrown nails,edema, fungal dermatitis, onychomycosis	
Potential confounders: -		
INTERNAL VALIDITY		
Outcome(s) measured [12] Existence of any foot wound in follow up time, rated with Seattle Wound classification system. Pateinet separated in result in to groups. Minor injury (≤1.2) and major injury (≥1.3)	**Comparator(s)** [8] Observation of foot ulcer	
Measurement bias [16] Eximanrs were blinded to patients' experimental condition, historic data.	**Follow-up** (ITT) [17] 89%	
Overall quality assessment (descriptive) [18] Study is of good quality		**Quality assessment:** ++

RESULTS				
Results: 63 patients had a blister or a wound graded between minor and full thickness. 30 patients had significant foot lesion, non ulcerated minor lesion to full thickness and 4 had amputation.				
assessment	Measure of effect/effect size [22]			
	Univariate SWC≥1.2	Univariate SWC≥1.3	Multivariate SWC≥1.2	Multivariate SWC≥1.3
Monofilament (5.07)	OR 3.37 [1.95, 5.80]	OR 5.46 [2.39, 12.45]	OR 2.75 [1.55, 4.88]	OR 5.23 [2.26, 12.13]
Thermal sensitivity	OR 2.82 [1.52, 5.25]	OR 3.04 [1.17, 7.88]	OR 2.18 [1.13, 4.21]	NS
Total cholesterol	OR 1.00[1.00, 1.00]	OR 1.00[1.00, 1.00]	ns	ns
HDL cholesterol	OR 1.19 [0.95, 1.50]*	OR 1.69 [1.18, 2.42]*	ns	OR 1.63 [1.11, 2.39]*
Triglycerides	OR 1.38 [0.93, 2.07]	OR 2.50 [1.44, 4.36]	ns	ns
Fasting plasma glucose	OR 1.00[1.00, 1.00]	OR 1.00[1.00, 1.00]	ns	ns
* based on a decreasing change in HDL of 386.7 mmol/l (10mg/l)				
EXTERNAL VALIDITY				
Generalisabilty [29] included a large proportion of patients with a low socio economic status, based on annual income.				
Applicability [30] The study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.				
Comments [31]				

STUDY DETAILS		
Reference [1] Pham, H., D. G. Armstrong, et al. (2000). "Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial." Diabetes Care 23(5): 606-611.		
Affiliation/source of funds [2] Departement of Medicine, Joslin Beth Israel Deaconess Foot centre and microcirculation Laboratory anddepartement of Surgery, Harvard Madical school, Boston, The division of Podiatry, Departement of Orthopedics, University of Texas Health Science Centre at San Antonio and the Californian College of Podiatric Medicine, San Francisco, California.		
Study design [3] Prospective cohort study	Level of evidence [4] Level II	Location/setting [5] Joslin Beth Israel Deaconess Foot centre and primary foot care clinic Boston, University Texas, Californian College of Podiatric Medicine, San Francisco, USA
Selection criteria Inclusion criteria : diagnosis of diabetes Exclusion criteria : -		
Patient characteristics [10] Intervention group Age 58±12 (20-83) Me/women 126/125 BMI 30.1±6.4 (15.4-57.1) Diabetes type (1/2) 49/ 199 Diabetes duration (years) 14±11 (1-54) History of Foot ulceration 87 NSS 3.9±4.1 (0-16) NDS 10±8 (0-28) VPT (V) 29±17 (1-51) SWF 5.4±1.4 (1.85-7.00) Maximal plantar pressure (kg/cm²) 5.71± 2.91 (1.50- 28.0)		Sample size [7] 248 Length of follow-up [11] Mean 30 months (range 6-40)
Prognostic factor(s):	Data collection method	
Neuropathy Symptom score (NNS); ≥3 abnormal	Questioned presence or absence of nocturnal exacerbation of muscle cramp, numbness, abnormal hot and cold sensations, tingling sensations, burning pain, aching pain and irritation from bed clothes in lower leg and foot.	
Neuropathy disability score (NDS) ≥5 abnormal	Physical examination Achilles/ patella tendon reflex (yes=0, no= 2) and sensory modalities, pinprick metal pointed or wooden pin, vibration with tuning fork, light touché with cotton ball and temp perception with cold water test tube. (score 1=failed to perceive stimulus at toe, 2= at midfoot, 3= at the heel, 4= at lower leg, 5=at the knee)	
Vibration Perception Threshold (VPT) ≥25V	Biothesiometer (biomedical Newbury, OH)vibration at 100hz, 0-50volt, mean of three readings. ≥25V risk of foot ulcer	
Semmes- Weinstein Filament (SWF) 5.07 SWF high risk ulceration	Set of 8 SWF's 1-100g applied to plantar espect of hallux. Inability to feel 5.07 SWF high risk ulceration	
Plantar foot pressure (PFP) ≥6kg/cm²	Fscan mat system (Tekscan, Boston, MA) mean reading of three, foot pressure ≥6kg/cm² at risk for foot ulcer.	
Joint mobility (JM)	Goniometer for total ROM at first metatarsophalangeal joint and subtalar joint. Average of three readings.	
Peripheral vascular disease (PVD)	Absence of foot pulses and or symptoms of claudication or a history of bypass operation.	
Potential confounders: Neuropathy and neuropathy symptoms limited Joint mobility, history of foot ulcer		
INTERNAL VALIDITY		
Outcome(s) measured [12] First incidence of foot ulcer	Comparator(s) [8] Observation of foot ulcer	

Measurement bias [16] Patients will go into a foot care program when at tested as high risk. This might influence the outcome of foot ulcer.		Follow-up (ITT) [17] 100%	
Overall quality assessment (descriptive) [18]			Quality assessment: ++
RESULTS			
Assessment	Measure of effect/effect size Sensitivity(%)	Specificty (%)	Positive predictive value (%)
High NDS	92	43	28
High VPT	86	56	32
High SWF	91	34	25
High foot pressure	59	69	31
High NDS and/or VPT	94	38	26
High NDS and/or SWF	99	22	23
High SWF and/or VPT	98	28	24
High NDS and/or foot pressure	58	78	38
assessment	Measure of effect/effect size [22] (multivariate; sex, duration DB, race and palpable pulses)		
High NDS	OR 3.1 (1.3, 7.6) p=0.013		
High VPT	OR 3.4 (1.7, 6.8) p=0.001		
High SWF	OR 2.4 (1.1, 5.3) p=0.036		
High foot pressure	OR 2.0 (1.2, 3.3) p=0.007		
Any other adverse effects [28] no			
EXTERNAL VALIDITY			
Generalisabilty [29] The study included a sample population attending foot or diabetes clinics, which makes them generalisable to the target population.			
Applicability [30] One study took place in the USA, which has similar health care for diabetes patients compared to the Australia health care context.			
Comments [31]			

STUDY DETAILS			
Reference [1] Veves, A., H. J. Murray, et al. (1992). "The risk of foot ulceration in diabetic patients with high foot pressure: a prospective study." Diabetologia 35(7): 660-663.			
Affiliation/source of funds [2] Diabetes Centre, Manchester Royal Infirmary, Manchester UK			
Study design [3] Prospective cohort study	Level of evidence [4] Level II	Location/setting [5] Manchester Diabetes Centre	
Selection criteria Inclusion criteria : diabetic patients attending clinics at Manchester Diabetes Centre Exclusion criteria : previous amputation, active foot ulcer or where unable to walk normally without aid for any reason			
Patient characteristics [10] Diabetic group N= 86 Age (years) (range) 53.4 (17-77) Weight 74.4 ±16.5 Male/female 61/25 Type i/ type II 36/50 Diabetes duration (years) (range) 16.8 (1-36)	Neuropathy group 58 56.3 (28-77) 74.8 ±17.2 71/17 25/33 19.1 (1-36)	Non neuropathy group 28 47.9 (17-66) 74.4 ±15.0 20/8 11/17 12.1 (1-32)	Sample size [7] 86 Length of follow-up [11] Mean 30 months (range 13-35)
Prognostic factor(s):	Data collection method		
Peak Plantar pressure	Measured with optical pedobarography under the metartasal heads, heel, the great toe and any other high area of pressure. >12.3kg/cm² is seen as abnormal Most normal gait footstep of three footsteps was measured		
Neuropathy NDS ≥5	Reduced or absence ankle reflex, reduced or absence sensation to pain, touché and vibration(Vibration perception threshold (Arnold Horwell, London, UK)) Average score of both feet was calculated. Neuropathy diagnosed if total score of reflex from both feet and the average sensory examination score was ≥5.		
Potential confounders: study excluded possible confounders by regular chiropody (callus removal),			
INTERNAL VALIDITY			
Outcome(s) measured [12] First incidence of foot ulcer	Comparator(s) [8] Observation of foot ulcer		
Measurement bias [16] Patients received foot education, chiropody care and appropriate foot wear as needed which might have influence on the development of ulcers over time when stated as high risk by the test.	Follow-up (ITT) [17] 64%		
Overall quality assessment (descriptive) [18] The study does not give sensitivity and specificity for the prediction of foot ulcer, but only reports absolute numbers.			Quality assessment: ++
RESULTS			
Results: After measuring plantar pressure in all three groups and a control groups at baseline and follow up, there were no significant different changes in any group and between groups			
Assessment	Measure of effect/effect size		

	Sensitivity(%)	Specificty (%)	Positive predictive value (%)	Negative predictive value (%)
High plantar peak pressure	100% (15/15) [CI95% 0.74, 1.00]	39% (28/71) [95%CI 0.28, 0.52]	26% (15/58) [95%CI 0.16, 0.39]	100% (43/43) [95%CI 0.85, 1.00]
Neuropathy + high plantar pressure	93% (14/15) [95%CI 0.66, 0.99]	39% (11/28) [95%CI 0.22, 0.59]	45% (14/31) [95%CI 0.28, 0.64]	92% (11/12) [95%CI 0.60, 0.99]
Any other adverse effects [28]				
EXTERNAL VALIDITY				
Generalisabilty [29] included diabetic patients (type I and II), with neuropathy and or history of ulceration, visiting foot or diabetes clinics, which makes them generelisable to the target population.				
Applicability [30] study took place in the UK, which has similar health care for diabetes patients compared to the Australia health care context.				
Comments [31]				

STUDY DETAILS

Reference [1]
Young, M. J., J. L. Breddy, et al. (1994). "The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds. A prospective study." Diabetes Care 17(6): 557-560.

Affiliation/source of funds [2]
Manchester Diabetes centre, Manchester Royal Infimary, asnd the Apllie Statistics Research Unit, University of Kent, Canterbury, UK

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective cohort study	Level II	Diabetes centre and foot clinic, Manchester UK

Selection criteria
Inclusion criteria: No history of foot ulceration and at least one pedal pulse in each foot.
Exclusion criteria : patients with ischemia

Patient characteristics [10] Intervention group
Age 53.7 (17-85)
Men/ women 228/241
Duration diabetic 12.4 (0-60 years)
Type II diabetes 58%
VPT<15V 209
VPT 16-24V 58
VPT>25V 202

Sample size [7]
469

Length of follow-up [11]
4 years

Prognostic factor(s):
VPT Vibration Perception Threshold (Arnold Horwell, London , UK) Reading at great toe with probe vertically on pulp of the toe. A mean of three readings was used for each foot

Data collection method
VPT<15V
VPT 16-24 V
VPT > 25V

Potential confounders:

INTERNAL VALIDITY

Outcome(s) measured [12]	Comparator(s) [8]
First incidence of foot ulcer	Observation of foot ulcer

Measurement bias [16]	Follow-up (ITT) [17]
No information on measurement bias	100%

Overall quality assessment (descriptive) [18]	Quality assessment:
	+

RESULTS

Groups	sensitivity	Specificity	Positive predictive value	Negative Predictive value	Odds ratio [95%CI]
VPT 16-24 V (reference VPT<15V)	25% [0.44, 0.64]	78% [0.72, 0.82]	3% [0.01, 0.13]	97% [0.93, 0.99]	1.21 [0.24,6.15]
VPT > 25V (reference VPT<15V)	87% [0.73, 0.95]	56% [0.5, 0.6]	20% [0.15, 0.26]	3% [0.03, 0.06]	7.99 [3.65, 17.5]
VPT >25V (reference VPT 16-24V)	95% [0.83, 0.99]	26% [0.20, 0.32]	20% [0.15, 0.26]	3% [0.01, 0.13]	6.91 [1.62, 29.5]
VPT >25V (reference VPT <25V)	83% [0.69, 0.92]	62% [0.57, 0.67]	20% [0.15, 0.26]	3% [0.01, 0.06]	8.24 [3.76, 18.0]

Any other adverse effects [28] no

EXTERNAL VALIDITY

Generalisabilty [29] included diabetes patients without ulcers and was generalisable to the target population.

Applicability [30] the Study took place in the UK., which has similar health care system for diabetes care to the Australian system and are therefore likely applicable for the Australian context
Comments [31]

Question 3

STUDY DETAILS

Reference [1]

Balsells, M., J. Viade, et al. (1997). "Prevalence of osteomyelitis in non-healing diabetic foot ulcers: usefulness of radiologic and scintigraphic findings." Diabetes Res Clin Pract 38(2): 123-127.

Affiliation/source of funds [2]

None reported

Study design [3]	Level of evidence [4]	Location/setting [5]
Cohort study	II	In patient setting, Spain

Patient characteristics [10]	Means ± SD or %	Sample size [7]
Age	65 ± 12 years	28 (33 episodes)
Male	12	
Ankle brachial index < 0.6	36%	Length of follow-up [11]
Neuropathy (vibration perception threshold > 30V)	29%	At least 12 months
Mixed vasculopathy and neuropathy	36%	
Previous amputation	25%	

Selection criteria

Inclusion criteria : - Not reported

Exclusion criteria : - Not reported

Predictor variable(s):	Data collection method
Osteomyelitis	Diagnosed by combined bone and leukocyte scans or plain x -ray

Potential confounders:

Vasculopathy, neuropathy, previous history

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Primary: Amputation	Not reported	Not reported

Measurement bias [16]	Follow-up (ITT) [17]
Not reported	100% (2 patients died but results/outcomes were still included)

Overall quality assessment (descriptive) [18]

The report of this study is limited by a lack of detail which markedly increases the potential for bias to be introduced. There is insufficient detail to indicate whether or not this was a retrospective or prospective study (which means the level of evidence applied earlier may be incorrect).

RESULTS

Outcome [19] Amputation		Quality assessment: SIGN: Poor QUADAS: Poor
Outcome [19]	Measure of effect/effect size + 95% CI [22] OR	Diagnostic accuracy
Combined bone and leukocyte scan		Sensitivity = 75% Specificity = 59%
Radiographic x-ray		Sensitivity = 69% Specificity = 88%
Osteomyelitis (no severe vasculopathy)	10.7 [1.7, 74]	
Osteomyelitis with severe vasculopathy	12 [0.5, 30]	
	Mantel-Hanzel OR = 11 [1.65, 74.2]	
Conclusion: This study suggests that patients with foot ulcer complicated by osteomyelitis are more likely to have poorer outcomes ie amputation. However, the substantially wide confidence intervals indicate that there is still significant uncertainty regarding the effect size.		
EXTERNAL VALIDITY		
Generalisabilty: This study can be generalisable to patients hospitalised with diabetic foot ulcer complications.		
Comments: This study is of poor quality, inadequately powered and poorly controlled in terms of potential confounders.		

STUDY DETAILS

Reference [1]

Rattan, R. and D. Nayak (2008). "High levels of plasma malondialdehyde, protein carbonyl, and fibrinogen have prognostic potential to predict poor outcomes in patients with diabetic foot wounds: a preliminary communication." Int J Low Extrem Wounds 7(4): 198-203.

Affiliation/source of funds [2]

None reported

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective cohort study	II	India. Setting is not reported.

Patient characteristics [10]		Means ± SD or %	Sample size [7]
Age		58.6 ± 7.3 years (range 50 - 70)	101 (61 with DFU)
Duration of diabetes		9.2 ± 3.8 years	
Males: Females		92:2	Length of follow-up [11]
BMI (kg/m^2)		26.3 ± 4.3	8 months
Systolic blood pressure (mmHg)		123 ± 13	
Diastolic blood pressure (mmHg)		77 ± 9	
Smoking (n)		18	
Site of ulcer -	Forefoot	22	
	Midfoot	4	
	Hind foot	33	
Grade of ulcer (Texas)	Grade 1	41	
	Grade 2	20	

Selection criteria

Inclusion criteria : - No episodes of ketoacidosis, > 30 years of age at diagnosis of diabetes, on insulin therapy if started on insulin after 5 years of diagnosis.

Exclusion criteria : - lower extremity amputation or vascular surgery, complications other than foot ulcer, clinical evidence of CVD, microalbuminuria and impaired renal function test. Females on hormone therapy were also excluded.

Predictor variable(s):	Data collection method
Plasma fibrinogen	Immunoturbimetric assay on plasma sample following overnight fast

Potential confounders:

Neuropathy, peripheral vascular disease.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Amputation	No significant differences were noted between diabetic patients with and without DFU	Not reported

Measurement bias [16]	Follow-up (ITT) [17]
All subjects appear to be measured in the same manner.	Not known if all patients had an 8 month follow-up

Overall quality assessment (descriptive) [18] It is difficult to determine which patients were included in the analysis. Outcomes appear to be reported only for subjects with Grade II foot ulcer. It is unclear if only these patients were included in the analysis of whether plasma fibrinogen predicts lower extremity amputation. Some uncertainty regarding the study design, the authors described it as a case-control study however, subjects do not appear to be selected based on outcome of amputation. Investigators have used restriction to control for potential confounders however, it is possible that the study has been confounder by other variables such as neuropathy or peripheral vascular disease.		
RESULTS		
Outcome [19] Amputation		Quality assessment: Poor
Outcome [19]	Measure of effect/effect size + 95% CI [22] AUC	
Plasma fibrinogen	0.976 [0.932, 1.019]	
Optimum cutoff value	300.4mg/dL (Sensitiviy = 100%, Specificity = 99.2%)	
Conclusion: These results suggest that the probability that a person who has undergone amputation would have a higher plasma fibrinogen score than a person who has not undergone an amputation, is 97.6%. However, it should be noted that the follow-up period for this study was relatively short (8 months) and therefore the most severe cases are likely to have undergone amputation. This study does not indicate that ability of plasma fibrinogen score to discriminate against people who would or would not undergo amputation in the longer term that is, beyond8 months.		
EXTERNAL VALIDITY		
Generalisabilty: It is difficult to make a judgement regarding the generalisability of this study as no information is given with respect to the setting or the actual patients included in the AUC analysis.		
Comments: This is a poor quality study which does little to inform of the value of plasma fibrinogen in predicting amputation in diabetic people with foot ulcer.		

DFU = diabetic foot ulcer; CVD = cardiovascular disease; AUC = area under curve

STUDY DETAILS

Reference [1]

Gul, A., A. Basit, et al. (2006). "Role of wound classification in predicting the outcome of diabetic foot ulcer." J Pak Med Assoc 56(10): 444-447.

Affiliation/source of funds [2]

PharmEvo (Pakistan)

Study design [3]	Level of evidence [4]	Location/setting [5]
Retrospective Cohort study	III-3	Baqai Institute of Diabetology and Endocrinology, Karachi, Pakistan

Patient characteristics [10]	Means ± SD or %	Sample size [7]
Males	65%	200
Age in males	53.0 ± 10.3	
Age in females	51.1 ± 9.9	Length of follow-up [11]
Duration of treatment - Males	109.7 ±82.3 days	Not reported
Females	85.1 ± 62.0 days	
Neuropathic ulcers	45%	
Neuro-ischaemic ulcers	54.5%	
Pure ischaemic ulcers	<1%	

Selection criteria

Inclusion criteria : - Diabetic subjects who visite the foot clinic at the Baqai Institute of Diabetology and Endocrinology from January 1997 to December 2003, whose medical records provided complete socio-demographic and clinical profiles.

Exclusion criteria : - Not reported

Predictor variable(s):	Data collection method
Wagner classification of diabetic foot ulcer	Grade 1 – superficial wound Grade 2 – deep wound involving tendons and capsules but not bone Grade 3 – bony involvement Grade 4 – localised gangrene Grade 5 – generalised gangrene
University of Texas classification of diabetic foot ulcer	Grade 1 – superficial wound Grade 2 – deep wound involving tendons but not bone Grade 3 – Bone involvement, localised and generalised gangrene Four stages in each grade; no infection or ischaemia (A); infection (B); ischaemia (C) and infection and ischaemia (D)

Potential confounders:

Presumably all potential confounders have been considered during the development of these classification systems.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Amputation	Not reported	Not reported

Measurement bias [16]	Follow-up (ITT) [17]
As a chart review of medical records, this is not known	Not reported

Overall quality assessment (descriptive) [18]

This study is limited by the retrospective nature of the study design. The follow up period is also unknown making the applicability of the results difficult to determine.

RESULTS		
Outcome [19] Amputation		Quality assessment: Poor
Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22] OR	
Wagner Grade 1 (referent) Grade 2 Grade 3 Grade 4 & 5	1.0 Not reported Not reported 45.5 [3.48, 594.68]	
University of Texas Grade 1 (referent) Grade 2 Grade 3 Grade 4 & 5	1.0 2.9 [0.37, 23.83] 9.5 [1.15, 77.27] Not reported	
University of Texas Stage A & B (referent) Stage C & D	 2.7 [1.31, 5.41]	
Conclusion: This study suggests that the Wagner and University of Texas classification systems for diabetic foot ulcer are able to classify foot ulcers according to their associated risk of amputation. The substantial width of the 95% confidence intervals suggest that there is significant uncertainty surrounding the exact effect size associated with the severity of foot ulcer. Additionally, the less severe foot ulcer grades may not be statistically significant in terms of amputation risk. It should be noted that these results have not been controlled for treatments received or other potential confounders and therefore may not be an accurate reflection of the predictive ability of these classification systems.		
EXTERNAL VALIDITY		
Generalisabilty: It is likely that these results are generalisable to the population of interest.		
Comments: Lack of control of potential confounders and the retrospective nature of the study have limited the results.		

STUDY DETAILS

Reference [1]

Oyibo, S., E. Jude, et al. (2000). "Comparison of two diabetic foot ulcer classification systems." Diabetes 49: 135.

Affiliation/source of funds [2]

None reported

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective cohort study	II	Two specialist diabetic foot clinics, Manchester, UK and San Antonio, Texas.

Patient characteristics [10]	Means ± SD or % or Median (interquartile range)
Age (years)	56.6 ± 12.6
Sex (M/F)	149/45
Diabetes (type 1 / type 2)	21/173
Ulcer size (cm^2)	1.48 (0.68 – 4.0)
Type of ulcer (underlying factor)	
Neuropathic	67.0
Neuroischaemic	26.3
Ischaemic	1
Non-neuropathic, nonischaemic	5.7
Site of ulcer	
Forefoot	77.8
Midfoot	11.9
Hindfoot	10.3

Sample size [7]

194

Length of follow-up [11]

Minimum = 6 months

Selection criteria

Inclusion criteria : - Diabetic patients who presented with a new diabetic foot ulcer

Exclusion criteria : - None reported

Predictor variable(s):	Data collection method
Wagner classification of diabetic foot ulcer	Grade 1 – superficial wound Grade 2 – deep wound involving tendons and capsules but not bone Grade 3 – bony involvement Grade 4 – localised gangrene Grade 5 – generalised gangrene
University of Texas classification of diabetic foot ulcer	Grade 1 – superficial wound Grade 2 – deep wound involving tendons but not bone Grade 3 – Bone involvement, localised and generalised gangrene Four stages in each grade; no infection or ischaemia (A); infection (B); ischaemia (C) and infection and ischaemia (D)

Potential confounders: Previous history of ulcer, sex, age, duration of diabetes, treatment.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Amputation, time to healing	The mean age and duration of diabetes for subjects with non-neuropathic, nonischaemic ulcers was much less than that of the rest of the group (47.6 v 57.1 ($p<0.05$) years and 8.0 v 15.9 years respectively ($p<0.01$)).	Not reported

Measurement bias [16]	Follow-up (ITT) [17]
All patients were measured and treated in the same way.	100%

Overall quality assessment (descriptive) [18] This was a well conducted and reported study. There is some potential for confounding due to previous clinical history and potentially treatment.		
RESULTS		
Outcome [19] Amputation and healing time		Quality assessment: Average
Outcome [19]	Measure of effect/effect size + 95% CI [22]	
	Wagner grade:	University of Texas
Amputation	= 21.0, p<0.0001	Grade: = 23.7, p<0.0001 Stage: = 15.1, p=0.0001 Stage B v Stage A OR=11.1 [95% CI 3.0, 41.0] p<0.0001 Stage C v Stage A OR=4.6 [95% CI 0.9, 24.7] p=0.09 Stage D v Stage A OR=14.7 [95%CI 3.7, 58.2] p<0.0001 Stage C & D v Stage A & B OR=2.8 [95%CI 1.2, 6.5] p<0.05
Median healing time	Grade 1: 8 weeks Grade 2: 16 weeks Grade 3: 11 weeks 5.68, df=3, p=0.13	Grade 1: 8 weeks Grade 2: 12 weeks Grade 3: 16 weeks 5.47, df=2, p=0.07 Stage A: 7 weeks Stage B: 11 weeks Stage C: 16 weeks Stage D: 20 weeks 10.24, df=3, p=0.02
Not healing within study period		Stage: Hazard ratio=0.8 [95% CI 0.67, 0.98] p<0.05
Conclusion: This study shows that both the Wagner and UT classifications indicate the severity of foot ulcer in terms of clinical outcomes (eg amputation). Additionally, the stage of the ulcer at presentation in terms of infection and ischaemia also indicate the severity of foot ulcer. It should be noted that the low numbers of Stage C subjects lead to a lack of statistical power for this stage to predict amputation. The authors also reported that the Stage of ulcer in the UT classification was able to predict the likelihood of ulcer healing within the study period (minimum of 6 months) with the more severe stages being less likely to heal. Unfortunately, the exact period of follow-up in the study was poorly described.		
EXTERNAL VALIDITY		
Generalisabilty: This study is generalisable to patients presenting at a specialised diabetic foot clinic with a new ulcer.		
Comments: This study provided evidence regarding the ability of the Wagner and UT classifications to predict amputation and healing time in people with a new foot ulcer. The study did not control for treatment or clinical history therefore it is uncertain if they had any impact on the results. Additionally, it is uncertain over what period of time these classifications are able to predict the outcome.		

STUDY DETAILS

Reference [1]

Leese, G., C. Schofield, et al. (2007). "Scottish foot ulcer risk score predicts foot ulcer healing in a regional specialist foot clinic." Diabetes Care 30(8): 2064-2069.

Affiliation/source of funds [2]

No sources of funding have been acknowledged.

Study design [3]	Level of evidence [4]	Location/setting [5]
Retrospective cohort study	III-3	Specialist foot clinic in Dundee, Scotland

Patient characteristics [10]	Means ± SD or %	Sample size [7]
Age (years)	67.3 ± 12.7	198 (221 referrals/episodes)
		Length of follow-up [11]: Maximum = 2 years 9 months

Selection criteria

Inclusion criteria : - Attending specialist diabetic foot clinic with foot ulcer

Exclusion criteria : - Not reported

Predictor variable(s):	Data collection method
Sex	Patient history
Age	Patient history
Ulcer site: meta head versus toe Dorsum versus toe Heel versus toe Other versus toe	As assessed by diabetes or vascular surgery consultant
Ulcer depth: Deep versus superficial bone versus superficial	As assessed by diabetes or vascular surgery consultant using University of Texas ulcer slcassifciation
High risk (according to foot ulcer risk score)	As assessed by diabetes or vascular surgery consultant using foot risk score (SIGN)
Absent pulses	As assessed by diabetes or vascular surgery consultant
Neuropathy	As assessed by diabetes or vascular surgery consultant using 10-g monofilament (absence of sensation indicated neuropathy)
Previous ulcer	Not reported
Foot deformity	As assessed by diabetes or vascular surgery consultant
Sepsis	Presence of surrounding cellulites or pus

Potential confounders:

Ulcer size, treatment

INTERNAL VALIDITY

Outcome measurement method [12] Nonhealing – requiring amputation or dying with ulcer Healing – complete re-epithelialisation of the wound.	Comparison of study groups [14] Not relevant/reported	Blinding [15] Not reported
Measurement bias [16] Uncertain how patients were treated	Follow-up (ITT) [17] Not reported	
Overall quality assessment (descriptive) [18] Lack of detail regarding measurement of predictor variables, outcomes and follow-up introduce some uncertainty into the study. Results are potentially confounded by ulcer size and treatment of patients.		
RESULTS		
Outcome [19] Non-healing	Quality assessment: Average	

Multivariate outcome [19]	OR + 95% CI + p-value[22]	
Male sex	0.67 [0.31, 1.45] NS	
Age (year)	1.04 [1.00, 1.08] p=0.04	
Ulcer site: meta head versus toe Dorsum versus toe Heel versus toe Other versus toe	1.59 [0.56, 4.5] NS 8.53 [0.23, 310.77] NS 1.56 [0.67, 3.65] NS 1.14 [0.24, 5.45] NS	
Ulcer depth: Deep versus superficial bone versus superficial	2.93 [1.08, 7.94] p=0.03 4.87 [1.85, 12.84] p=0.001	
High risk	-	
Absent pulses	4.78 [1.57, 15.53] p=0.006	
Neuropathy	4.98 [1.56, 15.95] p=0.006	
Previous ulcer	1.11 [0.55, 2.24] NS	
Foot deformity	0.68 [0.24, 1.98] NS	
Sepsis	1.14 [0.50, 2.60] NS	

Conclusion: While this study suggests that neuropathy (as defined by absence of monofilament sensation), ulcer depth, age and absence of pulses predict non-healing, it has failed to control for ulcer size and treatment. The impact of these two variables on the odds ratios and confidence intervals is uncertain. Furthermore, the follow-up period of the study has not been well defined nor has the exposure assessments.
EXTERNAL VALIDITY
Generalisabilty: This study would be generalisable to the target population of the guideline
Comments: Although the study may be generalisable, it is uncertain whether the results are entirely reliable due to the lack of controlling for potential confounders.

STUDY DETAILS

Reference [1]

Margolis, D. J., L. Allen-Taylor, et al. (2002). "Diabetic neuropathic foot ulcers - The association of wound size, wound duration, and wound grade on healing." Diabetes Care 25(10): 1835-1839.

Affiliation/source of funds [2]

Part funded by National Institutes of Health

Study design [3]	Level of evidence [4]	Location/setting [5]
Retrospective cohort study	III-3	Curative Health Center(s) (CHS), USA

Patient characteristics [10]	Means ± SD or %	Sample size [7]
Male	53.9%	75,525 wounds
Previously received care at a wound care centre	20.5%	
Age (years)	63.8	Length of follow-up [11]
CHS wound grade scale: 1 Partial thickness involving only dermis and epidermis 2 Full thickness and subcutaneous tissues 3 Grade 2 plus exposed tendons, ligament, and/or joint 4 Grade 3 plus abscess and/or osteomyelitis 5 Grade 3 plus necrotic tissue in wound 6 Grade 3 plus gangrene in the wound and surrounding tissue	≤ grade 2 76.2%	20 weeks
Duration of wound	Mean = 5.39 months median = 1.0 months	

Selection criteria

Inclusion criteria : - Treatment at a CHS center between 1988 and 2000 and had at least one diabetic neuropathic foot ulcer

Exclusion criteria : - Second office visit or documentation of a surgical procedure within 6 weeks of first office visit.

Predictor variable(s):	Data collection method
Patient age	
Patient sex	
Duration of wound	Not reported
Size of wound	Not reported
Wound grade	According to CHS classification above
Number of wounds	Not reported
Prior care at a CHS center	Full cycle of care (ie registered, treated and discharged by CHS)
CHS center	

Potential confounders:

Treatment, foot deformity, location of ulcer, nephropathy, retinopathy

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
The outcome was a healed wound by 20th week of care as determined by database	Not relevant/reported for this study.	Not reported

Measurement bias [16]	Follow-up (ITT) [17]
It is unclear what treatments patients received, or if they were all treated in the same way.	Not reported.

Overall quality assessment (descriptive) [18] This is an average quality study which has been limited by the retrospective nature of the study design and the use of a database. Inadequate detail regarding the assessment of potential predictors and outcomes ensures some difficulty in interpreting the results and assessing their applicability and generalisability.				
RESULTS				
Outcome [19] Not healing at 20 weeks			Quality assessment: Average	
Multivariate outcome [19]	OR + 95% CI [22]		First wound only	
Sex (male)	1.07	[1.03, 1.12]	1.14	[1.08, 1.20]
Prior wounds	0.92	[0.89, 0.96]	-	
Grade	2.05	[1.98, 2.13]	1.93	[1.82, 2.05]
Age	1.00	[1.00, 1.01]	1.01	[1.00, 1.01]
Count (number of wounds)	1.12	[1.11, 1.14]	-	
Wound duration	1.23	[1.21, 1.24]	1.30	[1.27, 1.32]
Wound size	1.31	[1.29, 1.32]	1.32	[1.30, 1.34]
Conclusion: The large sample size in this study has enabled very narrow confidence intervals. However, it also shows that the impact of the measured independent variables is marginal except for the grade of ulcer which has been dichotomised in this study to ≤ or > grade 2 (CHS scale), where people with ulcers classified as grade 2 or greater are twice as likely to not have a healed ulcer at 20 weeks after initial presentation. It should be noted that these results have not been controlled for potential confounders such as treatment, foot deformity, location of ulcer, nephropathy or retinopathy. Additionally, the use of a patient database is likely to introduce information bias and limits the study's results. The authors have taken into account potential effects of clustering due to wound care centre and patient.				
EXTERNAL VALIDITY				
Generalisabilty: This study can be generalisable to patients with neuropathic foot ulcers presenting for specialised wound care. It is not clear if these wound care centres specialise in diabetic foot ulcers.				
Comments:				

STUDY DETAILS

Reference [1]

Edelman, D., D. M. Hough, et al. (1997). "Prognostic value of the clinical examination of the diabetic foot ulcer." Journal of General Internal Medicine 12(9): 537-543.

Affiliation/source of funds [2]

No source of funding has been reported. The senior author is supported by the Veterans Affairs Health Services Research and Development Career Development and the Robert Wood Johnson Generalist Physician Faculty Scholars Programs.

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective Cohort	II	Outpatients and inpatients at the Durham Veterans Affairs Medical Center.

Patient characteristics [10]	Number of ulcers (%)
Element of clinical history:	
Painful ulcer	44 (56)
Claudication (affected leg)	26 (33)
Never been seen by physician before enrolment	22 (28)
Prior lower extremity amputation	20 (26)
Fever, chills or sweats	10 (13)
Smoking status	
Ex-smokers	41 (53)
Smokers	19 (24)
Never smoked	18 (23)
Median days since patient noticed ulcer (interquartile range)	33 (14-153)
Physical findings	
Leg	48 (62)
Right	30 (38)
Left	
Location	28 (36)
Metatarsal heads	28 (36)
Toes	22 (28)
Other	
Ankle-brachial index (n=53)	22 (42)
> 0.9	13 (25)
0.5 – 0.9	18 (34)
< 0.5	68 (87)
Induration	62 (80)
Edema	62 (80)
Erythaema	58 (74)
Necrosis	52 (67)
Purulence	42 (54)
Present dorsal pedal pulse	33 (42)
Present posterior tibial pulse	26 (33)
Cyanosis	7 (9)
Visible bone in ulcer	3 (4)
Crepitus	20mm (11-28mm)
Median width in largest dimension (interquartile range)	3mm (2-5mm)
median depth (interquartile range)	22 (28)
Physician estimate of likelihood of osteomyelitis	28 (36)
Low	28 (36)
Moderate	
High	

Sample size [7]

64 patients with 78 ulcers

Length of follow-up [11]

6 months

Selection criteria

Inclusion criteria: - Patients with diabetes and a wound through the full thickness of the dermis at or distal to the malleoli of the ankle.

Exclusion criteria: - Patients with lacerations and puncture wounds or previous diagnosis of osteomyelitis underlying the current ulcer and inability to tolerate MRI.

Predictor variable(s):	Data collection method
Clinical history including: Age; race; gender; smoking status; medication; duration of diabetes; duration of ulcer; previous amputation; fever, chills or sweats; painful ulcer; claudication	Structured clinical history

Physical examination including: leg; width; depth location of ulcer; crepitus; necrosis; purulence; erythema; induration; visible bone; dorsal pedal and posterior tibial pulses; cyanosis; edema; ankle-brachial index	Structured physical examination
MRI	MRI's were read independently by two radiologists blinded to clinical examination. Results were either positive or negative for osteomyelitis or abscess, indeterminate or inadequate for reading.

Potential confounders:

Treatment, neuropathy, retinopathy, nephropathy

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Ulcer healing – complete wound closure at 6 months follow up.	Not relevant/reported for this study.	Radiologists were blinded to clinical examination.

Measurement bias [16]	Follow-up (ITT) [17]
All patients were assessed in the same way with structured interviews for patient history and structured physical examinations.	62/64 (97%)

Overall quality assessment (descriptive) [18]

A good study to assess clinical factors which predict failure to heal in diabetic patients with foot ulcer. This study however, does fail to control for treatment (and type) and given that all patients with foot ulcer were eligible for enrolment and wide range of treatments may have been administered which would impact on the final outcome.

RESULTS

Outcome [19] Failure to heal	Quality assessment: Average

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22] OR	95% CI	c statistic
Absence of audible posterior tibial pulse	8.46	[1.54, 46.5]	0.742
Pain at site of ulcer	3.69	[1.03, 13.2]	
Analysis with elements of clinical examination requiring the use of a Doppler excluded:			
Prior amputation	6.45	[1.86, 22.4]	0.741
Pain at site of ulcer	2.85	[1.04, 7.81]	

Conclusion:

This study indicates that elements of a clinical examination may predict the failure of ulcers to heal however, this analysis did not control for the effects of treatment, or other diabetic complications.

EXTERNAL VALIDITY

Generalisabilty: The results of this study would apply to the general diabetic population with foot ulcer.

Comments:

MRI = magnetic resonance imaging

STUDY DETAILS

Reference [1]

Bishara, R. A., W. Taha, et al. (2009). "Ankle peak systolic velocity: new parameter to predict nonhealing in diabetic foot lesions." Vascular 17(5): 264-268.

Affiliation/source of funds [2]

No financial disclosures to report

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective cohort study	II	Not reported

Patient characteristics [10]	Means ± SD or %
Median age (range)	63 years (42-78 years)
Male	42 (68%)
Ischaemic heart disease	30 (49%)
Hypertension	29 (47%)
Smoking	15 (24%)
Stroke	6 (10%)
Renal impairment	6 (10%)
Dyslipidaemia	6 (10%)

Sample size [7]

100 limbs in 62 patients

Length of follow-up [11]

Uncertain

Selection criteria

Inclusion criteria : - Diabetic with absent dorsalis pedis and posterior tibial pulses in the affected leg, and had foot lesions in the form of ulcers, gangrene or tissue necrosis.

Exclusion criteria : - None reported

Predictor variable(s):	Data collection method
Age	
Gender	
Diabetes mellitus	
Hypertension	Not reported
Ischaemic heart disease	Not reported
Renal impairment	Not reported
Cerebrovascular accident	Not reported
Dyslipidaemia	Not reported
Ankle peak systolic velocity (APSV)	Mean of the peak systolic velocities of the anterior and posterior tibial arteries measured at the ankle level. Measured as part of the duplex scan.

Potential confounders:

Treatment

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Healed wound, a healing wound, revascularisation (not relevant to review), major amputation or death. Non-healing was defined as not showing signs of healthy granulations after 1 month of follow-up or if patient developed manifestations of critical limb ischaemia	Not reported	Not reported

Measurement bias [16] Patients with non-ischaemic lesions or lesions in revascularised limbs received standardised wound dressing. Patients with non-healing lesions or critical limb ischaemia underwent revascularisation procedures by endovascular or open surgical techniques.	Follow-up (ITT) [17] 4 patients lost to follow-up after receiving advice for revascularisation but these were considered as failure to heal.
Overall quality assessment (descriptive) [18] There is some uncertainty around the number of limbs included in the logistic regression analysis. The protocol suggests that if a limb lesion failed to heal and then underwent revascularisation, the limb re-entered the study. According to the number of limbs which underwent revascularisation, there would be 191 limbs considered in the analysis. This is not mentioned by the authors who have indicated that there were only 100 limbs. When the authors have reported the median APSV for limbs which have healed and not healed they have indicated that there are only 100 limbs.	
RESULTS	
Outcome [19] Non-healing	Quality assessment: Poor

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22]	
Using a cut-off APSV of 35 cm/s:	Sensitivity: 92.9% [95% CI 82, 97%] Specificity: 90.6% [95% CI 76, 96%] PPV: 92.9% NPV: 90.6% AUC: 0.9723 [95% CI 0.59, 1.0]	

Conclusion: The authors suggest that APSV is an independent predictor of non-healing in diabetic patients with foot lesions. The authors have also indicated that the variable diabetes mellitus is a non-significant predictor of non-healing however, as all patients were diabetic it makes no sense to consider this in the analysis. As indicated previously, the estimates reported in this study are likely to favour APSV due to the double counting of patients after treatment with surgery. Furthermore, treatment was not evaluated as a predictor variable.
EXTERNAL VALIDITY
Generalisabilty: This study is likely to be generalisable to people with diabetic foot ulcers and peripheral ischaemia.
Comments: Given the poor quality of the study, little weight should be given to the results.

PPV = positive predictive value; NPV = negative predictive value; AUC = area under curve

STUDY DETAILS

Reference [1]

Moriarty, K. T., A. C. Perkins, et al. (1994). "Investigating the capillary circulation of the foot with 99mTc-macroaggregated albumin: a prospective study in patients with diabetes and foot ulceration." Diabet Med 11(1): 22-27.

Affiliation/source of funds [2]

This study was financially supported by the British Diabetic Association, Synthelabo Recherche and the University of Nottingham Medical School Trust Fund.

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective cohort study	II	Foot clinic in the UK

Patient characteristics [10]	Means ± SD or %	Sample size [7]
Male	78%	23 patients with 41 ulcers
Type 2 diabetes	74%	
Age	68 ± 2 years (range 44–82 years)	
Current Smokers Ex-smokers Never smoked	13% 61% 26%	Length of follow-up [11] 3 months
Impalpable foot pulses	100%	
Mean ankle-brachial pressure	0.46 ±0.07	

Selection criteria

Inclusion criteria : -Not reported

Exclusion criteria : - Not reported

Predictor variable(s):	Data collection method
Capillary circulation	^{99m}Tc-macroaggregated albumin perfusion scanning. Scans were graded as poor, normal or increased perfusion; however, the criteria for these classifications were not reported.

Potential confounders:

Treatment

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
At the end of follow-up, ulcers were classified as healed or not healed. If patients required surgery for the ulcers (eg angioplasties, reconstructive surgery or amputation) then this was classified as non-healed. No formal definition of healed was provided.	Not reported	Radiologists and medical physicists evaluated the images of the feet without knowledge of the site of ulceration. Treatment was provided without knowledge of the results of the perfusion scan.

Measurement bias [16] Yes	Follow-up (ITT) [17] One person died (of malignancy) and was not included in the follow-up.
Overall quality assessment (descriptive) [18] The results of this study are weakened by the failure to take into account the treatments which patients underwent and furthermore by the absence of a definition by which ulcers were classified as healed.	
RESULTS	
Outcome [19] Healing	Quality assessment: Poor

Outcome [19]	Measure of effect/effect size + 95% CI [22] Healed	Not healed	Fisher's exact test
Poor perfusion	0 (0%)	5 (100%)	Poor v normal p=0.0005
Normal perfusion	12 (66%)	6 (33%)	
Increased perfusion	14 (82%)	3 (18%)	Increased v normal p=0.047

Conclusion: These results suggest that poor perfusion of capillary circulation, as evaluated by ^{99m}Tc-macroaggregated albumin perfusion scanning, is associated with non-healing of ulcers. However, the results of this study have not considered the impact of treatment on the outcome.
EXTERNAL VALIDITY
Generalisabilty: This study is particularly generalisable to people with ischaemic diabetic foot ulcers.
Comments: This is a weak study and it is not recommended that much weight be given to the results.

STUDY DETAILS

Reference [1]

Kalani, M., K. Brismar, et al. (1999). "Transcutaneous oxygen tension and toe blood pressure as predictors for outcome of diabetic foot ulcers." Diabetes Care 22(1): 147-151.

Affiliation/source of funds [2]

Financial support from the Swedish Medical Research Council , the Swedish Diabetes Association and the Karolinska Institute.

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective cohort study	II	Multidisciplinary foot care setting in Sweden

Patient characteristics [10]	Means ± SD or %	Sample size [7]
Men	37/50 (74%)	50 patients
Age	61 ± 12 years	
Diabetes duration	26 ± 14 years	Length of follow-up [11]
Ankle-Brachial index <0.6	32/50 (64%)	12 months
Reconstructive vascular surgery	1/50 (2%)	
Smokers Ex smokers	10/50 (20%) 10/50 (20%)	
Insulin therapy Oral antidiabetics	34/50 (68%) 16/50 (32%)	

Selection criteria

Inclusion criteria : - Diabetic patients referred to microcirculatory laboratory with chronic foot ulcers of > 2 months duration

Exclusion criteria : - Not reported

Predictor variable(s):	Data collection method
$TcPO_2$	Measured by electrochemical transducer at the dorsum of the foot in the first intertarsal space
Toe blood pressure (TBP)	Systolic TBP measured using a miniature cuff placed around the base of the great toe.

Potential confounders:

Smoking, type of diabetes and sex

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Ulcer healing (impaired or improved)	There were some differences in regard to potential confounders such as sex, type of diabetes and smoking	Not reported

Measurement bias [16]	Follow-up (ITT) [17]
They were all treated with standard care and measured by the same method.	There were no losses to follow-up

Overall quality assessment (descriptive) [18]

This was an average quality study to evaluate the predictive value of TcPO2 and TBP to predict ulcer healing in patients with chronic diabetic foot ulcers. Patients were classified into three groups based on their clinical outcome 12 months after baseline measurements. These three groups - impaired healing, improved healing and healed with intact skin were poorly defined but are likely to represent a change in ulcer area of ±25%. The study did not take into account potential confounders which may have influenced the outcome of healing.

RESULTS

Outcome [19] Impaired Ulcer healing		Quality assessment: QUADAS: Poor SIGN: Poor
outcome [19]	Measure of effect/effect size + 95% CI [22] TcPO2	TBP
Impaired healing	Sensitivity = 84.6% [95%CI 57., 95.7] Specificity = 91.8% [95%CI 78.7, 97.2] PPV = 79% NPV = 94%	Using a cut off of 30mmHg [a] Sensitivity = 15% Specificity = 97% PPV = 67% NPV = 77% Using a cut off of 45mmHg [b] Sensitivity = 46%] Specificity = 84% PPV = 50% [a] Raw data were not provided for these outcomes hence, confidence intervals could not be calculated
Conclusion: This study reports high specificity and good sensitivity for $TcPO_2$ measurement to predict impaired ulcer healing in patients with chronic diabetic foot ulcers. For TBP, a high specificity was reported but very low sensitivity. The confidence intervals suggest that there is some error in the reported estimates. The odds ratio calculated from the raw data indicates that there is a very strong relationship between $TcPO_2$ however, this effect measure does not control for the impact of smoking, type of diabetes and sex, and given the large confidence intervals, it is likely that this estimate is associated with substantial error. It would appear that $TcPO_2$ is a reasonable predictor of impaired healing in this group of patients however, the exact definition of impaired healing is still uncertain.		
EXTERNAL VALIDITY		
Generalisabilty: These results are generalisable to people with chronic diabetic foot ulcers.		
Comments:		

STUDY DETAILS

Reference [1]

Faris, I. and H. Duncan (1985). "Skin perfusion pressure in the prediction of healing in diabetic patients with ulcers or gangrene of the foot." J Vasc Surg 2(4): 536-540.

Affiliation/source of funds [2]

Financially supported by a grant from the Reeves surgical Research Fund.

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective cohort study	II (Prognosis) III-3 (Diagnostic)	Royal Adelaide Hospital, South Australia

Patient characteristics [10]	Means ± SD or %	Sample size [7]
Age (median)	72 years (38–86 years)	61
Male	37 (61%)	
Duration of diabetes (median)	10 years (0.5–40 years)	Length of follow-up [11]
Ulcer	35 (57%)	Not reported
Gangrene	26 (43%)	

Selection criteria

Inclusion criteria : - Not reported

Exclusion criteria : - Not reported

Predictor variable(s):	Data collection method
Skin perfusion pressure (SPP)	Measured by radioisotope clearance method

Potential confounders:

Previous history of foot ulcer or amputation,

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Healing (including with conservative treatment, local surgery, transmetatarsal amputation) Arterial surgery Below the knee amputation	Not reported	Not reported

Measurement bias [16]	Follow-up (ITT) [17]
Not reported	100%

Overall quality assessment (descriptive) [18]

This is a poorly reported study which has not provided sufficient information regarding the baseline characteristics and assessment of patients, the length of follow-up and details of conservative treatment.

RESULTS

Outcome [19] Healing	Quality assessment: QUADAS: Poor SIGN: Poor

Outcome [19]	Measure of effect/effect size + 95% CI [22] Calculated from raw data (2x2 table)	
Healing	Using a cut off value of 40mmHg: Sensitivity = 97.2% [95% CI 85.8, 99.5] Specificity = 80% [95% CI 60.9, 91.1] PPV = 87.5% NPV = 95.2% OR =	
Conclusion: This was a poor quality study which provided insufficient detail to ascertain whether the results are reliable. Interpreting these results should be done with care as the outcome of healing included patients who required local surgery and/or amputation, which indicates that there were problems with healing of lesions or gangrene which required more aggressive intervention. The authors have not indicated the length of follow-up in the study so it is not possible to determine over what period of time SPP might be able to predict the outcome of healing. Based on the raw data provided, the diagnostic accuracy outcomes have been calculated. These outcomes suggest that SPP has excellent sensitivity and good specificity. The high sensitivity could indicate that this measurement is able to identify patients who would not heal as those with a SPP measurement below 40mmHg. However, the poor quality of this study introduces significant uncertainty regarding any conclusions which may be drawn.		
EXTERNAL VALIDITY		
Generalisabilty: These results are likely to be generalisable to diabetic patients with foot ulcers or gangrene.		
Comments: Little weight should be given to these results.		

STUDY DETAILS

Reference [1]

Apelqvist, J., J. Castenfors, et al. (1989). "Prognostic value of systolic ankle and toe blood pressure levels in outcome of diabetic foot ulcer." Diabetes Care 12(6): 373-378.

Affiliation/source of funds [2]

Financially supported by the Swedish Medical Research Council

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective cohort study	II	Outpatient clinic in Sweden

Patient characteristics [10]		Means ± SD or %	Sample size [7]
Duration of foot ulcers		14.5 ± 26.1 weeks	314 consecutive patients
Wagner	Grade 1	150/314 (48%)	
	Grade 2	50/314 (16%)	Length of follow-up [11]
	Grade 3	40/314 (13%)	Not reported
	Grade 4	39/314 (12%)	
	Grade 5	29/314 (9%)	

Selection criteria

Inclusion criteria : - Patients with diabetes mellitus referred o the Department of Internal Medicine due to foot ulcer.

Exclusion criteria : - Not reported

Predictor variable(s):	Data collection method
Systolic ankle blood pressure Systolic toe blood pressure	Where possible, measured with same occluding cuff as used for toe pressure measurements. Measured every 6 months. Mean of three measurements was used for analysis. Using individually fitted occluding cuffs around base of toe. Mean of three measurements used for analysis. Measured at 6 month intervals. Toe pressure was measured simultaneously in both legs.
Systolic brachial pressure	Measured in both arms.

Potential confounders:

Treatment, duration of diabetes, age, sex, smoking, blood pressure, presence of neuropathy were all measured but not used in the analysis.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Primary healing – no further details were provided	Potential confounders were compared between those who had primary healing, amputation and those who died.	Not reported

Measurement bias [16]	Follow-up (ITT) [17]
It would appear that all patients had access to the same multidisciplinary care. However, patients would not necessarily received the same treatment.	100% 77 (25%) of patients underwent amputation, 40(13%) died during follow up.

Overall quality assessment (descriptive) [18]

Difficult to extract meaningful data from the article, the only measures which were explicitly reported were the mean toe- and ankle-brachial indices. The analysis only considered whether there were differences in indices between those who healed and those who did not.

RESULTS		
Outcome [19] Primary healing		Quality assessment: Poor
Outcome [19]	Measure of effect/effect size + 95% CI [22] Mean ± SD	Mann-Whitney U test (two tailed)
Ischaemic ankle index	Primary healed (n=179) 0.87 ± 0.29 Amputated (n=65) 0.55 ± 0.28	$p < 0.001$
Toe index	Primary healed (n=179) 0.55 ± 0.30 Amputated (n=65) 0.20 ± 0.18	$p < 0.001$
Conclusion: The results suggest that there is a statistically significant difference in the ratio of toe or ankle pressure with brachial artery pressure, and those who achieved primary healing and those who are amputated.		
EXTERNAL VALIDITY		
Generalisabilty: These results would be generalisable to the target population of this guideline ie people with diabetic foot ulcers receiving multidisciplinary care		
Comments:		

STUDY DETAILS			
Reference [1] Van Acker, K., C. De Block, et al. (2002). "The choice of diabetic foot ulcer classification in relation to the final outcome." Wounds-a Compendium of Clinical Research and Practice 14(1): 16-25.			
Affiliation/source of funds [2] Not reported			
Study design [3] Retrospective cohort study	Level of evidence [4] III-3	Location/setting [5] Antwerp diabetic foot clinic	
Patient characteristics [10] Age (years)	Means ± SD or % Healed with amputation healed without amputation 57.9 ± 12.7 57.9 ± 13.4	Sample size [7] 121 patients with253 ulcers.	
		Length of follow-up [11] Not reported	
Selection criteria Inclusion criteria : - All patients visiting the Antwerp Diabetic Foot Clinic between January, 1992 and December, 1997. Exclusion criteria : - Not reported			
Predictor variable(s): Wagner classification Van Acker/Peter (VA/P)classification	Data collection method		
Potential confounders:			
INTERNAL VALIDITY			
Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]	
Measurement bias [16]	Follow-up (ITT) [17]		
Overall quality assessment (descriptive) [18]			
RESULTS			
Outcome [19] Healing without amputation	Quality assessment:		
Outcome [19]	Measure of effect/effect size + 95% CI [22]		
	Healing with amputation	Healing without amputation	

VA/P horizontal axis Class 1 Class 2 Class 3 Class 4	5% 7.7% 13.8% 42.4%	95% 92.3% 86.2% 57.6%	^{2} test for linear trend, p < 0.001
VA/P vertical axis Class A Class BC Class DE	6.3% 6.8% 20.6%	93.8% 93.2% 79.4%	^{2} test for linear trend, p < 0.002
Correlation between Wagner and VA/P: Wagner v VA/P Wagner v VA/P horizontal Wagner v VA/P vertical VA/P v VA/P horizontal VA/P v VA/P vertical VA/P horizontal v VA/P vertical	Spearman's Correlation coefficient 0.473 0.274 0.665 0.931 0.415 0.072 (p > 0.05)		
Conclusion:			
EXTERNAL VALIDITY			
Generalisabilty:			
Comments:			

STUDY DETAILS

Reference [1]

Margolis, D., L. Allen-Taylor, et al. (2005). "Diabetic neuropathic foot ulcers and amputation." Wound Rep Reg 13: 230-236.

Affiliation/source of funds [2]

Supported by the National Institutes of Health

Study design [3]	Level of evidence [4]	Location/setting [5]
Retrospective cohort study	III-3	Curative Health Center(s) (CHS), USA

Patient characteristics [10]	Means ± SD, % No amputation	Means ± SD, % Amputation	Sample size [7]
			24,616
Duration (month)	2.75 ± 3.75	2.66 ± 3.28	
Area (cm^2)	5.05 ± 1.73	5.46 ± 1.64	
Gender (female)	43.7%	39.0%	Length of follow-up [11]
Age (years)	63.6 ± 13.9	65.7 ± 12.7	Not reported
CHS wound grade scale:			
1 Partial thickness involving only dermis and epidermis	4.7	2.0	
2 Full thickness and subcutaneous tissues	68.0	35.4	
3 Grade 2 plus exposed tendons, ligament, and/or joint	12.2	13.6	
4 Grade 3 plus abscess and/or osteomyelitis	10.4	26.9	
5 Grade 3 plus necrotic tissue in wound	4.3	14.0	
6 Grade 3 plus gangrene in the wound and surrounding tissue	0.6	7.6	
Number of wounds	2.12 ± 1.86	2.70 ± 2.18	

Selection criteria

Inclusion criteria : - Individuals with diabetic neuropathic foot ulcers who received treatment at a CHS center between 1988 and 2001.

Exclusion criteria : - Not first course of treatment at a CHS center.

Predictor variable(s):	Data collection method
Patient age	
Patients gender	
Size of wound	
Number of wounds	
Duration of wound	
Wound grade	According to CHS classification above
CHS center	
Center's length of experience	

Potential confounders:

Wound care, diabetes treatment, duration of diabetes, type of diabetes, location of ulcer, local infection, degree of neuropathy, degree of arterial insufficiency, comorbid illnesses, smoking status.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
First lower extremity amputation: Percentage of patients who had an amputation Amputation by the 20th week of care	Not relevant/reported for this study	Not reported

Measurement bias [16]	Follow-up (ITT) [17]
It is unclear what treatments patients received, or if they were all treated in the same way.	Not reported

Overall quality assessment (descriptive) [18] This is an average quality study which has been limited by the retrospective nature of the study design and the use of a database.		
RESULTS		
Outcome [19] Amputation by the 20th week of care		Quality assessment: Average
Multivariate outcome [19]	OR + 95% CI [22]	
Sex	1.33 [1.19, 1.48]	
Age	1.01 [1.01, 1.01]	
Number of wounds	1.32 [1.27, 1.38]	
Duration (months)	0.97 [0.93, 1.01]	
Area (cm^2)	0.97 [0.94, 1.00]	
Grade Grade 1 Grade 2 Grade 3 Grade 4 Grade 5 Grade 6	 Reference 1.28 [0.88, 1.86] 2.71 [1.83, 4.01] 6.30 [4.31, 9.21] 7.33 [4.93, 10.90] 31.57 [20.15, 49.47]	
Grade ≤2 Grade >2	Reference 4.35 [3.92, 4.82]	
Conclusion: The results of this study suggest that wound grade (CHS scale) at the initial assessment is most important predictor of amputation. Wound grade at the initial visit was strongly associated with the likelihood of amputation; patients with a wound grade greater than 2 are approximately four times as likely to have an ampututation within 20 weeks compared to those with a wound grade of 2 or less. When adjusted for wound grade, wound duration and wound size were not indicators of amputation risk. It should be noted that these results have not been controlled for potential confounders such as treatment, location of ulcer, duration of diabetes, type of diabetes and local infection. Additionally, the use of a patient database is likely to introduce information bias and limits the study's results. The authors have taken into account potential effects of clustering due to wound care centre and patient.		
EXTERNAL VALIDITY		
Generalisabilty: This study can be generalisable to patients with neuropathic foot ulcers presenting for specialised wound care. It is not clear if these wound care centres specialise in diabetic foot ulcers.		
Comments:		

STUDY DETAILS

Reference [1]

Van Houtum, W. H., L. A. Lavery et al. (1998). "Risk factors for above-knee amputations in diabetes mellitus." Southern Medical Journal 91(7): 643-649.

Affiliation/source of funds [2]

No sources of funding have been acknowledged.

Study design [3]	Level of evidence [4]	Location/setting [5]
Retrospective cohort study	III-3	Hospitals within six metropolitan areas in Texas, USA.

Patient characteristics [10]	Means ± SD or %	Sample size [7]
Sex (M/F)	616/427	1,043
Age (years)	64.8 ± 12.5	
Age group (years)		Length of follow-up [11]
25-44	5.7	Not reported
45-64	41.0	
64-74	30.7	
≥75	22.6	
Ethnicity		
Hispanic	78.1	
Non-Hispanic white	15.0	
Black	6.8	
Level of amputation		
Foot	45.7	
Below knee	32.3	
Above knee	22.0	

Selection criteria

Inclusion criteria : - All diabetic patients hospitalised for a lower extremity amputation from 1 January to 31 December, 1993.

Exclusion criteria : -

Predictor variable(s) for above-knee amputation vs below knee or foot amputaion:	Data collection method
Diabetes related comorbidities	Kaplan-Feinstein four-point ranking scale
Hyper tension	0=non disease
Cardiac disease	1=mild
Cerebrovascular disease	2=moderate
Respiratory disease	3=severe
Renal disease	
Hepatic disease	
Anaemia	
Peripheral vascular disease	
Malignancy	
Locomotor impairment	
Alcoholism	
Collagen vascular disease	
Age	
Sex	
Ethnicity	
Body mass index (BMI)	
Type of diabetes therapy	
Laboratory values at admission	
Renal function tests	
Hepatic function	
Triglyceride level	
Cholesterol level	
Blood glucose	

Potential confounders:

Variations in criteria for amputation between centers, location of ulcer, size and duration of ulcer, type of diabetes, duration of diabetes, presence of infection.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Level of amputation: foot, transtibial (below knee), transfemoral (above knee)	The following characteristics were more common in the above-knee amputation group, compared to patients who had a foot or below knee amputation: advanced age, female sex, black ethnicity, low BMI, history of amputation or vascular reconstruction of the lower extremity. Oral hypoglycemic therapy and previous coronary artery bypass grafting were more common in the below knee amputation group.	Not reported

Measurement bias [16]	Follow-up (ITT) [17]
Clinical information was analysed retrospectively using the Kaplan-Feinstein ranking scale. As this scale has a degree of subjectivity, there is potential for misclassification bias.	Not reported

Overall quality assessment (descriptive) [18]

This is an average quality study which has been limited by the retrospective nature of the study design and the use of medical records. It is not clear exactly which baseline parameters were assessed as potential predictors. The relevant information was not consistently reported in the medical records. The study does not report the number of patients for which the relevant information on each parameter was available, nor does it provide details on how missing data was handled. Due to the potential for bias and confounding, it is difficult to assess the applicability and generalisability of the results.

RESULTS

Outcome [19] Level of amputation (above knee vs below knee/foot amputation)	Quality assessment:
	Average

Multivariate outcome [19]	OR + 95% CI [22]	
Locomotor impairment	1.95 [1.68, 2.26]	
Anaemia	2.21 [1.46, 3.34]	
Cardiovascular disease	1.23 [1.18, 1.28]	
Cerebrovascular disease	1.35 [1.25, 1.46]	
Collagen vascular disease	0.50 [0.36, 0.71]	
Female sex	1.69 [1.33, 2.15]	
History of lower extremity bypass	1.89 [1.36, 2.62]	
BMI <20kg/m^2	2.08 [1.35, 3.21]	
SGOT (>40U/L)	1.79 [1.28, 2.49]	
Glucose (>11.1mmol/L)	0.51 [0.37, 0.70]	

Conclusion:

The results of the study suggest that in diabetic patients who require amputation of a lower extremity, advance locomotor impairment, anaemia, low BMI, female sex, and cerebrovascular, peripheral vascular, hepatic, and cardiovascular disease are significantly associated with an increased risk of above knee amputation. While many of the factors in the regression analysis are associated with increasing age, age is not found to be a risk factor for above knee amputation. Systemic collagen vascular disease and an admission blood glucose value >11.1mmol/L were associated with a decreased prevalence of above knee amputations. It is not clear exactly which potential confounders have been assessed. Important factors such as location of the underlying lesion and presence of infection are not reported. Additionally, the use of a patient database is likely to introduce information bias and limits the study's results.

EXTERNAL VALIDITY
Generalisabilty: The results of this study are of limited applicability to the population of interest, as it only identifies risk factors for above knee amputation in diabetic patients in whom amputation of a lower extremity is indicated, regardless of the underlying cause, rather than diabetic patients with foot ulceration.
Comments:

STUDY DETAILS

Reference [1]

Faglia, E., G. Clerici, et al. (2007). " Predictive values of transcutaneous oxygen tension for above-the-ankle amputation in diabetic patients with critical limb ischemia." European Journal of Vascular and Endovascular SurgeryU B33B: 731-736.

Affiliation/source of funds [2]

No sources of funding have been acknowledged.

Study design [3]	Level of evidence [4]	Location/setting [5]
Retrospective cohort study	III-3	Diabetic foot center, Italy

Patient characteristics [10]	Means ± SD or %
Age (years)	70.0 ± 9.6
Female/male	35.1/64.9
Insulin/oral therapy	60.6/39.4
Diabetes duration (years)	17.0 ± 11.1
Sensory motor neuropathy	82.4
Retinopathy	37.6
Albumin excretion (mg/L)	259.8 ± 529.7
Creatinine (mg/dL)	1.28 ± 0.56
Wagner grade	
0	15.6
1	14.7
2	13.8
3	9.8
4	46.1
Infected ulcer	64.2
$TcPO_2$ at admission (mmHg)	14.1 ± 11.8

Sample size [7]

564

Length of follow-up [11]

Not reported

Selection criteria

Inclusion criteria : - All patients admitted to the diabetic foot clinic from January 1999 to December 2005 for foot ulcer or rest pain and with a pedal $TcPO_2$ value lower than 50mmHg.

Exclusion criteria : -

Predictor variable(s):	Data collection method
Transcutaneous oxygen tension ($TcPO_2$)	All measurements were taken at the dorsum of the foot in the peri-lesional site with the patient resting in supine position, using a TCM™3 equipment. The calibration period was 10 minutes and the $TcPO_2$ signal was continuously recorded on paper for 30 minutes.

Potential confounders:

Insufficient data are provided in the study to assess the potential for confounding.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Above-the-ankle amputation	Not relevant	Not reported

Measurement bias [16]	Follow-up (ITT) [17]
Measurement of $TcPO_2$ is objective and determined prior to knowledge of the outcome. There is potential for knowledge of a patient's $TcPO_2$ level to influence management decisions.	All patients were included in the analysis

Overall quality assessment (descriptive) [18] The study is limited by the retrospective nature of the study design, although both the predictive variable and the outcome are objective and appear to have been assessed in a consistent manner. The study has not adequately addressed the potential for confounding.		
RESULTS		
Outcome [19] Above-the-ankle amputation		Quality assessment: Average
Multivariate outcome [19]	OR + 95% CI [22]	
Increase of 1mmHg of $TcPO_2$	0.90 [0.87, 0.93]	
$TcPO_2$ values (mmHg) <10 10 to <20 20 to <30 30 to <40 40 to <50 50 to <60	Predicted Probability (%) 68.0 [52.7, 80.0] 44.0 [33.1, 55.4] 22.5 [17.2, 28.8] 6.1 [4.1, 8.9] 2.6 [1.5, 4.4] 0.8 [0.4, 1.9]	
Conclusion: The study indicates that $TcPO_2$ levels may predict the likelihood of above-the-ankle amputation and indicate when revascularization is necessary. Factors which may influence the reliability of $TcPO_2$ levels as a predictive parameter have not been adequately assessed in the study. It is possible that patient management was influenced by the clinician's knowledge of the patient's $TcPO_2$ level, which would tend to reinforce any observed association with the probability of amputation.		
EXTERNAL VALIDITY		
Generalisabilty: The results of this study would apply to diabetic patients with critical limb ischaemia.		
Comments:		

STUDY DETAILS

Reference [1]

Oyibo, S. O., E. B. Jude, et al. (2001). "The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers." Diabetic Medicine 18(2): 133-138.

Affiliation/source of funds [2]

None reported

Study design [3]	Level of evidence [4]	Location/setting [5]
Cohort study	II	Outpatient setting, two diabetic foot centres (UK and Texas)

Patient characteristics [10]	Means ± SD or %
N=194	
Male	149/194 (77%)
Age	56.6 (±12.6) years
Type II diabetes	89%
Duration of diabetes	15.4 (±9.9) years
Ulcer Characteristics	
Neuropathic	67%
Neuroischaemic	26.3%
Ischaemic	1%
Superficial	68%
To Tendon	15%
To Bone	17%
Infection	40%
Area	1.5 (IQR 0.6-4.0) cm^2

Sample size [7]

194 (one primary ulcer per patient)

Length of follow-up [11]

At least 6 months

Selection criteria

Inclusion criteria : - All diabetic patients who presented with a new foot ulcer to two diabetic foot centres

Exclusion criteria : - none stated

Predictor variable(s):	Data collection method
Demographic and disease variables 1. Age (ns) 2. Sex (ns) 3. Diabetes Type (ns) 4. Diabetes Duration (ns) 5. Ulcer Size (significant predictor) 6. Ulcer Site (ns) 7. Ulcer Depth (ns) 8. Presence of infection (ns) 9. Presence of ischaemia (significant predictor)	Presumably by interview and clinical examination

Potential confounders:

Type of treatment given for ulcers will differ depending upon the severity (or perceived severity) of the ulcer.

Collinearity between ulcer variables – largest ulcers also tended to be the deepest and the most infected – and deep ulcers tended to predict amputation – and infected ulcers took longer to heal.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Time to healing and amputation.	Not applicable	Not reported

Measurement bias [16]	Follow-up (ITT) [17]
Not reported	It is unclear what proportion of patients were followed for a minimum of 6 months – though at the termination of the study (18 months post first enrolment) – 3.5% of patients were lost to death.

Overall quality assessment (descriptive) [18]

This study was a prospective cohort study. Patients with different levels of exposure (different baseline assessments of ulcers) are given disparate treatment regimens. Whilst it is unlikely that the treatments will have a detrimental effect upon the outcomes, and more rigorous treatment for ulcers assessed to be more severe is likely to bias the outcome toward a smaller difference between exposure groups, it remains unclear what the true effect of the exposures has upon outcomes.

Results are not clearly documented. It is unclear whether ulcers may still be classified as healed if this occurs following the first 6 months of follow up, or if amputations that take place outside of the first 6 months are regarded. Given the different lengths of time patients are followed for (minimum of 6 months and maximum of 18 months), there may be some problems interpreting statistics based on outcomes that may have occurred beyond 6 months. "Time to healing" has been modelled with a Cox Regression, however this is poorly presented and an optimum model has not been proposed nor have tests for variable interactions been performed.

RESULTS

Outcome [19]	Quality assessment:
Ulcer healing at the end of the study (healed, unhealed, amputation and death) Time to healing	Poor

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22] Relative Risk	
Ulcer not healed by end of study		
Ulcer Size	1.08 (1.01 – 1.14)	
Presence of Ischaemia	1.69 (1.06-2.70)	
The paper only poorly describes the above Cox Regression – given that a Cox Regression has been used, this is more likely to be measuring length of time an ulcer remains unhealed rather than a dichotomous outcome of healed or not. Presumably the relative risk for presence of ischaemia reflects a 1.69 times increase in risk of an unhealed ulcer with the presence of ischaemia compared to the absence of ischaemia. Whilst not explicitly stated, the paper indicates that Ulcer Size was a continuous variable in the model, and that for each increase of 1 cm^2 in ulcer area, the risk of not healing by the end of the study increased by 1.1 times. These results are spurious as the model contains many variables that are not predictors, and variables that may be strongly collinear.		

Conclusion:

This study has found that the size of a foot ulcer in diabetic patients is a predictor of outcomes (such as time to healing and likelihood of amputation). The presentation of results is poor and makes further conclusions difficult. Different treatments or management pathways for patients with differing levels of exposure further complicates the ability to extract a true measure of association between ulcer size and outcome.

EXTERNAL VALIDITY

Generalisabilty: This study may be generalisable to patients attending a diabetic foot clinic for the assessment of new ulcers.

Comments: The presentation of this study is poor and inadequate to extract meaningful information. The study design allows confounding and statistical efforts to control for potential associations are poorly executed. It is likely that the association between ulcer size and healing time is real, however the strength of this association remains uncertain.

STUDY DETAILS

Reference [1]

Parisi, M. C. R., D. E. Zantut-Wittmann, et al. (2008). "Comparison of three systems of classification in predicting the outcome of diabetic foot ulcers in a Brazilian population." European Journal of Endocrinology 159(4): 417-422.

Affiliation/source of funds [2]

None reported – authors declare no conflict of interest

Study design [3]	Level of evidence [4]	Location/setting [5]
Cohort study	II	Outpatient setting, specialist unit in Brazil

Patient characteristics [10]	Means ± SD or %
N=94	
Male	61%
Age	57.6 (±12.4) years
Duration of diabetes	16.91 (±8.2) years
Smoking	41%
Hypertension	81%
Cardiovascular disease	33%
Stroke	7%
Neuropathy	59%
Ischaemia	36%
Severe Ischaemia	5%
Plantar Ulcer	95%
Dorsal Ulcer	5%

Sample size [7]

94 (one primary ulcer per patient)

Length of follow-up [11]

At least 6 months

(no further detail given)

Selection criteria

Inclusion criteria : - All diabetic patients who presented with a foot ulcer to the specialist centre in Brazil

Exclusion criteria : - none stated

Predictor variable(s):	Data collection method
Ulcer Classification Systems 1. Wagner ulcer classification system 2. University of Texas classification system 3. Size (area, depth), sepsis, arteriopathy, denervation (S(AD)SAD) classification system	Clinical examination

Potential confounders:

Treatment is not controlled amongst the groups of different exposures. Therefore groups with perceived more aggressive ulcers are more likely to receive different / more drastic treatments.

11 patients from the initial 105 (10.5%) were excluded due to lack of data. There is insufficient detail in the report to ascertain whether these patients may be missing data for a reason that may be related to their level of exposure or outcome.

INTERNAL VALIDITY

Outcome measurement method [12] Primary: Healed ulcer at 6 months post enrolment Secondary: Amputation	Comparison of study groups [14] Whilst the data appears to have been collected on several baseline patient characteristics, there is no discussion whether these characteristics are uniform across all grades, or whether there are associations between certain characteristics and ulcer grades. The study has stated that there was no difference in outcome between gender, age or duration of diabetes groups.
Measurement bias [16] Not reported Patients are unlikely to have been treated the same – and their treatment will be contingent upon the perceived severity of the ulcer, and this is linked with exposure status.	Follow-up (ITT) [17] No patients were lost to follow up, however 11 patients had insufficient data for analysis and were excluded. It is unclear what the average follow up duration was, however the primary outcome was healed or not healed by 6 months.
Overall quality assessment (descriptive) [18] This study was a prospective cohort study. Consecutive patients attending a specialist clinic were enrolled (and refusals for the study are not mentioned and presumably did not occur). 11 patients of 105 were excluded for lack of data. Baseline characteristics of these patients were not compared to the remaining 94 patients. If the 11 patients excluded were different to the remaining patients, results may be biased. Whilst it is claimed that data is collected prospectively, it is not clear at what stage the raw data is converted into the ulcer grade and whether or not there is potential flexibility in the translation of clinical data into the grading systems. If the outcome of the patient is known at the time of assigning the ulcer grade, this may introduce serious bias into the study. Statistical analysis is presented as both univariate and multivariate models. Given the lack of information provided regarding the variables entered into the multivariate models ("stepwise inclusion of the selected variables"), it is unclear what variables are being corrected for in each model. Given that this study is comparing three different grading systems, it is important to know what each grading system is being modelled with. Without further detail of the analysis, it is difficult to state whether the study was sufficiently powered, though it is likely to be very underpowered (for example, healing probability is presented for 16 S(AD)SAD categories, which would mean, even if perfectly distributed amongst the categories, there will be as few as 5 patients in each category). Finally, treatment is not controlled amongst patients with different levels of exposure and this will bias outcomes. Overall, the study has some clear sources of bias or potential bias. The statistical analysis is not presented well and does not allow a clear assessment of the ability of the grading system to predict patient outcome.	
RESULTS	

Outcome [19] Primary: Ulcer healing at 6 months Secondary: Amputation	Quality assessment: Poor
Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22] Odds Ratio

Ulcer healing at 6 months University of Texas Stage A B C D Grade 1 2-3 (it is unclear whether the odds ratios were generated from a model involving both stage and grade, or it was done separately). Prediction of ulcer healing (this is presumably the Harrell's c index?) Wagner Grade 1 2-3 c index S(AD)SAD Score ≤9 >9 *Using the above cut off to predict healing* Sensitivity Specificity Accuracy If S(AD)SAD components are examined in a multivariate logistic regression, infection predicted likelihood of healing at 6 months. No Infected Lesions Cellulitis / Osteomyelitis NOT: IT IS NOT STATED WHAT VARIABLES ARE ENTERED INTO EACH MULTIVATIRATE MODEL THEREFORE IT IS DIFFICULT TO COMPARE THE OUTPUTS OF EACH MODEL.	 4.6 (1.37-15.49) 1.68 (0.46-6.11) –not sig 2.26 (0.62-8.32) –not sig 1 (reference) 2.87 (1.08-7.64) 1 (reference) c=0.723 3.48 (1.38-8.76) 1 (reference) c=0.631 7.64 (2.72-21.45) 1 (reference) 87.5% 52.2% 70.2% 4.26 (1.77-10.26) 1 (reference) c=0.668	Blinding [15] Not reported
Conclusion: This study has shown that all three considered staging / grading systems are able to predict the likelihood of healing at 6 months in an uncontrolled setting. Lack of information regarding the construction of the multivariate analyses, and the prediction indices (c), make a comparison of the three systems, which is the title of the paper, impossible, and other than the presentation of the healing probabilities in each category of the three systems, the authors did not attempt to compare the systems in any meaningful way. For these reasons, and the reasons stated in "Overall quality assessment" section, no true estimation of the odds of ulcer healing associated with different categories in the grading systems, nor any conclusion regarding which system discriminates risk of healing better, can be made.		
EXTERNAL VALIDITY		
Generalisabilty: This study may be generalisable to other centres with similar treatment regimes. There is the danger that the population studied may be substantially different to other countries (this is indeed a conclusion of the authors who found that arteriopathy was not a significant predictor in their population whilst it was a strong predictor in US series).		
Comments: This study conveys little if no useable information. At best it shows that the studied grading systems may provide a tool for judging patient risk of healing at 6 months.		

STUDY DETAILS

Reference [1]

Beckert, S., M. Witte, et al. (2006). "A new wound-based severity score for diabetic foot ulcers - A prospective analysis of 1,000 patients." Diabetes Care 29(5): 988-992.

Affiliation/source of funds [2]

Authors do not declare conflicts of interest or funding sources

Study design [3]	Level of evidence [4]	Location/setting [5]
Cohort study	II	Outpatient wound care unit, Germany

Patient characteristics [10]	Median (range) or %	Sample size [7]
Patients		1000
N=1000		
Male	67.5%	Length of follow-up [11]
Age (years)	69 (26-95)	365 days or until amputation or healing if earlier.
Number of visits	5 (2-60)	
Multiple ulcers	40.4%	
Time of follow up (days)	68 (3-365)	
Hospitalisation	62.1%	
Wounds		
Wound history (days)	31 (1-18, 708)	
Wound area (cm^2)	0.9 (0.1-123)	
Soft tissue infection at initial visit	35.4%	
Probing to bone	26.9%	
Ulcer location (toe% : foot%)	35.6% : 64.4%	
Palpable peripheral pulses	65.6%	
Wound grading (depth)		
1 (dermis)	2.9%	
2 (subcutaneous)	63.5%	
3 (fascia)	2.0%	
4 (muscle)	4.7%	
5 (bone)	26.9%	
Surgery		
Sharp debridement	100%	
Bone resection	13.6%	
Minor amputation	9.9%	
Major amputation	2.6%	

Selection criteria

Inclusion criteria : - All diabetic patients (WHO criteria) who presented with a foot ulcer to the outpatient wound care unit (Germany) – consecutive accrual.

Exclusion criteria : Patients with less than two visits during the study period were excluded.

Predictor variable(s):	Data collection method
1. Diabetic Ulcer Severity Score (DUSS) 2. Components of DUSS - Multiple ulcers - Probing to bone - Location (foot or toe) - Non-palpable pulses	Clinical examination

Potential confounders:

Whilst treatment has been described by the researchers, it is obvious that treatment is delivered on a need basis. Therefore, patients who have more severe ulcers are likely to need more aggressive treatment. Though, as the grading system is being correlated with outcome (healing vs not healing etc), there is a danger that the wound score is not correlated to the severity of the ulcer, but rather correlated with the ulcers that are non-responsive to treatment. For instance, because treatment is not controlled for or consistent amongst different grades of ulcer, an ulcer may become healed because it was a low risk ulcer, or because it was a successfully treated high risk ulcer. Therefore a grading system that predicts healing will categorise both of these ulcers as the same.

It is not stated how many patients were excluded because they had less than two visits during the study period. There was no comparison between these patients and those left in the study – it is possible that these patients were of a different risk profile (ie, they were high risk and were hospitalised or received amputation prior to the second visit, or they may have been low risk, with the ulcer healing prior to the second visit). This may have introduced bias and reduce the generalisability of the results.

INTERNAL VALIDITY	

Outcome measurement method [12] Primary: Time to healed ulcer	Comparison of study groups [14] There has been no discussion of whether there were differences in the patient demographics or other measures between those with different DUSS grades.
Measurement bias [16] The timing of the calculation of the DUSS is not clear. This may have been done retrospectively – increasing the likelihood of bias. Different DUSS will have received different treatments which will confound the outcome. It is unclear whether researchers are blinded to the DUSS at outcome assessment. Duration of ulcer at the time of attending the clinic (baseline) is known, though it is uncertain if healing time is calculated from baseline, or extended back to the onset of the ulcer.	Follow-up (ITT) [17] The authors have not stated if any patients were lost to follow up. An undisclosed number of patients attended the clinic only once and were excluded.

Overall quality assessment (descriptive) [18]

This study was a prospective cohort study. Levels of exposure were well defined. It is implied that the DUSS was generated retrospectively, which may introduce some bias in measuring if the outcome of individual patients is known, however this is considered unlikely.

Statistics take account of differences in follow up (Kaplan-Meier and Cox regression). The risk ratio (hazard ratio) quoted assumes equal increases in risk for every 1 increase in the DUSS score, however there is no indication that proportional hazards was tested prior to the use of Cox regression.

Overall, the study is large, and measurements and procedures are well described. However, there has been no attempt to control for treatment, and as such, the true measure of association between DUSS and outcome remains unknown. Unlike other papers in for this question, the treatment regime has at least been described, therefore, if a similar treatment regime is offered in another institution, we might have some confidence that we would observe the same correlation between DUSS and outcomes.

RESULTS

Outcome [19] Primary: Time to ulcer healing	Quality assessment: Poor / Fair

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22]			Blinding [15]
Time to Ulcer Healing Cox Regression <u>Diabetic Ulcer Severity Score</u> (Hazard Ratio / RR) It is not entirely clear how this regression is put together – it does not explain how amputations are handled (ie are they censored? Or considered not healed and continue to add time to the model?) <u>DUSS components</u> *(all entered in the same Cox Regression and all are independent predictors of time to healing)* Multiple Ulcers Probing to bone Location (foot ulcer) Non-palpable pulses	0.648 (0.589-0.714) (p<0.001) Ie, for every 1 increase in DUSS score there is a 35% decrease in the chance of healing. 0.648 (0.540-0.778) p<0.0001 0.777 (0.623-0.968) p<0.025 0.483 (0.402-0.580) p<0.0001 0.723 (0.603-0.868) p<0.0001			It is not stated whether the classification of "healed" or "not healed" is done by someone who is blinded to the original DUSS, or whether the calculation of the DUSS (if done retrospectively) is done by people who are blinded to the patients progress or outcome.

Conclusion:

This study has shown that the Diabetic Ulcer Severity Score (DUSS) is associated with time to healing in this population. There are serious risks of confounding and bias, however it is likely that the results of this study would be generalisable to a similar population who follow a similar treatment protocol. The authors failed to use multivariate analysis to correct for potential confounding, however the statistical tests used were felt to be appropriate. The proportional hazard assumption was not addressed, however the Kaplan-Meier plot indicated that this assumption was not unreasonable.

As with other studies assessed for Question3 – treatment is not controlled for between groups such that groups ascribed different scores will receive different management paths and the outcome may be related to both. Therefore, again, the true measure of association between the DUSS and time to healing is unknown.

This study is generally of fair quality.

EXTERNAL VALIDITY

Generalisabilty: This study may be generalisable to other centres with similar treatment regimes.

Comments: This study shows that an increase in the DUSS at baseline is associated with a decreased chance of healing.

STUDY DETAILS

Reference [1]

Beckert, S., A. M. Pietsch, et al. (2009). "MAID A Prognostic Score Estimating Probability of Healing in Chronic Lower Extremity Wounds." Annals of Surgery 249(4): 677-681.

Affiliation/source of funds [2]

Authors do not declare conflicts of interest or funding sources

Study design [3]	Level of evidence [4]	Location/setting [5]
Cohort study	II	Outpatient wound care unit, Germany

Patient characteristics [10]	Median (range) or n (%)		Sample size [7]
Patients			2019
N=2019			
Male	1162	(58)	Length of follow-up [11]
Age (years)	70	(15-98)	365 days or until amputation or healing if earlier.
Number of visits	5	(2-96)	
Multiple ulcers	914	(45.3)	
Time of follow up (days)	73	(2-365)	
Wounds			
Wound history (days)	65	(15-21229)	
Wound area (cm^2)	2	(0.1-500)	
Non-palpable pedal pulses	901	(44.6)	
Soft tissue infection at initial visit	720	(35.7)	
Probing to bone	434	(21.5)	
Ulcer location			
Toe	450	(22.3)	
Foot	919	(45.5)	
Heal	176	(8.7)	
Leg	474	(23.5)	
Aetiology			
Vasculitis	32	(1.6)	
Non-diabetic neuropathy	87	(4.3)	
Diabetes	1000	(49.5)	
Venous insufficiency	498	(24.7)	
PAOD	234	(11.6)	
Miscellaneous	168	(8.3)	
Wound grading (depth)			
1 (dermis)	38	(1.9)	
2 (subcutaneous)	1408	(69.7)	
3 (fascia)	46	(2.3)	
4 (muscle)	93	(4.6)	
5 (bone)	434	(21.5)	
Surgery			
Minor amputation	127	(6.3)	
Major amputation	26	(1.3)	

Selection criteria

Inclusion criteria : -
All patients presenting to an outpatient wound care unit (Germany) – consecutive accrual – with chronic ulcers of the lower extremity. Chronic ulcers defined as an ulcer that has been present for at least 14 days with no signs of healing despite local therapy

Exclusion criteria : Patients with less than two visits during the study period were excluded.

Predictor variable(s):	Data collection method
1. Chronic Lower Extremity Ulcer Score (MAID)	
2. Components of MAID	
- Multiple ulcers	Clinical examination
- Wound area (>4 cm^2)	Photoplanimetry
- Wound history (>130 days)	Clinical Interview
- Non-palpable pulses	Palpation by one of 4 specially trained general surgeons

Potential confounders:

Whilst treatment has been described by the researchers, it is obvious that treatment is delivered on a need basis. Therefore, patients who have more severe ulcers are likely to need more aggressive treatment. Though, as the grading system is being correlated with outcome (healing vs not healing etc), there is a danger that the wound score is not correlated to the severity of the ulcer, but rather correlated with the ulcers that are non-responsive to treatment. For instance, because treatment is not controlled for or consistent amongst different grades of ulcer, an ulcer may become healed because it was a low risk ulcer, or because it was a successfully treated high risk ulcer. Therefore a grading system that predicts healing will categorise both of these ulcers as the same.

It is not stated how many patients were excluded because they had less than two visits during the study period. There was no comparison between these patients and those left in the study – it is possible that these patients were of a different risk profile (ie, they were high risk and were hospitalised or received amputation prior to the second visit, or they may have been low risk, with the ulcer healing prior to the second visit). This may have introduced bias and reduce the generalisability of the results.

These comments are identical to that for Beckert 2006- this is nearly an identical study by the same author and the potential confounders mentioned above remain unchanged.

**** for Liz... A component of the MAID score is "wound history" which is scored as 0 if the duration of the wound has existed for less than or equal to 130 days, and scored as 1 if the wound has existed for greater than 130 days. The duration a wound has existed prior to clinic attendance may be related to many factors, such as referral patterns. Given any alterations in the causes of wound duration (that are unrelated to the severity of the wound), the timing of clinic attendance may be substantially altered and affect the MAID score (ie, a larger number of patients with severe wounds may be seen earlier than 130 days duration, and hence their score may be revised downward, or an increase in the waiting list may result in lower risk ulcers being delayed and being seen after 130 days, resulting in an increase in their MAID score – however, in both of these examples, the severity of the ulcer appears unchanged). – problem is, i'm not sure if this is confounding??? Still, if we are using likelihood of healing at 365 days as an outcome, and we include the duration of the ulcer prior to enrolment, are we not overfitting the model? Ie, we have used something highly correlated with the outcome but only known at outcome, and used it as a variable to predict outcome.*

INTERNAL VALIDITY	
Outcome measurement method [12] Primary: Time to healed ulcer	Comparison of study groups [14] Few differences between the MAID groups were discussed. It was found that there was a difference in the presence of infection between the groups at inception, and that a toe ulcer location tended to be more common in lower MAID groups, whist heel and leg ulcers were more common in the higher MAID groups.
Measurement bias [16] It is almost certain that the MAID score was calculated retrospectively from clinical records collected from patients at the time of their visits. If the MAID score is calculated knowing the outcome of the patient, there may be some bias introduced into the study. Different MAID score will have received different treatments which will confound the outcome. It is unclear whether researchers are blinded to the MAID score at outcome assessment. Duration of ulcer at the time of attending the clinic (baseline) is known, though it is uncertain if healing time is calculated from baseline, or extended back to the onset of the ulcer.	Follow-up (ITT) [17] The authors have not stated if any patients were lost to follow up. An undisclosed number of patients attended the clinic only once and were excluded.
Overall quality assessment (descriptive) [18] This study was a prospective cohort study. Levels of exposure were well defined. The MAID score was calculated retrospectively from prospectively collected data – and as the MAID score is reasonably straight forward requiring no subjective assessment of previously recorded data, bias is considered unlikely. Statistical methods are well presented and appropriate. There is some question surrounding whether time to healing incorporates previously recorded wound duration, and if so, the usefulness of this model may be questionable. If it does not include wound duration, the generalisability of this model may be questionable, given that wound duration is likely to be related to referral pathways which may differ between hospitals and countries. Again, different MAID scores will receive different treatments and hence outcome will be confounded by treatment. The MAID score has been shown to predict outcome, which is contingent on treatment success, which is in turn influenced by wound severity. This study is large, with a well defined population and measurements. However, this paper analyses a proportion of patients who are not diabetic (about one half) and patients with leg ulcers (about one quarter). As the results are not stratified by these groups, it is impossible to estimate the true performance of the MAID score in the target population (diabetic foot ulcers).	

RESULTS	
Outcome [19] Primary: Time to ulcer healing	Quality assessment: Poor
Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22]

Time to Ulcer Healing Cox Regression MAID Score (Hazard Ratio / RR) It is not entirely clear how this regression is put together – it does not explain how amputations are handled (ie are they censored? Or considered not healed and continue to add time to the model?) MAID components *(all entered in the same Cox Regression and all are independent predictors of time to healing)* Multiple Ulcers Wound Area (>4cm) Wound History (>130 days) Non-palpable pulses	0.625 (0.583-0.669) (p<0.0001) Ie, for every 1 increase in MAID score there is a 37% decrease in the chance of healing. 0.729 (0.697-0.835) p<0.0001 0.455 (0.388-0.535) p<0.0001 0.641 (0.547-0.752) p<0.0001 0.827 (0.723-0.947) p<0.01			Blinding [15] It is not stated whether the classification of "healed" or "not healed" is done by someone who is blinded to the original MAID score, or whether the calculation of the MAID score (which was done retrospectively) is done by people who are blinded to the patients progress or outcome.
Conclusion: This study has shown that the MAID score is associated with time to healing in this population. There are serious concerns regarding confounding, particularly with different treatments given to different MAID scores. It is not certain what the real effect of MAID score upon outcome is. In particular, this study does not solely include patients who are eligible for Question 3, and their outcomes may be different to patients who are ineligible for this review, further weakening confidence in accepting the study results.				
EXTERNAL VALIDITY				
Generalisabilty: For these results to be generalisable, centres must share the same treatment regime / protocol, and have a similar referral pattern for patients. Patients who on average present earlier or later than seen in this centre may have a different MAID score.				
Comments:				

STUDY DETAILS

Reference [1]

Margolis, D. J., L. Allen-Taylor, et al. (2003). "Diabetic neuropathic foot ulcers: Predicting which ones will not heal." American Journal of Medicine 115(8): 627-631.

Affiliation/source of funds [2]

Study is supported by grants from the National Institutes of Health, Bethesda, Maryland. No conflicts of interest are recorded.

Study design [3]	Level of evidence [4]	Location/setting [5]
Retrospective Cohort study	III-3	Multicentre, US

Patient characteristics [10]

Patients of modelling dataset

N=10,211 (not healed): 9,096 (healed)

	Median (IQR) or n (row %)			
	NOT HEALED*		HEALED*	
Male	5662	(55)	4682	(45)
Age (years)	65	(54-74)	65	(54-74)
Wounds				
Grade ≤ 2	6320	(47)	7173	(53)
Grade ≥3	3801	(67)	1846	(33)
Grade 1	312	(36)	544	(64)
Grade 2	6008	(48)	6629	(52)
Grade 3	1435	(62)	894	(38)
Grade 4	1484	(67)	738	(33)
Grade 5	691	(78)	198	(22)
Grade 6	191	(92)	16	(8)
Duration (log months)	1.18	(±1.30)	0.79	(±1.31)
Size (log mm^2)	5.46	(±1.70)	4.64	(±1.63)
1 wound	4331	(46)	5024	(54)
2 wounds	2214	(54)	1879	(46)
3 wounds	1428	(62)	875	(58)
4 or more wounds	2238	(63)	1291	(36)

*Healed or not healed by the end of 20 weeks follow up
Validation data set is provided in paper, I have not recreated it here.

Sample size [7]

27,630

Length of follow-up [11]

20 weeks post enrolment

Selection criteria

Inclusion criteria : -
Patients entered onto a database who were treated within the Curative Health Services system (>150 wound care centres in US).
Patients > 18 years of age with at least one diabetic neuropathic foot ulcer

Exclusion criteria : Patients who attended the clinic only once were excluded.

Predictor variable(s):

1. Composite Wound Score
2. Components of Score
   - Ulcer Size (>2cm^2)
   - Wound area (>4 cm^2)
   - Wound history (>2 months)

Data collection method

Methods of data collection are not recorded.

Potential confounders:

All patients received a "standardised treatment approach", though this involves differential levels of treatment depending upon the perceived severity of the ulcer. Therefore, whilst a score predicts whether an ulcer has healed by 20 weeks, it is impossible to separate out the effect of treatment on the likelihood of healing.

Not all prognostic factors were collected (or retrieved), therefore there may be several exposures that may be associated with a poor outcome and they may be spread unevenly amongst patients with different Wound Scores. Therefore, it is uncertain whether the variables chosen are truly causative, or whether they are surrogates for a confounding variable .

It is not stated how many patients were excluded because they had only one visit, nor how they compared with patients who were seen more than once (ie, were they higher or lower risk). This may introduce bias into the study.

When developing and validating the final model, 447 patients are excluded due to lack of data. There is no description of the excluded patients, though if these patients primarily belong to one group or the other, it may bias the model. This is unlikely, because 447 is very small compared to the 27,630 patients initially assessed.

INTERNAL VALIDITY

Outcome measurement method [12]

Primary: Ulcer healed at 20 weeks post enrolment.

Comparison of study groups [14]

A comparison of baseline data amongst the 4 wound score exposures is not made in the paper.

Measurement bias [16]

The Score was developed using data that was collected prospectively, however, the Score itself was defined after patient outcome was known (and was defined based upon patient outcome). However, it is unlikely, given the simplicity of the score, that there is any need for subjective interpretation when calculating the score, and bias is unlikely.

Follow-up (ITT) [17]

The authors have not stated if any patients were lost to follow up. An undisclosed number of patients attended the clinic only once and were excluded.

Overall quality assessment (descriptive) [18]

This study was a retrospective cohort study. Data on patients was collected over more than a decade and recorded in a database. This data was then used to create a model that predicts healing by 20 weeks (post first visit).

Good points: This study involves over 150 different centres throughout the US. It is very large (27,000+ patients). A random part of the data set has been set aside from the model generation for the purposes of validation. Differences in outcomes between centres was considered, tested and found to be non-existent. Treatments have been described (published elsewhere). Statistics are appropriate and robust (the outcome is dichotomous and ROC AUC is used).

Bad points: The study does not correct for treatment effects. Some patients will receive different treatments depending upon the severity of their ulcer. This will therefore alter the ulcer outcome. Therefore, results may not be generalisable to places that do not offer similar treatments as study population.

And whilst this is a retrospective cohort study, it is unlikely that it will suffer any greater bias than a prospective cohort study given that the variables / exposures collected are quite routine, and were only missed on a few occasions.

RESULTS

Outcome [19]

Primary: Ulcer not healed by 20 weeks

Quality assessment:

Average

Multivariate outcome [19]

Measure of effect/effect size + 95% CI [22]

Time to Ulcer Healing

Ulcer Severity Score		IN THE VALIDATION SET % not healed at 20 weeks	Likelihood Ratio (95% CI)
Count	0	35	0.48 (0.44-0.52)
	1	47	0.78 (0.74-0.83)
	2	66	1.77 (1.64-1.90)
	3	81	3.84 (3.20-4.62)

The likelihood ratio of less than 1 suggests that the severity category is associated with *not* not healed at 20 weeks, or presumably, is associated with healing at 20 weeks.

The likelihood ratio of more than 1 suggests that the severity category is associated with not healed at 20 weeks.

I cannot interpret it more than this....

Likelihood Ratio is the Probability of having an exposure amongst those with the disease divided by the Probability of having an exposure amongst those without the disease.

In this case – for Score =0
Pr(0|not healed)/Pr(0|healed)
= (618/4370) / (1148/3894)
= 0.4797
The confidence intervals are made by bootstrapping 1000 times from the validation set.

ROC Area Under Curve

Modeling Data Set = 0.65 Validation Data Set = 0.66

THE PAPER DOES NOT INCLUDE RELATIVE RISKS, THOUGH I CAN GENERATE THESE IF YOU LIKE.

Blinding [15]

The data collected (and entered onto the database) was done prospectively, and therefore was blinded to outcome. However, the data was drawn from the database once the outcome was known. This is not likely to create substantial bias.

Conclusion:

This study has shown that the Model produced that sums a score from three dichotomous variables (Size>2cm^2, Duration>2months and Ulcer Grade≥3) has can predict the likelihood of not healing by 20 weeks. Given that this is a multi-institutional study, with an enormous number of patients, and 30% of the patients were excluded from the model development to allow validation, it is likely that the variables used in the model, and the model itself, are able to predict the likelihood of healing at 20 weeks in populations that share a common treatment protocol.

EXTERNAL VALIDITY

Generalisabilty: For these results to be generalisable, centres must share the same treatment regime / protocol, and have a similar referral pattern for patients. Again, wound duration in this study may be both a reflection of the severity of the ulcer and/or the time it takes a patient to receive treatment in this health care setting. If the latter is different in another population, the predictive ability of wound duration (in particular the chosen cut point of 2 months) will suffer.

Comments:

STUDY DETAILS

Reference [1]

Widatalla, A. H., S. E. I. Mahadi, et al. (2009). "Implementation of diabetic foot ulcer classification system for research purposes to predict lower extremity amputation." International Journal of Diabetes in Developing Countries 29(1): 1-5.

Affiliation/source of funds [2]

Authors declare no conflicts of interest, and no source of funding.

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective Cohort study	II	Single Centre (Diabetic Foot Centre in Khartoum, Sudan)

Patient characteristics [10]	Mean (SD) or %	Sample size [7]
Patients of modelling dataset		2,321
N=2,321		
Age (years)	55.5 (± 12.3)	Length of follow-up [11]
Type 2 Diabetes (%)	71	Not Reported
Foot Ulcers (%)	83.5	
Blisters (%)	55.0	
Offensive Smell (%)	15.9	
Oedema (of effected limb) (%)	36.3	
Thrombophlebitis (%)	6.7	
Fever (%)	10	
General Weakness and Prostration (%)	25	
Tissue Necrosis (%)	39	
Gangrene (%)	12.5	
Pus Discharge (%)	46.4	
Cause of Wounds		
No Inflicting Cause (%)	40.4	
Sharp Injury (%)	17.8	
New Shoes (%)	13.0	
Thermal Injuries (%)	4.5	
Various Causes (%)	24.3	
Amputations		
All Amputations (%)	28.5	
Major Lower Extreme Amputation (MLEA) (%)	10	
-Below Knee (%)	*8.7*	
-Above Knee (%)	*1.3*	
First Toe (%)	9.9	
Neuropathy		
Grade 1 (none) (%)	42.6	
Grade 2 (no pressure / vibration) (%)	57.4	
Wound Depth		
Grade 1 (superficial) (%)	41.7	
Grade 2 (fascia, muscles and tendons) (%)	42.2	
Grade 3 (bone / joint) (%)	16.0	
Infection (%)	63.6	
Grade 1 (none) (%)	*36.4*	
Grade 2 (skin and subcutaneous only) (%)	*33.0*	
Grade 3 (deep abscess, osteomyelitis etc) (%)	*26.6*	
Grade 4 (systemic responses) (%)	*4.0*	
End Stage Renal Failure (%)	3.2	

Selection criteria

Inclusion criteria : -
All patients who presented at the Jabir Abu Eliz Diabetic Centre, Khartoum, Sudan between 2003 and 2005.

Exclusion criteria : none recorded

Predictor variable(s): Data collection method

Components of wound classification by the International Consensus for the Diabetic Foot 1. Limb Ischaemia 2. Sensory Neuropathy 3. Depth and Surface Area of Wound 4. Severity of Sepsis End Stage Renal Failure	Data Collection methods are poorly reported. Components of the wound classification are well defined.

Potential confounders:

This study does not report whether there are differences in treatment for patients who present with wounds of a different severity. This is a strong confounder and will limit the generalisability of the study results.

End stage renal failure is recorded, however no other co-morbidity is reported on. There remains the possibility of confounding with other co-morbidities.

INTERNAL VALIDITY	
Outcome measurement method [12] Primary: Major Amputation or Toe Amputation	Comparison of study groups [14] Few baseline characteristics are reported. Exposed groups (defined by the presence / severity of listed components of the wound classification) are compared only regarding the outcome variable (amputations).
Measurement bias [16] The observations were collected prospectively and outcome (amputation, death, loss to follow up) is unlikely to have influenced the measurement of exposure variables.	Follow-up (ITT) [17] The authors have not stated either the length of follow up, the date of the end of the study, alternative censor groups (ie died of ulcer, lost to follow up, died of other cause) and have not recorded the number of patients who were lost to follow up.

Overall quality assessment (descriptive) [18]

This study was a prospective cohort study. Data were collected from ALL patients who attended a Diabetic Centre in Khartoum over a two or three year period (2005-2007: precise dates not given). The data collected were variables recommended by the International Consensus of the Diabetic Foot and were well defined in the study.

Outcomes were major lower extreme amputation and toe amputation.

It is not known how many patients were lost to follow up, or how many continued to be at risk at the end of the study. As we are not provided with a follow up time, it is not clear whether the dichotomous outcome variable (amputation = yes or no) is appropriate, or whether a time component should have been used. Causes of removing a patient from the study are not stated.

A multivariate model is most likely used (though not explicitly stated) as the term "independent predictor" is used in the discussion. The model (a logistic regression was most likely used given that Odds Ratios are presented - which makes it clear that a dichotomous outcome was used) is not provided and therefore it is unclear what variables are controlled for, and which are removed from the model.

It is unclear that odds ratios presented in the results are generated from a univariate or multivariate model (though it is most likely a multivariate model).

Finally, the treatment provided to patients at the diabetic centre is not stated, and given the outcome (amputation vs no amputation) is likely to be highly associated with treatment type and quality, the true association between the presented risk variables and outcome remain unknown AND will be difficult to translate into other countries that have different treatment and referral regimes.

Overall, as there were a large number of patients in this study (2,321) and all appeared to be enrolled consecutively (negating selection / enrolment bias), it is likely that there is an association between the risk variables presented as significant predictors and amputation as an outcome, however the magnitude of the association is uncertain. This study is of poor quality.

RESULTS	
Outcome [19] Primary: Major Lower Extremities Amputation or Toe Amputation	Quality assessment: Average (from the methodology checklist below) – however, given the studies poor generalisability, and the limitations of the methodology checklist, this assessment over-rates the quality of this study (it really should be poor).

Multivariate outcome [19]			Measure of effect/effect size + 95% CI [22]
Time to Ulcer Healing			Blinding [15]
<u>Major Lower Extremity Amputation</u>	OR	(95% CI)	The data are collected prospectively, therefore exposure status is measured prior to outcome. Outcome is unlikely to be influenced by the knowledge of baseline characteristics.
Neuropathy	2.43	(1.08 – 5.45)	
End Stage Renal Disease (Failure)	4.39	(1.53 – 12.61)	
Ischaemia (G1 or 2 vs G3)	5.08	(2.56 – 10.07)	
<u>Toe Amputation</u>			
Neuropathy	2.16	(1.32 – 3.5)	
Grade of Infection (G1 or 2 vs G3 or 4)	2.4	(1.55 – 3.7)	
Depth of Wound (G1 vs G2 or 3)	3.45	(2.02 – 5.88)	

Conclusion: This study has shown that neuropathy, end stage renal failure and ischaemia are predictors of major amputation, and that neuropathy, grade of infection and depth of wound are predictors of toe amputation. The study design is poor and whilst the associations are likely to be true, the strength of the associations cannot be accepted without considering the confounding effect of treatment, and without more detail regarding referral, loss to follow up, and the logistic regression model parameters.		
EXTERNAL VALIDITY		
Generalisabilty: These results are only likely to be generalisable if centres have the same population, treatment and referral protocols. Given that these are not, or only poorly, described, an estimation of the generalisability is impossible.		
Comments:		

STUDY DETAILS

Reference [1]

Ince, P., D. Kendrick, et al. (2007). "The association between baseline characteristics and the outcome of foot lesions in a UK population with diabetes." Diabetic Medicine 24(9): 977-981.

Affiliation/source of funds [2]

Source of funds not recorded, no competing interests.

Study design [3]	Level of evidence [4]	Location/setting [5]
**LIZ - Prospective Cohort study with a retrospective component??	II or III-3	Single Specialist Multidisciplinary Foot Clinic (UK)

Patient characteristics [10]		Means (±SD) or Median (IQR)	
N=449			
Age		66.7	(±13.2) years
Years of diabetes		13.3	(7.6, 21.0) years
Ulcer History (to first presentation)		29	(11, 60.5) days
		Frequency n (%)	
Male		286	(63.7)
Type II diabetes		384	(86.1)
Ulcer Site	Toe	247	(55.5)
	MTP joint	78	(17.5)
	Mid and hind foot	120	(27.0)
Ulcer Area	1	272	(60.6)
	2	108	(24.1)
	3	69	(15.4)
Ulcer Depth	1	352	(78.4)
	2	57	(12.7)
	3	40	(8.9)
Sepsis	0	246	(54.8)
	1	90	(20.0)
	2	73	(16.3)
	3	40	(8.9)
Arteriopathy	0	163	(36.3)
	1	94	(20.9)
	2	182	(40.5)
	3	10	(2.2)
Denervation	0	90	(20.0)
	1	117	(26.1)
	2	236	(52.6)
	3	6	(1.3)
Healed		295	(68.3)
Person Years Follow Up		165.0 years	
All grades refer to S(AD)SAD system. Grade 0 is impossible for "ulcer area" or "ulcer depth" (as only patients with ulcers were included in the study).			

Sample size [7]

449 (one primary ulcer per patient)

Length of follow-up [11]

At least 1 year, or until amputation or death if earlier

Selection criteria

Inclusion criteria : - All patients referred to a specialist foot clinic between 1/JAN/2000 and 31/DEC/2003.

Exclusion criteria : - Patients whose epidermis was intact were excluded (therefore only including patients with ulcers).

Predictor variable(s): Data collection method

Demographic and disease variables 1. S(AD)SAD components 2. Age 3. Duration of Diabetes 4. Duration of Ulcer 5. Gender 6. Diabetes type 7. Socio-Economic Status 8. Ulcer Site	Collected prospectively, then later retrieved from database / registry (and medical records when necessary).

Potential confounders:

Depending upon the perceived severity of an ulcer, a patient is likely to receive different treatment. This will seriously confound the outcome an ulcer.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Time to healing (complete epithelialisation of wound). Patients who die are deemed to have not healed if there is no evidence of healing before death and censored at time of death. Patients who receive an amputation are categorised as "not healed" and censored at the date of amputation.	Not applicable – characteristics such as age, gender and SES are compared later in a multivariate model. Therefore, baseline differences are controlled for using statistical methods.	Data was collected prospectively on all ulcers. The study suggests that the selection of the primary ulcer was done without reference to the outcome.

Measurement bias [16]	Follow-up (ITT) [17]
Some imprecision regarding the duration of ulcer is reported. All patients have reported the month of onset, and the study presumes that the ulcer started on the 15th of that month. Depending upon the timing of the clinics, there may be some bias introduced into this variable (for instance, it is reported that ulcers that are calculated to have negative durations due to this protocol are assumed to have a duration of 0, thereby slightly increasing the mean duration in the cohort).	Patients are followed for one year, or until amputation or death if earlier. A small proportion of patients could not be classified according to outcome (but 96% of cases could).

Overall quality assessment (descriptive) [18]

This is a cohort study in which data were collected prospectively, however, were retrieved from a registry / database or medical records at a later date. The paper suggests that sufficient data were collected for all but 17 cases (of 449), and necessitated a different ulcer to be chosen for these patients (though the selection of the primary ulcer was done blinded to patient outcome). However, the data were not collected specifically for this use, and hence the study is probably a retrospective cohort study.

A large number of variables were considered in this study, and a time component to ulcer healing was incorporated into the Cox regression. The model is multivariate and the authors have described how the final model was constructed (and how variables were included or excluded based upon their influence on the model – log likelihood test). Statistical methods are robust (and well described). A consequence of the large number of variables (both ulcer related and demographics), confounding can (to a certain extent) be controlled for in a multivariate model (for instance SES is tested for an effect on ulcer outcome before being discarded from a multivariate model). Correlation between variables was tested and the more predictive variable was kept in the model.

A major drawback to the study is the lack of description of the treatment process. It is likely that more severe ulcers receive more intensive treatment, and this effect cannot be removed from the outcomes. However, similar centres servicing similar populations would be likely to observe associations of approximately the same magnitude between variables in this paper and time to healing.

The study has inherent weaknesses, however much of what could be done, has been done to reduce bias and confounding. The quality is therefore average.

RESULTS

Outcome [19]	Quality assessment:
Time to healing (amputation and death are censored and regarded as not healed).	Average

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22]	
	Relative Risk / Hazard Ratio	

Ulcer Healing (Multivariate Cox Model)				
Ulcer Area	1	1.0	(Reference)	
	2	0.75	(0.54, 1.04)	
	3	0.40	(0.24, 0.67)	
Arteriopathy	0	1.0	(Reference)	
	1	0.76	(0.54, 1.06)	
	2 & 3	0.50	(0.37, 0.67)	
Ulcer Site	Toe	1.0	(Reference)	
	MTP	0.73	(0.51, 1.05)	
	Mid and hind foot	0.68	0.49, 0.96)	
Duration of Diabetes	<10 years	1.0	(Reference)	
	10-19 years	0.72	(0.53, 0.98)	
	≥20 years	0.66	(0.48, 0.92)	
S(AD)SAD definition of area / arteriopathy grades		To read this, we would say that an ulcer area less than 1cm^2 is two and a half times more likely to heal than an ulcer area greater than 3cm^2, when adjusted for by other predictors such as ulcer site, arteriopathy and duration of diabetes.		

Conclusion:

This study was well presented. The authors have considered potential bias and claim that although the selection of primary ulcer was done retrospectively, it was done without reference to patient outcome. All data was collected prospectively, and was sufficient for the vast majority of patients. Outcome was ascertained in 96% of cases. Sadly, the treatment protocol was not described, and this is likely to be a strong confounder of outcome.

EXTERNAL VALIDITY

Generalisabilty: This study may be generalisable to similar patients attending a diabetic foot clinic in the UK or other country with similar resources and treatment protocols.

Comments:

STUDY DETAILS

Reference [1]

Khaodhiar, L., T. Dinh, et al. (2007). "The use of medical hyperspectral technology to evaluate microcirculatory chaves in diabetic foot ulcers and to predict clinical outcomes." Diabetes Care 30(4): 903-910.

Affiliation/source of funds [2]

4 authors are employees of Hypermed, 2 authors own stock in Hypermed and one author is a paid consultant of Hypermed and also owns stock in Hypermed. Hypermed Inc. is the company that creates the HyperMed CombiVu-R System (referred to as hyperspectral technology, HT, in the study) used to measure oxy- and deoxy-haemoglobin (which is the "exposure" that is linked with time to ulcer healing).

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective observational study – most likely classified as a cohort study (there is no description of patient accrual, nor how the "control" group was chosen) -	II	"A large number of practices".

Patient characteristics [10]	Mean (±SD) or Median (IQR)	
N=10 type 1 diabetic patients with foot ulceration		
Age (years)	51	(38-64) ?median or mean, and IQR or range?
Male	N=6	ie 60%
BMI (kg/m^2)	29	(±7)
Years of diabetes	31	(±12)
Systolic blood pressure (mm/Hg)	133	(±20)
Diastolic blood pressure (mm/Hg)	76	(±8)
Ankle-brachial pressure index	1.14	(±0.19)
Transcutaneous oxygenation monitor (mmHg)	46	(±16)
Laser Doppler (Aus flux)	116	(±18)
Neuropathy Symptom Score	5	(±3)
Neuropathy Disability Score	15	(±8)
Vibration Perception Threshold (V)	44	(±10)
Semmes-Weinstein filaments (marking number)	6.2	(±0.9)
N=13 type 1 diabetic without foot ulcer (details not relevant to data extraction)		
N= 14 non-diabetic, non-foot ulcer patients (details not relevant to data extraction)		

Sample size [7]

10

Length of follow-up [11]

6 months

Selection criteria

Inclusion criteria : - 10 type 1 diabetic patients with at least 1 foot ulcer

Exclusion criteria : - peripheral arterial occlusive disease requiring surgery, heart failure resulting in oedema, stroke or TIA with residual nerve dysfunction, uncontrolled hypertension, end stage renal disease, other serious chronic diseases that affect healing, treatment with steroids or chemotherapy, pregnant or lactating women.

Predictor variable(s):	Data collection method
Demographic and disease variables 1. HT oxy-haemoglobin 2. HT deoxy-haemoglobin	Ulcer healing measured at clinic visits, or by phone if patient did not attend clinic. HT measured for all patients in clinic at baseline.

Potential confounders:

So few variables are reported that it is not clear how thoroughly confounding has been explored. Potential confounders are other ulcer characteristics (size, depth, infection etc). There may have been differences in treatment between the patients, therefore treatment may be a confounder for ulcer healing. Given that patients were selected from a "large number of practices" and were given "regular care" from their physicians, it is very likely that they type of care between the practices will be different, and the population attending the practices will be different.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Healed ulcer at the end of 6 months follow up.	A comparison between subjects that heal or not heal is not made. A comparison between patients with ulcers and those without (diabetic and non-diabetic "controls") is made, however this is not helpful in the context of this question.	Physicians who were treating the patients were blinded to the data collection of the study. It is not obvious whether it is this same physician who is deciding whether the patient has healed – in fact, it is likely that for a few patients who required phone follow up, it may have been a study person who was not blinded to the HT-oxy / deoxy measurements who ascertains the patient outcome.

Measurement bias [16]	Follow-up (ITT) [17]
Unclear. One very large ulcer is broken into 4 ulcer sites (and the analysis is done on ulcer sites) – therefore the characteristics of this ulcer and its outcome are likely to overly influence the findings (given that some of the causes of non-ulcer healing or ulcer healing will be related to the patient, and not to local factors). When comparing ulcer patients with "controls" there may be some measurement bias related to the position of the HT scan, however this is not relevant to this extraction.	Patients were followed for 6 months – no loss to follow up is recorded

Overall quality assessment (descriptive) [18]

This is a very low quality study. There is little description of how subjects were selected, over what time period, how many subjects refused etc. Subjects were not chosen consecutively and may have received vastly different treatments at different institutions. It is not clear whether every subject received the measurement of HT-oxy / deoxy (or other baseline variables) by the same physician, or whether there may have been differences in how the measurements were done. Confounding by ulcer stage / patient characteristics etc is not addressed.

The low quality and lack of transparency regarding the study design is not improved by the financial ties between several of the authors and the company providing the technology that measures the "exposures".

There is no mention of the power of the study, and given that there were only 10 patients, it is likely that the study was substantially underpowered. Several ulcer sites per patient are used as individual cases rather than selecting the primary ulcer per patient. This will introduce uncertainty into the study. If a patient has one ulcer that heals, presumably they are more likely to have other ulcers heal for reasons unrelated to the measurements taken (better self care / better treatment / better glycaemic control / non-smoker etc). Using several ulcers per patient will enhance this effect. The merit of recording one ulcer as four ulcers due to its size is also highly questionable.

The Healing Index appears to be generated from data that was only created at the time of statistical analysis – more specifically, the healing index seems to be related to a value of oxy and deoxy that best separates healed from non-healed ulcers. Therefore, the level of exposure is being defined by a metric which involves outcome – this may be difficult to apply in a prospective fashion to a new population.

RESULTS

Outcome [19]	Quality assessment:
Healed at six months – specificity, sensitivity, positive and negative predictive values of HT healing index (HT healing index is the distance between the mean oxy and deoxy measure and a discriminant line that best separates healing from non-healing).	??

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22]	
Ulcer Healing at 6 months – Healing Index		
Sensitivity	93% (66-100)	
Specificity	86% (42-100)	
PPV	93% (66-100)	
NPV	86% (42-100)	

Conclusion:

This study was poorly presented. The comparison groups add little to the study and are irrelevant to this question. The small size of the study introduces substantial uncertainty (outcome measures have wide 95% CIs), and using the same patient several times over for different ulcers presents an enormous problem when patient characteristics are not involved as confounders in any statistical model. Creating a measurement that relies upon the outcome (healing index) to predict whether an ulcer heals is of limited prognostic value.

EXTERNAL VALIDITY

Generalisabilty: There is no way of knowing how generalisable this study is to the Australian population. It was done in many centres and patient selection was not clearly stated. Only type 1 diabetes is studied.

Comments:

STUDY DETAILS

Reference [1]

Nouvong, A., B. Hoogwerf, et al. (2009). "Evaluation of diabetic foot ulcer healing with hyperspectral imaging of oxyhemoglobin and deoxyhemoglobin." Diabetes Care 32(11): 2056-2061.

Affiliation/source of funds [2]

No competing interests are disclosed. Funded by a grant from the National Institute of Diabetes and digestive and Kidney Diseases and by the Cleveland Clinic (National Institutes of Health).

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospectively collected data – prospective cohort (very poorly defined population).	II	3 centers in US – no date or period specified.

Patient characteristics [10]

N=66 (12 lost to follow up and characteristics not presented)

Means (±SD) or Median (IQR)	HEALED (n=38)		NOT HEALED (n=16)	
Male (n)	35		14	
Age (median (range))	51	(34-68)	52	(25-63)
Diabetes (type1 / type2)	15 / 23		8 / 8	
Diabetes Duration (years)	13	(±10)	12	(±8)
A1C (presumably haemoglobin A1c) %	9.7	(±2.6)	9.5	(±2.4)
BMI (kg/m^2)	34	(±10)	31	(±12)
Systolic BP (mm/Hg)	135	(±24)	142	(±21)
Diastolic BP (mm/Hg)	76	(±13)	79	(±9)
Neuropathy Symptoms Score	5.3	(±3.3)	4.9	(±3.0)
Neuropathy Disability Score	7.7	(±3.4)	6.7	(±4.9)

Sample size [7]

66 patients

54 completed with 73 ulcers.

Length of follow-up [11]

At least 1 year, or until amputation or death if earlier

Selection criteria

Inclusion criteria : - Patients aged 21 – 45 with type 1 or 2 diabetes with at least one diabetic foot ulcer.

Exclusion criteria : - peripheral arterial occlusive disease requiring surgery, heart failure resulting in oedema, stroke or TIA with residual nerve dysfunction, uncontrolled hypertension, end stage renal disease, severe peripheral oedema, other serious chronic diseases that affect healing, treatment with steroids or chemotherapy, pregnant or lactating women.

Predictor variable(s):

Healing Index (a measurement requiring oxyhaemoglobin and deoxyhaemoglobin measured at 0.5 or 1cm radius around the ulcer (depending upon ulcer size), as well as the value of oxy and deoxy that best discriminates healed and non healed ulcers).

Data collection method

Demographic and wound characteristics were collected prospectively – healing index was calculated retrospectively once outcome was known (and using the outcome to generate the index).

Potential confounders:

Differences in treatment will change the outcome of the ulcer. Different ulcer severities may receive different treatments. Treating physicians are, however, blinded to the results of the superficial tissue oxyhaemoglobin and deoxyhaemoglobin. Several wound and demographic characteristics are recorded, and are analysed for associations with wound healing, however many are not (ulcer depth, infection etc). 12 patients were excluded from the study for not finishing. In two cases, the patient required amputation (yet was still excluded from the study). In the remaining 10 cases, it is not clear why they did not finish, nor are the baseline characteristics presented to check if the group is different to the group who finished the study. This may be a major source of bias.

Many ulcers are measured from each patient. This will introduce confounding if patient characteristics are involved in outcome (diet, self care etc).

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Healed at 24 weeks. (complete reepithelialisation and no exudates = healing).	Characteristics of patients with healed ulcers were compared with patients with non-healed ulcers.	Treating physicians were blinded to the study values of oxy and deoxy haemoglobin.

Measurement bias [16]

Oxy and deoxy haemoglobin are measured by a commercial HyperSpectral Imaging system. For wounds greater than 1cm in diameter, a 1cm radial border of is used to measure the mean oxy and deoxy values, though for a wound less than 1cm in diameter, a border of 0.5cm was used. [though i am no mathematics expert – this appears to be problematic]. A wound with a diameter of 0.95cm will have the measurements based upon an area surrounding the wound of about 2.1cm^2 compared with 6.4cm^2 for a wound with a diameter of 1.05cm. There may be a systematic bias introduced around this "pivot" of wound diameter of 1cm, with measurements taken further from the wound if the wound is slightly bigger than if slightly smaller. There was no explanation of why this pivot was chosen except that changing the size of the border improved the discrimination of the test (therefore, the border was selected AFTER results were known!). By introducing this cut point, there is the danger that the measure may be a proxy or surrogate for something else, like ulcer size. It is not clear how this might bias results.

Follow-up (ITT) [17]

Patients are followed for 24 weeks, though 12 patients were "lost" – 2 receiving amputation and 10 for reasons not reported.

Overall quality assessment (descriptive) [18]

This is a prospective cohort study. The cohort is very poorly defined: there is no date range for when patients were recruited; there is no mention of how patients were recruited, (consecutive, all, random, single consultant from each centre etc) therefore we do not know whether patients were "selected" to suit the study; we do not know anything about the 12 patients (nearly 20%) of patients who were excluded from the study; it is not clear why the 2 patients excluded due to amputation are not included with the did not heal group; there is no description of treatment except that physicians were blinded to hyperspectral imaging data; whilst it appears "exposure" – the measure of oxy and deoxy-haemoglobin – were recorded prospectively, the area in which it was measured around the wound was adjusted to create better sensitivity and specificity for predicting wound outcome, therefore the measurement is, in part, linked to the outcome; and finally, the HEALING INDEX is a metric that requires statistical analysis of patient outcomes to generate and therefore has limited usefulness as a prognostic marker and whilst it relies upon there being a difference between oxy and deoxy haemoglobin in patients who heal and do not heal, the cut point can only be ascertained after the outcome – and the sensitivity / specificity of the test is therefore highly exaggerated. If a cut-point were decided prospectively (as would be required if this were to be validated as a prognostic marker for wound healing), the sensitivity and specificity would be much lower due to variations in population etc.

Many ulcers may be used from one patient – increasing the likelihood for confounding if patient characteristics influence healing rather than just oxy / deoxy measures.

This is a low quality study.

RESULTS

Outcome [19]	Quality assessment:
Ulcer Healed at 24 weeks	Average quality (according to the checklist below)

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22] *** no confidence intervals are provided	
Ulcer Healing at 24 weeks – Healing Index		
Sensitivity Specificity PPV	80% 74% 90%	
#After excluding ulcers with callused skin and with underlying osteomyelitis		
Sensitivity Specificity PPV	86% 88% 96%	
(#note: it is not clear whether the authors went back and looked at all ulcers or only the ulcers for which the healing index wrongly predicted outcome – in fact, it is implied that it is the latter – therefore these results are (more or less) pointless).		

Conclusion:

This study is poorly presented. Little information is known regarding the selection of patients and patients are discarded from the analysis without presenting characteristics nor performing a sensitivity analysis. Treatment as a confounder is not addressed. The healing index can only be calculated after it is known whether a patient heals or not. Exposure (oxy / deoxy) was defined, in part, after healing was known (ie the area around the wound that gave the most accurate results was defined post outcome – and using the outcome). There remains little confidence that this test (even if healing index was defined prior to the outcome) could predict ulcer healing at the level of sensitivity / specificity that has been reported.

EXTERNAL VALIDITY

Generalisabilty: There is no way of knowing whether the population is the same as few demographics are presented, and we do not know what treatments are given. The sensitivity and specificity of the test is specific to this population and contingent upon their rate of healing.

Comments:

STUDY DETAILS

Reference [1]

Younes, N. A. and A. M. Albsoul (2004). "The DEPA scoring system and its correlation with the healing rate of diabetic foot ulcers." J Foot Ankle Surg 43(4): 209-213.

Affiliation/source of funds [2]

None reported

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective Cohort Study	II	Single institution (Jordan University Hospital, Jordan) between 1997 and 2002

Patient characteristics [10]	Means ± SD or %	Sample size [7]
N=84 (consecutive)		84
Male (n)	52 (62%)	
Age	62 (range: 30 - 93) years	Length of follow-up [11]
Ulcer Location*:	n	20 weeks (or until healed or amputated if earlier)
• Toe	41 (49%)	
• Forefoot	24 (29%)	
• Lateral	7 (8%)	
• Dorsal	3 (4%)	
• Ankle / Heel	9 (11%)	
DEPA Score:	n	
≤6	32 (38%)	
7-9	35 (42%)	
≥10	17 (20%)	
*percents do not sum to 100 due to rounding		

Selection criteria

Inclusion criteria : - All patients with type 1 or 2 diabetes with at least 1 foot ulcer.

Exclusion criteria : - Osteomyelitis affecting the heel, large ulcers (>40cm^2) with sepsis, heel ulcers with necrotizing fasciitis extending to the ankle, foot ulcers with acute foot ischaemia.

Predictor variable(s):

Data collection method

Demographic and disease variables

1. DEPA Score (categorical)

≤6
7-9
≥10

Score:	1	2	3
Depth	Skin	Soft Tissue	Bone
Extent of bacterial colonization	Contamination	Infection	Necrotising Infection
Phase of Ulcer	Granulating	Inflammatory	Nonhealing
Associated Aetiology	Neuropathy	Bone deformity	Ischaemia

Presumably by clinical examination

Potential confounders:

Different ulcer severity (it is implied that the DEPA score or components of the DEPA score are used in the assessment of severity) receive different treatments. Presumably treatment will alter the outcome of the ulcer and therefore is a major confounder in this study. Ulcer duration is used as a component of the DEPA score. If there is a variable that allows a patient to access a clinic earlier than another patient, they are less likely to be graded a 3 for "phase of ulcer" and if this variable is also linked to ulcer healing, it will be a confounder of the study (for example, a patient with a high level of self care may access help earlier, therefore be graded lower, than a patient who is slower to present – and the patient with higher levels of self care is probably more likely to heal than one who is incapable of self care – therefore, the "Phase of Ulcer" component acts not only as a marker of more resilient ulcers, but as a surrogate for patients who present earlier.)

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Ulcer healing at 10 weeks vs 20 weeks vs not healed by 20 weeks vs Amputation	Patients with different DEPA scores are not compared for baseline variables (other than the components of the DEPA score).	Not reported – physicians giving treatment are not blinded to the DEPA score – and are unlikely to be blinded at the time of deciding whether a patient has "healed".

Measurement bias [16] Not reported – Healing was defined as "complete closure of the ulcer without the need of dressing." There may be some subjective assessment required in measuring this outcome and as physicians are unlikely to be blinded to original DEPA score, some bias may be introduced.	Follow-up (ITT) [17] Patients are followed up for 20 weeks, or until ulcer healing or amputation (if earlier).

Overall quality assessment (descriptive) [18]

This is a prospective cohort study with 84 consecutively recruited patients. Treatment is a major confounder, and will alter time to healing. This is particularly true for this study because the treatment regime is selected for patients DEPENDING UPON THEIR DEPA SCORE. However, as the treatment is the same for all patients within specific DEPA categories, and if we assume that more intensive treatment (given to the higher DEPA score patients) results in better outcomes, then this confounding will act to reduce the predictive value of DEPA. Therefore, any association between DEPA score and time to healing would be far greater if disparate treatments were removed from the study.

There may be some bias introduced by not blinding physicians to the DEPA score when they are deciding whether an ulcer is healed or not.

No multivariate model is used adjusting for known baseline factors such as age, duration of diabetes, ulcer size, smoking etc

One very good part of this paper is that the authors have explicitly stated the treatment protocols for different DEPA scores, therefore an informed decision regarding generalisability (to another institution) may be made. However, only very few demographics have been given regarding patients, which will reduce the generalisability. This is a well presented study of average quality.

RESULTS

Outcome [19] Categorical outcome - Ulcer healed at 10 weeks; ulcer healed at 20 weeks; ulcer not healed at 20 weeks; amputation required.	Quality assessment: Average

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22] Relative Risk	
No effect sizes are given. Spearman non-parametric correlation Linear regression model	Correlation coefficient 0.78 (0.68-0.86) p<0.0001 r = 0.85 slope best-fit = 0.51 (0.44-0.59) p<0.0001	

Conclusion:

This study has shown that a higher DEPA score can predict poor outcomes (less likely to heal at 10 weeks, 20 weeks, and more likely to receive amputation).

The lack of effect size or relative risks reduces the score's utility.

EXTERNAL VALIDITY

Generalisabilty: This study may be generalisable to other hospitals / clinics that have a similar treatment regime and similar waiting times (given that a component of the score is duration of ulcer).

Comments:

STUDY DETAILS

Reference [1]

Apelqvist, J., J. Castenfors, et al. (1989). "Wound classification is more important than site of ulceration in the outcome of diabetic foot ulcers." Diabet Med 6(6): 526-530.

Affiliation/source of funds [2]

No conflicts of interest are reported, research is supported by a Swedish Medical Research Council grant.

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective Cohort Study	II	Single institution (Department of Internal Medicine, University Hospital, Lund, Sweden) – accrual occurred between 1983 and 1987.

Patient characteristics [10]	Means ± SD or %		Sample size [7]
N=314 (consecutive)			314
Male (n)	156	(49.7%)	
Age	64	(± 17) years	Length of follow-up [11]
Duration of diabetes	17	(± 12) years	Not explicitly stated.
Treatment for diabetes*:			
Insulin	201	(64%)	
Oral hypoglycaemic	78	(25%)	
Both	5	(2%)	
Diet alone	30	(10%)	
Duration of Ulcer	5	(range 0 – 208) weeks	
*percents do not sum to 100 due to rounding			

Selection criteria

Inclusion criteria : - All patients with a diagnosis of diabetes with at least one foot ulcer referred to the clinic.

Exclusion criteria : - Non-stated

Predictor variable(s):

1. Wound Grade (Wagner)
2. Ulcer Site (Digit 1, Digits II-V, Metatarsal head, Mid-foot and heel, Dorsum of the foot, multiple ulcers)
3. Ankle and toe blood pressure.

Data collection method

By single team of physicians.

Potential confounders:

Different ulcer severity will receive different treatments (which will affect outcome). Whilst other possible predictor variables (ankle / toe pressures and wound site) were presented, they were not sensibly stratified or assessed in a multivariate model – therefore the predictive capacity of the wound grade is likely confounded by these variables, however we are unsure by how much.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Ulcer healing (6 months of intact skin) – if a patient dies within 6 months of achieving intact skin, it is recorded as "healed".	Patients of different Ulcer Grade are compared for ankle and toe pressures, though not for any other baseline characteristics.	Healing is unlikely to be recorded by those blinded to the Wagner grade. Nor is treatment likely to be delivered by those blinded to the grade.

Measurement bias [16]	Follow-up (ITT) [17]
As physicians are unlikely to be blinded to Wagner score at the time of establishing "healed" status, there may be some possibility of bias, though it is deemed unlikely given that there is no time limit placed upon healing, therefore if a physician decided that a wound was not quite healed, s/he would confirm it healed on the subsequent visit and the patient would be classified in the same category as if s/he had been "healed" the previous visit.	Not obvious from the paper.

Overall quality assessment (descriptive) [18]

This is a prospective cohort study with a large number of patients. Only very few baseline characteristics have been presented and none have been used in a multivariate analysis of the Wagner Grade, therefore the grading system may merely be a surrogate for other (more accurate or stronger predicting) variables. Treatment is disparate between patients of different ulcer severity and this will confound the results. No time component has been used in this study, and therefore an ulcer which heals in 2 weeks is classified the same as an ulcer that takes a year to heal. In addition, patients who die with non-healed ulcers are classified as non-healed, though clearly if a patient dies of unrelated causes 2 weeks after presenting to the clinic, this ulcer should not be classified as non-healed, but the patient should be censored from the study. Alternatively, time to healing should have been studied allowing appropriate statistical censoring to deal with deceased patients.

The methods and presentation are poor, and the study design suffers significant uncertainty.

RESULTS

Outcome [19]	Quality assessment:
Primary healed vs not (primary healing rate%)	Average

Multivariate outcome [19]

No effect sizes are given (therefore i have calculated relative risk for the Wagner Grades using grade 1 as a reference).

ULCER GRADE (WAGNER)

- 1 (superficial)
- 2 (deep)
- 3 (abscess / osteomyelitis)
- 4 and 5* (minor and major gangrene)

*5 is included with 4 as there are no patients in the "healed" category for Wagner Grade 5 (making RR difficult to generate), and there is no difference in healing rates between grade 4 and 5 (reported by the authors).

ULCER LOCATION

- Digit I
- Digits II – V
- Metatarsal Head
- Mid-foot & Heel
- Dorsum of Foot
- Multiple Ulcers (>2 ulcers)

Ankle / Toe blood pressure – is greater in grade 1, 2 and 3 compared with grades 4&5 combined (p<0.001). These measures are not reported with the outcome of healing.

Measure of effect/effect size + 95% CI [22]

Relative Risk

HEALING RATES:

grade 1 > grade 2 (p<0.05) grade 1 > grade 3 (p<0.001)
grade 1 > grade 4&5 (p<0.001) grade 2&3 > grade 4&5 (p<0.001)

HEALED	NOT HEALED	TOTAL	RR (of not healing)	
132	18	150	1	(*reference*)
37	13	50	2.17	
26	20	46	3.62	
2	66	68	8.09	

n	Primary Healed	% Healed
88	62	70
72	43	59
41	32	78
46	31	67
45	28	62
22	1	5

Conclusion:

This study has shown that the Wagner grade is associated with the likelihood of an ulcer healing. From these data, a Wagner grade 2 has about twice the chance of not healing as a Wagner grade 1. There appears to be some association with wound location also, however these data were not combined with Wagner grade, therefore the relative importance of either variable is unknown. Ankle and Toe blood pressure appear to be lower in higher Wagner grades and may be associated with reduced likelihood of healing (though this is not presented by the authors).

EXTERNAL VALIDITY

Generalisabilty: This study followed patients between 1983 and 1987. Treatment for ulcers is likely to have changed during this period, as well as treatment of co-morbid conditions that are likely to slow ulcer healing (diabetes, peripheral vascular disease etc). It is uncertain how applicable these results are today, nor how generalisable they may be to an Australian setting.

Comments:

STUDY DETAILS

Reference [1] Armstrong, D. G., L. A. Lavery, et al. (1998). "Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation." Diabetes Care 21(5): 855-859.

Affiliation/source of funds [2]

No conflicts of interest are reported, funding source not identified.

Study design [3]	Level of evidence [4]	Location/setting [5]
Retrospective Cohort	III-3	Single institution (University of Texas Health Science Center).

Patient characteristics [10]		Means ± SD or %			Sample size [7]
N=360 (how the patients were selected is not recorded)					360
Male (n)		68.6%			
Age		53.9	(± 10.4) years		Length of follow-up [11]
Duration of diabetes		14	(± 9.2) years		6 months
Race:	Mexican/American	79.2%			
	Non-Hispanic White	12.5%			
	African American	6.7%			
	Asian	1.6%			
		Palpable pedal pulses%		*Ankle Brachial Index*	
Stage (n):	A (164)	78%		1.03	(± 0.15)
	B (158)	83.5%		1.02	(± 0.14)
	C (21)	14.3%		0.71	(± 0.18)
	D (17)	5.9%		0.66	(± 0.19)
Age, Duration of diabetes, % men and race are also separated out by stage.					

Selection criteria

Inclusion criteria : - Patients with a complicated foot wound (below the ankle) between 1st Jan 1994 and 1st July 1996 presenting to a multidisciplinary tertiary care diabetic foot clinic. All patients have verified diabetes.

Exclusion criteria : - None-stated

Predictor variable(s):	Data collection method
1. Wound Grade (0=healed, 1=superficial, 2=to tendon or capsule, 3=bone or joint) 2. Wound Stage (A=clean, B=non-ischaemic infected, C=ischaemic non-infected, D=ischaemic and infected)	Wounds graded by one principle investigator

Potential confounders:

Wounds graded more severely will receive more rigorous treatment (which will in turn result in improved outcomes). There is also wide variability of race between the groups (when separated by stage). There appear to be more Mexican Americans in the highest stage and fewer non-Hispanic white patients. This trend is unlikely to be statistically significant, though if there are differences in the genetics or cultures that predispose better or worse outcomes, this may be a small confounding factor.

There is no measure of ulcer duration used in this analysis. Given that the outcome (amputation y/n at six months) will be contingent (in part) upon the length of time an ulcer is present and not healing, patients seen with earlier ulcers may not have sufficient time to progress to higher grade ulcers and receive an amputation compared with those who are seen by the clinic with higher grade / higher stage ulcers to begin with. It seems likely that many high stage and high grade ulcers would have begun as lower stage / grade ulcers before progressing – therefore without controlling for duration of ulcer, amputation as a dichotomous outcome may be related to grade / stage but partly as a surrogate for duration spent with the ulcer. A study based elsewhere that sees the same patients at different times after the inception of their ulcer may find a different relationship between grade, stage and amputation.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Prevalence of amputation at 6 months.	Patients of different Ulcer Grade and different ulcer stage are compared baseline characteristics.	The classification of the wound (stage and grade) is unlikely to have occurred blinded to the outcome (amputation) and there exists the potential for bias.

Measurement bias [16] Many measurements were made on a clinical basis. It might be possible that more worrying diagnoses are made of more worrying appearing wounds. Infection, for instance, is diagnosed by several local signs, and if it is missed, it is more likely to be missed in smaller and less worrying looking wounds. Again, vascular insufficiency (another variable diagnosed clinically) may be more scrutinised in wounds that look more severe. Therefore, variables defined clinically may be discovered more frequently in "severe looking" wounds though the prevalence of the variables may be biased by inconsistent measurements.	Follow-up (ITT) [17] No loss to follow up is recorded, all patients are followed to 6 months.

Overall quality assessment (descriptive) [18]

This is a retrospective cohort study. It is not clear how the population was recruited or how many people were excluded, and for what reasons, in the creation of the sample, therefore we cannot comment on selection bias. An investigator has assigned stages and grades to the population from the medical records (retrospectively) and the outcome is likely to be at hand during this process, therefore there is the potential for allocation bias. The patients were originally assessed by a clinic though not in a controlled environment; therefore it is uncertain whether the same protocol was followed for each patient.

Finally, treatment is likely to be different for patients with different severity of wounds, therefore confounding outcome.

This study quality is generally poor, with insufficient detail in the published paper to provide confidence regarding sources of bias.

RESULTS

Outcome [19]	Quality assessment:
Amputation at 6 months	Average

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22]
	Relative Risk

Prevalence of amputations within each wound category

		GRADE			
STAGE	0	I	II	III	
A	0%	0%	0%	0%	no difference
B	12.5%	8.5%	28.6%	92%	p<0.0001
C	26.0%	24.0%*	26.0%	100%	p<0.001*
D	50.0%	50.0%	100%	100%	p=0.02

*some figures are almost illegible – even when extracted from a pdf on the computer screen

Grade III vs Grade 0-II

18.3% vs 2.0%, p<0.001, OR = 11.1, 95% CI 4.0 – 30.3

Stage D vs Stage A-C

76.5% vs 3.5%, p<0.001, OR=89.6, 95% CI 25 – 316

Conclusion:

This study shows that patients with stage D cancer are nearly 90 times more likely to receive an amputation in the first 6 months after attending a clinic than patients with lesser stages, and patients with Grade III cancer are more than 11 times more likely to receive an amputation than patients with lower grades in the 6 months after presentation.

However, treatment is a confounder for outcome, and no account for the duration of the ulcer has been made. There may be some confounding due to a difference in race across different ulcer grades. Also, this study was not done in a controlled environment, and it is not explained how the original assessments (pre-assigning of the grade and stage – which were done using medical records) were done, and whether there may have been problems with inter-rater reliability.

Whilst the effect is likely to be real, we cannot be certain how much of the effect is real and how much is due to bias and/or confounding.

EXTERNAL VALIDITY

Generalisabilty: Nearly 80% of patients were recorded as being of Mexican-American race. If race is linked to outcome, it may be difficult to know if this data is generalisable. Also, treatment may be very different in Texas then Australia, and as it was not described, it is impossible to know whether these outcomes are generalisable.

Comments:

Question 5

STUDY DETAILS

Reference [1]

Oyibo, S. O., E. B. Jude, et al. (2001). "The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers." Diabetic Medicine 18(2): 133-138.

Affiliation/source of funds [2]

None reported

Study design [3]	Level of evidence [4]	Location/setting [5]
Cohort study	II	Outpatient setting, two diabetic foot centres (UK and Texas)

Patient characteristics [10]	Means ± SD or %
N=194	
Male	149/194 (77%)
Age	56.6 (±12.6) years
Type II diabetes	89%
Duration of diabetes	15.4 (±9.9) years
Ulcer Characteristics	
Neuropathic	67%
Neuroischaemic	26.3%
Ischaemic	1%
Superficial	68%
To Tendon	15%
To Bone	17%
Infection	40%
Area	1.5 (IQR 0.6-4.0) cm^2

Sample size [7]

194 (one primary ulcer per patient)

Length of follow-up [11]

At least 6 months

Selection criteria

Inclusion criteria : - All diabetic patients who presented with a new foot ulcer to two diabetic foot centres

Exclusion criteria : - none stated

Predictor variable(s):	Data collection method
Demographic and disease variables 10. Age (ns) 11. Sex (ns) 12. Diabetes Type (ns) 13. Diabetes Duration (ns) 14. Ulcer Size (significant predictor) 15. Ulcer Site (ns) 16. Ulcer Depth (ns) 17. Presence of infection (ns) 18. Presence of ischaemia (significant predictor)	Presumably by interview and clinical examination

Potential confounders:

Type of treatment given for ulcers will differ depending upon the severity (or perceived severity) of the ulcer.

Collinearity between ulcer variables – largest ulcers also tended to be the deepest and the most infected – and deep ulcers tended to predict amputation – and infected ulcers took longer to heal.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Time to healing and amputation.	Not applicable	Not reported

Measurement bias [16]	Follow-up (ITT) [17]
Not reported	It is unclear what proportion of patients were followed for a minimum of 6 months – though at the termination of the study (18 months post first enrolment) – 3.5% of patients were lost to death.

Overall quality assessment (descriptive) [18]

This study was a prospective cohort study. Patients with different levels of exposure (different baseline assessments of ulcers) are given disparate treatment regimens. Whilst it is unlikely that the treatments will have a detrimental effect upon the outcomes, and more rigorous treatment for ulcers assessed to be more severe is likely to bias the outcome toward a smaller difference between exposure groups, it remains unclear what the true effect of the exposures has upon outcomes.

Results are not clearly documented. It is unclear whether ulcers may still be classified as healed if this occurs following the first 6 months of follow up, or if amputations that take place outside of the first 6 months are regarded. Given the different lengths of time patients are followed for (minimum of 6 months and maximum of 18 months), there may be some problems interpreting statistics based on outcomes that may have occurred beyond 6 months. "Time to healing" has been modelled with a Cox Regression, however this is poorly presented and an optimum model has not been proposed nor have tests for variable interactions been performed.

RESULTS

Outcome [19]	Quality assessment:
Ulcer healing at the end of the study (healed, unhealed, amputation and death) Time to healing	Poor

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22] Relative Risk	
Ulcer not healed by end of study		
Ulcer Size	1.08 (1.01 – 1.14)	
Presence of Ischaemia	1.69 (1.06-2.70)	
The paper only poorly describes the above Cox Regression – given that a Cox Regression has been used, this is more likely to be measuring length of time an ulcer remains unhealed rather than a dichotomous outcome of healed or not. Presumably the relative risk for presence of ischaemia reflects a 1.69 times increase in risk of an unhealed ulcer with the presence of ischaemia compared to the absence of ischaemia. Whilst not explicitly stated, the paper indicates that Ulcer Size was a continuous variable in the model, and that for each increase of 1 cm^2 in ulcer area, the risk of not healing by the end of the study increased by 1.1 times. These results are spurious as the model contains many variables that are not predictors, and variables that may be strongly collinear.		

Conclusion: This study has found that the size of a foot ulcer in diabetic patients is a predictor of outcomes (such as time to healing and likelihood of amputation). The presentation of results is poor and makes further conclusions difficult. Different treatments or management pathways for patients with differing levels of exposure further complicates the ability to extract a true measure of association between ulcer size and outcome.		
EXTERNAL VALIDITY		
Generalisabilty: This study may be generalisable to patients attending a diabetic foot clinic for the assessment of new ulcers.		
Comments: The presentation of this study is poor and inadequate to extract meaningful information. The study design allows confounding and statistical efforts to control for potential associations are poorly executed. It is likely that the association between ulcer size and healing time is real, however the strength of this association remains uncertain.		

STUDY DETAILS

Reference [1]

Parisi, M. C. R., D. E. Zantut-Wittmann, et al. (2008). "Comparison of three systems of classification in predicting the outcome of diabetic foot ulcers in a Brazilian population." European Journal of Endocrinology 159(4): 417-422.

Affiliation/source of funds [2]

None reported – authors declare no conflict of interest

Study design [3]	Level of evidence [4]	Location/setting [5]
Cohort study	II	Outpatient setting, specialist unit in Brazil

Patient characteristics [10]	Means ± SD or %
N=94	
Male	61%
Age	57.6 (±12.4) years
Duration of diabetes	16.91 (±8.2) years
Smoking	41%
Hypertension	81%
Cardiovascular disease	33%
Stroke	7%
Neuropathy	59%
Ischaemia	36%
Severe Ischaemia	5%
Plantar Ulcer	95%
Dorsal Ulcer	5%

Sample size [7]

94 (one primary ulcer per patient)

Length of follow-up [11]

At least 6 months

(no further detail given)

Selection criteria

Inclusion criteria : - All diabetic patients who presented with a foot ulcer to the specialist centre in Brazil

Exclusion criteria : - none stated

Predictor variable(s):	Data collection method
Ulcer Classification Systems 4. Wagner ulcer classification system 5. University of Texas classification system 6. Size (area, depth), sepsis, arteriopathy, denervation (S(AD)SAD) classification system	Clinical examination

Potential confounders:

Treatment is not controlled amongst the groups of different exposures. Therefore groups with perceived more aggressive ulcers are more likely to receive different / more drastic treatments.

11 patients from the initial 105 (10.5%) were excluded due to lack of data. There is insufficient detail in the report to ascertain whether these patients may be missing data for a reason that may be related to their level of exposure or outcome.

INTERNAL VALIDITY

Outcome measurement method [12]

Primary: Healed ulcer at 6 months post enrolment

Secondary: Amputation

Comparison of study groups [14]

Whilst the data appears to have been collected on several baseline patient characteristics, there is no discussion whether these characteristics are uniform across all grades, or whether there are associations between certain characteristics and ulcer grades.

The study has stated that there was no difference in outcome between gender, age or duration of diabetes groups.

Measurement bias [16] Not reported Patients are unlikely to have been treated the same – and their treatment will be contingent upon the perceived severity of the ulcer, and this is linked with exposure status.	Follow-up (ITT) [17] No patients were lost to follow up, however 11 patients had insufficient data for analysis and were excluded. It is unclear what the average follow up duration was, however the primary outcome was healed or not healed by 6 months.

Overall quality assessment (descriptive) [18]

This study was a prospective cohort study. Consecutive patients attending a specialist clinic were enrolled (and refusals for the study are not mentioned and presumably did not occur).

11 patients of 105 were excluded for lack of data. Baseline characteristics of these patients were not compared to the remaining 94 patients. If the 11 patients excluded were different to the remaining patients, results may be biased.

Whilst it is claimed that data is collected prospectively, it is not clear at what stage the raw data is converted into the ulcer grade and whether or not there is potential flexibility in the translation of clinical data into the grading systems. If the outcome of the patient is known at the time of assigning the ulcer grade, this may introduce serious bias into the study.

Statistical analysis is presented as both univariate and multivariate models. Given the lack of information provided regarding the variables entered into the multivariate models ("stepwise inclusion of the selected variables"), it is unclear what variables are being corrected for in each model. Given that this study is comparing three different grading systems, it is important to know what each grading system is being modelled with. Without further detail of the analysis, it is difficult to state whether the study was sufficiently powered, though it is likely to be very underpowered (for example, healing probability is presented for 16 S(AD)SAD categories, which would mean, even if perfectly distributed amongst the categories, there will be as few as 5 patients in each category).

Finally, treatment is not controlled amongst patients with different levels of exposure and this will bias outcomes.

Overall, the study has some clear sources of bias or potential bias. The statistical analysis is not presented well and does not allow a clear assessment of the ability of the grading system to predict patient outcome.

RESULTS

Outcome [19] Primary: Ulcer healing at 6 months Secondary: Amputation	Quality assessment: Poor

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22] Odds Ratio	
Ulcer healing at 6 months <u>University of Texas</u> Stage A B C D Grade 1 2-3 (it is unclear whether the odds ratios were generated from a model involving both stage and grade, or it was done separately). Prediction of ulcer healing (this is presumably the Harrell's c index?) <u>Wagner</u> Grade 1 2-3 c index <u>S(AD)SAD</u> Score ≤9 >9 *Using the above cut off to predict healing* Sensitivity Specificity Accuracy If S(AD)SAD components are examined in a multivariate logistic regression, infection predicted likelihood of healing at 6 months. No Infected Lesions Cellulitis / Osteomyelitis NOTE: IT IS NOT STATED WHAT VARIABLES ARE ENTERED INTO EACH MULTIVATIRATE MODEL THEREFORE IT IS DIFFICULT TO COMPARE THE OUTPUTS OF EACH MODEL.	 4.6 (1.37-15.49) 1.68 (0.46-6.11) –not sig 2.26 (0.62-8.32) –not sig 1 (reference) 2.87 (1.08-7.64) 1 (reference) c=0.723 3.48 (1.38-8.76) 1 (reference) c=0.631 7.64 (2.72-21.45) 1 (reference) 87.5% 52.2% 70.2% 4.26 (1.77-10.26) 1 (reference) c=0.668	Blinding [15] Not reported

Conclusion: This study has shown that all three considered staging / grading systems are able to predict the likelihood of healing at 6 months in an uncontrolled setting. Lack of information regarding the construction of the multivariate analyses, and the prediction indices (c), make a comparison of the three systems, which is the title of the paper, impossible, and other than the presentation of the healing probabilities in each category of the three systems, the authors did not attempt to compare the systems in any meaningful way. For these reasons, and the reasons stated in "Overall quality assessment" section, no true estimation of the odds of ulcer healing associated with different categories in the grading systems, nor any conclusion regarding which system discriminates risk of healing better, can be made.		
EXTERNAL VALIDITY		
Generalisabilty: This study may be generalisable to other centres with similar treatment regimes. There is the danger that the population studied may be substantially different to other countries (this is indeed a conclusion of the authors who found that arteriopathy was not a significant predictor in their population whilst it was a strong predictor in US series).		
Comments: This study conveys little if no useable information. At best it shows that the studied grading systems may provide a tool for judging patient risk of healing at 6 months.		

STUDY DETAILS

Reference [1]

Beckert, S., M. Witte, et al. (2006). "A new wound-based severity score for diabetic foot ulcers - A prospective analysis of 1,000 patients." Diabetes Care 29(5): 988-992.

Affiliation/source of funds [2]

Authors do not declare conflicts of interest or funding sources

Study design [3]	Level of evidence [4]	Location/setting [5]
Cohort study	II	Outpatient wound care unit, Germany

Patient characteristics [10]	Median (range) or %	Sample size [7]
Patients		1000
N=1000		
Male	67.5%	Length of follow-up [11]
Age (years)	69 (26-95)	365 days or until amputation or healing if earlier.
Number of visits	5 (2-60)	
Multiple ulcers	40.4%	
Time of follow up (days)	68 (3-365)	
Hospitalisation	62.1%	
Wounds		
Wound history (days)	31 (1-18, 708)	
Wound area (cm^2)	0.9 (0.1-123)	
Soft tissue infection at initial visit	35.4%	
Probing to bone	26.9%	
Ulcer location (toe% : foot%)	35.6% : 64.4%	
Palpable peripheral pulses	65.6%	
Wound grading (depth)		
1 (dermis)	2.9%	
2 (subcutaneous)	63.5%	
3 (fascia)	2.0%	
4 (muscle)	4.7%	
5 (bone)	26.9%	
Surgery		
Sharp debridement	100%	
Bone resection	13.6%	
Minor amputation	9.9%	
Major amputation	2.6%	

Selection criteria

Inclusion criteria : - All diabetic patients (WHO criteria) who presented with a foot ulcer to the outpatient wound care unit (Germany) – consecutive accrual.

Exclusion criteria : Patients with less than two visits during the study period were excluded.

Predictor variable(s):	Data collection method
3. Diabetic Ulcer Severity Score (DUSS) 4. Components of DUSS - Multiple ulcers - Probing to bone - Location (foot or toe) - Non-palpable pulses	Clinical examination

Potential confounders:

Whilst treatment has been described by the researchers, it is obvious that treatment is delivered on a need basis. Therefore, patients who have more severe ulcers are likely to need more aggressive treatment. Though, as the grading system is being correlated with outcome (healing vs not healing etc), there is a danger that the wound score is not correlated to the severity of the ulcer, but rather correlated with the ulcers that are non-responsive to treatment. For instance, because treatment is not controlled for or consistent amongst different grades of ulcer, an ulcer may become healed because it was a low risk ulcer, or because it was a successfully treated high risk ulcer. Therefore a grading system that predicts healing will categorise both of these ulcers as the same.

It is not stated how many patients were excluded because they had less than two visits during the study period. There was no comparison between these patients and those left in the study – it is possible that these patients were of a different risk profile (ie, they were high risk and were hospitalised or received amputation prior to the second visit, or they may have been low risk, with the ulcer healing prior to the second visit). This may have introduced bias and reduce the generalisability of the results.

INTERNAL VALIDITY	

Outcome measurement method [12] Primary: Time to healed ulcer	Comparison of study groups [14] There has been no discussion of whether there were differences in the patient demographics or other measures between those with different DUSS grades.
Measurement bias [16] The timing of the calculation of the DUSS is not clear. This may have been done retrospectively – increasing the likelihood of bias. Different DUSS will have received different treatments which will confound the outcome. It is unclear whether researchers are blinded to the DUSS at outcome assessment. Duration of ulcer at the time of attending the clinic (baseline) is known, though it is uncertain if healing time is calculated from baseline, or extended back to the onset of the ulcer.	Follow-up (ITT) [17] The authors have not stated if any patients were lost to follow up. An undisclosed number of patients attended the clinic only once and were excluded.

Overall quality assessment (descriptive) [18]

This study was a prospective cohort study. Levels of exposure were well defined. It is implied that the DUSS was generated retrospectively, which may introduce some bias in measuring if the outcome of individual patients is known, however this is considered unlikely.

Statistics take account of differences in follow up (Kaplan-Meier and Cox regression). The risk ratio (hazard ratio) quoted assumes equal increases in risk for every 1 increase in the DUSS score, however there is no indication that proportional hazards was tested prior to the use of Cox regression.

Overall, the study is large, and measurements and procedures are well described. However, there has been no attempt to control for treatment, and as such, the true measure of association between DUSS and outcome remains unknown. Unlike other papers in for this question, the treatment regime has at least been described, therefore, if a similar treatment regime is offered in another institution, we might have some confidence that we would observe the same correlation between DUSS and outcomes.

RESULTS

Outcome [19] Primary: Time to ulcer healing	Quality assessment: Poor / Fair

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22]	Blinding [15]
Time to Ulcer Healing Cox Regression <u>Diabetic Ulcer Severity Score</u> (Hazard Ratio / RR) It is not entirely clear how this regression is put together – it does not explain how amputations are handled (ie are they censored? Or considered not healed and continue to add time to the model?) <u>DUSS components</u> *(all entered in the same Cox Regression and all are independent predictors of time to healing)* Multiple Ulcers Probing to bone Location (foot ulcer) Non-palpable pulses	0.648 (0.589-0.714) (p<0.001) Ie, for every 1 increase in DUSS score there is a 35% decrease in the chance of healing. 0.648 (0.540-0.778) p<0.0001 0.777 (0.623-0.968) p<0.025 0.483 (0.402-0.580) p<0.0001 0.723 (0.603-0.868) p<0.0001	It is not stated whether the classification of "healed" or "not healed" is done by someone who is blinded to the original DUSS, or whether the calculation of the DUSS (if done retrospectively) is done by people who are blinded to the patients progress or outcome.

Conclusion:

This study has shown that the Diabetic Ulcer Severity Score (DUSS) is associated with time to healing in this population. There are serious risks of confounding and bias, however it is likely that the results of this study would be generalisable to a similar population who follow a similar treatment protocol. The authors failed to use multivariate analysis to correct for potential confounding, however the statistical tests used were felt to be appropriate. The proportional hazard assumption was not addressed, however the Kaplan-Meier plot indicated that this assumption was not unreasonable.

As with other studies assessed for Question3 – treatment is not controlled for between groups such that groups ascribed different scores will receive different management paths and the outcome may be related to both. Therefore, again, the true measure of association between the DUSS and time to healing is unknown.

This study is generally of fair quality.

EXTERNAL VALIDITY

Generalisabilty: This study may be generalisable to other centres with similar treatment regimes.

Comments: This study shows that an increase in the DUSS at baseline is associated with a decreased chance of healing.

STUDY DETAILS

Reference [1]

Beckert, S., A. M. Pietsch, et al. (2009). "MAID A Prognostic Score Estimating Probability of Healing in Chronic Lower Extremity Wounds." Annals of Surgery 249(4): 677-681.

Affiliation/source of funds [2]

Authors do not declare conflicts of interest or funding sources

Study design [3]	Level of evidence [4]	Location/setting [5]
Cohort study	II	Outpatient wound care unit, Germany

Patient characteristics [10]	Median (range) or n (%)		Sample size [7]
Patients			2019
N=2019			
Male	1162	(58)	Length of follow-up [11]
Age (years)	70	(15-98)	365 days or until amputation or healing if earlier.
Number of visits	5	(2-96)	
Multiple ulcers	914	(45.3)	
Time of follow up (days)	73	(2-365)	
Wounds			
Wound history (days)	65	(15-21229)	
Wound area (cm^2)	2	(0.1-500)	
Non-palpable pedal pulses	901	(44.6)	
Soft tissue infection at initial visit	720	(35.7)	
Probing to bone	434	(21.5)	
Ulcer location			
Toe	450	(22.3)	
Foot	919	(45.5)	
Heal	176	(8.7)	
Leg	474	(23.5)	
Aetiology			
Vasculitis	32	(1.6)	
Non-diabetic neuropathy	87	(4.3)	
Diabetes	1000	(49.5)	
Venous insufficiency	498	(24.7)	
PAOD	234	(11.6)	
Miscellaneous	168	(8.3)	
Wound grading (depth)			
1 (dermis)	38	(1.9)	
2 (subcutaneous)	1408	(69.7)	
3 (fascia)	46	(2.3)	
4 (muscle)	93	(4.6)	
5 (bone)	434	(21.5)	
Surgery			
Minor amputation	127	(6.3)	
Major amputation	26	(1.3)	

Selection criteria

Inclusion criteria : -
All patients presenting to an outpatient wound care unit (Germany) – consecutive accrual – with chronic ulcers of the lower extremity. Chronic ulcers defined as an ulcer that has been present for at least 14 days with no signs of healing despite local therapy

Exclusion criteria : Patients with less than two visits during the study period were excluded.

Predictor variable(s):	Data collection method
3. Chronic Lower Extremity Ulcer Score (MAID)	
4. Components of MAID	
- Multiple ulcers	Clinical examination
- Wound area (>4 cm^2)	Photoplanimetry
- Wound history (>130 days)	Clinical Interview
- Non-palpable pulses	Palpation by one of 4 specially trained general surgeons

Potential confounders:

Whilst treatment has been described by the researchers, it is obvious that treatment is delivered on a need basis. Therefore, patients who have more severe ulcers are likely to need more aggressive treatment. Though, as the grading system is being correlated with outcome (healing vs not healing etc), there is a danger that the wound score is not correlated to the severity of the ulcer, but rather correlated with the ulcers that are non-responsive to treatment. For instance, because treatment is not controlled for or consistent amongst different grades of ulcer, an ulcer may become healed because it was a low risk ulcer, or because it was a successfully treated high risk ulcer. Therefore a grading system that predicts healing will categorise both of these ulcers as the same.

It is not stated how many patients were excluded because they had less than two visits during the study period. There was no comparison between these patients and those left in the study – it is possible that these patients were of a different risk profile (ie, they were high risk and were hospitalised or received amputation prior to the second visit, or they may have been low risk, with the ulcer healing prior to the second visit). This may have introduced bias and reduce the generalisability of the results.

These comments are identical to that for Beckert 2006- this is nearly an identical study by the same author and the potential confounders mentioned above remain unchanged.

**** for Liz... A component of the MAID score is "wound history" which is scored as 0 if the duration of the wound has existed for less than or equal to 130 days, and scored as 1 if the wound has existed for greater than 130 days. The duration a wound has existed prior to clinic attendance may be related to many factors, such as referral patterns. Given any alterations in the causes of wound duration (that are unrelated to the severity of the wound), the timing of clinic attendance may be substantially altered and affect the MAID score (ie, a larger number of patients with severe wounds may be seen earlier than 130 days duration, and hence their score may be revised downward, or an increase in the waiting list may result in lower risk ulcers being delayed and being seen after 130 days, resulting in an increase in their MAID score – however, in both of these examples, the severity of the ulcer appears unchanged). – problem is, i'm not sure if this is confounding??? Still, if we are using likelihood of healing at 365 days as an outcome, and we include the duration of the ulcer prior to enrolment, are we not overfitting the model? Ie, we have used something highly correlated with the outcome but only known at outcome, and used it as a variable to predict outcome.*

INTERNAL VALIDITY	
Outcome measurement method [12] Primary: Time to healed ulcer	Comparison of study groups [14] Few differences between the MAID groups were discussed. It was found that there was a difference in the presence of infection between the groups at inception, and that a toe ulcer location tended to be more common in lower MAID groups, whist heel and leg ulcers were more common in the higher MAID groups.
Measurement bias [16] It is almost certain that the MAID score was calculated retrospectively from clinical records collected from patients at the time of their visits. If the MAID score is calculated knowing the outcome of the patient, there may be some bias introduced into the study. Different MAID score will have received different treatments which will confound the outcome. It is unclear whether researchers are blinded to the MAID score at outcome assessment. Duration of ulcer at the time of attending the clinic (baseline) is known, though it is uncertain if healing time is calculated from baseline, or extended back to the onset of the ulcer.	Follow-up (ITT) [17] The authors have not stated if any patients were lost to follow up. An undisclosed number of patients attended the clinic only once and were excluded.
Overall quality assessment (descriptive) [18] This study was a prospective cohort study. Levels of exposure were well defined. The MAID score was calculated retrospectively from prospectively collected data – and as the MAID score is reasonably straight forward requiring no subjective assessment of previously recorded data, bias is considered unlikely. Statistical methods are well presented and appropriate. There is some question surrounding whether time to healing incorporates previously recorded wound duration, and if so, the usefulness of this model may be questionable. If it does not include wound duration, the generalisability of this model may be questionable, given that wound duration is likely to be related to referral pathways which may differ between hospitals and countries. Again, different MAID scores will receive different treatments and hence outcome will be confounded by treatment. The MAID score has been shown to predict outcome, which is contingent on treatment success, which is in turn influenced by wound severity. This study is large, with a well defined population and measurements. However, this paper analyses a proportion of patients who are not diabetic (about one half) and patients with leg ulcers (about one quarter). As the results are not stratified by these groups, it is impossible to estimate the true performance of the MAID score in the target population (diabetic foot ulcers).	

RESULTS	
Outcome [19] Primary: Time to ulcer healing	Quality assessment: Poor
Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22]

Time to Ulcer Healing Cox Regression MAID Score (Hazard Ratio / RR) It is not entirely clear how this regression is put together – it does not explain how amputations are handled (ie are they censored? Or considered not healed and continue to add time to the model?) MAID components *(all entered in the same Cox Regression and all are independent predictors of time to healing)* Multiple Ulcers Wound Area (>4cm) Wound History (>130 days) Non-palpable pulses	0.625 (0.583-0.669) (p<0.0001) Ie, for every 1 increase in MAID score there is a 37% decrease in the chance of healing. 0.729 (0.697-0.835) p<0.0001 0.455 (0.388-0.535) p<0.0001 0.641 (0.547-0.752) p<0.0001 0.827 (0.723-0.947) p<0.01	Blinding [15] It is not stated whether the classification of "healed" or "not healed" is done by someone who is blinded to the original MAID score, or whether the calculation of the MAID score (which was done retrospectively) is done by people who are blinded to the patients progress or outcome.
Conclusion: This study has shown that the MAID score is associated with time to healing in this population. There are serious concerns regarding confounding, particularly with different treatments given to different MAID scores. It is not certain what the real effect of MAID score upon outcome is. In particular, this study does not solely include patients who are eligible for Question 3, and their outcomes may be different to patients who are ineligible for this review, further weakening confidence in accepting the study results.		
EXTERNAL VALIDITY		
Generalisabilty: For these results to be generalisable, centres must share the same treatment regime / protocol, and have a similar referral pattern for patients. Patients who on average present earlier or later than seen in this centre may have a different MAID score.		
Comments:		

STUDY DETAILS

Reference [1]

Margolis, D. J., L. Allen-Taylor, et al. (2003). "Diabetic neuropathic foot ulcers: Predicting which ones will not heal." American Journal of Medicine 115(8): 627-631.

Affiliation/source of funds [2]

Study is supported by grants from the National Institutes of Health, Bethesda, Maryland. No conflicts of interest are recorded.

Study design [3]	Level of evidence [4]	Location/setting [5]
Retrospective Cohort study	III-3	Multicentre, US

Patient characteristics [10]	Median (IQR) or n (row %)				Sample size [7]
Patients of modelling dataset					27,630
N=10,211 (not healed): 9,096 (healed)	NOT HEALED*		HEALED*		
Male	5662	(55)	4682	(45)	
Age (years)	65	(54-74)	65	(54-74)	Length of follow-up [11]
Wounds					20 weeks post enrolment
Grade ≤ 2	6320	(47)	7173	(53)	
Grade ≥3	3801	(67)	1846	(33)	
Grade 1	312	(36)	544	(64)	
Grade 2	6008	(48)	6629	(52)	
Grade 3	1435	(62)	894	(38)	
Grade 4	1484	(67)	738	(33)	
Grade 5	691	(78)	198	(22)	
Grade 6	191	(92)	16	(8)	
Duration (log months)	1.18	(±1.30)	0.79	(±1.31)	
Size (log mm^2)	5.46	(±1.70)	4.64	(±1.63)	
1 wound	4331	(46)	5024	(54)	
2 wounds	2214	(54)	1879	(46)	
3 wounds	1428	(62)	875	(58)	
4 or more wounds	2238	(63)	1291	(36)	

*Healed or not healed by the end of 20 weeks follow up
Validation data set is provided in paper, I have not recreated it here.

Selection criteria

Inclusion criteria : -
Patients entered onto a database who were treated within the Curative Health Services system (>150 wound care centres in US).
Patients > 18 years of age with at least one diabetic neuropathic foot ulcer

Exclusion criteria : Patients who attended the clinic only once were excluded.

Predictor variable(s):

3. Composite Wound Score
4. Components of Score
   - Ulcer Size (>2cm^2)
   - Wound area (>4 cm^2)
   - Wound history (>2 months)

Data collection method

Methods of data collection are not recorded.

Potential confounders:

All patients received a "standardised treatment approach", though this involves differential levels of treatment depending upon the perceived severity of the ulcer. Therefore, whilst a score predicts whether an ulcer has healed by 20 weeks, it is impossible to separate out the effect of treatment on the likelihood of healing.

Not all prognostic factors were collected (or retrieved), therefore there may be several exposures that may be associated with a poor outcome and they may be spread unevenly amongst patients with different Wound Scores. Therefore, it is uncertain whether the variables chosen are truly causative, or whether they are surrogates for a confounding variable .

It is not stated how many patients were excluded because they had only one visit, nor how they compared with patients who were seen more than once (ie, were they higher or lower risk). This may introduce bias into the study.

When developing and validating the final model, 447 patients are excluded due to lack of data. There is no description of the excluded patients, though if these patients primarily belong to one group or the other, it may bias the model. This is unlikely, because 447 is very small compared to the 27,630 patients initially assessed.

INTERNAL VALIDITY

Outcome measurement method [12]

Primary: Ulcer healed at 20 weeks post enrolment.

Comparison of study groups [14]

A comparison of baseline data amongst the 4 wound score exposures is not made in the paper.

Measurement bias [16]

The Score was developed using data that was collected prospectively, however, the Score itself was defined after patient outcome was known (and was defined based upon patient outcome). However, it is unlikely, given the simplicity of the score, that there is any need for subjective interpretation when calculating the score, and bias is unlikely.

Follow-up (ITT) [17]

The authors have not stated if any patients were lost to follow up. An undisclosed number of patients attended the clinic only once and were excluded.

Overall quality assessment (descriptive) [18]

This study was a retrospective cohort study. Data on patients was collected over more than a decade and recorded in a database. This data was then used to create a model that predicts healing by 20 weeks (post first visit).

Good points: This study involves over 150 different centres throughout the US. It is very large (27,000+ patients). A random part of the data set has been set aside from the model generation for the purposes of validation. Differences in outcomes between centres was considered, tested and found to be non-existent. Treatments have been described (published elsewhere). Statistics are appropriate and robust (the outcome is dichotomous and ROC AUC is used).

Bad points: The study does not correct for treatment effects. Some patients will receive different treatments depending upon the severity of their ulcer. This will therefore alter the ulcer outcome. Therefore, results may not be generalisable to places that do not offer similar treatments as study population.

And whilst this is a retrospective cohort study, it is unlikely that it will suffer any greater bias than a prospective cohort study given that the variables / exposures collected are quite routine, and were only missed on a few occasions.

RESULTS

Outcome [19]

Primary: Ulcer not healed by 20 weeks

Quality assessment:

Average

Multivariate outcome [19]

Measure of effect/effect size + 95% CI [22]

Time to Ulcer Healing

Ulcer Severity Score		IN THE VALIDATION SET % not healed at 20 weeks	Likelihood Ratio (95% CI)	
Count	0	35	0.48	(0.44-0.52)
	1	47	0.78	(0.74-0.83)
	2	66	1.77	(1.64-1.90)
	3	81	3.84	(3.20-4.62)

The likelihood ratio of less than 1 suggests that the severity category is associated with *not* not healed at 20 weeks, or presumably, is associated with healing at 20 weeks.

The likelihood ratio of more than 1 suggests that the severity category is associated with not healed at 20 weeks.

I cannot interpret it more than this....

Likelihood Ratio is the Probability of having an exposure amongst those with the disease divided by the Probability of having an exposure amongst those without the disease.

In this case – for Score =0
Pr(0|not healed)/Pr(0|healed)
= (618/4370) / (1148/3894)
= 0.4797
The confidence intervals are made by bootstrapping 1000 times from the validation set.

ROC Area Under Curve

Modeling Data Set = 0.65 Validation Data Set = 0.66

THE PAPER DOES NOT INCLUDE RELATIVE RISKS, THOUGH I CAN GENERATE THESE IF YOU LIKE.

Blinding [15]

The data collected (and entered onto the database) was done prospectively, and therefore was blinded to outcome. However, the data was drawn from the database once the outcome was known. This is not likely to create substantial bias.

Conclusion:

This study has shown that the Model produced that sums a score from three dichotomous variables (Size>2cm^2, Duration>2months and Ulcer Grade≥3) has can predict the likelihood of not healing by 20 weeks. Given that this is a multi-institutional study, with an enormous number of patients, and 30% of the patients were excluded from the model development to allow validation, it is likely that the variables used in the model, and the model itself, are able to predict the likelihood of healing at 20 weeks in populations that share a common treatment protocol.

EXTERNAL VALIDITY

Generalisabilty: For these results to be generalisable, centres must share the same treatment regime / protocol, and have a similar referral pattern for patients. Again, wound duration in this study may be both a reflection of the severity of the ulcer and/or the time it takes a patient to receive treatment in this health care setting. If the latter is different in another population, the predictive ability of wound duration (in particular the chosen cut point of 2 months) will suffer.

Comments:

STUDY DETAILS

Reference [1]

Widatalla, A. H., S. E. I. Mahadi, et al. (2009). "Implementation of diabetic foot ulcer classification system for research purposes to predict lower extremity amputation." International Journal of Diabetes in Developing Countries 29(1): 1-5.

Affiliation/source of funds [2]

Authors declare no conflicts of interest, and no source of funding.

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective Cohort study	II	Single Centre (Diabetic Foot Centre in Khartoum, Sudan)

Patient characteristics [10]	Mean (SD) or %	Sample size [7]
Patients of modelling dataset		2,321
N=2,321		
Age (years)	55.5 (± 12.3)	Length of follow-up [11]
Type 2 Diabetes (%)	71	Not Reported
Foot Ulcers (%)	83.5	
Blisters (%)	55.0	
Offensive Smell (%)	15.9	
Oedema (of effected limb) (%)	36.3	
Thrombophlebitis (%)	6.7	
Fever (%)	10	
General Weakness and Prostration (%)	25	
Tissue Necrosis (%)	39	
Gangrene (%)	12.5	
Pus Discharge (%)	46.4	
Cause of Wounds		
No Inflicting Cause (%)	40.4	
Sharp Injury (%)	17.8	
New Shoes (%)	13.0	
Thermal Injuries (%)	4.5	
Various Causes (%)	24.3	
Amputations		
All Amputations (%)	28.5	
Major Lower Extreme Amputation (MLEA) (%)	10	
-Below Knee (%)	*8.7*	
-Above Knee (%)	*1.3*	
First Toe (%)	9.9	
Neuropathy		
Grade 1 (none) (%)	42.6	
Grade 2 (no pressure / vibration) (%)	57.4	
Wound Depth		
Grade 1 (superficial) (%)	41.7	
Grade 2 (fascia, muscles and tendons) (%)	42.2	
Grade 3 (bone / joint) (%)	16.0	
Infection (%)	63.6	
Grade 1 (none) (%)	*36.4*	
Grade 2 (skin and subcutaneous only) (%)	*33.0*	
Grade 3 (deep abscess, osteomyelitis etc) (%)	*26.6*	
Grade 4 (systemic responses) (%)	*4.0*	
End Stage Renal Failure (%)	3.2	

Selection criteria

Inclusion criteria : -
All patients who presented at the Jabir Abu Eliz Diabetic Centre, Khartoum, Sudan between 2003 and 2005.

Exclusion criteria : none recorded

Predictor variable(s): Data collection method

Components of wound classification by the International Consensus for the Diabetic Foot 5. Limb Ischaemia 6. Sensory Neuropathy 7. Depth and Surface Area of Wound 8. Severity of Sepsis End Stage Renal Failure	Data Collection methods are poorly reported. Components of the wound classification are well defined.

Potential confounders:

This study does not report whether there are differences in treatment for patients who present with wounds of a different severity. This is a strong confounder and will limit the generalisability of the study results.

End stage renal failure is recorded, however no other co-morbidity is reported on. There remains the possibility of confounding with other co-morbidities.

INTERNAL VALIDITY	
Outcome measurement method [12] Primary: Major Amputation or Toe Amputation	Comparison of study groups [14] Few baseline characteristics are reported. Exposed groups (defined by the presence / severity of listed components of the wound classification) are compared only regarding the outcome variable (amputations).
Measurement bias [16] The observations were collected prospectively and outcome (amputation, death, loss to follow up) is unlikely to have influenced the measurement of exposure variables.	Follow-up (ITT) [17] The authors have not stated either the length of follow up, the date of the end of the study, alternative censor groups (ie died of ulcer, lost to follow up, died of other cause) and have not recorded the number of patients who were lost to follow up.

Overall quality assessment (descriptive) [18]

This study was a prospective cohort study. Data were collected from ALL patients who attended a Diabetic Centre in Khartoum over a two or three year period (2005-2007: precise dates not given). The data collected were variables recommended by the International Consensus of the Diabetic Foot and were well defined in the study.

Outcomes were major lower extreme amputation and toe amputation.

It is not known how many patients were lost to follow up, or how many continued to be at risk at the end of the study. As we are not provided with a follow up time, it is not clear whether the dichotomous outcome variable (amputation = yes or no) is appropriate, or whether a time component should have been used. Causes of removing a patient from the study are not stated.

A multivariate model is most likely used (though not explicitly stated) as the term "independent predictor" is used in the discussion. The model (a logistic regression was most likely used given that Odds Ratios are presented - which makes it clear that a dichotomous outcome was used) is not provided and therefore it is unclear what variables are controlled for, and which are removed from the model.

It is unclear that odds ratios presented in the results are generated from a univariate or multivariate model (though it is most likely a multivariate model).

Finally, the treatment provided to patients at the diabetic centre is not stated, and given the outcome (amputation vs no amputation) is likely to be highly associated with treatment type and quality, the true association between the presented risk variables and outcome remain unknown AND will be difficult to translate into other countries that have different treatment and referral regimes.

Overall, as there were a large number of patients in this study (2,321) and all appeared to be enrolled consecutively (negating selection / enrolment bias), it is likely that there is an association between the risk variables presented as significant predictors and amputation as an outcome, however the magnitude of the association is uncertain. This study is of poor quality.

RESULTS	
Outcome [19] Primary: Major Lower Extremities Amputation or Toe Amputation	Quality assessment: Average (from the methodology checklist below) – however, given the studies poor generalisability, and the limitations of the methodology checklist, this assessment over-rates the quality of this study (it really should be poor).

Multivariate outcome [19]			Measure of effect/effect size + 95% CI [22]
Time to Ulcer Healing			Blinding [15]
<u>Major Lower Extremity Amputation</u>	OR	(95% CI)	The data are collected prospectively, therefore exposure status is measured prior to outcome. Outcome is unlikely to be influenced by the knowledge of baseline characteristics.
Neuropathy	2.43	(1.08 – 5.45)	
End Stage Renal Disease (Failure)	4.39	(1.53 – 12.61)	
Ischaemia (G1 or 2 vs G3)	5.08	(2.56 – 10.07)	
<u>Toe Amputation</u>			
Neuropathy	2.16	(1.32 – 3.5)	
Grade of Infection (G1 or 2 vs G3 or 4)	2.4	(1.55 – 3.7)	
Depth of Wound (G1 vs G2 or 3)	3.45	(2.02 – 5.88)	

Conclusion: This study has shown that neuropathy, end stage renal failure and ischaemia are predictors of major amputation, and that neuropathy, grade of infection and depth of wound are predictors of toe amputation. The study design is poor and whilst the associations are likely to be true, the strength of the associations cannot be accepted without considering the confounding effect of treatment, and without more detail regarding referral, loss to follow up, and the logistic regression model parameters.		
EXTERNAL VALIDITY		
Generalisabilty: These results are only likely to be generalisable if centres have the same population, treatment and referral protocols. Given that these are not, or only poorly, described, an estimation of the generalisability is impossible.		
Comments:		

STUDY DETAILS

Reference [1]

Ince, P., D. Kendrick, et al. (2007). "The association between baseline characteristics and the outcome of foot lesions in a UK population with diabetes." Diabetic Medicine 24(9): 977-981.

Affiliation/source of funds [2]

Source of funds not recorded, no competing interests.

Study design [3]	Level of evidence [4]	Location/setting [5]
**LIZ - Prospective Cohort study with a retrospective component??	II or III-3	Single Specialist Multidisciplinary Foot Clinic (UK)

Patient characteristics [10]		Means (±SD) or Median (IQR)	
N=449			
Age		66.7	(±13.2) years
Years of diabetes		13.3	(7.6, 21.0) years
Ulcer History (to first presentation)		29	(11, 60.5) days
		Frequency n (%)	
Male		286	(63.7)
Type II diabetes		384	(86.1)
Ulcer Site	Toe	247	(55.5)
	MTP joint	78	(17.5)
	Mid and hind foot	120	(27.0)
Ulcer Area	1	272	(60.6)
	2	108	(24.1)
	3	69	(15.4)
Ulcer Depth	1	352	(78.4)
	2	57	(12.7)
	3	40	(8.9)
Sepsis	0	246	(54.8)
	1	90	(20.0)
	2	73	(16.3)
	3	40	(8.9)
Arteriopathy	0	163	(36.3)
	1	94	(20.9)
	2	182	(40.5)
	3	10	(2.2)
Denervation	0	90	(20.0)
	1	117	(26.1)
	2	236	(52.6)
	3	6	(1.3)
Healed		295	(68.3)
Person Years Follow Up		165.0 years	
All grades refer to S(AD)SAD system. Grade 0 is impossible for "ulcer area" or "ulcer depth" (as only patients with ulcers were included in the study).			

Sample size [7]

449 (one primary ulcer per patient)

Length of follow-up [11]

At least 1 year, or until amputation or death if earlier

Selection criteria

Inclusion criteria : - All patients referred to a specialist foot clinic between 1/JAN/2000 and 31/DEC/2003.

Exclusion criteria : - Patients whose epidermis was intact were excluded (therefore only including patients with ulcers).

Predictor variable(s): Data collection method

Demographic and disease variables 9. S(AD)SAD components 10. Age 11. Duration of Diabetes 12. Duration of Ulcer 13. Gender 14. Diabetes type 15. Socio-Economic Status 16. Ulcer Site	Collected prospectively, then later retrieved from database / registry (and medical records when necessary).

Potential confounders:

Depending upon the perceived severity of an ulcer, a patient is likely to receive different treatment. This will seriously confound the outcome an ulcer.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Time to healing (complete epithelialisation of wound). Patients who die are deemed to have not healed if there is no evidence of healing before death and censored at time of death. Patients who receive an amputation are categorised as "not healed" and censored at the date of amputation.	Not applicable – characteristics such as age, gender and SES are compared later in a multivariate model. Therefore, baseline differences are controlled for using statistical methods.	Data was collected prospectively on all ulcers. The study suggests that the selection of the primary ulcer was done without reference to the outcome.

Measurement bias [16]	Follow-up (ITT) [17]
Some imprecision regarding the duration of ulcer is reported. All patients have reported the month of onset, and the study presumes that the ulcer started on the 15th of that month. Depending upon the timing of the clinics, there may be some bias introduced into this variable (for instance, it is reported that ulcers that are calculated to have negative durations due to this protocol are assumed to have a duration of 0, thereby slightly increasing the mean duration in the cohort).	Patients are followed for one year, or until amputation or death if earlier. A small proportion of patients could not be classified according to outcome (but 96% of cases could).

Overall quality assessment (descriptive) [18]

This is a cohort study in which data were collected prospectively, however, were retrieved from a registry / database or medical records at a later date. The paper suggests that sufficient data were collected for all but 17 cases (of 449), and necessitated a different ulcer to be chosen for these patients (though the selection of the primary ulcer was done blinded to patient outcome). However, the data were not collected specifically for this use, and hence the study is probably a retrospective cohort study.

A large number of variables were considered in this study, and a time component to ulcer healing was incorporated into the Cox regression. The model is multivariate and the authors have described how the final model was constructed (and how variables were included or excluded based upon their influence on the model – log likelihood test). Statistical methods are robust (and well described). A consequence of the large number of variables (both ulcer related and demographics), confounding can (to a certain extent) be controlled for in a multivariate model (for instance SES is tested for an effect on ulcer outcome before being discarded from a multivariate model). Correlation between variables was tested and the more predictive variable was kept in the model.

A major drawback to the study is the lack of description of the treatment process. It is likely that more severe ulcers receive more intensive treatment, and this effect cannot be removed from the outcomes. However, similar centres servicing similar populations would be likely to observe associations of approximately the same magnitude between variables in this paper and time to healing.

The study has inherent weaknesses, however much of what could be done, has been done to reduce bias and confounding. The quality is therefore average.

RESULTS

Outcome [19]	Quality assessment:
Time to healing (amputation and death are censored and regarded as not healed).	Average

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22]	
	Relative Risk / Hazard Ratio	

Ulcer Healing (Multivariate Cox Model)				
Ulcer Area	1	1.0	(Reference)	
	2	0.75	(0.54, 1.04)	
	3	0.40	(0.24, 0.67)	
Arteriopathy	0	1.0	(Reference)	
	1	0.76	(0.54, 1.06)	
	2 & 3	0.50	(0.37, 0.67)	
Ulcer Site	Toe	1.0	(Reference)	
	MTP	0.73	(0.51, 1.05)	
	Mid and hind foot	0.68	0.49, 0.96)	
Duration of Diabetes	<10 years	1.0	(Reference)	
	10-19 years	0.72	(0.53, 0.98)	
	≥20 years	0.66	(0.48, 0.92)	
S(AD)SAD definition of area / arteriopathy grades		To read this, we would say that an ulcer area less than 1cm^2 is two and a half times more likely to heal than an ulcer area greater than 3cm^2, when adjusted for by other predictors such as ulcer site, arteriopathy and duration of diabetes.		

Conclusion:

This study was well presented. The authors have considered potential bias and claim that although the selection of primary ulcer was done retrospectively, it was done without reference to patient outcome. All data was collected prospectively, and was sufficient for the vast majority of patients. Outcome was ascertained in 96% of cases. Sadly, the treatment protocol was not described, and this is likely to be a strong confounder of outcome.

EXTERNAL VALIDITY

Generalisabilty: This study may be generalisable to similar patients attending a diabetic foot clinic in the UK or other country with similar resources and treatment protocols.

Comments:

STUDY DETAILS

Reference [1]

Khaodhiar, L., T. Dinh, et al. (2007). "The use of medical hyperspectral technology to evaluate microcirculatory chaves in diabetic foot ulcers and to predict clinical outcomes." Diabetes Care 30(4): 903-910.

Affiliation/source of funds [2]

4 authors are employees of Hypermed, 2 authors own stock in Hypermed and one author is a paid consultant of Hypermed and also owns stock in Hypermed. Hypermed Inc. is the company that creates the HyperMed CombiVu-R System (referred to as hyperspectral technology, HT, in the study) used to measure oxy- and deoxy-haemoglobin (which is the "exposure" that is linked with time to ulcer healing).

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective observational study – most likely classified as a cohort study (there is no description of patient accrual, nor how the "control" group was chosen) -	II	"A large number of practices".

Patient characteristics [10]	Mean (±SD) or Median (IQR)		Sample size [7]
N=10 type 1 diabetic patients with foot ulceration			10
Age (years)	51	(38-64) ?median or mean, and IQR or range?	
Male	N=6	ie 60%	Length of follow-up [11]
BMI (kg/m^2)	29	(±7)	6 months
Years of diabetes	31	(±12)	
Systolic blood pressure (mm/Hg)	133	(±20)	
Diastolic blood pressure (mm/Hg)	76	(±8)	
Ankle-brachial pressure index	1.14	(±0.19)	
Transcutaneous oxygenation monitor (mmHg)	46	(±16)	
Laser Doppler (Aus flux)	116	(±18)	
Neuropathy Symptom Score	5	(±3)	
Neuropathy Disability Score	15	(±8)	
Vibration Perception Threshold (V)	44	(±10)	
Semmes-Weinstein filaments (marking number)	6.2	(±0.9)	
N=13 type 1 diabetic without foot ulcer (details not relevant to data extraction)			
N= 14 non-diabetic, non-foot ulcer patients (details not relevant to data extraction)			

Selection criteria

Inclusion criteria : - 10 type 1 diabetic patients with at least 1 foot ulcer

Exclusion criteria : - peripheral arterial occlusive disease requiring surgery, heart failure resulting in oedema, stroke or TIA with residual nerve dysfunction, uncontrolled hypertension, end stage renal disease, other serious chronic diseases that affect healing, treatment with steroids or chemotherapy, pregnant or lactating women.

Predictor variable(s):	Data collection method
Demographic and disease variables 3. HT oxy-haemoglobin 4. HT deoxy-haemoglobin	Ulcer healing measured at clinic visits, or by phone if patient did not attend clinic. HT measured for all patients in clinic at baseline.

Potential confounders:

So few variables are reported that it is not clear how thoroughly confounding has been explored. Potential confounders are other ulcer characteristics (size, depth, infection etc). There may have been differences in treatment between the patients, therefore treatment may be a confounder for ulcer healing. Given that patients were selected from a "large number of practices" and were given "regular care" from their physicians, it is very likely that they type of care between the practices will be different, and the population attending the practices will be different.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Healed ulcer at the end of 6 months follow up.	A comparison between subjects that heal or not heal is not made. A comparison between patients with ulcers and those without (diabetic and non-diabetic "controls") is made, however this is not helpful in the context of this question.	Physicians who were treating the patients were blinded to the data collection of the study. It is not obvious whether it is this same physician who is deciding whether the patient has healed – in fact, it is likely that for a few patients who required phone follow up, it may have been a study person who was not blinded to the HT-oxy / deoxy measurements who ascertains the patient outcome.

Measurement bias [16]	Follow-up (ITT) [17]
Unclear. One very large ulcer is broken into 4 ulcer sites (and the analysis is done on ulcer sites) – therefore the characteristics of this ulcer and its outcome are likely to overly influence the findings (given that some of the causes of non-ulcer healing or ulcer healing will be related to the patient, and not to local factors). When comparing ulcer patients with "controls" there may be some measurement bias related to the position of the HT scan, however this is not relevant to this extraction.	Patients were followed for 6 months – no loss to follow up is recorded

Overall quality assessment (descriptive) [18]

This is a very low quality study. There is little description of how subjects were selected, over what time period, how many subjects refused etc. Subjects were not chosen consecutively and may have received vastly different treatments at different institutions. It is not clear whether every subject received the measurement of HT-oxy / deoxy (or other baseline variables) by the same physician, or whether there may have been differences in how the measurements were done. Confounding by ulcer stage / patient characteristics etc is not addressed.

The low quality and lack of transparency regarding the study design is not improved by the financial ties between several of the authors and the company providing the technology that measures the "exposures".

There is no mention of the power of the study, and given that there were only 10 patients, it is likely that the study was substantially underpowered. Several ulcer sites per patient are used as individual cases rather than selecting the primary ulcer per patient. This will introduce uncertainty into the study. If a patient has one ulcer that heals, presumably they are more likely to have other ulcers heal for reasons unrelated to the measurements taken (better self care / better treatment / better glycaemic control / non-smoker etc). Using several ulcers per patient will enhance this effect. The merit of recording one ulcer as four ulcers due to its size is also highly questionable.

The Healing Index appears to be generated from data that was only created at the time of statistical analysis – more specifically, the healing index seems to be related to a value of oxy and deoxy that best separates healed from non-healed ulcers. Therefore, the level of exposure is being defined by a metric which involves outcome – this may be difficult to apply in a prospective fashion to a new population.

RESULTS

Outcome [19]	Quality assessment:
Healed at six months – specificity, sensitivity, positive and negative predictive values of HT healing index (HT healing index is the distance between the mean oxy and deoxy measure and a discriminant line that best separates healing from non-healing).	??

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22]	
Ulcer Healing at 6 months – Healing Index		
Sensitivity	93% (66-100)	
Specificity	86% (42-100)	
PPV	93% (66-100)	
NPV	86% (42-100)	

Conclusion:

This study was poorly presented. The comparison groups add little to the study and are irrelevant to this question. The small size of the study introduces substantial uncertainty (outcome measures have wide 95% CIs), and using the same patient several times over for different ulcers presents an enormous problem when patient characteristics are not involved as confounders in any statistical model. Creating a measurement that relies upon the outcome (healing index) to predict whether an ulcer heals is of limited prognostic value.

EXTERNAL VALIDITY

Generalisabilty: There is no way of knowing how generalisable this study is to the Australian population. It was done in many centres and patient selection was not clearly stated. Only type 1 diabetes is studied.

Comments:

STUDY DETAILS

Reference [1]

Nouvong, A., B. Hoogwerf, et al. (2009). "Evaluation of diabetic foot ulcer healing with hyperspectral imaging of oxyhemoglobin and deoxyhemoglobin." Diabetes Care 32(11): 2056-2061.

Affiliation/source of funds [2]

No competing interests are disclosed. Funded by a grant from the National Institute of Diabetes and digestive and Kidney Diseases and by the Cleveland Clinic (National Institutes of Health).

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospectively collected data – prospective cohort (very poorly defined population).	II	3 centers in US – no date or period specified.

Patient characteristics [10]

N=66 (12 lost to follow up and characteristics not presented)

Means (±SD) or Median (IQR)	HEALED (n=38)		NOT HEALED (n=16)	
Male (n)	35		14	
Age (median (range))	51	(34-68)	52	(25-63)
Diabetes (type1 / type2)	15 / 23		8 / 8	
Diabetes Duration (years)	13	(±10)	12	(±8)
A1C (presumably haemoglobin A1c) %	9.7	(±2.6)	9.5	(±2.4)
BMI (kg/m^2)	34	(±10)	31	(±12)
Systolic BP (mm/Hg)	135	(±24)	142	(±21)
Diastolic BP (mm/Hg)	76	(±13)	79	(±9)
Neuropathy Symptoms Score	5.3	(±3.3)	4.9	(±3.0)
Neuropathy Disability Score	7.7	(±3.4)	6.7	(±4.9)

Sample size [7]

66 patients

54 completed with 73 ulcers.

Length of follow-up [11]

At least 1 year, or until amputation or death if earlier

Selection criteria

Inclusion criteria : - Patients aged 21 – 45 with type 1 or 2 diabetes with at least one diabetic foot ulcer.

Exclusion criteria : - peripheral arterial occlusive disease requiring surgery, heart failure resulting in oedema, stroke or TIA with residual nerve dysfunction, uncontrolled hypertension, end stage renal disease, severe peripheral oedema, other serious chronic diseases that affect healing, treatment with steroids or chemotherapy, pregnant or lactating women.

Predictor variable(s):

Healing Index (a measurement requiring oxyhaemoglobin and deoxyhaemoglobin measured at 0.5 or 1cm radius around the ulcer (depending upon ulcer size), as well as the value of oxy and deoxy that best discriminates healed and non healed ulcers).

Data collection method

Demographic and wound characteristics were collected prospectively – healing index was calculated retrospectively once outcome was known (and using the outcome to generate the index).

Potential confounders:

Differences in treatment will change the outcome of the ulcer. Different ulcer severities may receive different treatments. Treating physicians are, however, blinded to the results of the superficial tissue oxyhaemoglobin and deoxyhaemoglobin. Several wound and demographic characteristics are recorded, and are analysed for associations with wound healing, however many are not (ulcer depth, infection etc). 12 patients were excluded from the study for not finishing. In two cases, the patient required amputation (yet was still excluded from the study). In the remaining 10 cases, it is not clear why they did not finish, nor are the baseline characteristics presented to check if the group is different to the group who finished the study. This may be a major source of bias.

Many ulcers are measured from each patient. This will introduce confounding if patient characteristics are involved in outcome (diet, self care etc).

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Healed at 24 weeks. (complete reepithelialisation and no exudates = healing).	Characteristics of patients with healed ulcers were compared with patients with non-healed ulcers.	Treating physicians were blinded to the study values of oxy and deoxy haemoglobin.

Measurement bias [16]

Oxy and deoxy haemoglobin are measured by a commercial HyperSpectral Imaging system. For wounds greater than 1cm in diameter, a 1cm radial border of is used to measure the mean oxy and deoxy values, though for a wound less than 1cm in diameter, a border of 0.5cm was used. [though i am no mathematics expert – this appears to be problematic]. A wound with a diameter of 0.95cm will have the measurements based upon an area surrounding the wound of about 2.1cm^2 compared with 6.4cm^2 for a wound with a diameter of 1.05cm. There may be a systematic bias introduced around this "pivot" of wound diameter of 1cm, with measurements taken further from the wound if the wound is slightly bigger than if slightly smaller. There was no explanation of why this pivot was chosen except that changing the size of the border improved the discrimination of the test (therefore, the border was selected AFTER results were known!). By introducing this cut point, there is the danger that the measure may be a proxy or surrogate for something else, like ulcer size. It is not clear how this might bias results.

Follow-up (ITT) [17]

Patients are followed for 24 weeks, though 12 patients were "lost" – 2 receiving amputation and 10 for reasons not reported.

Overall quality assessment (descriptive) [18]

This is a prospective cohort study. The cohort is very poorly defined: there is no date range for when patients were recruited; there is no mention of how patients were recruited, (consecutive, all, random, single consultant from each centre etc) therefore we do not know whether patients were "selected" to suit the study; we do not know anything about the 12 patients (nearly 20%) of patients who were excluded from the study; it is not clear why the 2 patients excluded due to amputation are not included with the did not heal group; there is no description of treatment except that physicians were blinded to hyperspectral imaging data; whilst it appears "exposure" – the measure of oxy and deoxy-haemoglobin – were recorded prospectively, the area in which it was measured around the wound was adjusted to create better sensitivity and specificity for predicting wound outcome, therefore the measurement is, in part, linked to the outcome; and finally, the HEALING INDEX is a metric that requires statistical analysis of patient outcomes to generate and therefore has limited usefulness as a prognostic marker and whilst it relies upon there being a difference between oxy and deoxy haemoglobin in patients who heal and do not heal, the cut point can only be ascertained after the outcome – and the sensitivity / specificity of the test is therefore highly exaggerated. If a cut-point were decided prospectively (as would be required if this were to be validated as a prognostic marker for wound healing), the sensitivity and specificity would be much lower due to variations in population etc.

Many ulcers may be used from one patient – increasing the likelihood for confounding if patient characteristics influence healing rather than just oxy / deoxy measures.

This is a low quality study.

RESULTS

Outcome [19]	Quality assessment:
Ulcer Healed at 24 weeks	Average quality (according to the checklist below)

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22] *** no confidence intervals are provided	
Ulcer Healing at 24 weeks – Healing Index		
Sensitivity Specificity PPV	80% 74% 90%	
#After excluding ulcers with callused skin and with underlying osteomyelitis		
Sensitivity Specificity PPV	86% 88% 96%	
(#note: it is not clear whether the authors went back and looked at all ulcers or only the ulcers for which the healing index wrongly predicted outcome – in fact, it is implied that it is the latter – therefore these results are (more or less) pointless).		

Conclusion:

This study is poorly presented. Little information is known regarding the selection of patients and patients are discarded from the analysis without presenting characteristics nor performing a sensitivity analysis. Treatment as a confounder is not addressed. The healing index can only be calculated after it is known whether a patient heals or not. Exposure (oxy / deoxy) was defined, in part, after healing was known (ie the area around the wound that gave the most accurate results was defined post outcome – and using the outcome). There remains little confidence that this test (even if healing index was defined prior to the outcome) could predict ulcer healing at the level of sensitivity / specificity that has been reported.

EXTERNAL VALIDITY

Generalisabilty: There is no way of knowing whether the population is the same as few demographics are presented, and we do not know what treatments are given. The sensitivity and specificity of the test is specific to this population and contingent upon their rate of healing.

Comments:

STUDY DETAILS

Reference [1]

Younes, N. A. and A. M. Albsoul (2004). "The DEPA scoring system and its correlation with the healing rate of diabetic foot ulcers." J Foot Ankle Surg 43(4): 209-213.

Affiliation/source of funds [2]

None reported

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective Cohort Study	II	Single institution (Jordan University Hospital, Jordan) between 1997 and 2002

Patient characteristics [10]	Means ± SD or %	Sample size [7]
N=84 (consecutive)		84
Male (n)	52 (62%)	
Age	62 (range: 30 - 93) years	Length of follow-up [11]
Ulcer Location*:	n	20 weeks (or until healed or amputated if earlier)
• Toe	41 (49%)	
• Forefoot	24 (29%)	
• Lateral	7 (8%)	
• Dorsal	3 (4%)	
• Ankle / Heel	9 (11%)	
DEPA Score:	n	
≤6	32 (38%)	
7-9	35 (42%)	
≥10	17 (20%)	
*percents do not sum to 100 due to rounding		

Selection criteria

Inclusion criteria : - All patients with type 1 or 2 diabetes with at least 1 foot ulcer.

Exclusion criteria : - Osteomyelitis affecting the heel, large ulcers (>40cm^2) with sepsis, heel ulcers with necrotizing fasciitis extending to the ankle, foot ulcers with acute foot ischaemia.

Predictor variable(s):

Demographic and disease variables

2. DEPA Score (categorical)

≤6
7-9
≥10

Score:	1	2	3
Depth	Skin	Soft Tissue	Bone
Extent of bacterial colonization	Contamination	Infection	Necrotising Infection
Phase of Ulcer	Granulating	Inflammatory	Nonhealing
Associated Aetiology	Neuropathy	Bone deformity	Ischaemia

Data collection method

Presumably by clinical examination

Potential confounders:

Different ulcer severity (it is implied that the DEPA score or components of the DEPA score are used in the assessment of severity) receive different treatments. Presumably treatment will alter the outcome of the ulcer and therefore is a major confounder in this study. Ulcer duration is used as a component of the DEPA score. If there is a variable that allows a patient to access a clinic earlier than another patient, they are less likely to be graded a 3 for "phase of ulcer" and if this variable is also linked to ulcer healing, it will be a confounder of the study (for example, a patient with a high level of self care may access help earlier, therefore be graded lower, than a patient who is slower to present – and the patient with higher levels of self care is probably more likely to heal than one who is incapable of self care – therefore, the "Phase of Ulcer" component acts not only as a marker of more resilient ulcers, but as a surrogate for patients who present earlier.)

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Ulcer healing at 10 weeks vs 20 weeks vs not healed by 20 weeks vs Amputation	Patients with different DEPA scores are not compared for baseline variables (other than the components of the DEPA score).	Not reported – physicians giving treatment are not blinded to the DEPA score – and are unlikely to be blinded at the time of deciding whether a patient has "healed".

Measurement bias [16] Not reported – Healing was defined as "complete closure of the ulcer without the need of dressing." There may be some subjective assessment required in measuring this outcome and as physicians are unlikely to be blinded to original DEPA score, some bias may be introduced.	Follow-up (ITT) [17] Patients are followed up for 20 weeks, or until ulcer healing or amputation (if earlier).

Overall quality assessment (descriptive) [18]

This is a prospective cohort study with 84 consecutively recruited patients. Treatment is a major confounder, and will alter time to healing. This is particularly true for this study because the treatment regime is selected for patients DEPENDING UPON THEIR DEPA SCORE. However, as the treatment is the same for all patients within specific DEPA categories, and if we assume that more intensive treatment (given to the higher DEPA score patients) results in better outcomes, then this confounding will act to reduce the predictive value of DEPA. Therefore, any association between DEPA score and time to healing would be far greater if disparate treatments were removed from the study.

There may be some bias introduced by not blinding physicians to the DEPA score when they are deciding whether an ulcer is healed or not.

No multivariate model is used adjusting for known baseline factors such as age, duration of diabetes, ulcer size, smoking etc

One very good part of this paper is that the authors have explicitly stated the treatment protocols for different DEPA scores, therefore an informed decision regarding generalisability (to another institution) may be made. However, only very few demographics have been given regarding patients, which will reduce the generalisability. This is a well presented study of average quality.

RESULTS

Outcome [19] Categorical outcome - Ulcer healed at 10 weeks; ulcer healed at 20 weeks; ulcer not healed at 20 weeks; amputation required.	Quality assessment: Average

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22] Relative Risk	
No effect sizes are given. Spearman non-parametric correlation Linear regression model	Correlation coefficient 0.78 (0.68-0.86) p<0.0001 r = 0.85 slope best-fit = 0.51 (0.44-0.59) p<0.0001	

Conclusion:

This study has shown that a higher DEPA score can predict poor outcomes (less likely to heal at 10 weeks, 20 weeks, and more likely to receive amputation).

The lack of effect size or relative risks reduces the score's utility.

EXTERNAL VALIDITY

Generalisabilty: This study may be generalisable to other hospitals / clinics that have a similar treatment regime and similar waiting times (given that a component of the score is duration of ulcer).

Comments:

STUDY DETAILS

Reference [1]

Apelqvist, J., J. Castenfors, et al. (1989). "Wound classification is more important than site of ulceration in the outcome of diabetic foot ulcers." Diabet Med 6(6): 526-530.

Affiliation/source of funds [2]

No conflicts of interest are reported, research is supported by a Swedish Medical Research Council grant.

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective Cohort Study	II	Single institution (Department of Internal Medicine, University Hospital, Lund, Sweden) – accrual occurred between 1983 and 1987.

Patient characteristics [10]	Means ± SD or %		Sample size [7]
N=314 (consecutive)			314
Male (n)	156	(49.7%)	
Age	64	(± 17) years	Length of follow-up [11]
Duration of diabetes	17	(± 12) years	Not explicitly stated.
Treatment for diabetes*:			
Insulin	201	(64%)	
Oral hypoglycaemic	78	(25%)	
Both	5	(2%)	
Diet alone	30	(10%)	
Duration of Ulcer	5	(range 0 – 208) weeks	
*percents do not sum to 100 due to rounding			

Selection criteria

Inclusion criteria : - All patients with a diagnosis of diabetes with at least one foot ulcer referred to the clinic.

Exclusion criteria : - Non-stated

Predictor variable(s):

4. Wound Grade (Wagner)
5. Ulcer Site (Digit 1, Digits II-V, Metatarsal head, Mid-foot and heel, Dorsum of the foot, multiple ulcers)
6. Ankle and toe blood pressure.

Data collection method

By single team of physicians.

Potential confounders:

Different ulcer severity will receive different treatments (which will affect outcome). Whilst other possible predictor variables (ankle / toe pressures and wound site) were presented, they were not sensibly stratified or assessed in a multivariate model – therefore the predictive capacity of the wound grade is likely confounded by these variables, however we are unsure by how much.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Ulcer healing (6 months of intact skin) – if a patient dies within 6 months of achieving intact skin, it is recorded as "healed".	Patients of different Ulcer Grade are compared for ankle and toe pressures, though not for any other baseline characteristics.	Healing is unlikely to be recorded by those blinded to the Wagner grade. Nor is treatment likely to be delivered by those blinded to the grade.

Measurement bias [16]	Follow-up (ITT) [17]
As physicians are unlikely to be blinded to Wagner score at the time of establishing "healed" status, there may be some possibility of bias, though it is deemed unlikely given that there is no time limit placed upon healing, therefore if a physician decided that a wound was not quite healed, s/he would confirm it healed on the subsequent visit and the patient would be classified in the same category as if s/he had been "healed" the previous visit.	Not obvious from the paper.

Overall quality assessment (descriptive) [18]

This is a prospective cohort study with a large number of patients. Only very few baseline characteristics have been presented and none have been used in a multivariate analysis of the Wagner Grade, therefore the grading system may merely be a surrogate for other (more accurate or stronger predicting) variables. Treatment is disparate between patients of different ulcer severity and this will confound the results. No time component has been used in this study, and therefore an ulcer which heals in 2 weeks is classified the same as an ulcer that takes a year to heal. In addition, patients who die with non-healed ulcers are classified as non-healed, though clearly if a patient dies of unrelated causes 2 weeks after presenting to the clinic, this ulcer should not be classified as non-healed, but the patient should be censored from the study. Alternatively, time to healing should have been studied allowing appropriate statistical censoring to deal with deceased patients.

The methods and presentation are poor, and the study design suffers significant uncertainty.

RESULTS

Outcome [19]	Quality assessment:
Primary healed vs not (primary healing rate%)	Average

Multivariate outcome [19]

No effect sizes are given (therefore i have calculated relative risk for the Wagner Grades using grade 1 as a reference).

ULCER GRADE (WAGNER)

- 1 (superficial)
- 2 (deep)
- 3 (abscess / osteomyelitis)
- 4 and 5* (minor and major gangrene)

*5 is included with 4 as there are no patients in the "healed" category for Wagner Grade 5 (making RR difficult to generate), and there is no difference in healing rates between grade 4 and 5 (reported by the authors).

ULCER LOCATION

- Digit I
- Digits II – V
- Metatarsal Head
- Mid-foot & Heel
- Dorsum of Foot
- Multiple Ulcers (>2 ulcers)

Ankle / Toe blood pressure – is greater in grade 1, 2 and 3 compared with grades 4&5 combined (p<0.001). These measures are not reported with the outcome of healing.

Measure of effect/effect size + 95% CI [22]

Relative Risk

HEALING RATES:

grade 1 > grade 2 (p<0.05) grade 1 > grade 3 (p<0.001)
grade 1 > grade 4&5 (p<0.001) grade 2&3 > grade 4&5 (p<0.001)

HEALED	NOT HEALED	TOTAL	RR (of not healing)	
132	18	150	1	(*reference*)
37	13	50	2.17	
26	20	46	3.62	
2	66	68	8.09	

n	Primary Healed	% Healed
88	62	70
72	43	59
41	32	78
46	31	67
45	28	62
22	1	5

Conclusion:

This study has shown that the Wagner grade is associated with the likelihood of an ulcer healing. From these data, a Wagner grade 2 has about twice the chance of not healing as a Wagner grade 1. There appears to be some association with wound location also, however these data were not combined with Wagner grade, therefore the relative importance of either variable is unknown. Ankle and Toe blood pressure appear to be lower in higher Wagner grades and may be associated with reduced likelihood of healing (though this is not presented by the authors).

EXTERNAL VALIDITY

Generalisabilty: This study followed patients between 1983 and 1987. Treatment for ulcers is likely to have changed during this period, as well as treatment of co-morbid conditions that are likely to slow ulcer healing (diabetes, peripheral vascular disease etc). It is uncertain how applicable these results are today, nor how generalisable they may be to an Australian setting.

Comments:

STUDY DETAILS

Reference [1] Armstrong, D. G., L. A. Lavery, et al. (1998). "Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation." Diabetes Care 21(5): 855-859.

Affiliation/source of funds [2]

No conflicts of interest are reported, funding source not identified.

Study design [3]	Level of evidence [4]	Location/setting [5]
Retrospective Cohort	III-3	Single institution (University of Texas Health Science Center).

Patient characteristics [10]		Means ± SD or %			Sample size [7]
N=360 (how the patients were selected is not recorded)					360
Male (n)		68.6%			
Age		53.9	(± 10.4) years		Length of follow-up [11]
Duration of diabetes		14	(± 9.2) years		6 months
Race:	Mexican/American	79.2%			
	Non-Hispanic White	12.5%			
	African American	6.7%			
	Asian	1.6%			
		Palpable pedal pulses%		*Ankle Brachial Index*	
Stage (n):	A (164)	78%		1.03	(± 0.15)
	B (158)	83.5%		1.02	(± 0.14)
	C (21)	14.3%		0.71	(± 0.18)
	D (17)	5.9%		0.66	(± 0.19)
Age, Duration of diabetes, % men and race are also separated out by stage.					

Selection criteria

Inclusion criteria : - Patients with a complicated foot wound (below the ankle) between 1st Jan 1994 and 1st July 1996 presenting to a multidisciplinary tertiary care diabetic foot clinic. All patients have verified diabetes.

Exclusion criteria : - None-stated

Predictor variable(s):	Data collection method
3. Wound Grade (0=healed, 1=superficial, 2=to tendon or capsule, 3=bone or joint) 4. Wound Stage (A=clean, B=non-ischaemic infected, C=ischaemic non-infected, D=ischaemic and infected)	Wounds graded by one principle investigator

Potential confounders:

Wounds graded more severely will receive more rigorous treatment (which will in turn result in improved outcomes). There is also wide variability of race between the groups (when separated by stage). There appear to be more Mexican Americans in the highest stage and fewer non-Hispanic white patients. This trend is unlikely to be statistically significant, though if there are differences in the genetics or cultures that predispose better or worse outcomes, this may be a small confounding factor.

There is no measure of ulcer duration used in this analysis. Given that the outcome (amputation y/n at six months) will be contingent (in part) upon the length of time an ulcer is present and not healing, patients seen with earlier ulcers may not have sufficient time to progress to higher grade ulcers and receive an amputation compared with those who are seen by the clinic with higher grade / higher stage ulcers to begin with. It seems likely that many high stage and high grade ulcers would have begun as lower stage / grade ulcers before progressing – therefore without controlling for duration of ulcer, amputation as a dichotomous outcome may be related to grade / stage but partly as a surrogate for duration spent with the ulcer. A study based elsewhere that sees the same patients at different times after the inception of their ulcer may find a different relationship between grade, stage and amputation.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Prevalence of amputation at 6 months.	Patients of different Ulcer Grade and different ulcer stage are compared baseline characteristics.	The classification of the wound (stage and grade) is unlikely to have occurred blinded to the outcome (amputation) and there exists the potential for bias.

Measurement bias [16]

Many measurements were made on a clinical basis. It might be possible that more worrying diagnoses are made of more worrying appearing wounds. Infection, for instance, is diagnosed by several local signs, and if it is missed, it is more likely to be missed in smaller and less worrying looking wounds. Again, vascular insufficiency (another variable diagnosed clinically) may be more scrutinised in wounds that look more severe. Therefore, variables defined clinically may be discovered more frequently in "severe looking" wounds though the prevalence of the variables may be biased by inconsistent measurements.

Follow-up (ITT) [17]

No loss to follow up is recorded, all patients are followed to 6 months.

Overall quality assessment (descriptive) [18]

This is a retrospective cohort study. It is not clear how the population was recruited or how many people were excluded, and for what reasons, in the creation of the sample, therefore we cannot comment on selection bias. An investigator has assigned stages and grades to the population from the medical records (retrospectively) and the outcome is likely to be at hand during this process, therefore there is the potential for allocation bias. The patients were originally assessed by a clinic though not in a controlled environment; therefore it is uncertain whether the same protocol was followed for each patient.

Finally, treatment is likely to be different for patients with different severity of wounds, therefore confounding outcome.

This study quality is generally poor, with insufficient detail in the published paper to provide confidence regarding sources of bias.

RESULTS

Outcome [19]

Amputation at 6 months

Quality assessment:

Average

Multivariate outcome [19]

Measure of effect/effect size + 95% CI [22]

Relative Risk

Prevalence of amputations within each wound category

		GRADE			
STAGE	0	I	II	III	
A	0%	0%	0%	0%	no difference
B	12.5%	8.5%	28.6%	92%	p<0.0001
C	26.0%	24.0%*	26.0%	100%	p<0.001*
D	50.0%	50.0%	100%	100%	p=0.02

*some figures are almost illegible – even when extracted from a pdf on the computer screen

Grade III vs Grade 0-II

18.3% vs 2.0%, p<0.001, OR = 11.1, 95% CI 4.0 – 30.3

Stage D vs Stage A-C

76.5% vs 3.5%, p<0.001, OR=89.6, 95% CI 25 – 316

Conclusion:

This study shows that patients with stage D cancer are nearly 90 times more likely to receive an amputation in the first 6 months after attending a clinic than patients with lesser stages, and patients with Grade III cancer are more than 11 times more likely to receive an amputation than patients with lower grades in the 6 months after presentation.

However, treatment is a confounder for outcome, and no account for the duration of the ulcer has been made. There may be some confounding due to a difference in race across different ulcer grades. Also, this study was not done in a controlled environment, and it is not explained how the original assessments (pre-assigning of the grade and stage – which were done using medical records) were done, and whether there may have been problems with inter-rater reliability.

Whilst the effect is likely to be real, we cannot be certain how much of the effect is real and how much is due to bias and/or confounding.

EXTERNAL VALIDITY

Generalisabilty: Nearly 80% of patients were recorded as being of Mexican-American race. If race is linked to outcome, it may be difficult to know if this data is generalisable. Also, treatment may be very different in Texas then Australia, and as it was not described, it is impossible to know whether these outcomes are generalisable.

Comments:

STUDY DETAILS

Reference [1] Abbott, C. A., L. Vileikyte, et al. (1998). "Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration." Care 21(7): 1071-1075.

Affiliation/source of funds [2] Department of Medicine, Manchester Royal Infirmary, Manchester, U.K. Source of funding was not stated

Study design [3] Prospective, originally started as a RCT (stopped due to lack of efficacy of the drug under trial)

Level of evidence [4] II

Location/setting [5] A total of 44 centers (29 from U.K., 9 from U.S., 6 from Canada)

Patient characteristics [10]

Characteristics	N=1,035
Mean age, (range)	60 (23–70)
Female %	25.4
Type 1 diabetes %	24.6
Caucasian % Black Oriental Other	94.8 2.0 3.9 2.8
BMI (kg/m^2)	28.4 (16.9–84.7)

Sample size [7]

1,035 patients

Length of follow-up [11]

1 year

Selection criteria

Inclusion criteria: - Patients were included in the study if they were diagnosed with insulin dependent or non-insulin dependent diabetes mellitus according to World Health Organization criteria, were ages 18–70 years, were men or non pregnant women, had a vibration perception threshold (VPT) >=25 V on at least one foot and <=50 V on both feet (determined at the hallux by neurothesiometer), and had at least one palpable pedal pulse on each foot.

Exclusion criteria : -The main exclusion criteria were as follows: 1) past or present foot ulcers, defined as any full-thickness skin lesion that required treatment in hospital, with general practitioner or chiropodist, excluding minor abrasions or blisters; 2) lower limb amputation; 3) presence of any other cause of diffuse peripheral neuropathy (malignancy, alcohol abuse, drug abuse, peripheral ischemia, anaemia, known vitamin B12 deficiency, or untreated hypothyroidism); 4) significant neurological disorder other than diabetic polyneuropathy (DPN) (e.g., stroke with significant neurological deficit, transient ischemic attacks, multiple sclerosis, epilepsy, and dementia); 5) alcohol abuse or other drug dependence; 6) previous or present treatment with cytotoxic drugs and/or radiotherapy; 7) uncontrolled hypertension (systolic blood pressure >=175 mmHg or diastolic blood pressure>= 105 mmHg); 8) renal disease with serum creatinine 160 µmol/l.

Predictor variable(s):	Data collection method
Treatment either surgical or non-surgical to ulcers that were developed	Routine or medical or surgical
Number of visits of patients to the clinic	
Basic education about foot care	Each patient was provided with a standardized foot care education leaflet at baseline, and the details in it were discussed. At every subsequent visit, the subject of foot care was raised, and patients were reminded of its importance. However this was not objectively evaluated for each patient.
Vibration perception threshold (VPT)	VPT was assessed at the great toe of both feet in triplicate using a neurothesiometer at baseline and after 52 weeks.
Severity of Michigan diabetic polyneuropathy (DPN) score Sum of muscle strength and reflex component of component of Michigan DPN scores at baseline Age Diabetes status and duration of diabetes at study entry Race Socioeconomic status	The severity of Michigan diabetic polyneuropathy (DPN) score was determined at baseline and after 52 weeks. This score has three components: sensory impairment (assessed by vibration perception at the great toe using a tuning fork, 10-g Semmes-Weinstein monofilament at the great toe, and a pinprick on the dorsum of the great toe); muscle strength testing (assessing finger spread, great toe extension, and ankle dorsi flexion); and re flexes (assessing biceps brachii, triceps brachii, quadriceps femoris, and Achilles tendon) Socioeconomic status was classified from the occupation of the main wage earner of the household

Potential confounders: Age, sum of muscle strength and reflex component of Michigan DPN scores at baseline, sum of the 10-g monofilament scores from the sensory component of the Michigan DPN scores at baseline, sum of the VPT scores at baseline, diabetes status, race, economic status (classified from the occupation of the main wage earner of the household), and duration of diabetes at study entry. The models did not control for gender, obesity, or medical/surgical treatment provided or antibiotic treatment in case of infection.

INTERNAL VALIDITY

Outcome measurement method [12] The outcomes were measured at baseline and at weeks 13, 26, 39, and 52 with patients undergoing a thorough examination. If ulcers were found, the patients underwent surgical or other treatment as thought appropriate by their physicians.	Comparison of study groups [14] N/A	Blinding [15] Initially was a double blind study for drug under investigation. However, here there was no blinding. The investigator was aware of the outcome (ulcer) and providing the scores was not blinded to outcome.
Measurement bias [16] Cannot evaluate because of the 44 different centres that were involved and no information was provided about the uniformity in treatments or assessments provided by the many different investigators at the many different centres.	Follow-up (ITT) [17] Withdrawal: 206/1,035=19.9%; ITT was provided. However, the authors do not state that all patients including the 206 withdrawals were followed up till one year (or till occurrence of ulcer)	
Overall quality assessment (descriptive) [18] Of moderate quality; The results were not controlled for treatment or surgery or antibiotics given for any sign of infection that could have eventually developed into an open ulcer; no adjustment was done to gender, and obesity. Furthermore, we cannot assume that foot care was similar in all 44 centres, or whether patient awareness and education was the same and this was also not controlled for. Full output of the models was not provided and confidence intervals were not stated. Confounding by factors mentioned above and measurement bias cannot be excluded.		
RESULTS		
Outcome [19] See below: Time to onset of the first foot ulcer was defined as the number of days between starting the study and a patient's first foot ulcer being found. The authors did not provide full output of models.	Quality assessment: Moderate	

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22]	
Age	Only stated as *P*<0.001, stated as age having a protective effect	
Baseline VPT	Only stated as *P*<0.001; possibly with HR=1.056	
Baseline Michigan DPN score	Only stated as *P*<0.001; possibly with HR=1.050	

No other information about the other variables introduced into the model was provided.
Conclusion: VPT, age, and Michigan DPN scores for muscle strength and reflexes were significant independent predictors for first foot ulceration (P< 0.001). However, confounding by treatment cannot be excluded and measurement bias among the 44 different centres, also pose a potential problem.
EXTERNAL VALIDITY
Generalisabilty: Good generalisability, a multi centre study.
Comments:

STUDY DETAILS

Reference [1] Boyko, E. J., J. H. Ahroni, et al. (1996). "Increased mortality associated with diabetic foot ulcer." Diabet Med 13(11): 967-972.

Affiliation/source of funds [2] Veterans Affairs Puget Sound Health Care System, Seattle, WA 98108, USA. The study was funded by the Veterans affairs Merit review rehabilitation research and Development.

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective study	II	Ambulatory general internal medicine clinic patients at Seattle VA Medical centre, Seattle, WA, USA

Patient characteristics [10]

More characteristics are reported in the univariate analysis (by death status). However, very minimal characteristics were reported by the authors for the whole cohort

Characterisitcs	
Male gender%	98.0%
Married status %	59.0%
Race (white)	78.0%
With non-insulin diabetes mellitus %	92.1%

Sample size [7]

725 diabetic subjects

Length of follow-up [11]

Mean follow-up was 691.8 days (± SD 339.9, range 28-1436 days)

Selection criteria

Inclusion criteria: - Ambulatory general internal medicine clinic diabetic patients at Seattle VA Medical centre, diagnosed as having diabetes mellitus by a physician or who received oral hypoglycaemic medication or insulin. Patients on oral medication or diet only were considered as having non insulin dependent diabetes mellitus. Those who were diagnosed before age 30 years, used insulin continuously since diagnosis, had ketoacidosis, and lean body habitus at the time of the diagnosis were considered as having insulin dependent diabetes mellitus type 1. All patients meeting these criteria duting 1 October, 1990 and 1 October, 1994 were eligible to participate.

Exclusion criteria: - Non ambulatory, declined to participate or too ill to take part in the study. Patients with a foot ulcer at the initial examination were also excluded.

Predictor variable(s):	Data collection method
Demographic, diabetes, and medical and foot health history	Medical history and demographics were collected by nurse practitioners
Glycosylated haemoglobin (blood test)	
Ankle-arm index (AAI)	AAI was calculated as the higher of the dorsalis pedis or posterior tibialis arterial Doopler blood pressure in both limbs
Lower limb neuropathy	Lower limb sensory neuropathy was assessed using the Semmes-Weinstein monofilaments with insensitivity defined as inability to feel the 5.07 monofilament at one or more of nine locations on the foot.
Ulcers and diabetic complications	Patients were asked to report to staff any foot lesions. Every 3 months the patients were mailed a questionnaire about foot health; Medical staff was asked to examine the feet of the patients and if the patient was hospitalized because of a foot problem, the researchers interviewed the patients for a diabetic foot problem. A phone interview was done with patients who reported any foot lesions.
	Ulcer was defined as a full thickness defect present for at least 14 days.

Potential confounders:

Age; diabetes type, duration, and treatment; glycosylated haemoglobin level; history of lower extremity amputation; and cumulative pack years smoked and major co-morbidites.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
Death was ascertained from the VA records, reports by family or friends, clinic providers or hospital discharge records. In addition to this, death was detected using national and insurance databases.	Compared those who died and who survived in terms of their characteristics	Not blinded

Measurement bias [16]	Follow-up (ITT) [17]
Similar; the outcome was not ascertained in patients who eventually were lost to follow-up, but loss to follow up was similar among those who had an ulcer and those who were without an ulcer (11.4% and 13.2%, respectively)	Of the 745 initially enrolled patients, 725 (97.3%) finally participated. From the 725 patients, 13% (94 patients) were lost to follow-up, but the analysis included time that all the patients donated.

Overall quality assessment (descriptive) [18] Of moderate quality. The authors assessed the association of an incident foot ulcer with the risk of death given risk factors. However, they chose to run two separate models controlling for a separate set of confounders at a time. They did not include all confounders in one separate model. Moreover, in the model that included self-reported major co-morbidities, the authors stated that "incident foot ulcer" was included and that its independent association with death remained. However, they chose not to report the adjusted hazard ratio of incident foot ulcer in the second model. Confounding cannot be excluded.

RESULTS

Outcome [19] See below

Quality assessment: Moderate

Multivariate outcome [19] Measure of effect/effect size + 95% CI [22]

Cox proportional hazards model of risk of death: Model 1

	HR (95%CI)	*P value*
Incident foot ulcer	2.21 (1.09-4.48)	0.027
Age at entry	1.02 (0.99-1.05)	0.317
Diabetes duration at entry	1.02 (1.00-1.05)	0.083
NIDDM vs. IDDM	2.99 (0.64-13.87)	0.162
Oral hypoglycaemic agent vs. diet	2.52 (0.89-7.12)	0.082
Insulin vs diet	1.85 (0.63-5.38)	0.262
Pack-years smoked	1.01 (1.00-1.01)	<0.001
Prior lower extremity amputation	1.46 (0.66-3.23)	0.354
Self-reported prior leg/foot ulcer	1.01 (0.59-1.73)	0.962

Cox proportional hazards model of risk of death: Model 2

	HR (95%CI)	*P value*
Ankle-arm index	2.23 (1.13-4.39)	*0.020*
Sensory neuropathy	2.14 (1.09-4.20)	0.028
Congestive heart failure*	2.38 (1.22-4.63)	0.011
Myocardial infarction*	2.38 (1.22-4.63)	0.011
Cerebrovascular disease*	2.36 (1.21-4.59)	0.012
Diabetic retinopathy*	2.38 (1.22-4.63)	0.011
Laser photocoagulation*	2.29 (1.17-4.51)	0.016
Renal disease*	2.38 (1.22-4.63)	0.011
Claudication symptoms*	2.30 (1.18-4.46)	0.014
Numbness in feet*	2.44 (1.25-4.76)	0.009

*The co-morbidities were self-reported

The authors stated that they included "incident foot ulcer" in the model, but they did not report the hazard ratio together with the confidence interval

Moreover, the authors did not control for risk factors presented in model 1.

Conclusion: The authors concluded that the risk of dying was significantly higher among patients with ulcers after adjustment for age; diabetes type, duration, and treatment; glycosylated hemoglobin level; history of lower extremity amputation; and cumulative pack years smoked.

EXTERNAL VALIDITY

Generalisabilty: Moderate generalisability, a predominantly male study population (98%)

Comments: The findings must be interpreted with caution as confounding by major co-morbidities cannot be excluded.

STUDY DETAILS

Reference [1] Cowley, M. S., E. J. Boyko, et al. (2008). "Foot ulcer risk and location in relation to prospective clinical assessment of foot shape and mobility among persons with diabetes." Diabetes Res Clin Pract 82(2): 226-232.

Affiliation/source of funds [2]

Department of Veterans Affairs, RR&D Center of Excellence for Limb Loss Prevention and Prosthetic Engineering, VA Puget Sound Health Care System, Seattle; Epidemiologic Research and Information Center, VA Puget Sound Health Care System, Seattle; Department of General Internal Medicine, University of Washington, Seattle; Department of Biobehavioral Nursing and Health Systems, University of Washington, Seattle; Northwest Weight Loss Surgery, Everett; Department of Mechanical Engineering, University of Washington, Seattle; Department of Orthopaedics and Sports Medicine, University of Washington, Seattle, WA 98195; United States. The research was supported by the Department of Veterans Affairs (VA) Rehabilitation Research and Development.

Study design [3] Prospective study	Level of evidence [4] II	Location/setting [5] VA Puget Sound Health Care System, Seattle, USA

Patient characteristics [10] Means ± SD or %

Characteristic	
Age at baseline, mean (SD)	62.4 (10.6) years
Male %	98.1%
Mean years of duration of diabetes (SD)	10.2 (9.3)
Type 2 diabetes	95.3%
Use of insulin %	40.7%
Past history of ulceration %	22.0%

Sample size [7]

3040 feet (from 1520 subjects)

Length of follow-up [11]

Subjects were followed prospectively for a mean of 4.7 years (S.D. 2.8 years).

Selection criteria

Inclusion criteria: - All patients at the General Internal Medicine Clinic with diabetes were eligible for the study. All patients provided informed consent. Subjects with diabetes were identified by reviews of: (1) hospital computerized pharmacy data for receipt of insulin, oral hypoglycemic medication, or blood or urine glucose test strips, (2) laboratory data, or (3) medical record problem lists for the diagnosis of diabetes. Diagnoses were confirmed through clinical providers or medical record review.

Exclusion criteria : - Exclusion criteria included a current foot ulcer, inability to ambulate, bilateral foot amputations, inability to participate in the study due to cognitive impairment, or other illness or condition that would not allow the subject to participate.

Predictor variable(s):	Data collection method
Diabetes type, duration, and treatment; neuropathic symptoms; past history of foot or leg ulcer, and past history of any foot amputation.	Collected by patient interview
Foot type, hammer/claw toe, hallux valgus, hallux limitus, prominent metatarsal heads, bony prominences, plantar callus, muscle atrophy, and ankle and hallux mobility.	Assessed by a physical examination by a research nurse
	Foot type was considered to be pes cavus (high arched with an inverted calcaneus), neutrally aligned (normal arch height during weight bearing, calcaneus perpendicular to the ground), pes planus (low arched with an everted calcaneus) and other, such as Charcot deformity, drop foot or partial foot amputation. The pes planus feet were further subdivided as rigid (nonreducible during weightbearing) or flexible (reducible during weight bearing).
Age at onset, presenting weight and symptoms, family history, onset of insulin treatment, and history of ketoacidosis.	
Foot ulcer	A foot ulcer was defined as a skin defect that penetrated its full thickness and that took more than 14 days to heal.

Potential confounders: Models were adjusted for age, gender, body mass index (BMI), insulin medication, neuropathy, amputation history and ulcer history

INTERNAL VALIDITY

Outcome measurement method [12]

The patients were re-examined at 12–18 month intervals (mean interval = 13 months) to review whether an outcome had occurred. Subjects were contacted quarterly by mail. They were also encouraged to call study staff or come by the research clinic if they suspected that they had a foot ulcer. Subjects who did not return mailed questionnaires were contacted, if possible, in person at their next clinic visit at the medical center. Special attention was called to the need for clinical providers to inform study personnel of all incident ulcers seen in ambulatory urgent care, surgical specialty clinics, and other clinical settings.

Comparison of study groups [14]

Ulcerated vs. non-ulcerated patients

Blinding [15]

Not blinded

Measurement bias [16]

Similar

Follow-up (ITT) [17] The number of eligible feet that remained in the study was 2939 out of 3040, or 96.7%, from 1502 subjects. No ITT

Overall quality assessment (descriptive) [18] Of good quality. However, the authors make selective conclusions based on a model that did not control for neuropathy. When neuropathy was controlled in the final model, no significant associations remained between foot shape and higher risk of ulceration.

RESULTS

Outcome [19] See below

Quality assessment:Good

Multivariate outcome [19] Cox proportional hazards models for new ulceration

Measure of effect/effect size + 95% CI [22]

	Hazard ratio (95% CI)	**P value**
Hallux valgus	0.8 (0.60-1.06)	0.1
Hallux limitus	1.11 (0.83-1.49)	0.5
Hammer/claw toes	1.40 (1.03-1.90)	0.09
Graded hammer/claw toes: Absent	1:00	
Slight	1.22 (0.81-1.87)	0.4
Moderate	0.99 (0.67-1.50)	0.99
Marked	1.43 (0.95-2.17)	0.09
Not graded	1.49 (0.95-2.43)	0.1
Prominent metatarsal head	1.19 (0.90-1.59)	0.2
Plantar callus	0.99 (0.76-1.29)	0.9
Ankle dorsiflexion (100)	1.02 (0.83-1.25)	0.8
MTPJ dorsiflexion (100)	0.95 (0.84-1.07)	0.4
MTPJ plantar flexion (108)	0.92 (0.82-1.04)	0.2
Muscle atrophy	1.08 (0.80-1.46)	0.6
Bony prominences	1.29 (0.95-1.76)	0.1
Foot type		
Neutrally aligned	1:00	
Pes cavus	1.01 (0.72-1.40)	0.99
Pes planua rigid	0.72 (0.40-1.27)	0.3
Pes Planus flexible	1.00 (0.60-1.66)	0.99
Other	1.76 (1.04-3.04)	0.05

The model was adjusted for neuropathy, age, BMI, insulin medication, ulcer history and amputation history; stratified by gender.

Conclusion: The authors concluded that foot shape was significantly associated with a higher risk of ulceration. However, when the final model also adjusted for neuropathy, no significant associations remained as demonstrated in the above model. The association of foot shape with any ulceration risk was confounded by neuropathy. Therefore, any association between foot shape and higher risk of ulceration was not proved.

EXTERNAL VALIDITY

Generalisabilty: Moderate generalisability, predominantly male (98%)

Comments:

STUDY DETAILS

Reference [1] Ledoux, W. R., J. B. Shofer, et al. (2005). "Relationship between foot type, foot deformity, and ulcer occurrence in the high-risk diabetic foot." Journal of Rehabilitation Research & Development 42(5): 665-672.

Affiliation/source of funds [2]

Department of Veterans Affairs (VA), Rehabilitation Research and Development Center of Excellence for Limb Loss Prevention and Prosthetic Engineering, VA Puget Sound Health Care System, Seattle, WA; Departments of Mechanical Engineering and 3Orthopaedics and Sports Medicine, University of Washington, Seattle, WA; Department of Medicine, Harborview Medical Center, University of Washington, Seattle, WA; 5Health Services Research and Development Service, VA Puget Sound Health Care System, Seattle, WA; Departments of 6 Health Services and 7Epidemiology, University of Washington, Seattle, WA; USA.
The study was supported by the VA Rehabilitation Research and Development and the VA Health Services Research and Development Service, and the National Institute of Diabetes and Digestive and Kidney Diseases.

Study design [3] Prospective	Level of evidence [4] II	Location/setting [5] The Department of Veterans Affairs [VA] Puget Sound Health Care System and the Group Health Cooperative [GHC], Seattle, WA, USA.

Patient characteristics [10] (by feet)

Characteristics by feet	
Mean age, (SD)	62 .4 (10.1)
Male %	77.4%
Mean BMI (kg/m^2)	32.9 (7.0)
Neuropathy %	57.7

Patient characteristics (by patient)

Characteristics by patients	
Mean age	62
Mean years of education	14 years
White race %	78%
Married %	61%

Sample size [7]

400 diabetic subjects

Length of follow-up [11]

2 years

Selection criteria

Inclusion criteria: - Study subjects were recruited from two Western Washington healthcare organizations (the Department of Veterans Affairs [VA] Puget Sound Health Care System and the Group Health Cooperative [GHC]), for a randomized trial of footwear. Study eligibility criteria of subjects were diagnosed diabetes, ages between 45 and 84, men from either the VA or GHC and women from GHC (few female veterans met the eligibility criteria), history of a full thickness foot lesion, no foot deformities requiring a custom shoe, and ability to walk one block and climb one flight of stairs a day.

Exclusion criteria: - Exclusion criteria were a prior lower-limb amputation of more than one digit; presence of either an unhealed lesion or healed ulcer in the prior month; requirement of boots, custom shoes, or non-traditional footwear for daily activities; non-ambulatory status; or a terminal illness with a 2-year survival unlikely. Subjects with severe foot deformities and Charcot feet were also excluded. Ulcers that were related to external trauma, self-care, decubitus, paronychia, or critical ischemia were excluded from the analysis.

Predictor variable(s):

Foot type (pes planus, neutrally aligned, and pes cavus), foot deformities (hallux valgus, hallux limitus, and hammer/claw toes, either fixed or supple), response to 5.07 monofilament, and peripheral pulses.

Body mass index (kg/m^2)
Age
Gender
Neuropathy
Duration of diabetes mellitus

Data collection method

Data on diabetes, health, foot, and functional status were collected from patients at baseline and after 1 and 2 years. Each foot was evaluated and examined during study visits every 17 weeks.

Definitions: Pes cavus feet have a high arch with or without an inverted hind foot, neutrally aligned feet have a normal arch with a well-aligned hind foot, and pes planus feet have a low arch with or without an everted hind foot. Hallux valgus is considered present if the great toe is deviated toward the lateral side of the foot with a prominence developed over the medial side of the first metatarsal head. Hallux limitus is present if the dorsiflexion and plantar flexion of the great toe is limited at the metatarsophalangeal joint. Hammer/claw toes are present if the metatarsophalangeal joint is hyperextended, the proximal interphalangeal joint is flexed, and the distal interphalangeal joint either is flexed or extended. The hammer/ claw toe deformity is supple if it can be passively corrected with the joints returning to a neutral position. If it cannot be passively corrected, the deformity is fixed.

An ulcer was defined as cutaneous erosion extending into or through the dermis to deeper tissue or other cuts not healing in 30 days. Only the first ulcer episode on each foot was included. Ulcers from factors deemed not footwear-related (e.g., minor trauma, self-care, critical ischemia, paronychia, or decubitus) were excluded.

Potential confounders: Age, sex, BMI, duration of diabetes, foot shape and neuropathy

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15] A panel of three foot-care specialists were blinded to the study group determined final ulcer classification.
Each foot was evaluated and examined during study visits every 17 weeks. Ulcers were photographed and medical records were reviewed.	With vs. without ulcers	

Measurement bias [16] Similar to all patients	Follow-up (ITT) [17] 398/400=99.5% had full follow-up

Overall quality assessment (descriptive) [18] Of good quality

RESULTS

Outcome [19] See below

Quality assessment: Good

Multivariate outcome [19] Logistic regression model for first new ulcer

Measure of effect/effect size + 95% CI [22]

	OR (95% CI)	P value
Male	2.38 (0.71-7.99)	0.2
Age	1.43 (0.95-2.16)	0.09
BMI	0.78 (0.56-1.07)	0.1
Duration of diabetes mellitus	1.55 (0.71-3.38)	0.3
Neuropathy	6.28 (1.88-21.0)	0.003
Foot type: Neutrally aligned	1:00	
Pes Planus	1.25 (0.53-2.98)	0.6
Pes Cavus	0.77 (0.25-2.37)	0.7
Hallux Valgus	1.97 (0.9-4.31)	0.09
Hammer / Claw toes; None	1:00	
Supple	0.68 (0.25-1.87)	0.5
Fixed	3.91 (1.57-9.71)	0.003
Hallux Limitus	3.02 (1.37-6.66)	0.006

Conclusion: Given age, sex, neuropathy, duration of diabetes and BMI, fixed hammer/claw toes and hallux limitus were associated with increased risk of any ulcer occurrence.

EXTERNAL VALIDITY

Generalisabilty: Moderate generalisability; Recruitment process is not stated. The authors did not state how many people were asked to participate, did so.

Comments:

STUDY DETAILS

Reference [1] LeMaster, J. W., G. E. Reiber, et al. (2003). "Daily weight-bearing activity does not increase the risk of diabetic foot ulcers." Medicine & Science in Sports & Exercise 35(7): 1093-1099.

Affiliation/source of funds [2] Department of Family and Community Medicine, University of Missouri, Columbia, MO, USA; the University of Washington, Seattle, WA, USA; VA Puget Sound Health Care System, Department of Veterans Affairs, Seattle, WA, USA. The study was supported by Rehabilitation Research and Development, the epidemiology Research and Information Centre, Department of Veterans Affairs, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Health and the Centres for Disease Control and Prevention.

Study design [3] Prospective	Level of evidence [4] II	Location/setting [5] Participants were from the Veterans Affairs Puget Sound Health Care System and Group Health Cooperative in Seattle, WA, USA

Patient characteristics [10]

Characteristic	N=390	Characteristic	N=390
Mean age, (SD)	62.5 (9)	Diabetes diagnosis >25 yeras %	12%
Female %	23%	Severe fixed foot deformities %	32%
Non white ethnicity %	22%	History of congestive heart failure %	13%
Currently unmarried %	39%	History of stroke %	15%
High school not completed%	28%	History of respiratory problems %	39%
Self monitors blood glucose %	44%	History of cancer %	18%
BMI >30 %	62%	History of depression %	41%
Past surgery for narrowed cardiovascular vessels %	15%	Any co-morbid condition %	75%
Insensate feet %	58%	Current smokers %	16%
Drank alcohol in the past year	55%	SF-36, standardised general health, mean (SD)	46 (1)
SF-36, standardised physical score, mean (SD)	35 (5)	SF-36, standardised mental score, mean (SD)	47 (1)

*For the SF-36 measures, the sample size was 386

Sample size [7]
400 participants

Length of follow-up [11]
2 years

Selection criteria

Inclusion criteria: - Participants were from the Veterans Affairs Puget Sound Health Care System and Group Health Cooperative in Seattle, WA, and were originally assembled for a randomized controlled trial that investigated the effect of therapeutic footwear and insoles on foot ulceration among diabetic patients who had a history of prior foot ulcers. Inclusion criteria included: diagnosed diabetes, ages 45-84, men from either the VA or GHC and women from GHC, history of a full thickness foot lesion or a foot infection requiring antibiotic treatment, no foot deformities requiring a custom shoe, and reported ability to walk one block and climb one flight of stairs per day.

Exclusion criteria : - Exclusion criteria were: Lower extremity amputation of more than one digit, a lesion either unhealed or healed for less than 1 month, requirement of boots, custom shoes, or non-traditional footwear for daily activities, a history of or active Charcot foot deformity, or a terminal illness that would make 2-year survival unlikely.

Predictor variable(s):	Data collection method
	Feet were examined and demographic and health history information was collected at enrolment. Daily weight-bearing activity was reported at enrolment and every 17 wk thereafter for 2 yr. All incident foot lesions were recorded.
Insensate feet	Feet were regarded as insensate when the 5.07 Semmes-Weinstein monofilament response was absent at any point on either foot. This as well as the presence of dorsalis pedis and posterior tibial pulses was re-assessed 1 year into follow-up.
Demographic and health status measures included age, gender, marital status, completion of high school, ethnicity, BMI, current smoker, history of stroke, congestive heart failure, respiratory illness, cancer, depression, or cardiovascular surgery. Other information included time since diagnosis of diabetes, compliance with blood glucose monitoring, and quality of life.	Quality of life was assessed using the SF-36 tool
The study outcome was re-ulceration	Re-ulceration was defined as a break in the cutaneous barrier extending into or through the dermis to deeper tissue that did not heal within 30 days. Ulcers that were not related to daily activity were excluded (decubitus ulcer, trauma-related, acute vascular insufficiency). Ulcers that resulted from patient-induced minor trauma were included.
Activity levels	An active hour was 60 minutes that participants reported they accumulated in any weight-bearing activity (standing, walking or more activity). Activity was reported in 15-minute intervals.
	Current activity was the reported number of the 24-hour before a given follow-up visit that were active hours.
	Long term activity was the cumulative average number of active hours measured from enrolment through a given follow-up visit.
	Short-term activity change for a participant was obtained by subtracting the number of active hours per day reported at a given follow-up visit from the number of active hours reported at the prior visit.
	Average activity intensity was the average metabolic equivalent task (MET) intensity above and beyond resting and was reported for weight-bearing activities at a given follow-up visit

Potential confounders:

Demographic and health status measures including age, gender, marital status, completion of high school, ethnicity, BMI, current smoker, history of stroke, congestive heart failure, respiratory illness, cancer, depression, or cardiovascular surgery, time since diagnosis of diabetes, compliance with blood glucose monitoring, and quality of life.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15] Blinding was done in the RCT setting. (those assessing the ulcers were blinded to the treatment allocation)
A panel of three foot-care specialists blinded to the clinical trial treatment arm determined ulcer classification. The ulcer date was the date the participant first noticed the ulcer.	N/A	

Measurement bias [16]	Follow-up (ITT) [17] Dropped out: 9/400=2.2%. The reported results are for the remaining 391 patients
The participants were interviewed once every 17 weeks using a 24-hour activity questionnaire to elicit information on daily-weight bearing activity. The questionnaire was validated.	

Overall quality assessment (descriptive) [18]

Of good quality

RESULTS

Outcome [19] See below	Quality assessment: Good

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22]	
Logistic regression models for re-ulceration		

	Without imputed data OR (95% CI)	With imputed data OR (95% CI)
Current activity	0.82 (0.86-1.01)	0.84 (0.68-1.02)
Long term activity	0.77 (0.81-0.96)	0.80 (0.64-1.0)
Short term activity	1.10 (0.99-1.22)	1.07 (0.96-1.20)

	Without imputed data OR (95% CI)	With imputed data OR (95% CI)
Least active (reference)	1.0	1.0
Moderately active	0.50 (0.22-1.16)	0.56 (0.25-1.25)
Most active	0.20 (0.04-0.87)	0.23 (0.06-0.97)

The models were adjusted for time in study, foot and health characteristics (age, marital status, presence of a co-morbidity, education, ethnicity, duration of diabetes, frequency of self-monitoring of blood glucose, BMI, history of current smoking, and physical and mental health status as measured by SF-36.

Conclusion:

The authors concluded that increased weight-bearing activity did not increase the risk of foot re-ulceration. Patients who were most active were at a lower risk of experiencing a re-ulceration compared to the less active patient.

EXTERNAL VALIDITY

Generalisabilty: Generalisable to those who had a prior history of foot ulcer

Comments:

STUDY DETAILS

Reference [1] Moss, S. E., R. Klein, et al. (1992). "The prevalence and incidence of lower extremity amputation in a diabetic population." Arch Intern Med 152(3): 610-616.

Affiliation/source of funds [2] Department of Ophthalmology, University of Wisconsin Medical School, Madison, USA. The study was funded by the National Eye Institute, Bethesda, MD., USA.

Study design [3] Cohort

Level of evidence [4] II

Location/setting [5] Setting not clear; patients were invited to participate in the study (not clear if these patients belonged to the outpatient clinic); University of Wisconsin Medical School, Madison, USA.

Patient characteristics [10] for younger age group (N=996)

Baseline characteristic	
Age: 0-29	574/996=57.6%
30-39	227/996=22.8%

Patient characteristics [10] for older age group (N=1370)

Baseline characteristic	
Age: 30-59	373/1367=27.3%
60-69	453/1367=33.1%

Sample size [7]

(for those who had baseline data)

Younger group=996

Older group= 1370

40-69	195/996=19.6%	70 +	541/1367=39.6%	Length of follow-up [11]
Duration of diabetes, yrs		Duration of diabetes, yrs		4 years
0-4	172/996=17.3%	0-4	353/1367=25.8%	
5-9	246/996=24.7%	5-9	338/1367=24.7%	
10-14	174/996=17.5%	10-14	180/1367=13.2%	
15-19	134/996=13.4%	15-19	251/1367=18.4%	
>=20	270/996=27.1%	>=20	245/1367=17.9%	
Systolic blood pressure, mmHg		Systolic blood pressure, mmHg		
78-110	218/873=24.9%	80-130	243/955=25.4%	
111-120	241/873=27.6%	131-144	266/955=27.9%	
121-134	224/873=25.6%	145-160	239/955=25.0%	
135-221	190/873=21.8%	161 +	207/955=21.7%	
Diastolic blood pressure, mmHg		Diastolic blood pressure, mmHg		
<=71	228/871=26.2%	<=70	213/952=22.4%	
72-78	223/871=25.6%	71-78	254/952=26.7%	
79-85	203/871=23.3%	79-87	254/952=26.7%	
86 +	217/871=24.9%	88 +	231/952=24.3%	
Pulse pressure, mmHg		Pulse pressure, mmHg		
<=33	217/871=24.9%	<=50	239/952=25.1%	
34-41	219/871=25.1%	51-64	235/952=24.7%	
42-52	220/871=25.3%	65-79	243/952=25.5%	
53+	215/871=24.7%	80+	235/952=24.7%	
Body Mass Index, kg/m^2		Body Mass Index, kg/m^2		
<=20.9	225/877=25.6%	<=24.6	206/956=21.5%	
21-23	215/877=24.5%	24.7-28.1	241/956=25.2%	
23.1-25.5	222/877=25.3%	28.2-31.7	245/956=25.6%	
>=25.6	215/877=24.5%	>=31.8	264/956=27.6%	
Glycosylated haemoglobin, %		Glycosylated haemoglobin, %		
<=10.8	211/834=25.3%	<=9.2	230/878=26.2%	
10.9-12.2	207/834=24.8%	9.2-10.8	220/878=25.0%	
12.3-14.1	215/834=25.8%	10.9-12.6	214/878=24.4%	
14.2+	201/834=24.1%	12.7+	214/878=24.4%	
Male gender%	442/879=50.3%	Male gender%	423/956=44.2%	
Proteinuria, %	156/844=18.5%	Proteinuria, %	101/921=10.9%	
History of sores, %	96/879=10.9%	History of sores, %	98/955=10.3%	
Retinopathy, %		Retinopathy, %		
Mild	298/879=33.9%	Mild	291/956=30.4%	
Moderate	142/879=16.1%	Moderate	129/956=13.5%	
Proliferative diabetic retinopathy	166/879=18.9%	Proliferative diabetic retinopathy	59/956=6.2%	
Smoking: Ex-smoker %	115/696=16.5%	Smoking: Ex-smoker %	286/956=29.9%	
Current smoker	197/696=28.3%	Current smoker	133/956=13.9%	
		Taking insulin %	459/956=48.0%	

Selection criteria

Inclusion criteria: - Case identification method is not stated. The authors refer the reader to a published article. In brief, two study samples of diabetic patients were invited to participate in the baseline examination from 1980 to 1982; the first (N=1910) consisted of the entire population of insulin-taking patients diagnosed before 30 years of age (referred to as the younger group); and the second group (N=1780) consisted of a random group stratified by duration of diabetes, of person diagnosed at 30 years of age or older (referred to as the older group). The surviving participants were further invited to participate in a follow-up examination 4 years later from 1984 to 1986.

Exclusion criteria : - Not reported

Predictor variable(s):	Data collection method
Severity of retinopathy	All fundus photographs were graded using a modified Airlie House classification scheme.
Pulse pressure	Pulse pressure is defined as systolic minus diastolic blood pressure.
Proteinuria	Proteinuria defined as a level of 0.30 g/L or greater.
Body Mass Index (BMI)	BMI= weight/height^2
Non smoker	Non smoker was any person who smoked less than 100 cigarettes in his/her lifetime

Potential confounders: Age, gender, duration of diabetes, history of sores, diabetes control, blood pressure, BMI, smoking, retinopathy, proteinuria. The authors did not control for any other co-morbidity or for the use of medications.

INTERNAL VALIDITY

Outcome measurement method [12] New sores of the feet and ankles and amputation of toes and legs based on *self-reported* medical history questionnaire. All traumatic amputations were excluded	Comparison of study groups [14] N/A	Blinding [15] Not blinded
Measurement bias [16] Measurements of variables followed similar protocols to all participants: this included measuring blood pressure, administering medical history questionnaire, taking stereoscopic colour fundus photographs of seven standard fields, determining urine protein level using a reagent strip and determining glycosylated haemoglobin levels.	Follow-up (ITT) [17] 4-year follow-up: Younger group: 891/996=89.4% Older group: 987/1370=72.0%. ITT was not applied	

Overall quality assessment (descriptive) [18] Of moderate quality: The good sides of the study: a large sample with 4-year follow up for the majority of the sample, multivariate analysis was applied to control for a selected number of potential confounders. The negative sides of the study: the outcomes were self-reported and this could have introduced some information or recall bias by the participants. Furthermore, patients who had the event (i.e. amputation) and got complicated and died were not identified; The authors did not validate the outcomes. The results were not controlled for other potential confounders such as socioeconomic status, or other co-morbidities, or medication use (such as corticosteroids); ITT was not applied and the characteristics of those without a full follow-up were not provided

RESULTS

Outcome [19] See below Stepwise logistic regression models separately for each age group and for each outcome	Quality assessment: Moderate

Multivariate outcome [19] Modelling AMPUTATION

Patient group: Younger group			
	OR	95% CI	P value
Age, 10 y	2.0	1.2-3.1	<0.005
History of sores	10.5	3.7-29.8	<0.001
Diastolic blood pressure, 10 mmHg	2.1	1.3-3.5	<0.005
Glycosylated haemoglobin, 2%	1.4	1.0-2.1	0.07
Retinopathy, 2 steps	1.4	1.0-1.9	0.06

Patient group: Younger sample >=18 years of age			
	OR	95% CI	P value
Age, 10 y	1.6	1.0-2.7	0.07
History of sores	8.7	3.0-25.0	<0.001
Diastolic blood pressure, 10 mmHg	2.2	1.3-3.6	<0.005
Glycosylated haemoglobin, 2%	1.5	1.1-2.2	<0.05
Pack-years smoked, 10 y	1.3	1.0-1.6	0.05
Retinopathy, 2 steps	1.4	0.9-1.9	0.10

Patient group: Older sample			
	OR	95% CI	P value
History of sores	4.6	1.7-12.2	<0.005
Proteinuria	4.3	1.6-11.5	<0.01
Glycosylated haemoglobin, 2%	1.5	1.0-2.2	<0.05
Male sex	2.8	1.0-7.5	<0.05
Duration of diabetes, 10 y	1.8	1.0-3.2	<0.05

Multivariate outcome [19] Modelling ULCERATION

Patient group: Younger group			
	OR	95% CI	P value
Age, 10 y	1.1	0.8-1.4	0.62
Glycosylated haemoglobin, 2%	1.6	1.3-2.0	<0.001
Retinopathy, 2 steps	1.3	1.1-1.6	<0.001

Patient group: Younger sample >=18 years of age			
	OR	95% CI	P value
Age, 10 y	1.1	0.9-1.5	0.35
Glycosylated haemoglobin, 2%	1.7	1.4-2.1	<0.001
Retinopathy, 2 steps	1.3	1.1-1.5	<0.01
Current smoker	1.0	0.4-2.4	<0.05
Diastolic blood pressure, 10 mmHg	2.3	1.0-5.6	0.06

Patient group: Older sample			
	OR	95% CI	P value
Glycosylated haemoglobin, 2%	1.6	1.3-2.0	<0.001
Duration of diabetes, 10 y	1.5	1.0-2.1	<0.05
Proteinuria	2.2	1.1-4.3	<0.05
Male sex	1.6	1.0-2.7	0.06
Diastolic blood pressure, 10 mmHg	0.8	0.6-1.0	<0.05
Retinopathy, 2 steps	1.2	1.0-1.4	0.08

Conclusion: The incidence of ulceration was similar in both age groups, though different risk factors for amputation or ulceration were observed for each group.

In younger-onset persons, significant risk factors for amputation included age, history of sores or ulcers, high diastolic blood pressure, and pack-years smoked. Risk factors for sores or ulcers included glycosylated hemoglobin, retinopathy, and current smoking.

In older-onset persons, risk factors for amputation were history of sores or ulcers, proteinuria, glycosylated hemoglobin, male sex, and duration of diabetes. For sores or ulcers, risk factors were glycosylated hemoglobin, duration of diabetes, proteinuria, and diastolic blood pressure.

EXTERNAL VALIDITY

Generalisabilty: Moderate generalisability. Despite the relatively large sample, it is not clear how the researchers got to the original lists and how did they select the patients that were invited. Exclusion criteria were not mentioned.

Comments:

STUDY DETAILS

Reference [1] Otiniano, M. E., K. S. Markides, et al. (2003). "Self-reported diabetic complications and 7-year mortality in Mexican American elders - Findings from a community-based study of five Southwestern states." Journal of diabetes and its complications 17(5): 243-248.

Affiliation/source of funds [2]

Sealy Center on Aging, University of Texas Medical Branch, Galveston, TX; Department of Endocrinology, Baylor College of Medicine, Houston, TX; Department of Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston, TX; School of Allied Health, University of Texas Medical Branch, Galveston, TX; Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX, USA. The study was supported by the National Institute on Aging, the National Institute of Diabetes, Digestive, and Kidney Diseases, and the Agency for Health Research and Quality.

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective	II	Non-institutionalised American Mexicans who were part of a population-based sample that formed the Epidemiological Study of the Elderly (H-EPESE) living in Texas, USA

Patient characteristics [10]

Characteristic		Characteristic	
Age:		BMI <22 %	19.3%
65-74 %	71.6%	22-26	28.1%
75-84	24.1%	27-29	21.0%
85+	4.3%	30 +	31.6%
Male %	42.2%	Any complications	59.7%
Ever smoked %	41.1%	Ever drank alcohol %	45.1%
Years of diabetes: <10	43.0%	Eye problems	38.9%
10-19	27.9%	Kidney problems	14.3%
20 +	21.4%	Circulation problems	40.6%
Unknown	7.5%	Amputations	8.9%
Co-morbidities:		Living alone %	18.3%
Stroke	11.0%	Living with others	81.7%
Heart attack	15.2%		
Hypertension	57.1%		
Hip fracture	3.3%		
Depression	26.9%		

Sample size [7]

690 patients

Length of follow-up [11]

7 years

Selection criteria

Inclusion criteria: - The Hispanic Established Population for the Epidemiological Study of the Elderly (H-EPESE) is a population based study of non institutionalized Mexican Americans aged 65 and older from five South-western states (Arizona, California, Colorado, New Mexico, and Texas). Subjects were selected by using the area probability sampling procedures that involved selection of counties and households within selected census tracts. Those who reported in the baseline interview having received a physician's diagnosis of diabetes (690 respondents) were included in this study.
Exclusion criteria : - Not stated

Predictor variable(s):	Data collection method
	Face-to-face interviews in either Spanish or English. The baseline interview was obtained in 1993–1994, the first follow-up in 1995–1996, the second follow-up in 1998– 1999, and the third follow-up in 2000–2001.
Diabetes	Diabetes was patient self-reported (stating that they received a physician's diagnosis of diabetes)
Co-morbidities were self-reported.	Respondents were asked if they were ever been told by a doctor that they had a stroke, heart attack, hypertension, or hip fracture.
Depression	Depression was measured with the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). A dichotomous measure was derived based on a score of 16 or greater on the CES-D, indicative of high levels of depressive symptomatology
Causes of death	Causes of death were obtained from family members or proxies at the time of the interviews. Causes of death were categorized as heart attack or heart disease, cancer, pneumonia, stroke, diabetic complications, Alzheimer's disease, any injury such as car accident, falls, suicide, drowning, and other causes of death.

Potential confounders:

Age, gender, co-morbidities, smoking, alcohol consumption, diabetes-related complications and social factors such as living alone

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
The authors did not state how information on death was collected. Possibly, this information was collected by interviewing relatives who also provided the causes of death. The authors did not ascertain the deaths. It is possible that some deaths were missed.	With diabetes-related complication vs. Without diabetes-related complications.	Not blinded

Measurement bias [16]	Follow-up (ITT) [17]
The methods used to collect all in the information may lack reliability and validity. The authors relied on self-reported co-morbidities as reported by the respondents and also causes of deaths were only taken from the respondents' relatives. Information and recall biases cannot be excluded.	The authors state that there were some who were lost to follow-up but they do not provide data. The information on all respondents was included till event, or till loss to follow up or till last day of follow-up.

Overall quality assessment (descriptive) [18] Moderate quality. The study relies on non-reliable and non-validated methods to collect most of the study's data. No effort was done to try to validate the information they gathered by either interviewing the patient or the relative. No information was given on number of patients who were lost to follow up.

RESULTS

Outcome [19] See below	Quality assessment:Moderate
Multivariate outcome [19] Cox proportional hazards model of 7-year mortality	Measure of effect/effect size + 95% CI [22]

	HR (95%CI)
Eyes problems	1.26 (0.97-1.63)
Kidney problems	1.56 (1.13-2.16)
Circulation problems	1.09 (0.83-1.45)
Amputations	1.32 (0.87-1.99)

*The model was controlled for age, sex, living arrangements, smoking, alcohol consumption, and self-reported history of stroke, heart attack, hypertension, cancer, and hip fracture

Conclusion:

The risk of 7-year mortality increased with the number of diabetic complications among Mexican American older adults. However, only self-reported diabetes-related kidney problems significantly increased the risk of dying within 7 years after baseline.

EXTERNAL VALIDITY

Generalisabilty: Poor generalisability. The study sample belong to one ethic group (Mexican American)

Comments:

STUDY DETAILS

Reference [1] Rith-Najarian, S. J., T. Stolusky, et al. (1992). "Identifying diabetic patients at high risk for lower-extremity amputation in a primary health care setting. A prospective evaluation of simple screening criteria." Diabetes Care 15(10): 1386-1389.

Affiliation/source of funds [2] Bemidji Area Indian Health Service Diabetes Program, Minnesota, USA. The study was supported by the Red Lake Tribal Council

Study design [3] Prospective study	Level of evidence [4] II	Location/setting [5] A primary-care setting at Red Lake, Minnesota, USA

Patient characteristics [10] Means ± SD or %

Characteristic	
Mean age (SD)	55.0 (12.3)
Male %	44%
Duration of diabetes, yrs (SD)	12.3 (6.7)
Risk category: 0 1 2 3	 74.3% 8.4% 4.5% 12.8%

Sample size [7]

358 diabetic patients out of all 405 patients that were registered in the diabetes registry

Length of follow-up [11]

32 months of follow-up or till censoring (death or loss to follow up)

Selection criteria

Inclusion criteria: - Cases for the study and complications were identified through active clinic and community screenings and followed with a diabetes registry (from 1 July 1988 to 28 February 1991).

Exclusion criteria : - Not stated

Predictor variable(s):	Data collection method
Risk categories	Individuals were assigned to one of four categories based on the presence of a foot deformity, history of lower extremity events (i.e. ulceration, amputation), and the ability to perceive the 5.07-U monofilament. Sensation status was determined by applying the 5.07 monofilamant to eight points on the plantar surface of each foot. Patients were considered sensate if they correctly identified the time at which the monofilament was applied to all areas on both feet. Patients who failed to identify the monofilament were retested twice before they were classified as insensate.
Feet deformities	Feet deformities were identified by clinical examination and these included hallux varus or valgus, claw and hammer toes, bony prominence, or Charcot foot on either foot.
Medical history information	History of ulceration or amputation was determined by interview, medical record review and examination.
Ulceration	Ulceration was defined as full thickness penetration of the dermis on the plantar aspect of the foot.

Potential confounders:

The risk score that was formed was based on major confounders such as history of ulceration or amputation, and foot deformity. However, no further adjustment was done for other major confounders such as duration of diabetes, neuropathy, age, gender, BMI, and co-morbidities.

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
The authors do not state how the outcomes were ascertained.	N/A	Not blinded

Measurement bias [16]	Follow-up (ITT) [17]
Similar to all patients	Death: 19/358=5.3%, Loss to follow-up: 2/358=0.6%. The denominator was based on person-years at risk. All donated time till event, or till censoring

Overall quality assessment (descriptive) [18] Of moderate quality. Crude results are shown. Confounding cannot be excluded.

RESULTS

Outcome [19] See below	Quality assessment:Moderate

Multivariate outcome [19] Not performed. The analysis done was Univariate	Measure of effect/effect size + 95% CI [22]	

	Crude OR for an amputation or ulceration
Risk category	
0 (reference)	1:00
1	15
2	32
3	78

Conclusion:

The authors concluded that the risk categorization described in the study could identify patients at risk for lower extremity events who are followed in a primary-care setting. However, these conclusions must be regarded with caution as confounding by major risk factors cannot be excluded. Confounding could have occurred by factors such as age, gender, duration of diabetes, and neuropathy.

EXTERNAL VALIDITY

Generalisabilty: Low generalisability. An Indian American indigenous population with 4 times more the risk of diabetes than the general American population.

Comments:

STUDY DETAILS

Reference [1] Roy, M. S. and B. Peng (2008). "Six-year incidence of lower extremity arterial disease and associated risk factors in Type 1 diabetic African-Americans." Medicine 25(5): 550-556.

Affiliation/source of funds [2] The University of Medicine and Dentistry, New Jersey Medical School; The Institute of Ophthalmology and Visual Sciences and Department of Preventive Medicine, Newark, NJ, USA. The study was funded by the National Eye Institute, Bethesda, MD, USA.

Study design [3] Cohort study	Level of evidence [4] II	Location/setting [5] Patients with a hospital discharge diagnosis of diabetes mellitus were selected randomly from 116 hospitals in New Jersey

Patient characteristics [10]

Baseline characteristics (N=483)			Baseline characteristics (N=483)	
Mean age, yr (SD)	27.5 (10.8)		Body mass index, kg/m^2 (SD)	27.9 (8.5)
Mean duration of diabetes, yr (SD)	10.4 (8.6)		Mean glycated haemoglobin, % (SD)	13.5 (4.3)
Male %	40.4		Systemic hypertension, yes	40.6
Socioeconomic status: Middle-high %	54.4		Education: <=High school %	52.1
Low	45.6		>= College	47.9
Smoking: Never %	55.4		Normoalbuminuria %	58.8
Past	11.1		Microalbuminuria	21.0
Current	33.5		Overt proteinuria	20.2
Age at diagnosis of diabetes <13 years	8.1		Retinopathy: None %	40.6
>= 13 years	91.9		Mild	35.0
			Moderate-severe	24.4
Macroangiopathy, yes %	11.8		Neuropathy, yes %	46.8
Use of statin medication, yes %	3.1			

Sample size [7]

N=483

Length of follow-up [11]

Mean follow-up: 6.1 ± 0.5 years;

Median follow-up: 5.96 years

Selection criteria

Inclusion criteria: - Initially the patients were selected randomly from 116 hospitals based on the presence of a hospital discharge diagnosis of diabetes mellitus as reported to the New Jersey Department of Health. In the database were listed 68,455 patients of African-American background. From these, 13,615 patients identified from 31 hospitals (lying within a 20-mile radius of New Jersey Medical School) had type1 diabetes. A random sample was selected from this list. The inclusion criteria included acute onset of diabetes before 30 years of age, insulin therapy started within 6 months from the diagnosis of diabetes, and continuous insulin therapy since that time.

Exclusion criteria: - Excluded were patients with type 2 diabetes, those diagnosed after age of 30 years whether on insulin or not, and patients with maturity-onset diabetes of youth.

Predictor variable(s):	Data collection method
Low extremity arterial disease (LEAD)	LEAD was defined if the patient had either of the following (as reported in the medical charts)1) toe, foot, or leg amputation, 2) angioplasty for poor circulation in the lower limb, or 3) absence of one or more major arterial pulses in the lower limbs.
Systemic hypertension	Systemic hypertension was defined as either systolic >=140 mmHg and or/diastolic >=90 mm Hg, and/or current use of antihypertensive medication. Blood pressure was taken twice, both in sitting and standing and the average of both measurements was recorded.
Pulse pressure	Pulse pressure defined as the difference the mean systolic and mean diastolic
Age at the time of baseline examination	
Age at the time diabetes was first diagnosed	
Socioeconomic status	Socioeconomic status was classified from the Golthorpe and Hope classification of occupations into middle-high and lower class using the occupation of the head of the family.
Alcohol consumption	Alcohol consumption was considered heavy if patient drank (currently or had a history of) 4 or more alcoholic drinks per day for at least one year – as documented in the hospital discharge summaries.
Smoking	Pack-years was calculated using the average number of packs of cigarettes (or cigars) per day multiplied by the number of years the patient smoked.
Exercise	Exercise was considered present if patient exercised at least one half-hour at least three times per week and this was associated with sweating.
Retinopathy	Eye examination was done after dilating fundus and fundus photographs were taken using standard stereoscopic methods for each eye. Severity of retinopathy was defined by the grading of the worse eye. Retinopathy levels: (10-15 none; 20-35 minimal non-proliferative; 43-53 moderate non-proliferative; >=61 severe proliferative retinopathy)

Potential confounders: Age, gender, duration of diabetes, retinopathy, socioeconomic status, smoking, blood pressure, body mass index, exercise, alcohol consumption, education, C peptide, blood cholesterol, proteinuria, gluycated haemoglobin, pulse pressure and peripheral neuropathy		
INTERNAL VALIDITY		
Outcome measurement method [12] First via structured interview and later the presence of low extremity artery disease or amputation was confirmed by chart review.	Comparison of study groups [14] N/A	Blinding [15] Not blinded
Measurement bias [16] Measurements were similar to all patients. The patient's medical history was obtained via a structured interview done by a physician. The medical information was further validated by reviewing medical charts. Medical examinations were also performed including eye examination and measuring the blood pressure. Also urine and blood samples were taken to assess the albumin, creatinine in urine and the levels of glycated haemoglobin, C-peptide and cholesterol in blood.	Follow-up (ITT) [17] Of the original sample that had baseline screening (725 patients), 508 participated in the 6-year follow up. However, only those still on insulin were included: 483 patients (483/725=66.6%). Results are only provided for this final sample.	
Overall quality assessment (descriptive) [18] Of moderate quality. "Researcher bias" at the level of analysis cannot be excluded. The multivariate analysis was done in two manners once including hypertension while excluding retinopathy and the second time the opposite was done. The researcher did not report a model that included both variables together (hypertension and retinopathy). Possibly the strengths of the association of "retinopathy" with LEAD could have been weakened (but results are not provided). Therefore, confounding cannot be excluded. The researchers do not give the characteristics of those lost to follow-up. The methods only identify survivors and do not recruit patients who might have had an amputation but died.		
RESULTS		
Outcome [19] See below	Quality assessment: Moderate, though confounding cannot be excluded	
Multivariate outcome [19] Multiple logistic regression model assessing LEAD as outcome		

	Model 1, including blood pressure but not retinopathy		Model 2, including retinopathy but not blood pressure	
	OR (95%CI)	*P value*	OR (95%CI)	*P value*
Duration of diabetes, year	1.08 (1.03-1.13)	<0.001	1.07 (1.01-1.13)	0.01
Systolic blood pressure	1.02 (1.005-1.04)	0.01	*Not included in model*	-
Foot/ankle ulcer	2.90 (1.02-8.19)	0.04	2.51 (0.86-7.29)	0.09
Male gender	2.28 (0.94-5.56)	0.07	2.70 (1.11-6.53)	0.03
Retinopathy severity None Minimal Moderate Severe	*Not included in model*		1.00 0.95 (0.23-3.98) 2.64 (0.62-11.31) 4.93 (1.13-21.55)	<0.001

Conclusion: The only variable that stays statistically significant in both models is duration of diabetes. Blood pressure that was significantly associated in first model is not included in the second and retinopathy is not included in the first model. Male gender is associated with a worse outcome, however, it does not reach statistical significance when blood pressure is included.

EXTERNAL VALIDITY

Generalisabilty: Weak generalisability, the study sample were all of African-American origin.

Comments:

STUDY DETAILS

Reference [1] Soedamah-Muthu, S. S., N. Chaturvedi, et al. (2008). "Relationship between risk factors and mortality in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study (PCS)." Care 31(7): 1360-1366.

Affiliation/source of funds [2] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; Epidemiology and Public Health, Royal Free and University College London Medical School, London, U.K.; the National Heart and Lung Institute, Imperial College, London, U.K.; and Medicine, University of Turin, Turin, Italy.
The EURODIAB study was supported by grants from the Wellcome Trust, the European Community, and Diabetes UK.

Study design [3] Prospective cohort study	Level of evidence [4] II	Location/setting [5] 16 European countries

Patient characteristics [10]	Means ± SD or %	Sample size [7]
The authors do not provide baseline characteristics for all the cohort except for two variables: Gender Mean age at baseline: The authors report the univariate analysis by their outcome (mortality); however, these are not the baseline characteristics of the whole cohort.	Gender: 51% males, and 49% females Age: 33 years ranging from 15 to 61 years.	2,787 type 1 diabetic patients (with full follow-up data) Length of follow-up [11] 7-year follow-up

Selection criteria

Inclusion criteria: - the EURODIAB Prospective Complications Study (PCS) recruited 1 diabetic patients between 1989 and 1991 from 16 European countries. Full details of the design, methods, and recruitment were not provided in this article. This clinic-based prospective cohort study examined 3,250 type 1 diabetic patients between 1989 and 1991. Participants were aged between 15 and 60 years and were recruited from 31 centres in 16 European countries. The sampling frame was all type 1 diabetic patients attending each centre at least once in the past year. Patients were stratified by age (three categories), diabetes duration (three categories), and sex. Ten patients were then randomly selected from each stratum. Type 1 diabetes was defined as diabetes diagnosed before the age of 36 years with a continuous need for insulin within 1 year of diagnosis. Of those invited, 85% participated.

Exclusion criteria: - Those with duration of diabetes < 1 year and pregnant women were excluded.

Predictor variable(s):	Data collection method
	All risk factors and microvascular complications were measured at baseline according to a standardized protocol.
Blood pressure Hypertension Pulse pressure Retinopathy Distal neuropathy "Pure" peripheral neuropathy Autonomic neuropathy Urine albumin excretion rate Plasma lipids (fasting triglycerides, cholesterol, and HDL cholesterol) and A1C.	Blood pressure was recorded in a sitting position with a random zero sphygmomanometer and taken as the mean of two measurements. Hypertension was defined as systolic blood pressure >=140 mmHg or diastolic blood pressure >=90 mmHg and/or the current use of blood pressure–lowering drugs (including ACE inhibitors, calcium channel antagonists, beta-blockers, diuretics, and alpha-blockers). Pulse pressure was calculated as the difference between systolic and diastolic blood pressure. Retinopathy was assessed by retinal photographs according to study protocol. Retinopathy was classified as none (level 0), nonproliferative (levels 1–3), and proliferative (levels 4 and 5). Distal neuropathy was diagnosed in patients with two or more of the following four measures: 1) the presence of one or more symptoms, 2) the absence of two or more reflexes of the ankle or knee tendons, 3) a vibration perception threshold that was abnormal for the patient's age, 4) and abnormal autonomic function (loss of heart rate variability with an RR ratio of <1.04 and/or postural hypotension with a fall in systolic blood pressure of >=20 mmHg). "Pure" peripheral neuropathy was defined as distal neuropathy without autonomic symptoms or abnormal autonomic function test results. Autonomic neuropathy was defined in two ways: 1) according to the above description or 2) at least two abnormal tests with a RR ratio of <1.04 and postural hypotension with a fall in systolic blood pressure of >=30 mmHg. Urine albumin: A single 24-h urine collection was performed to calculate albumin excretion rate (AER) after excluding proteinuria due to urinary tract infection using a Nephur dip-stick test for bacteria. Albuminuria was defined as micro- and macroalbuminuria. Triglyceride and cholesterol concentrations of plasma and the cholesterol concentration of HDL were assayed by standard enzymatic methods.

Potential confounders: Age, gender, major co-morbidities, life events (injury, surgery, etc.), duration of diabetes, treatments such as antihypertensive treatment

INTERNAL VALIDITY

Outcome measurement method [12]	Comparison of study groups [14]	Blinding [15]
All-cause mortality was ascertained from hospital records and death certificates.	N/A	Not blinded

Measurement bias [16] Endpoints were obtained similarly for all patients	Follow-up (ITT) [17] At baseline the cohort sample was 3,250, but full data were available only for 2,787 (86%). Outcomes were followed only for these 2,787 patients. ITT was not applied.
Overall quality assessment (descriptive) [18] Moderate quality. Only 86% of the initial sample was followed. A multivariate analysis was done while controlling for cardiovascular risk factors and diabetes-related complications. However, the model did not control for some potential confounders such as gender, other major co-morbidities such as cancer, cerebrovascular accidents, or other major events that could have occurred during the 7-year follow-up period (events such as injury, surgery, or other major health problem)	
RESULTS	
Outcome [19] See below (Cox proportional hazards model for all-cause mortality)	Quality assessment: Moderate

Multivariate outcome [19]	Measure of effect/effect size + 95% CI [22]	
Age at baseline (years)	1.87 (1.44–2.45)	
Age at diabetes diagnosis (years)	1.65 (1.33–2.04)	
Duration of diabetes (years)	1.20 (0.94–1.53)	
A1C (%)*	1.30 (1.07–1.58)	
Systolic blood pressure (mmHg)	1.46 (1.24–1.73)	
Diastolic blood pressure (mmHg)	1.26 (1.05–1.52)	
Pulse pressure (mmHg)	1.34 (1.14–1.57)	
Cholesterol (mmol/l)	1.31 (1.09–1.58)	
LDL cholesterol (mmol/l)	1.32 (1.06–1.63)	
HDL cholesterol (mmol/l)	0.70 (0.56–0.87)	
Fasting triglycerides (mmol/l)*	1.44 (1.17–1.78)	
Non-HDL cholesterol (mmol/l)	1.40 (1.18–1.67)	
Waist-to-hip ratio	1.34 (1.17–1.54)	
BMI (kg/m2)	0.93 (0.76–1.14)	
Insulin dose (units per day per kg)	0.88 (0.70–1.09)	
AER (_g/min)*	1.75 (1.51–2.03)	
Current smoking	1.23 (0.80–1.88)	
Low physical activity	1.36 (0.92–2.02)	
2–3 insulin injections/day vs. 1 injection	0.58 (0.29–1.15)	
Hypertension	2.44 (1.61–3.72)	
Antihypertensive medication	3.15 (2.04–4.85)	
Microalbuminuria	1.20 (0.75–1.92)	
Macroalbuminuria	4.27 (2.75–6.64)	
Albuminuria	2.94 (1.93–4.46)	
Non-proliferative retinopathy	0.82 (0.49–1.37)	
Proliferative retinopathy	3.58 (1.97–6.51)	
Retinopathy	2.23 (1.21–4.12)	
Autonomic neuropathy: 1)†	2.83 (1.82–4.38)	

Autonomic neuropathy: 2)†	2.45 (1.21–4.96)	
Peripheral neuropathy	2.83 (1.84–4.34)	
Cardiovascular disease	2.38 (1.50–3.77)	

*Log-transformed corrected A1C values according to the Diabetes Control and Complications Trial method. Cox proportional hazards analyses were performed, with baseline age and diabetes duration adjustments.
†Autonomic neuropathy was defined in two ways: *1*) loss of heart rate variability with an RR ratio of <1.04 and/or postural hypotension with a fall in systolic blood pressure of_20 mmHg or *2*) loss of heart rate variability with an RR ratio of <1.04 and postural hypotension with a fall in systolic BP of >=30 mmHg.

Conclusion: The study suggests that important risk factors for the increased total and non-CVD mortality in type 1 diabetic patients are age, Waist-to-hip ratio (thought this could have been confounded by gender), pulse pressure, and non-HDL cholesterol. Microvascular complications from macroalbuminuria and peripheral and autonomic neuropathy were shown to be strong risk markers for future mortality.

EXTERNAL VALIDITY

Generalisabilty: Moderate generalisability to type 1 diabetic patients (a multicentre study and a fairly large sample that was randomly selected according to age, gender and duration of diabetes). However, the authors do not clarify how the participants were initially recruited and why were they referred to this study. A referral bias cannot be excluded.

Comments:

STUDY DETAILS

Reference [1] Winkley, K., D. Stahl, et al. (2007). "Risk factors associated with adverse outcomes in a population-based prospective cohort study of people with their first diabetic foot ulcer." Journal of and its Complications 21(6): 341-349.

Affiliation/source of funds [2] Department of Psychological Medicine, Institute of Psychiatry, King's College London, Weston Education Centre, UK; Department of Biostatistics, Institute of Psychiatry, King's College London, London, UK; Diabetic Foot Clinic, King's College Hospital, London, UK. Source of funding was not stated.

Study design [3]	Level of evidence [4]	Location/setting [5]
Prospective cohort study	II	All the community chiropody and hospital foot clinics within 5 National Health Service health authorities in South London, UK

Patient characteristics [10]		Sample size [7]
Explanatory variable	Explanatory variable	253 patients

Mean age, yrs (SD)	62.0 (13.9)		Mean duration of diabetes, yrs (SD)	14.7 (13.2)	Length of follow-up [11]
Male gender %	63.6		Mean duration of ulcer, months (SD)	3.1 (3.6)	18-month follow-up
Type 2 diabetes %	83.0		Mean glycated haemoglobin (%)	8.2 (1.7)	
Insulin treated diabetes%	45.1		Non – or ex-smoker %	84.2	
Tablet treated diabetes %	54.9		Current smoker	15.8	
Microvascular complications ≥1 %	87.4		Macrovascular complications ≥1 %	26.9	
Texas severity of ulcer %			Mean ulcer size (cm^2)		
Superficial	74.3		≤ 1	48.6	
Deep	25.7		>1	51.4	
ABPI			Vibration perception threshold		
≥0.9	76.3		<25 V	18.6	
≥0.5, <0.9	23.7		≥ 25V	81.4	
Location of ulcer			DSM-IV-depression		
Plantar	43.9		None	67.6	
Dorsal	56.1		Any	32.4	
Alcohol problems	11.9%				

Selection criteria

Inclusion criteria : - Between October 2001 and February 2003, adults with type 1 or type 2 diabetes and presenting with their first (baseline) diabetic foot ulcer were identified through fortnightly contact with each participating clinic and review of previous fortnight's records using a standardised checklist of case definition and exclusion criteria for all current and all new patients. Diabetes was defined according to the World Health Organization (WHO) criteria. Informed consent was obtained for each participant. A clinically significant case definition of diabetic foot ulcer was used: (i) the ulceration was in the anatomical foot; (ii) there was a full thickness break in the epithelium with a minimum width of 5 mm; and (iii) to exclude severely ischaemic feet, the ankle:brachial ratio was >0.5 and no greater than 1.5 (to exclude those with potential calcification of the medial arteries) at either the dorsalis pedis or posterior tibial sites using Doppler pressure readings. When subjects had more than one ulcer at first presentation, the largest ulcer was defined as the baseline ulcer. Subjects whose first ulcer healed within 3 months from the start of the study were included.

Exclusion criteria: - The exclusion criteria were (i) not being fluent in English; (ii) current independent co-morbid medical condition (such as rheumatoid arthritis); and (iii) severe mental illness, such as schizophrenia, other psychoses, dementia. Any first diabetic foot ulcers with duration of greater than 1 year at recruitment were excluded.

Predictor variable(s):	Data collection method
Ulcer size, and the degree of neuropathy and ischaemia; surface area calculated in square centimeters. Severity of the ulcer was determined using the University of Texas Diabetic Wound Classification System Duration of ulceration Degree of ischaemia was assessed using the ankle brachial pressure index (ABPI). Foot pulses identified by a handheld Doppler. Brachial and ankle systolic pressure measured with a sphygmanometer. Protective pain sensation Glycosylated hemoglobin was measured at baseline and at 12 and 18 months Macrovascular complications Microvascular complications Depressive disorder Substance use Smoking (non- or ex-smoker vs. Smokers) Demographic variables: age and gender	Size was determined using digital imaging. Severity of the ulcer was determined using the University of Texas Diabetic Wound Classification System. (Wounds extending through the epidermis or dermis only were coded as superficial. Wounds penetrating tendons, joint capsule, bone, or joint were coded as severe). Duration of ulceration was recorded from first presentation (using medical records) to the date of recruitment. Degree of ischaemia was assessed using the ankle brachial pressure index (ABPI). Assessment of protective pain sensation and sensory neuropathy was made using a neurosthesiometer (participants with a vibration perception threshold (VPT) of ≥25 V were defined as neuropathic) The mean percentage of glycosylated haemoglobin values were derived from baseline and 12 and 18 months to capture the assumed close temporal association between glycaemic control and risk of ulceration Macrovascular complications were defined as prior myocardial infarct, coronary angioplasty, coronary artery bypass, and peripheral angioplasty or cerebrovascular accident. Microvascular complications were defined as retinopathy (background or proliferative) measured using digital fundal examination, nephropathy (macroalbuminuria or on dialysis) and neuropathy (VPT ≥25 V). Depression was assessed using the WHO's SCAN 2.1 (WHO, 1997) that is based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria. The information is collected by means of an interview The Alcohol Use Disorders Identification Test was used to classify patients who reported hazardous and harmful alcohol consumption; those scoring above 8 were defined as having an alcohol problem.
Potential confounders: Age, Sex, major co-morbidities, major events (injury, surgery, if they occurred during the 18 month follow up) when mortality was the outcome; also severity of ulcer and treatment for ulcer when outcome was re-ulceration or amputation	
INTERNAL VALIDITY	
Outcome measurement method [12] Checked at baseline, 6, 12, and 18 months after baseline.	**Comparison of study groups** [14] N/A **Blinding** [15] Blinded only to depression status
Measurement bias [16] Measurements were based on ICD-10 diagnostic codes obtained from the UK Central register Office and these were similar for all patients	**Follow-up** (ITT) [17] N=253; Follow-up for mortality outcome - all (100%); 92.0% and 90.5% for amputation (N=233) and recurrence (N=229), respectively
Overall quality assessment (descriptive) [18] The study is of good quality based on a population-based sample but may lack statistical power due to a relatively small sample size. The results were controlled for major confounder for each of the outcomes.	
RESULTS	
Outcome [19] See below: Using multivariate Cox proportional hazards regression modelling	**Quality assessment:** Good

Multivariate outcome [19] Multivariate Cox proportional hazards regression models by different outcomes (N=253)

Variable	Mortality (n=40)	Amputation (N=36)	Recurrence (N=99)
	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Mean age	1.07 (1.04 – 1.11)	0.99 (0.97–1.02)	0.99 (0.97–1.00)
Male gender	0.88 (0.41 – 1.89)	1.12 (0.56–2.26)	1.42 (0.87–2.33)
Type II diabetes; (reference: type 1 diabetes)	-	-	0.84 (0.49–1.45)
Insulin treatment; (reference: tablet treatment)	-	-	0.69 (0.44–1.06)
Smoker; (reference: ex, or non smoker)	1.36 (0.61–3.06)	0.88 (0.36–2.14)	1.16 (0.64–2.11)
Alcohol use	-	-	-
Microvascular complication	-	-	3.34 (1.17–9.56)
Macrovascular complications	1.11 (0.51–2.40)	-	-
Mean duration of ulcer	-	-	-
Mean duration of diabetes	-	-	-
Mean glycated haemoglobin	0.73 (0.56–0.96)	-	-
Deep ulcer (reference: superficial)	1.70 (0.86–3.38)	3.18 (1.53–6.59)	-
Mean ulcer size (cm^2) >1 (reference $\leq$1)	-	1.40 (0.69–2.85)	-
VPT $\geq$25 V (reference <25V)	1.80 (0.63–5.12)	-	-
ABPI $\geq$0.5, <0.9 (reference $\geq$0.9)	2.74 (1.46–5.14)	-	-
Dorsal location of ulcer, (reference plantar)	-	-	0.68 (0.45–1.05)
Any DSM-IV-depression, (reference none)	2.51 (1.33–4.73)	1.38 (0.70–2.72)	1.18 (0.77–1.81)

*All the listed variables were first tested in univariate Cox models and in the second stage only 'relevant' variables (authors do not state how was that decided) were included in the presented multivariate analysis.

Conclusion: The study showed that being older, having better gkycemic control, moderate ischaemia, and suffering from depression were independent risk factors of mortality following first ulceration. Severity of ulcer was independently associated with amputation and microvascular complications were associated with recurrent ulceration.

EXTERNAL VALIDITY

Generalisabilty: Good generalisability

Comments: Some of the results are hard to comprehend on clinical basis. They found that those who were better managed in terms of glucose control were more likely to die compared to those who had worse glycemic control. Maybe this was confounded by factors not accounted for such as socioeconomic status

Question 6

<table>
<tr><td colspan="5">STUDY DETAILS</td></tr>
<tr><td colspan="5">Reference [1] Katz, I. R., A. Harlan, et al. (2005). "A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers." Diabetes Care 28(3): 555-559.</td></tr>
<tr><td colspan="5">Affiliation/source of funds [2] Source of funding not stated. Authors are affiliated with University of Miami School of Medicine, Tucson Veterans Administration Medical Affairs Center and the Rosalind Franklin University of Medicine and Science (Scholl's Center for Lower Extremity Ambulatory Research). It is not obvious that any of these affiliations are related to either the experimental or control intervention.</td></tr>
<tr><td colspan="2">Study design [3] RCT</td><td colspan="2">Level of evidence [4] II – randomised control trial using pre-prepared random number tables</td><td>Location/setting [5] Referral clinic dedicated to the treatment of diabetic foot ulcers</td></tr>
<tr><td colspan="3">Intervention [6] Removable Cast Walker rendered irremovable by fibreglass casting material (iTCC)

Sample size [7] 21</td><td colspan="2">Comparator(s) [8] Standard total contact cast (TCC)

Sample size [9] 20</td></tr>
<tr><td colspan="5">Selection criteria
Inclusion criteria –
Diagnosis of diabetes
Chronic (≥ 7 days with surrounding callus), non-ischaemic, non-infected University of Texas stage IA or IIA ulcers.
Moderate to severe neuropathy (neuropathy disability score ≥ 6) and biothesiometer vibration perception threshold score ≥ 25 volts at the apex of the hallux on the affected side.
Exclusion criteria –
Clinical evidence of active infection at the ulcer site
Charcot neuroarthropathy
Significant peripheral arterial disease (absent dorsalis pedis or posterior tibial pulse)
Inability to walk</td></tr>
<tr><td colspan="5">Patient characteristics [10]
Intervention group –

Comparator group(s) –</td></tr>
<tr><td colspan="3">Length of follow-up [11]</td><td colspan="2">Outcome(s) measured [12]</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]</td><td>Comparison of study groups [14]</td><td>Blinding [15]</td><td>Treatment/ measurement bias [16]</td><td>Follow-up (ITT) [17]</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18]</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td rowspan="3">Outcome [19]</td><td rowspan="2">Intervention group [20]</td><td rowspan="2">Control group [21]</td><td rowspan="2">Measure of effect/effect size [22]

95% CI [25]</td><td>Benefits (NNT) [23]

95% CI [25]</td></tr>
<tr><td>Harms (NNH) [24]

95% CI [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26]</td><td colspan="2">Relevance (1-5) [27]</td></tr>
<tr><td colspan="5">Any other adverse effects [28]</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29]</td></tr>
</table>

Applicability [30]
Comments [31] It is not clear how the random number table is used to allocate the patient to the study or control intervention and therefore it is not certain that the randomisation is entirely masked. Inclusion and Exclusion criteria are well defined, however, it is not clear how well

STUDY DETAILS				
Reference [1] : Ahroni, J. H., E. J. Boyko, et al. (1993). "Diabetic Foot Ulcer Healing - Extrinsic Vs Intrinsic-Factors." Wounds-a Compendium of Clinical Research and Practice 5(5): 245-255.				
Affiliation/source of funds [2] Seattle Veterans Affairs Medical Center and the university of Wahinton, USA, supported by grant from Dow B. Hickam, Inc. And Veterans affairs Rehabilitation, Research and Development.				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] hospital and clinics (walk-in, medical, surgical subspecialty clinics and diabetes foot clinic)		
Intervention [6] Ulcer throroughly debrided with sharp instrument. Wounds are cleansed with half strength hydrogen peroxide and rinsed with normal saline. Daily dressing changes of two layers of moist wound dressing (Sorban™ Dow B Hickam Inc, Sugar Land, Texas) Sorbson is calcium alginate dressing. Held in place with gauze wrap.No other concurrent treatment. Antibiotics prescribed when infection of soft tissue for 2 weeks . Sample size [7] N= 20		Comparator(s) [8] Ulcer throroughly debrided with sharp instrument. Wounds blotted dry with gauze. Twice daily dressing changes with single layer of dry fine maze gauze (Owens Non-adherent dressing™, American Cyanamid Co, Danburry, Connecticut) Held in place with gauze wrap. No other concurrent treatment. Antibiotics prescribed when infection of soft tissue for 2 weeks . Sample size [9] N=19		
Selection criteria: Inclusion criteria – ulcers that penetrated the epidermis but did not significantly involved joint spaces, tendon or bone. Exclusion criteria – previously enrolled in this study, required inpatient management of their ulcers (i.e., severe infection, ischemia, extensive cellulitis, lymphantgitis, deep necrosis, gangrene, crepitus or gas in the tissue, osteomyelitis or presumed deep-space infection), evidence of systemic toxicity (i.e., high fever, hypotension or metabolic decompensation) unable or unwilling to comply with either daily wound care regiment or to come to weekly clinic visist.				
Patient characteristics [10] Intervention group – age mean(yrs) 61.2±11.0, Male 100% (n=20), NIDMM 85% (n=17), IDDM 26% (n=5), Insulin 70% (n=14), OHA 20% (n=4), Diet only 10% (n=2), mean Diabetes duration (yrs) 15.6±10.5, smoking never 10% (n=2), ex smoker 85% (n=17), current smoker 5% (n=1), , mean HbA1 (%) 12.4±3.3, Hematocrit 41.9±5.1, total lymphocyte count 2248±1337, creatinine 1.4±0.6, blood urea nitrogen 22.6±9.4, ulcer characteristics: mean wound duration (days) (range)132.9±320.6 (1-1460) chonic wounds (>4weeks) 60% (n=12),partial thickness 10% (n=2), full thickness 85% (n=17), necrotic tissue 5% (n=1) Eschar 0, mean Wound surface (mm²) 193.2±346.4, total wound score 18.3±6.6,ulcer cause, chronic pressure 55% (n=11) dysvascular 25% (n=5) other trauma 20% (n=4), ulcerlocation plantar forefoot 50% (n=10), heel 35% (n=7), dorsal toe 5% (n=1), dorsal foot 10% (n=2) Comparator group(s) – age mean(yrs) 65.4±9.3, Male 100% (n=20), NIDMM 74% (n=14), IDDM 26% (n=5), Insulin 68% (n=13), OHA 26% (n=5), Diet only 5% (n=1), mean Diabetes duration (yrs) 17.2±8.0, smoking never 37% (n=7), ex smoker 53% (n=10), current smoker 11% (n=2), , mean HbA1 (%) 13.1±2.9, Hematocrit 40.9±4.5, total lymphocyte count 2160±792, creatinine 1.6±0.6, blood urea nitrogen 31.8±27.2, ulcer characteristics: mean wound duration (days) (range)74.9±130.4 (1-480) chonic wounds (>4weeks) 47% (n=9),partial thickness 21% (n=4), full thickness 63% (n=12), necrotic tissue 11% (n=2) Eschar5% (n=1)0, mean Wound surface (mm²) 166.7±211.1, total wound score 20.4±8.5,ulcer cause, chronic pressure 63% (n=12) dysvascular 21% (n=4) other trauma 16% (n=3), ulcer location: plantar forefoot 53% (n=10), heel 16% (n=3), dorsal toe 11% (n=2), dorsal foot 21% (n=4)				
Length of follow-up [11] 4 weeks		Outcome(s) measured [12] healing : granulation tissue over 75% of wound area and 40% decrease in wound surface area. And number or adverse events		

INTERNAL VALIDITY				
Allocation [13] Randomised	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] No possibility for blinding	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] 8 drop out, 79% follow up (2 surgery, 4 amputation, 2 expired)
Overall quality assessment (descriptive) [18] good quality study				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size	Benefits (NNT) [23] 95% CI [25]
Healed at 4 weeks	25% (n=5)	37% (n=7)	P=0.65	
Unhealed at 4 weeks	50% (n=10)	47% (n=9)		
Withdrawn	25% (n=5)	16% (n=3)		

Healing rate area, mm^2/day	-2.19±4.0 (5 missing)	-2.04±2.61 (3 missing)	p>0.99	
Healing rate, linear, mm^2/day	0.094±0.147 (5 missing)	0.084±0.100 (3 missing)	P=0.87	
There was no significant difference between moist and dry dressings for healing or healing rate.				
	Clinical importance (1-4) [26] so no clinically important benefit		Relevance (1-5) [27] Evidence confined to unproven surrogate outcomes.	
Any other adverse effects [28]				
EXTERNAL VALIDITY				
Generalisabilty [29] likely generalisable to the target population				
Applicability [30] benefits do not outweigh harms				
Comments [31]				

STUDY DETAILS				
Reference [1] : Apelqvist, J., J. Larsson, et al. (1990). "Topical treatment of necrotic foot ulcers in diabetic patients: a comparative trial of DuoDerm and MeZinc." The British journal of dermatology 123(6): 787-792.				
Affiliation/source of funds [2] Department of Internal Medicine and Orthopaedic Surgery, University Hospital Lund, Sweden.				
Study design [3] Randomised controlled trial	Level of evidence [4] II	Location/setting [5] outpatient combined foot Care Team		
Intervention [6] corrected foot wear when necessary and relieve of external pressure on the ulcer. Ulcers were cleaned with sterile saline and dressed adhesive zinc oxide tape (MeZinc) (Mölnlycke Health Care, Sweden). Dressing changed daily in first week followed by every 3 days. Sample size [7] N= 22		Comparator(s) [8] corrected foot wear when necessary and relieve of external pressure on the ulcer. Ulcers were cleaned with sterile saline and dressed occlusive hydrocolloid dressing (DuoDerm or Granuflex or Varhesive) (ConVatec, USA). Dressing changed daily in first week followed by every 3 days. Sample size [9] N=22		
Selection criteria: Inclusion criteria –previous diabetes mellitus and superficial full thickness skin ulcer below the ankle, systolic blood pressure above 45mmHg or an absence of cutaneous erythema. Ulcer size between 1-25cm² in area with more than 50% of the area covered with dry or wet necrotic tissue. Exclusion criteria – positive patch test, showing clinical signs of cellulitis and ulcers where dressing would be inappropriate.				
Patient characteristics [10] Intervention group – age (yrs) 63 ±13, male 45% (n=10), female 55% (n=12), duration of diabetes (yrs) 22±15, Diet 5% (n=1), Oral hypoglycaemic agents 18% (n=4), Insulin 77% (n=17), Systolic blood pressure (mmHg) 66±33, Systolic ankle pressure (mmHg) 104±41, fB-glukos (mmol/l)9.1±4.8, HbA1c (%) 8.4±1.4, Zinc (µg/ml) 0.74±0.05; ulcer characteristics ulcer area (cm²) 2.2 (1 – 10.5), necrotic area (cm²) 1.5 (0.5-10.5), dry necrotic ulcer 68% (n=15), wet necrotic ulcer 32% (n=7), localisation: dig I 23% (n=5), Dig II-V 14% (n=3), Plantar surface 5% (n=1), Dorsal area 5% (n=1), Malleolus 32%(n=7), Heel 23% (n=5) Comparator group(s) – age (yrs) 62 ±18, male 73% (n=16), female 36% (n=8), duration of diabetes (yrs) 19±12, Diet 0% (n=0), Oral hypoglycaemic agents 18% (n=4), Insulin 82% (n=18), Systolic blood pressure (mmHg) 68±32, Systolic ankle pressure (mmHg) 114±52, fB-glukos (mmol/l) 9.0±4.0, HbA1c (%) 8.0±2.1, Zinc (µg/ml) 0.76±0.05; ulcer characteristics ulcer area (cm²) 2.2 (0.9 – 20.4), necrotic area (cm²) 1.6 (0.9-19.2), dry necrotic ulcer 73% (n=16), wet necrotic ulcer 27% (n=6), localisation: Dig I 18% (n=4), Dig II-V 14% (n=3), Plantar surface 0% (n=0), Dorsal area 9% (n=2), Malleolus 36%(n=8), Heel 23% (n=5)				
Length of follow-up [11] 5 weeks		Outcome(s) measured [12] necrotic area totally dissolved or decreased by at least 50%		

INTERNAL VALIDITY				
Allocation [13] Randomised	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] Blinded evaluation	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] 100%

Overall quality assessment (descriptive) [18] good quality study				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size	Benefits (NNT) [23] 95% CI [25]
Totally dissolved or decrease >50%	67% (14/22)	11% (6/22)	RR= 2.33 [95%CI 1.17, 4.81]	NNT = 3 [2,13]
No remaining necrosis	43% (9/21)	23% (5/21)	RR= 1.80 [0.75, 4.45]	
Decrease >50%	23% (5/21)	5% (1/21)	RR = 5.00 [0.86, 31.8]	
Decrease 25-50%	5% (n=1)	9% (n=2)		Harms (NNH) [24]
No change (±25%)	5% (n=1)	14% (n=3)		
Increase 25-50%	5% (n=1)	23% (n=5)		95% CI [25]
Increase >50%	18% (n=4)	23% (n=5)		
excluded	5% (n=1)	5% (n=1)		

	Clinical importance (1-4) [26] A clinically important benefit	Relevance (1-5) [27] evidence of an effect on patient relevant clinical outcome, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] Maceration of the skin edges in both groups, increase of necrosis in area associated with pain and oedema. One patient showed signs of cellulitis due to staphylococcus aureus.		
EXTERNAL VALIDITY		
Generalisabilty [29] likely generalisable to the target population		
Applicability [30] benefits outweigh harms		
Comments [31] The use of DuoDerm is not recommended for the treatment of necrotic foot ulcers. Although the adhesive zinc oxide tape reduced the initial necrosis, there are still risks involved and should be used for necrosis that is limited to the skin and does not involve deep tissue.Compliance was excellent in the study.		

STUDY DETAILS				
Reference [1] : Barth, R., L. V. Campbell, et al. (1991). "Intensive education improves knowledge, compliance, and foot problems in type 2 diabetes." Diabetic medicine : a journal of the British Diabetic Association 8(2): 111-117.				
Affiliation/source of funds [2] Diabetes Centre and Carvan Institute of Medical Research, st Vincent's Hospital, Sydney, Australia				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Patients recruited through radio and newspaper ads and from referrals by GP and people attending Diabetes centres in Sydney		
Intervention [6] intensive foot care intervention over 4 weekly sessions of 1,5 to 2.5 hrs after the diet intervention. Three sessions with podiatrist and one of psychologist for cognitive motivation (Heckhausen & Kuhl) Sample size [7] N= 33		Comparator(s) [8] a 1 hour session with a podiatrist covering main areas like washing, drying suitable foot wear cutting toe nails, inspecting feet etc. Sample size [9] N=29		
Selection criteria: Inclusion criteria –Type II diabetic patients (on any type of treatment), age of onset >30 years, duration of diabetes > 3 months, duration of current type of treatment > 1 month, suboptimal blood glucose control (HbA1c ≥9.5%, normal reference range 6.0, 9.0%), overweight (BMI≥25 kg/m², total energy intake as fat ≥35%, no attendance at a diabetes education program in the previous 6 months, competence in English and no major physical or mental disabilities preventing full participation in the program. Exclusion criteria –				
Patient characteristics [10] Intervention group – N=33 age mean(yrs) 58±9, Male 55% (n=18), Female 45% (n=15), mother tongue (English) 76% (n=25), other language 24% (n=8), mean time from diagnosis DM (mths) 104±94, treatement with tablet 76% (n=25), treatment with insulin 24% (n=8), GHb (%) 12.0±1.9, number of foot problems requiring treatment 4.0±1.2, peripheral vascular disease 58% (n=19) Comparator group(s) – N=29 age mean(yrs) 59±5, Male 59% (n=17), Female 41% (n=12), mother tongue (English) 86% (n=25), other language 14% (n=4), mean time from diagnosis DM (mths) 76±72, treatement with tablet 79% (n=23), treatment with insulin 21% (n=6), GHb (%) 11.2±1.8, num,ber of foot problems requiring treatment 3.6±2.2, peripheral vascular disease 21% (n=6)				
Length of follow-up [11] 6 months		Outcome(s) measured [12] compliance , foot problems		
INTERNAL VALIDITY				
Allocation [13] Randomised	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] Not stated	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] unknown
Overall quality assessment (descriptive) [18] average quality study				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size	Benefits (NNT) [23] 95% CI [25]
Number of foot problems	-	-	P<0.0006 at first follow up P= 0.062 3 months follow up P=0.216 6 months follow up	
	Clinical importance (1-4) [26] -		Relevance (1-5) [27] evidence of an effect on patient relevant clinical outcome, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] not stated				
EXTERNAL VALIDITY				
Generalisabilty [29] likely generalisable to the target population				
Applicability [30] benefits outweigh harms				

Comments [31] patients recruited through campaign in paper and radio, referrals from GP and people attending the center.

STUDY DETAILS				
Reference [1] : Blackman, J. D., D. Senseng, et al. (1994). "Clinical-Evaluation of a Semipermeable Polymeric Membrane Dressing for the Treatment of Chronic Diabetic Foot Ulcers." Diabetes Care 17(4): 322-325.				
Affiliation/source of funds [2] Department of Medicine, Section of Endocrinology, Rush Presbyterian St; Luke's Medical Centre and the department of Medicine and Endocrinology, Cook County Hospital, Illinois, USA				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] 8 Endocrinology, 4 rehabilitation centres, 1 plastic surgery centre, France		
Intervention [6] surgical debridement when necessary (n=4) followed by polymeric membrane treatment. No topical antibiotics or desinfectants or ulcer debridement. Change once daily minimal or when saturated. None of the wounds were packed. Sample size [7] N= 11		Comparator(s) [8] surgical debridement when necessary (n=4) followed by saline-soaked gauze dressing. Change once daily minimal or when saturated. None of the wounds were packed. Sample size [9] N=7 5 Cross over to intervention group after 2 months		
Selection criteria: Inclusion criteria – Insulin dependent and non insulin dependent diabetes mellitus patients with partial or full thickness open wound or foot ulcer, free of hard eschar. Wagner grade 1 and 2. Exclusion criteria – Wagner grade 3 or more foot ulcers, subjects that progressed to a Wagner 3 ulcer, subject needing vascular surgical therapy, ulcers from Charcot joints or subjects with ulcers of non diabetic origin.				
Patient characteristics [10] Intervention group – age mean(yrs) 51±4, Male 86% (n=6), Female 14% (n=1), mean Diabetes duration (wks) 28±6, initial ulcer size (cm^2) 1.81±0.75, GHb (%) 9.5±1.1 Comparator group(s) – age mean(yrs) 59±5, Male 100% (n=11), Female 0% (n=0), mean Diabetes duration (wks) 25±7, initial ulcer size (cm^2) 2.67±1.20, GHb (%) 8.4±0.9				
Length of follow-up [11] 8 weeks (2 months)		Outcome(s) measured [12] healing : granulation tissue over 75% of wound area and 40% decrease in wound surface area. And number or adverse events		
INTERNAL VALIDITY				
Allocation [13] Randomised	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] Not stated	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] 4 drop out, (2 form intervention, 2 from control; developed to Wagner III)
Overall quality assessment (descriptive) [18] average quality study				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size	Benefits (NNT) [23] 95% CI [25]
Healed	27% (n=3)	0% (n=0)	-	
Ulcer size reduction (%)	35±16	105±26	-	
	Clinical importance (1-4) [26] -		Relevance (1-5) [27] evidence of an effect on patient relevant clinical outcome, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] not stated				
EXTERNAL VALIDITY				
Generalisabilty [29] likely generalisable to the target population				
Applicability [30] benefits outweigh harms				
Comments [31] Calcium alginate seems to be a more appropriate for topical treatment than Vaseline gauze.				

STUDY DETAILS				
Reference [1] :(Dargis et al 1999) Dargis, V., O. Pantelejeva, et al. (1999). "Benefits of a multidisciplinary approach in the management of recurrent diabetic foot ulceration in Lithuania: a prospective study." Diabetes Care 22(9): 1428-31.				
Affiliation/source of funds [2] Rehabilitation Hospital, Kaunas, Lithuania; Department of Medicine, The Royal Infirmary, Manchester, UK;				
Study design [3] Prospective Cohort	Level of evidence [4] III-2	Location/setting [5] rehabilitation hospital in Kaunas, Lithuania and 7 outpatient clinics in other parts of Lithuania		
Intervention [6] Patients attending the outpatient clinic in the Kaunas Rehabilitation hospital were provided with podiatry care from a multidisciplinary team including dietician, diabetologist, podiatrist, shoemaker and orthopaedic surgeon which included education and specialty footwear for 2 years. Podiatry care received at least every 3 months and more if required. Including callus removal, cutting and grinding of toenails and individual silicone orthoses to redistribute pressure. Extra depth shoes were also provided. Sample size [7] N= 56		Comparator(s) [8] Patients attending 7 outpatients clinics in areas of Lithuania were provided standard care from a diabetologist and nurse with education and advice at the first visit from the same staff as the Kaunas group Sample size [9] N=89		
Selection criteria: Diabetic patients with a history of previous ulceration (Wagner grades I and II, Inclusion criteria – diabetic patients with a previous history of ulceration (Wagner grades I and II), Neuropathy Disability Score ≥6 and/or Vibratory Perception Threshold ≥25 V, Ankle Brachial Pressure Index ≥0.9, palpable pulse per foot ≥1, Exclusion criteria – past history of amputations, Charcot neuroarthropathy, or inability to follow simple instructions,				
Patient characteristics [10] Intervention group – 48.2% (n=27) males, 51.8% (n=29) females, 59.2±13.4 years of age, 14.0±7.1 years with diabetes, 83.9% (n=47) type II diabetes, 16.1% (n=9) type I diabetes, 71.5% (n=40) on insulin, 28.5% (n=16) taking oral medication for diabetes, number of previous ulcers 2.3±0.9, foot deformities 87.5%, Neuropathy Disability Score (NDS) 8.1±1.4, Vibratory Perception Threshold (VPT), 31.1±12.1, Ankle Brachial Pressure Index (ABPI) 1.14±0.14, Comparator group(s) – 47.2% (n=42) males, 52.8% (n=47) females, 58.5±11.5 years of age, 15.6±7.8 years with diabetes, 75.3% (n=67) type II diabetes, 24.7% (n=22) type I diabetes, 80% (n=71) on insulin, 20% (n=18) taking oral medication for diabetes, number of previous ulcers 2.1±1.0, foot deformities 85.4%, Neuropathy Disability Score (NDS) 7.9±1.7, Vibratory Perception Threshold (VPT) 33.9±11.2, Ankle Brachial Pressure Index (ABPI) 1.10±0.17,				
Length of follow-up [11] 2 years		Outcome(s) measured [12] ulcer recurrence and amputations		
INTERNAL VALIDITY				
Allocation [13] Not randomised	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] Not stated	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] 13 patients died before the end of the study so no follow up (4 intervention 9 control)
Overall quality assessment (descriptive) [18] average quality study				
RESULTS				
Outcome [19] Recurrence of ulcers	Intervention group [20] 30.4%	Control group [21] 58.4%	Measure of effect/effect size [22] 95% CI [25] OR 0.31 [0.14-0.67] $\chi^2$10.86, P<0.001	
Amputations	3% (3 minor, 1 major)	13.7% (8 minor, 1 major)		
	Clinical importance (1-4) [26] significant reduction in serious foot lesions and amputations		Relevance (1-5) [27] 80% of amputations are preceded by recurring ulcers, reducing recurrence of ulcers reduces the incidence of amputation	
Any other adverse effects [28] none stated				
EXTERNAL VALIDITY				
Generalisabilty [29] likely generalisable to the target population				
Applicability [30] benefits outweigh harms				
Comments [31] no indication of costs associated with extra multidisciplinary supervision				

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1]: Dimauro, C., A. M. Ossino, et al. (1991). "Lyophilized Collagen in the Treatment of Diabetic Ulcers." Drugs under experimental and clinical research 17(7): 371-373.</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2]
Institute of General Clinical Medicine, university of Catania, Catania; Clinical Research Department, Instituto Gentili, Pisa, Italy</td></tr>
<tr><td colspan="2">Study design [3] RCT</td><td colspan="2">Level of evidence [4] II</td><td colspan="2">Location/setting [5] -</td></tr>
<tr><td colspan="3">Intervention [6] treated by debridement, repeated saline solution washing and local antibiotic therapy, after adequate debridement, Lyophilized collagen (LC) was applied on the surface of the ulcer or inside fitulas. Tablets were moistened with saline or antibiotic solution when applied on the ulcer; tablets were dry, cut and suitable moulded when inserted in fistulas. Dressing was renewed every two days.
Sample size [7] N= ?</td><td colspan="3">Comparator(s) [8] treated by debridement, repeated saline solution washing and local antibiotic therapy, after adequate debridement, hyaluronic acid acid medicated gauze was applied.

Sample size [9] N=?</td></tr>
<tr><td colspan="6">Selection criteria:
Inclusion criteria –
Exclusion criteria –</td></tr>
<tr><td colspan="6">Patient characteristics [10] age range (yrs) 60-78 affected by non insulin dependent DM and ulcer. Foot ulcer (n) 19, wrist ulcer (n) 1
Intervention group –
Comparator group(s) –</td></tr>
<tr><td colspan="3">Length of follow-up [11]</td><td colspan="3">Outcome(s) measured [12] wound healing</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Randomised</td><td>Comparison of study groups [14]
Groups identical except for intervention</td><td>Blinding [15]
Not stated</td><td>Treatment/ measurement bias [16]
Both groups measured the same</td><td colspan="2">Follow-up (ITT) [17]
Not stated.</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18] poor quality study</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="2">Outcome [19]

Mean time to complete wound healing (days)</td><td>Intervention group [20]

32.4±8.6</td><td>Control group [21]

49.0±11.0</td><td colspan="2">Measure of effect/effect size [22]
95% CI [25]
P<0.001</td><td>Benefits (NNT) [23]

95% CI [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] significant clinical effect</td><td colspan="3">Relevance (1-5) [27] evidence of an effect on patient relevant clinical outcome, including benefits and harms, and quality of life and survival.</td></tr>
<tr><td colspan="6">Any other adverse effects [28] not stated</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisabilty [29] likely generalisable to the target population, except for the wrist patients, which was only 5% of the population (n=20)</td></tr>
<tr><td colspan="6">Applicability [30] benefits outweigh harms</td></tr>
<tr><td colspan="6">Comments [31] there is benefit in using LC instead of Hyaluronic gauze.</td></tr>
</table>

STUDY DETAILS				
Reference [1] : Jude, E. B., J. Apelqvist, et al. (2007). "Prospective randomized controlled study of Hydrofiber dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers." Diabetic medicine : a journal of the British Diabetic Association 24(3): 280-288.				
Affiliation/source of funds [2] Department of Diabetes Medicine, Tameside General Hospital, Ashton-under-lyne, UK; Department of Endocrinology, Malmo University Hospital,Malmo, Sweden; Mathias Hospital, Diabetology, Rheine, Germany and Hospital de Rangueil, Service Diabetologie & Endocrinologie, Toulouse, France				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] 18 european centers (8 UK, 5 France, 4 Germany and one Sweden)		
Intervention [6] standardised surgical debridement at baseline and at subsequent dressing changes to remove callus and ensure there was no more than 5% slough or eschar on the ulcer. Wound cleansed with saline and covered with sterile, non woven sodium carboxymethylcellulose primary AQAg dressing with 1.2% ionic silver (AQUACEL®Ag with Hydrofiber® technology) which was left for 7 days or changed earlier as clinically indicated. Primary dressing was covered by sterile, non adherent foam dressing. Footwear was accomadated where necessary. Sample size [7] N= 67		Comparator(s) [8] standardised surgical debridement at baseline and at subsequent dressing changes to remove callus and ensure there was no more than 5% slough or eschar on the ulcer. Wound cleansed with saline and covered with sterile, non woven calcium alginate dressing (Algosteril®), which has to moistened before putting on dry wound and once daily changed on infected wounds. Primary dressing was covered by sterile, non adherent foam dressing. Footwear was accomadated where necessary. Sample size [9] N=67		
Selection criteria: Inclusion criteria – type I or Ii DM, with HbA1c≤12.0%, serum creatinine ≤200µmol/l and with Wagner grade 1 or 2 DFU's of non ischaemic aetiology (neuropathic or neuro-ischaemic ulcers, none solely ischaemic). Wound ≥1cm² in area. Exclusion criteria – allergic to a component of the dressings studied, know or suspected malignancy local to the study ulcer, been on systemic antibiotics >7 days prior to enrolment or had inadequate arterial perfusion (AAI<0.8, great toe systolic blood pressure <40mmHg or forefoot TcPO2 <30mmHg (supine position) or <40mmHg (sitting))				
Patient characteristics [10] Intervention group – male 69% (n=46), Female31% (n=21), age (yrs) 58.9±12.6, DM type I 34% (n=23), DM type II 66% (n=44), serum creatinine (µmol/l) 90.5±30.1, Glycated haemoglobin (%) 8.1±1.9(n=66), ABPI (ratio) 2.4±9.7 9 (n=53), forefoot TcPO2 (mmHg) 49.4±22.8 (n=9), toe systolic pressure (mmHg) 105.3±25.8 (n=4), ulcer characteristics: Wagner I 79% (n=53), Wagner II 21% (n=14), neuro-ischaemic 19% (n=13), Neuropathic 81% (n=54), plantar location 66% (n=44), non-plantar 34% (n=23),antibiotics prescribed 19% (n=13), ulcer duration (yrs) 1.2±2.1, ulcer depth (cm) 0.40±0.45, ulcer baseline area (cm²) 3.1±4.1, epithelium (%) 7.9±21.4, granulation (%) 76.8±31.7, Slough (%) 11.4±22.6, Eschar (%) 0.2±1.3, Other appearance of ulcer bed (%) 3.8±14.1, sharp debridement (yes) 75% (n=50),amount of exudates: none 5% (n=3), minimal 40% (n=27), moderate 49% (n=33), heavy 6% (n=4), condition periulcer skin: normal 46% (n=31), erythematous 27% (n=18), macerated 33% (n=22), callus 58% (n=39), cellulitis 5% (n=4) Comparator group(s) – male 79% (n=53), Female21% (n=14), age (yrs) 61.1±11.4, DM type I 24% (n=16), DM type II 76% (n=51), serum creatinine (µmol/l) 98/.2±30.8 (n=64), Glycated haemoglobin (%) 7.9±1.8, ABPI (ratio) 1.1±0.2 (n=49), forefoot TcPO2 (mmHg) 37.7±22.2 (n=16), toe systolic pressure (mmHg) 68.3±12.8 (n=4), ulcer characteristics: Wagner I 72% (n=48), Wagner II 28% (n=19), neuro-ischaemic 30% (n=20), Neuropathic 70% (n=47), plantar location 70% (n=47), non-plantar 30% (n=20),antibiotics prescribed 12% (n=8), ulcer duration (yrs) 1.4±2.6, ulcer depth (cm) 0.40±0.39, ulcer baseline area (cm²) 4.2±7.8, epithelium (%) 6.4±14.2, granulation (%) 72.4±31.6, Slough (%) 15.9±25.6, Eschar (%) 0.2±1.0, Other appearance of ulcer bed (%) 5.1±16.6, sharp debridement (yes) 81% (n=54),amount of exudates: none 8% (n=5), minimal 36% (n=24), moderate 40% (n=27), heavy 16% (n=11), condition periulcer skin: normal 46% (n=31), erythematous 33% (n=22), macerated 34% (n=23), callus 55% (n=37), cellulitis 5% (n=3)				
Length of follow-up [11] 8 weeks ±2 days (mid study evaluation 4 weeks ± 2 days)		Outcome(s) measured [12] % healed, time to healing		

INTERNAL VALIDITY				
Allocation [13] Randomised (sealed envelope) stratified by systemic antibiotics	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] No blinding	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] 8 drop out intervention 88%, 13 in control group 81%
Overall quality assessment (descriptive) [18] good quality study				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size	Benefits (NNT) [23]
Rate of healing (cm² per wk)	0.29±0.33	0.26±0.90	P=0.795	95% CI [25]

Rate of healing (% per week)	11.6±17.7	10.0±15.5	P=0.993	
Mean time to 100% healing (days)	52.6±1.8	57.7±1.7	P=0.340	
Proportion 100% healed during study	31.3 % (21/67)	22.4% (15/67)	RR = 1.40 [0.80, 2.48]	
8 weeks % reduction in area	58.1±53.1	60.5±42.7	P=0.948	
Ulcer depth reduction (cm)	0.25±0.49	0.13±0.37	P=0.042	
Study related adverse events	16% (11/67)	13% (9/67)	RR = 1.22 [0.55, 2.73]	
	Clinical importance (1-4) [26] so no clinically important benefit		Relevance (1-5) [27] Evidence confined to unproven surrogate outcomes.	
Any other adverse effects [28] infection (16% AQAg group (n=11) and 12% in control (n=8); maceration (n=2 in control); red and/ or hot and/or swollen and/or painful and/or rash (n=2 control)musculoskeletal events (n=1 intervention, n=1 control)				
EXTERNAL VALIDITY				
Generalisabilty [29] likely generalisable to the target population				
Applicability [30] benefits do not outweigh harms				
Comments [31] Both dressing performed similar.intervention dressing improved ulcer depth reduction and wound bed improvement.				

STUDY DETAILS				
Reference [1] : Lalau, J. D., R. Bresson, et al. (2002). "Efficacy and tolerance of calcium alginate versus vaseline gauze dressings in the treatment of diabetic foot lesions." Diabetes & metabolism 28(3): 223-229.				
Affiliation/source of funds [2] Service d'Endocrinogie-Nutrition, Hôpital Sud, Amiens, Service de Diabétologie, Centre Hospitalier, Douai, Service de Rééducation et Réadaptation pour Adulte, Coubert, Service de Diabétologie, Centre Hospitalier, Boulogne sur Mer, Centre de Rééducation Fonctionnelle Clémenceau, Strasbourg, Service de Diabétologie, Centre Hospitalier Pitié-Salpétrière, Paris, Service de Chirurgie Plastique Réparatrice et Esthétique, Hôpital de la Conception, Marseille, Service de Diabétologie, Hôpital Rangueil, Toulouse, Centre Médical du Château St-Bernard, Touverac, Service d'Endocrinologie, CHU, Grenoble, Centre de Rééducation Fonctionnelle Les Massues, Lyon, Service de Médecine-Endocrinologie, Centre Hospitalier Universitaire, Lille and Centre Médical, Le Grau du Roi. France				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] 8 Endocrinology, 4 rehabilitation centers, 1 plastic surgery centre, France		
Intervention [6] Calcium alginate (Algosteril, laboratories Brothier, Nanterre,France). Applied directly on to wound to cover entire area. Dressings changed every day initially until throrough debridement then every 2 to 3 days. No other local treatment permitted, except saline solution. Second dressing was sterile gauze. Sample size [7] N= 39		Comparator(s) [8] Vaseline gauze (Vaselitulle, Solvay Pharma, Suresnes, France) Applied directly on to wound to cover entire area. Dressings changed every day initially until throrough debridement then every 2 to 3 days. No other local treatment permitted, except saline solution. Second dressing was sterile gauze. Sample size [9] N=38		
Selection criteria: Inclusion criteria – <75 years of age, suffering from diabetes of either type I or II, having a foot ulcer in the phase of cleansing which surface area between 1cm² and 50 cm². Partial cleansibng defined as granulation tissue surface <50% of wound area surface. Exclusion criteria – HbA1c level >10%, presence of clinical infection with redness,swelling, warmth and periwound erythema: osteomyelitis on plain radiography or probing of bone; a tunnelled wound , any severe hypovascularsation (defined on the basis of transcutaneous pressure of oxygen of < 30mmHg).				
Patient characteristics [10] Intervention group – age mean(yrs) 60.8±10.7, Male 56% (n=22), Female 44% (n=17), mean BMI (kg/m²) 27.6±5.11, Diabetes type 1 38% (n=15), DM type 2 62% (n=24), mean Diabetes duration (yrs) 19.2±11.8, mean HbA1 (%) 7.6±2.0, Revascularisation procedures (n) 13, mean TcPO2 (mmHg) 44.6±12.3, ulcer characteristics: mean Wound surface (cm²) 8.0±10.5, mean wound duration (months) 4.9±7.8, acute lesion 33% (n=13), chronic lesion 67% (n=26), acute wound duration (days) 37±14,chroni wound duration (days) 205±273, acute wound area (cm²) 13.5±15.5, chronic wound area (cm²) 5.3±5.4 Comparator group(s) – age mean(yrs) 63.5±12.8, Male 61% (n=23), Female 39% (n=15), mean BMI (kg/m²) 27.3±5.52, Diabetes type 1 42% (n=16), DM type 2 58% (n=22), mean Diabetes duration (yrs) 16.9±8.9, mean HbA1 (%) 7.9±1.5, Revascularisation procedures (n) 4, mean TcPO2 (mmHg) 42.6±10.3, ulcer characteristics:mean Wound surface (cm²) 8.8±16.0, mean wound duration (months) 9.1±13.1, acute lesion 37% (n=14), chronic lesion 63% (n=24), acute wound duration (days) 29±16,chroni wound duration (days) 417±589, acute wound area (cm²) 11.6±17.5, chronic wound area (cm²) 7.2±15.2				
Length of follow-up [11] originally 6 weeks, shorted for analysis to 4 weeks (due to 13 attrition)		Outcome(s) measured [12] healing : granulation tissue over 75% of wound area and 40% decrease in wound surface area. And number or adverse events		
INTERNAL VALIDITY				
Allocation [13] Randomised	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] evaluator blinded	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] 13 drop out, follow up 83%
Overall quality assessment (descriptive) [18] average quality study				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size	Benefits (NNT) [23] 95% CI [25]
Mean % reduction wound area	35.7±30.7	34.9±41.1	P=NS	
No. ulcers healed	42.8%	28.5%	p = NS	
No. acute ulcers healed	54.5%	23%	p = NS	

	Clinical importance (1-4) [26] A clinically important benefit	Relevance (1-5) [27] evidence of an effect on patient relevant clinical outcome, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] local adverse events were; osteitis, osteoarthritis in intervention group, wound infection, osteitis in control group. General adverse events; cardiac arythmia, fatal myocardial infarction in intervention group, fatal pulmonary embolism, aggravation of arteriopathy, renal failure in control group.		
EXTERNAL VALIDITY		
Generalisabilty [29] likely generalisable to the target population		
Applicability [30] benefits outweigh harms		
Comments [31] Calcium alginate seems to be a more appropriate for topical treatment than Vaseline gauze.		

STUDY DETAILS		
Reference [1]: Litzelman, D. K., C. W. Slemenda, et al. (1993). "Reduction of Lower-Extremity Clinical Abnormalities in Patients with Noninsulin-Dependent Diabetes-Mellitus - a Randomized, Controlled Trial." Annals of internal medicine 119(1): 36-41.		
Affiliation/source of funds [2] Regenstrief Institute for Health Care and Indiana University School of Medicine, Indianapolis, Indiana; and Centres for Disease Control and Prevention, Atlanta, Georgia.		
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] academic medical centre
Intervention 1 [6] patient: education by nurse in groups of 1 to 4 involving appropriate foot care behaviour and foot wear using slides and pamphlets,, behavioural contracts, phone (2wks after session) and postcard reminders (1 and 3 months). System intervention; folder to remind practitioner to ask patient to remove foot wear, to perform foot examination and providing foot care education at each visit. Sample size [7] N= 191	Comparator(s) [8] usual care Sample size [9] N=205	
Selection criteria: Inclusion criteria – Patients with non insulin dependent diabetes mellitus based on National Diabetes Data Group criteria or the presence of disease requiring medication for hyperglycemia control, seen at least two times by the same provider in the preceding year, diagnosis of diabetes after 30 years of age, age greater than 40 years, intention to obtain care at general medicine practice for next 2 years, body weight either ideal or heavier than ideal. Exclusion criteria – pregnancy, major psychiatric illness (dementia, terminal illness likely to cause death within 1 year, renal failure (serum creatinine >440μmol/l), previous bilateral amputations above the knee or below, inability to provide any self care. Patients of investigators involved in the study.		
Patient characteristics [10] Intervention group – N=191, black 75%, female 82%, mean age (yrs) 60.9±9.8, annual income <$10000 (%) 77, mean education level (yrs) 9.9±2.7, mean body mass index (kg/m²) 34.0±7.7, mean duration of diabetes (yrs) 9.6±8.0, mean haemoglobin A1c (%) 10.5±2.3, mean C-peptide (nmol/l) 0.55±0.50, mean plasma glucose (mmol/l) 11.48±4.81, taking insulin (%) 52, oral hypoglycaemic agents (%) 43, mean serum cholesterol (mmol/l) 5.88±1.25, mean serum triglycerides (mmol/l) 2.72±2.83, mean serum HDL (mmol/l) 1.12±0.29 Comparator group(s) – N=205, black 77%, female 80%, mean age (yrs) 59.9±9.4, annual income <$10000 (%) 77, mean education level (yrs) 9.7±2.8, mean body mass index (kg/m²) 33.4±6.9, mean duration of diabetes (yrs) 10.1±8.1, mean haemoglobin A1c (%) 10.0±2.6, mean C-peptide (nmol/l) 0.59±0.47, mean plasma glucose (mmol/l) 11.40±4.41, taking insulin (%) 47, oral hypoglycaemic agents (%) 46, mean serum cholesterol (mmol/l) 5.71±1.14, mean serum triglycerides (mmol/l) 2.49±2.14, mean serum HDL (mmol/l) 1.12±0.34		
Length of follow-up [11] 1 year (11.8±1.5 months)	Outcome(s) measured [12]	

INTERNAL VALIDITY				
Allocation [13] randomised	Comparison of study groups [14] Groups identical except for intervention and haemoglobin A1c.	Blinding [15] Nurse-clinician blinded	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] 11% drop out (n=43); death (11), change residence (15), illness (6), transportation (3), miscellaneous reasons (8).
Overall quality assessment (descriptive) [18] good quality study				

RESULTS				
Outcome [19]	Intervention group 1 [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Serious foot lesion	-	-	OR 0.41 [0.16, 1.00], significant at alfa 0.05.	
All foot lesion	-	-	OR 0.65 [0.36, 1.17]	
Dry or cracked skin	-	-	OR 0.62 [0.39, 0.98]	
Ingrown nails	-	-	OR 0.59 [0.39, 0.92]	
Fungal nail; infection	-	-	OR0.70 [0.46, 1.07]	
Fungal skin infection	-	-	OR 0.58 [0.30, 1.12]	
Interdigit maceration	-	-	OR 0.63 [0.34, 1.15]	

amputation	1% (n=1)	2% (n=4)	ns	
	Clinical importance (1-4) [26] no significant reduction. Point estimate is clinically important but the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] evidence of an effect on patient relevant clinical outcome, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] no adverse events				
EXTERNAL VALIDITY				
Generalisabilty [29] likely generalisable to the target population				
Applicability [30] benefits outweigh harms				
Comments [31]				

STUDY DETAILS					
Reference [1] : Martínez De Jesús, F. R., A. Ramos De la Medina, et al. (2007). "Efficacy and safety of neutral pH superoxidised solution in severe diabetic foot infections." International Wound Journal 4(4): 353-362.					
Affiliation/source of funds [2] Diabetic Foot Salvage and Prevention Center San Elian, Veracruz; Academia Mexicana de Cirugia, International Working Group on the Diabetic Foot, Mexico; Department of Education and Research, Veracruz Regional Hospital, Mexico; Department of Surgery; College of Podiatric Medicine at Roslind Franklin University of Medicine and Science; Center for Lower Extremity Ambulatory Research (CLEAR); Diabetic Foot Unit, Universidad Complutense de Madrid, Spain					
Study design [3] Randomised controlled trial	Level of evidence [4] II	Location/setting [5] San Elian Diabetic Foot Salavge and Prevention Center, Veracruz, Mexico			
Intervention [6])+ initial 15 to 20 minutes immersion of affected foot in neutral pH superoxidised solution (NpHSS) weekly or biweekly followed by NpHSS spray cleansing between immersions and to remove gauze. Sample size [7] N= 21		Comparator(s) [8] initial 15 to 20 minutes immersion of affected foot in saline weekly or biweekly followed by Povidone iodine spray cleansing between immersions. When infection resolved only surgical soap (Dermo Clean) with saline rinse was used.. Sample size [9] N=16			
All patients received: outpatient care included appropriate surgical debridement, aggressive parenteral/ intramuscular broad spectrum antimicrobial administration, appropriate off loading and strict glycaemic control. Antibiotics (pentoxyphylline 1200mg/day)used for 10 days (except for continued infections and conventional method of wound care (gauze with triticum vulgare to moisten, exudating wounds; calcium alginate gauze					
Selection criteria: Inclusion criteria –type II diabetes older than 18 years with infected deep wound at distal to the malleoli, presence of mal odour, active peri owund cellulites, loss of protective sensation and at least one dopplerable pedal pulse. Exclusion criteria – sever arterial disease (diagnosed based on absence of both foot pedal pulses on the affected side), brachial/ankle index below 0.5, diagnosis of osteomyelitis total gangrene of the study foot or forefoot, severe cardio vascular and renal failure and severe neurological problems that would make the patient a poor candidate for study (bed confined) and no family assistance.					
Patient characteristics [10] Intervention group – mean age (yrs) 61.9±11.9, male 45% (n=9), Female 55% (n=12), mean diabetes duration (yrs) 16.4±8.1, mean HbA1c 7.1±2, mean fasting glucose (mg/dl) 163±59,Obesity (chisquared and yates correction) 30% (n=6), ulcer duration (wks) 13.7±24, B/A index (Yao) 0.9±0.5 Comparator group(s) – mean age (yrs) 67.8±11.6, male 50% (n=8), Female 50% (n=8), mean diabetes duration (yrs) 17±10.2, mean HbA1c 6.7±1.8, mean fasting glucose (mg/dl) 152±65.8,Obesity (chisquared and yates correction) 25% (n=4), ulcer duration (wks) 15.1±16.3, B/A index (Yao) 1.14±0.7					
Length of follow-up [11] 20 weeks		Outcome(s) measured [12] Cellulitis reduction round wound (>50 % decrease) , improvement of skin around the ulcer, advances from infection to granulating tissue), Odour reduction			
INTERNAL VALIDITY					
Allocation [13] Randomised	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] Patient blinded	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] 100%	
Overall quality assessment (descriptive) [18] good quality study					
RESULTS					
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size	Absolute risk reduction [95%CI]	Benefits (NNT) [23]
Odour reduction(%)	100% (21/21)	25% (4/16)	P<0.001	ARR = 75% [54, 96}	2
Cellulitis reduction (effected area of erythema decreased >50%)	80.9% (17/21)	43.7% (7/16)	P<0.01 RR = 1.85 [1.10, 2.97]	37% [7.7, 67]	3 [2, 16]
Absence of periulcer skin donidtions around wound (absence of dryness, erythema, induration, rash, epidermolysis or blisterformation)	90.4% (n=19)	31.2% (n=5)	P<0.001 RR = 2.90 [1.61, 4.29]	59% [33, 85]	2 [1, 3]

% granulating tissue observed in the wound	90.4% (n=19)	62.5% (n=10)	P<0.05 RR = 1.45 [1.02, 1.81]	27% [1.1, 55]	4 [2, 88]
	Clinical importance (1-4) [26] A clinically important benefit		Relevance (1-5) [27] evidence of an effect on patient relevant clinical outcome, including benefits and harms, and quality of life and survival.		
Any other adverse effects [28] no side effects					
EXTERNAL VALIDITY					
Generalisabilty [29] likely generalisable to the target population					
Applicability [30] benefits outweigh harms					
Comments [31] NpHSS more effective in infection control than conventional disinfectants in treatment of diabetes foot infections.					

STUDY DETAILS		
Reference [1] : Martínez Sánchez, G., S. M. Al Dalain, et al. (2005). "Therapeutic efficacy of ozone in patients with diabetic foot." European journal of pharmacology **523**(1-3): 151-161.		
Affiliation/source of funds [2] Center of Studies for Research and Biological Evaluation (CEIEB-IFAL), university of Havana, Cuba; Ozon Research Center, Cuba; Laboratory of Pharmaceutical Biotechnology, University of Ancona, Italy; Department of Chemistry and Medical Biochemistry, University of Milan, Italy; Institute of Angiology and Vascular Surgery, Cuba.		
Study design [3] Randomised controlled trial	Level of evidence [4] II	Location/setting [5] patients hospitalised in the Institute of Angiology and Vascular Surgery
Intervention [6] patients treated daily with ozone (generated by OZOMED equipment, Cuba), 20 sessions, by rectal insufflations (with ozone dose of 10mg, ozone concentration: 50mg'L) and locally. For local ozone treatment, the lesion was covert with a plastic bag, sealed at the leg and in vacuum and filled with ozone concentration of 60mg/l. The patients remained with the bag for 1 hour before bag was removed and the lesion was covered with ozonised sunflower oil (Oleozone©) + debridement and gauze dressing Sample size [7] N= 51	Comparator(s) [8] patients were treated with systemic antibiotic therapy (according to microbe present), using conventional method for treatment, with topical application to the lesion (for 20 days). + debridement and gauze dressing Sample size [9] N=49	
Selection criteria: Inclusion criteria –adult patients of both sexes with different ethnic origin with diagnosis of neuroinfectious diabetes foot, according to the classification by McCook, suffering from ulcer of the feet and lower extremities and hospitalised in Institue of Angiology and Vascular Surgery. Exclusion criteria – severe septic conditions, hypersensitivity to the medication in use, hepatic dysfunction, renal failure (serum creatinine level >1.23µmol/l), pregnancy, cancer or other serious disease, inability to cooperate with the requirements of the study, recent history of alcohol and drug abuse, current therapy with any immunosuppressive agent or anticonvulsant, concurrent participation in another clinical trial or current treatment with an investigational drug.		
Patient characteristics [10] Intervention group – N= 51, 20-40 years of age 9% (n=5), 40-60 years of age 32% (n=17), ≥60 years of age 57% (n=30), white 75% (n=39), black 13% (n=7), mixed ethnicity 11% (n=6), female 50% (n=26), male 50% (n=26), hypertension 38% (n=20), renal dysfunction 3% (n=2), cardiovascular disease 19% (n=10), evolution time of disease (ETD) 17±11 years (range 1-50 years) Comparator group(s) – N= 49, 20-40 years of age 14% (n=7), 40-60 years of age 40% (n=20), ≥60 years of age 44% (n=22), white 61% (n=30), black 16% (n=8), mixed ethnicity 22% (n=11), female 38% (n=19), male 61% (n=30), hypertension 46% (n=23), renal dysfunction 4% (n=2), cardiovascular disease 14% (n=7), evolution time of disease (ETD) 18±8 years (range 1-42 years)		
Length of follow-up [11] 20 days	Outcome(s) measured [12] measurement of the area and perimeter of the lesion, duration of hospitalisation	

INTERNAL VALIDITY				
Allocation [13] Randomised	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] Not stated	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] Not stated.
Overall quality assessment (descriptive) [18] average quality study				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23]
Area (cm^2) reduction	75±0.35%	50±0.17%	P<0.02	95% CI [25]
Perimeter (cm) reduction	42%±0.25%	27±0.17%	P<0.01	
Healing rate with respect to area (cm^2/day)	2.66±0.05	1.21±0.01	P<0.01	Harms (NNH) [24]
Healing rate with respect to perimeter (cm/day)	0.34±0.00	0.24±0.00	P=0.04	95% CI [25]
Expected total recovery (days)	21±10	45±11	P<0.01	

Clinic evaluation (cured/ not cured)	39 (78%)/ 12 (24%)	34 (69%)/ 15 (30%)	RR=1.1 [95%CI 0.87, 1.4]
Duration hospitalisation (days)	26 (6-58) SD 13	34 (7-383) SD 18	P=0.01
	Clinical importance (1-4) [26] no significant reduction. Point estimate is clinically important but the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] evidence of an effect on patient relevant clinical outcome, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] no side effects			
EXTERNAL VALIDITY			
Generalisabilty [29] likely generalisable to the target population			
Applicability [30] benefits outweigh harms			
Comments [31] patients treated with ozon had a faster recovery of their lesions compared to those treated with antibiotic therapy (26 days vs 34 days)			

STUDY DETAILS				
Reference [1] : Mulder, G. D., L. M. Patt, et al. (1994). "Enhanced healing of ulcers in patients with diabetes by topical treatment with glycyl-L-histidyl-L-lysine copper." Wound Repair & Regeneration 2(4): 259-269.				
Affiliation/source of funds [2] Wound Healing Institute, Aurora, Colo; ProCyte Corporation, Kirkland, Wash; Veterans Administration Medical Center, Lebanon; Diabetes and Endocrine Center, Dallas, Texas; California College of Podiatric Medicine, San Fransisco.				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] multicenter;		
Intervention 1 [6] Direct addressed; Iamin Gel, 8 weeks of treatment with Iamin 2% Gel (2% Glycyl-L–histidyl-L–lysine (GHK) -Copper, 3% hydroxypropylmethylcellulose (HPMC)) after initial sharp debridement followed by 6 weeks of observation and wound measurement. Gel is once daily applied by patient Sample size [7] N= 28		Comparator(s) [8] treatment of 8 weeks with vehicle after initial sharp debridement followed by 6 weeks of observation and wound measurement. Placebo gel (0% GHK-Copper, 3%HPMC) once daily applied by patient. Sample size [9] N=32		
Intervention 2 [6] delayed an initial 4 week treatment with vehicle applied immediately after sharp debridement after vehicle phase, treatment for an additional 8 weeks with Iamin 2% gel (2% GHK-Copper, 3%HPMC) once daily applied by patient. Sample size [7] N= 39		Intervention 3 [6] delayed an initial 4 week treatment with vehicle applied immediately after sharp debridement after vehicle phase, treatment for an additional 8 weeks with Iamin 4% gel (4% GHK-Copper, 3%HPMC) once daily applied by patient Sample size [7] N= 42		
All patients were enrolled in standard protocol: sharp debridement included removal of all eschar, necrotic tissue and fibrin. Superficial and cleansing were performed weekly, daily dressing changes after application of rug with single thickness gauze, standardised pressure relieving footwear was fitted and dispensed and instructed to minimize weight bearing activity, metered dosing of gel based on surface area and applied daily in outpatient basis. Patient education on foot elevation, daily cleansing proper diabetes control and activity modification. Lesions that were clinically infected were cultured and aggressively treated with systemic antibiotics. Patients with limb edema received supported care.				
Selection criteria: Inclusion criteria –patients between 21-90 years of age, general health confirmed by physical and laboratory examination. Adequately controlled diabetes, as diagnosed by physician and a full thickness ulcer of the lower extremity below the knee. Minimum ulcer size on the two logest axes was 0.5x0.5 cm (25mm²). Maximum ulcer size was approximately 2700mm². Doppler blood pressure ≥40mmHg Exclusion criteria – pre-existing infection of bone 9osteomyelitis) or gangrene of the target limb, disease associated with hypercupremia (Wilson disease), no palpable pedal pulse, or other conditions known to cause cutenous ulceration such as venous stasis or vasculitis. Participated in an experimental protocol within 30 days or had received any systemic immunosuppressive or cytotoxic therapy with 30 days before the study entry. No palpable dorsal pedis or posterior tibialis pulse.				
Patient characteristics [10] mean age (yrs) 60, diabetes duration (yrs) 15 Type I DM 24% (n=44), Type II DM 76% (n=137), insulin dependent 63% (n=114), plantar foot ulcer 80% (n=145), lower extremity ulcer 20% (n=36) Intervention group – Comparator group(s) –				
Length of follow-up [11] direct= 14 weeks, delayed= 12 weeks		Outcome(s) measured [12] percentage of wound closure		
INTERNAL VALIDITY				
Allocation [13] randomised	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] Evaluator blinded	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] 4 patients dropped out
Overall quality assessment (descriptive) [18] average quality study				
RESULTS				
Outcome [19]	Intervention group 1 [20] All ulcers	Control group [21] All ulcers	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Median area of wound closure (%)	98.5%	60.8%	P<0.05	
Number of ulcers with ≥98% wound closure	54% (15/28)	31% (10/32)	RR = 1.71 [0.94, 3.14]	
	Intervention group 1 with small ulcer	Control group with small ulcer	Measure of effect/effect size [22] 95% CI [25]	NNT

Median area of wound closure (%)	100%	99.6%		
Number of ulcers with ≥98% wound closure	64% (9/14)	56% (9/16)	RR = 1.14 [0.64, 1.93]	
	Intervention group 1 with large ulcer	Control group with large ulcer		
Median area of wound closure (%)	89.2%	-10.6% (increase)	P<0.01	
Number of ulcers with ≥98% wound closure	43% (6/14)	6% (1/16)	RR = 6.86 [1.31, 42.26] P<0.05	NNT = 3 [2, 16]
Number of ulcers that developed infections	7% (2/28)	34% (11/32)	RR = 0.21 [0.05, 0.73	NNT = 4 [3, 15]

	Intervention 1	Intervention 2	Intervention 3	Control group
Wound closure (mm/day) mean±SEM (medium)	70.4±10.2 (98.5), p<0.05	31.1±10.1 (40)	33.9±12.9 (68.2)	10.4±21.1 (60.8)

Clinical importance (1-4) [26] no significant reduction. Point estimate is clinically important but the confidence interval includes clinically unimportant effects.	Relevance (1-5) [27] evidence of an effect on patient relevant clinical outcome, including benefits and harms, and quality of life and survival.

Any other adverse effects [28] no adverse events
EXTERNAL VALIDITY
Generalisabilty [29] likely generalisable to the target population
Applicability [30] benefits outweigh harms
Comments [31] values of mean percentage of closure can be affected by the a small number of wounds which showed a marked deterioration. Immediated treatment with Iamin Gel 2% significantly enhanced median wound clodure (p<0.05)

STUDY DETAILS					
Reference [1] : Pai, M. R., N. Sitaraman, et al. (2001). "Topical phenytoin in diabetic ulcers: a double blind controlled trial." Indian journal of medical sciences **55**(11): 593-599.					
Affiliation/source of funds [2] Funded by Karnataka Sate Council for Science and Technology and Dreyfus Health Foundation, New York.					
Study design [3] Randomised controlled trial	Level of evidence [4] II	Location/setting [5] patients hospitalised in 3 teaching hospitals.			
Intervention [6] surgical debridement when necessary and slough removed, followed by wound measurement. Gentle Saline cleaning, topical phenytoin and a sterile dressing cover was applied daily for a period of 6 weeks or until healing Powder quantity dusted depend on surface area: 0-5 cm^2 = 100mg; <5.1-9 cm^2 = 150mg; 9.1-15cm^2= 200mg; >15 cm^2= 300mg Sample size [7] N= 36		Comparator(s) [8] surgical debridement when necessary and slough removed, followed by wound measurement. Gentle Saline cleaning, control application (combination of talc and colloidal silicon dioxide) and a sterile dressing cover was applied daily for a period of 6 weeks or until healing Powder quantity dusted depend on surface area: 0-5 cm^2 = 100mg; <5.1-9 cm^2 = 150mg; 9.1-15cm^2= 200mg; >15 cm^2= 300mg Sample size [9] N=34			
Selection criteria: Inclusion criteria – Age 35-70 years, Grade I and II foot ulcers according to Meggitts clinical classification (Grade 1 were superficial ulcers and grade 2 were deep ulcers with slough) Control of diabetes with oral hypoglycaemic agents or insulin based on fasting blood sugar of 110-130 mg/dl. Exclusion criteria - presence of Grade III, IV and V foot ulcers.					
Patient characteristics [10] Intervention group – male 69% (n=25), female 41% (n=11), medium age (yrs) 55.5, average duration DM (yrs) 8.7, Pedal pulse presence 81% (n=29), pedal pulse diminished 19% (n=7), peripheral neuropathy changes 36% (n=13), neuroischaemic changes 14% (n=5) Comparator group(s) – male 65% (n=22), female 35% (n=12), medium age (yrs) 60.0, average duration DM (yrs) 9, Pedal pulse presence 71% (n=24), pedal pulse diminished 29% (n=10), peripheral neuropathy changes 41% (n=14), neuroischaemic changes 29% (n=10)					
Length of follow-up [11] 6 weeks		Outcome(s) measured [12] reduction in wound surface area (cm^2)			
INTERNAL VALIDITY					
Allocation [13] Randomised	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] Observer blinded, patient blinded	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] 13 dropped out	
Overall quality assessment (descriptive) [18] average quality study					
RESULTS					
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23]	
Mean difference in wound area (cm^2) (total study sample n=70)	6.45±1.53	5.44±1.49 73.5%		95% CI [25]	
Mean difference in wound area (cm^2) (completed study n=57)	8.47±1.58	7.82±1.52	Mean difference -0.65 [-1.47, 0.17]		
Deep ulcer healed	10% (n=2 out of 20)	32% (n=8 out of 25)	RR= 0.31 [0.07, 1.3]		
	Clinical importance (1-4) [26] no significance effect		Relevance (1-5) [27] evidence of an effect on patient relevant clinical outcome, including benefits and harms, and quality of life and survival.		
Any other adverse effects [28] no side effects					
EXTERNAL VALIDITY					
Generalisabilty [29] likely generalisable to the target population					
Applicability [30] benefits outweigh harms					

Comments [31] patients treated with ozon had a faster recovery of their lesions compared to those treated with antibiotic therapy (26 days vs 34 days)

STUDY DETAILS				
Reference [1] : Piaggesi, A., F. Baccetti, et al. (2001). "Sodium carboxyl-methyl-cellulose dressings in the management of deep ulcerations of diabetic foot." Diabetic medicine : a journal of the British Diabetic Association 18(4): 320-324.				
Affiliation/source of funds [2] Department of Endocrinology and Metabolism, University of Pisa, Italy; Department of Dermatology, University of Pisa, Italy				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] out-patients attending the foot clinic of the Department of Metabolic Diseases		
Intervention [6] treated with Carboxyl-methyl-cellulose dressings (hydro-fibre dressing, Aquacel™, ConvaTec, UK), used and changed every second or third day, depending on the extent of exudates produced by the wound. Sample size [7] N= 10		Comparator(s) [8] treated with saline moistened gauze, renewed twice a day with saline to prevent drying out. Sample size [9] N=10		
At baseline all lesions were aggressively surgically debrided with the complete elimination of all necrotic tissue and debris up to the bleeding healthy tissue; then ulcers were staged and measured, after treatment All patients in both groups received special post-operative shoes (Podiabetes; Zeno Buratto, Treviso, Italy) and crutches until complete re-epithelialization				
Selection criteria: Inclusion criteria – age 18-75 years, type 1 or 2 diabetes for over 5 years, foot ulcer deeper than 1 cm for > 3 weeks, good peripheral blood supply (palpable peripheral pulses or ABPI > 0.9) Exclusion criteria – active infection, as evident from clinical signs (purulent discharge, redness, swelling, tenderness) and confirmed by culture exams, plasma creatinine > 2 mg/dl, recent episodes of ketoacidosis, malignancies, and any therapy or pathology which might interfere with the healing process. Candidates for major amputation.				
Patient characteristics [10] Intervention group – type I DM 20% (n=2), type 2 DM 80% (n=8), mean age (yrs) 63.1±4.6, duration DM (yrs) 14.8±6.2, Glycated haemoglobin (%) 8.1±2.7, ABPI (ratio) 1.1±0.2, VPT (voltd) 36.3±9.9, ulcer characteristics: ulcer duration (wks) 6.8±2.6, maximum diameter (cm) 4.9±2.4, maximum depth (cm) 2.3±1.4, volume (cm^3) 22.6±8.4 Comparator group(s) – type I DM 10% (n=1), type 2 Dm 90% (n=9), mean age (yrs) 61.3±7.5, duration DM (yrs) 16.1±8.9, Glycated haemoglobin (%) 8.9±3.1, ABPI (ratio) 1.0±0.2, VPT (voltd) 32.4±12.8, ulcer characteristics: ulcer duration (wks) 5.9±1.3, maximum diameter (cm) 4.5±1.9, maximum depth (cm) 2.9±1.1, volume (cm^3) 19.2±6.4				
Length of follow-up [11] 8 weeks		Outcome(s) measured [12] the rate of reduction of lesional volume (RLV), rate of granulation tissue (GT), number of infective complications (IC)		
INTERNAL VALIDITY				
Allocation [13] Randomised (computer generated list)	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] evaluator blinded	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] 100%
Overall quality assessment (descriptive) [18] good quality study				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size	Benefits (NNT) [23] 95% CI [25]
Healed wounds	100% (n=10)	90% (n=9)		
Days till healing (mean±SD)	127±46	234±61	P<0.001	
Days till healing (mean±SD) (excluded infection cases	123±46	206±62	P<0.05	
	Clinical importance (1-4) [26] A clinically important benefit		Relevance (1-5) [27] evidence of an effect on patient relevant clinical outcome, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] maceration of peri lesion skin which was observed in 2 of control and 1 in intervention group. In the control group, 21 dressings in 8 patients were found dry and attached to the bottom of the lesion. Irrigation was necessary with saline to detach the dressing. Ifective complications (intervention 1/10, control 3/10) treated with amoxicillin an clavulanic acid.				
EXTERNAL VALIDITY				

Generalisabilty [29] likely generalisable to the target population
Applicability [30] benefits outweigh harms
Comments [31] Carboxyl-methyl-cellulose dressings can play role in management of wound healing of deep neuropathic ulcers of diabetic foot as they reduce time to healing.

STUDY DETAILS				
Reference [1]: Ramos Cuevas, F., A. A. Velazquez Mendez, et al. (2007). "[Zinc hyaluronate effects on ulcers in diabetic patients]." Gerokomos 18(2): 91-101.				
Affiliation/source of funds [2] Diabetes Foot Clinic of the hospital of Specialisations of the Adolfo Ruiz Cortines National Medical Centre; Continuous Medical Care of the Family Medicine Unit Nº 61, Mexico				
Study design [3] Randomised controlled trial	Level of evidence [4] II	Location/setting [5] tertiary care centre. Diabetic Foot Clinic, mexico		
Intervention [6] Treatment with zinc hyaluronic acid, application once a day, previous cure at home and follow up 20 weeks Sample size [7] N= 25		Comparator(s) [8] conventional treatment with daily cure at the assigned clinicand/or patients's home Sample size [9] N=25		
Selection criteria: Inclusion criteria – Exclusion criteria –				
Patient characteristics [10] Intervention group –female 44% (n=11), male56% (n=14), average age (yrs) 56.76±8.78, duration Type II DM (yrs) 14.74±6.72, oral hypoglycemiants n=16, insulin use n=8, diet n=1, average glycemia (mg/dl) 163.64±86.4, peripheral neuropathy diagnosis 100% (n=25), average AAI (mmHg) 1.06±0.18,SO_2 (%) 82-100 Comparator group(s) – female 44% (n=11), male56% (n=14), average age (yrs) 60.12±8.42, duration Type II DM (yrs) 16.40±5.84, oral hypoglycemiants n=15, insulin use n=9, diet n=1, average glycemia (mg/dl) 182.4±68.3, peripheral neuropathy diagnosis 96% (n=25), average AAI (mmHg) 0.96±0.15, SO_2 (%) 92-99				
Length of follow-up [11] 20 weeks		Outcome(s) measured [12] closure time		
INTERNAL VALIDITY				
Allocation [13] Not stated	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] Not stated	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] 100% in intervention group, 1 in conventional treatment group due to death.
Overall quality assessment (descriptive) [18] poor quality study				
RESULTS				
Outcome [19] Average closure time of ulcer (weeks)	Intervention group [20] 7.80±3.49	Control group [21] ≥12 weeks (except one 7 and one 9 weeks)	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
	Clinical importance (1-4) [26] non important results		Relevance (1-5) [27] not relevant	
Any other adverse effects [28] not stated				
EXTERNAL VALIDITY				
Generalisabilty [29] likely generalisable to the target population				
Applicability [30]				
Comments [31] There was no analysis on the results, poor presentation of result and not enough information to calculated effect.				

STUDY DETAILS				
Reference [1] Rönnemaa, T., H. Hämäläinen, et al. (1997). "Evaluation of the impact of podiatrist care in the primary prevention of foot problems in diabetic subjects." Diabetes Care 20(12): 1833-7 (Hamalainen et al 1998), Hamalainen, H., T. Ronnemaa, et al. (1998). "Long-term effects of one year of intensified podiatric activities on foot-care knowledge and self-care habits in patients with diabetes." Diabetes Educ 24(6): 734-740.				
Affiliation/source of funds [2] Department of Medicine, University of Turka, Finland; The Research and Development Centre, Social Insurance Institution, Turka, Finland; Helsinki Polytechnic, IV College for Health Care Professionals, Podiatric Education, Helsinki, Finland;				
Study design [3]RCT	Level of evidence [4] II Intervention		Location/setting [5] Turka, Finland	
Intervention [6] Individual education by podiatrist over 12 months as many times as judged appropriate by podiatrist. Education involved use of appropriate footwear, daily hygiene, cutting toenail, use of cream, avoidance of high risk situations and foot gymnastics. Foot care was also provided. Sample size [7] n=267		Comparator(s) [8] Written information and instructions only. Sample size [9] n=263		
Selection criteria; Diabetic patients on the national drug imbursement register receiving diabetic drugs in Finland Inclusion criteria – diabetic patient requiring medication not currently attending a podiatrist Exclusion criteria – attended a podiatrist during the previous 6 months, presence of a chronic foot problem requiring immediate attention, presence of ulcer or infection, presence of deformity such as Charcot joint, high risk of ulcer, previous amputation,				
Patient characteristics [10] 733 patients, 51% (n=369) males, 49% (n=364) females, age range 10-79 years, mean age 46.9±19.1 years, 110 patients had attended a podiatrist in previous 6 months and 93 required immediate foot care leaving 530 patients Intervention group – mean age 43.9 years Comparator group(s) – mean age 44.1 years				
Length of follow-up [11] 1 year and 7 years	Outcome(s) measured [12] visual examination of foot for ischemic or neuropathic ulcers, presence of inflammation or infection, and abnormal foot posture. Knowledge of foot care assessed by questionnaire with maximum score of 57, and serum fructosamine concentration measurement.			
INTERNAL VALIDITY				
Allocation [13] Randomisation not specified	Comparison of study groups [14] No significant differences between groups	Blinding [15] podiatrist conducting baseline and follow-up examinations blinded to treatment	Treatment/ measurement bias [16] both groups measured the same	Follow-up (ITT) [17] Over 1 year 88.6% Over 7 years control 77% (48 died, 50 non participants), intervention 73% (44 died, 56 non participants)
Overall quality assessment (descriptive) [18] average quality study				
RESULTS				
Results over 1 year (Rönnemaa et al 1997)				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22]	Benefits (NNT) [23] 95% CI [25]
% Callosities in calcaneal region	N=233 Baseline 18.5 12 months 12.0 P=0.003	N=226 Baseline 16.8 12 months 15.5 P=0.62	Difference in change between groups p= 0.14	Harms (NNH) [24] 95% CI [25]
% Callosities in other regions	Baseline 54.5 12 months 39.5 P<0.001	Baseline 51.3 12 months 48.2 P=0.33	Difference in change between groups p=0.009	
% Corns	Baseline 36.9 12 months 27.0 P=0.001	Baseline 33.6 12 months 29.7 P=0.16	Difference in change between groups p=0.16	
% Ingrown toenail	Baseline 19.3 12 months 24.0 P=0.054	Baseline 23.0 12 months 31.4 P=0.004	Difference in change between groups p=0.33	

% Inability to spread out toes	Baseline 50.6 12 months 39.1 P<0.001	Baseline 53.1 12 months 46.5 P=0.034	Difference in change between groups p=0.23	
% Inability to flex toes	Baseline 23.2 12 months 18.0 P=0.044	Baseline 29.7 12 months 24.8 P=0.11	Difference in change between groups p=0.94	
% Diameter of greatest callosity in calcaneal region	N=49 Baseline 40.5±30.8 12 months 25.5±28.8 P=0.001	N=55 Baseline 30.6±28.5 12 months 28.3±26.8 P=0.65	Difference in change between groups p=0.065	
% Diameter of greatest callosity in other regions	N=141 Baseline 16.6±10.2 12 months 11.4±10.3 P<0.001	N=138 Baseline 15.2±9.8 12 months 14.4±9.9 P=0.39	Difference in change between groups P<0.001	
Results over 7 years Hamalainen, 1998				
Reduced forefoot arch	69%	72%	p=0.61	
Hallux valgus	34%	40%	p= 0.35	
Claw toe	27%	26%	p=0.96	
Any abnormality in posture	93%	94%	p= 0.89	
Mild interdigital fungal infection	2%	2%	p= 1.0	
Marked interdigital fungal infection	3.0%	1%	p=0.45	
Fungal infection of toenail	21%	27%	p= 0.28	
Ingrown toenail	29%	41%	p= 0.03	
Callosity in calcaneous	12%	13%	p=1.0	
Callosity in other region	23%	30%	p= 0.19	
Fissure in calcaneous	15%	22%	p=1.54	
Corn other than interdigit	8%	13%	p=0.24	
Interdigit corn	1%	2%	p=0.68	
verruca	11%	6%	p= 0.13	
Any hyperkeratotic change	68%	67%	p=0.91	
ulcer	1%	1%	p=1.0	
Amputation	1%	0%	p=0.50	
	Clinical importance (1-4) [26] regular podiatrist care significantly reduced foot complications in the target population		**Relevance** (1-5) [27] podiatrist supervision improved patient knowledge and self care practices achieved better outcomes than educational material alone	
Any other adverse effects [28] nil stated				

EXTERNAL VALIDITY
Generalisabilty [29] likely generalisable to the target population
Applicability [30] benefits likely to outweigh harms
Comments [31] cost associated with podiatrist supervision in relation to benefits not established, and only a one year follow-up so no long term benefit identified from treatment

STUDY DETAILS				
Reference [1] : Scire, V., E. Leporati, et al. (2009). "Effectiveness and Safety of Using Podikon Digital Silicone Padding in the Primary Prevention of Neuropathic Lesions in the Forefoot of Diabetic Patients." Journal of the American Podiatric Medical Association 99(1): 28-34.				
Affiliation/source of funds [2] Department of Endocrinology and Metabolism, University of Pisa, Italy,				
Study design [3] RCT	Level of evidence [4] Level II Intervention		Location/setting [5] outpatient diabetic foot clinic, Italy	
Intervention [6] Clinical examination and mechanical keratolysis and elimination of hyperkeratotic areas, soft insole and deep shoes, digital orthoses made to measure with silicone (corrective, additive or protective, and hardness 10-22 shores varied by patient characteristics), 3 month follow-up and examination Sample size [7] N=89			Comparator(s) [8] Same examination and treatment but no orthotic protection Sample size [9] N=78	
Selection criteria: attendance at a outpatient diabetic foot clinic between January 1 and July 1, 2005 Inclusion criteria – Age ≥18 years, diagnosis with type I or type II diabetes mellitus for at least 5 years, peripheral neuropathy documented by a threshold of vibratory sensitivity >25 V measured in the hallux by a biothesiometer, and deformity or preulcerative conditions of the forefoot, Exclusion criteria – Active ulcerative lesions, peripheral macroangiopathy documented by a systolic pressure ankle/arm index <0.9, local clinical symptoms (erythema, oedema, increase in temperature, secretions, skin macerations, pain or tenderness) or systemic symptoms (fever, leukocytosis) of infection, clinically visible rhagades or dyshidrosis, Charcot's neuroarthropathy in an active or stabilizing phase, and presence of peripheral neuropathies other than peripheral neuropathy				
Patient characteristics [10] Intervention group – N=89, 13.5% (n=12) type I diabetes, 86.5% (n=77) type II diabetes, 58.2±17.1 years of age,15.2±8.9 years a diabetic, HbA_{1c} 8.2±1.7, Vibration perception threshold-hallux (VPT) 37.4±10.2 V, presence of deformity 6% (n=5), presence of hyperkeratosis 5% (n=4), presence of deformity and hyperkeratosis 89% (n=79), Comparator group(s) – N=78, 10.3% (n=8) type I diabetes, 89.7% (n=70) type II diabetes,54.9±18.2 years of age, 16.4±9.4 years a diabetic, HbA_{1c} 7.9±0.9, VPT-hallux 34.1±9.9 V, presence of deformity 8% (n=6), presence of hyperkeratosis 6% (n=5), presence of deformity and hyperkeratosis 86% (n=68),				
Length of follow-up [11] 3 months		Outcome(s) measured [12] prevalence of hyperkeratosis, skin hardness, presence of ulcer, reduction in peak pressure,		
INTERNAL VALIDITY				
Allocation [13] Randomisation via computer-generated randomising list	Comparison of study groups [14] No significant differences between groups	Blinding [15] Examiners at baseline and 3 months blinded to treatment and patient group assignment	Treatment/ measurement bias [16] All participants treated and measured the same except for orthotics	Follow-up (ITT) [17] No withdrawals from either group
Overall quality assessment (descriptive) [18] good quality study				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22]	
Areas of hyperkeratosis at baseline	71.7±12.4 International Units	69.8±16.1 International Units	P=0.4271	
Presence of hyperkeratosis at 3 months	41% overall (61%plantar region 23% dorsal region 11% interdigital region)	84% overall (70% plantar region 20% dorsal region 10% interdigital region	P=0.0002 95% CI [25]	
Number of ulcers occurring during study period	1.1% (n=1)	15.4% (n=12)	P<0.001	
	Clinical importance (1-4) [26] a clinically important benefit for the full range of plausible estimates		Relevance (1-5) [27] evidence of an effect on patient relevant clinical outcomes, including benefits and harms and quality of life and survival	
Any other adverse effects [28] none stated				

EXTERNAL VALIDITY
Generalisabilty [29] likely generalisable to target population
Applicability [30] benefits outweigh harms
Comments [31] authors claim a significant reduction in numbers of foot ulcers and hyperkeratosis which are risk factors for ulcers, by using silicone orthotics

STUDY DETAILS				
Reference [1] : Varma, A. K., A. Bal, et al. (2006). "Efficacy of polyurethane foam dressing in debrided diabetic lower limb wounds." Wounds: A Compendium of Clinical Research & Practice 18(10): 300-306.				
Affiliation/source of funds [2] Amrita Institute of Medical Sciences and Research Center, Kochi, South Indian Sate of Kerala.Divison of Diabetic Foot Surgery and department of endocrinology				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] territairy referral hospital		
Intervention [6] surgical debridement, wound cleaned with sterile normal saline solution; bedside sharp debridement of necrotic tissue and slough performed when necessary and again cleaned with normal saline. Polyurethane foam sheet soaked in sterile saline and manually squeezed, this was directly placed on the wound surface. Sterile gamgee pads were placed over foam sheet and held in place with bandage with light compression elastrocrepe bandage overlap 50%. (no topical antibiotics, de-sloughing ointment or other topical agents) Foam had a Shore hardness of 10, pore size 0.4mm diameter and 65 pores per inch^2. Sample size [7] N= 24		Comparator(s) [8] surgical debridement, bedside sharp debridement and wounds were dressed daily with conventional techniques using topical antibiotics, de-sloughing agents (collagenase, papain-urea, hyaluronidase ointment), or hydrogel and hydrocolloid dressing as deemed necessary. Limb was offloaded after operation. Sample size [9] N=24		
split skin grafting (SSG) for >5cm or 20 cm^2 once clean, devoid of slough and granulated well and culture of surface swab without bacterial growth.				
Selection criteria: Inclusion criteria – type II diabetes patients. With lower limb wound after debridement reformation of slough with or without excessive exudates in the immediate postoperative period (with 72 hours) Exclusion criteria – patients that, after debridement, did not reform slough and remain clean in the immediate postoperative period (within 72 hours).				
Patient characteristics [10] Intervention group – N = 24; age (yrs) 58.8 ± 9.4; duration of diabetes (yrs) 14 ± 8; exposed bone 16/24 (66.7%); peripheral occlusive vascular disease 8/24 (34.8%); neuropathy 15/24 (60%); blood urea nitrogen (mg%) 44.6 ± 28.3; serum creatinine (mg%) 1.7 ± 1.4; white blood cell count (cells/mm^3) 23.2 ± 8.5; ulcer area (cm^2) 208.9 ± 196.3; no. ulcers > 5 cm diameter 19/24 (79.2%); ulcer location: thigh 2/24 (8.3%); leg 8/24 (33.3%); foot 14/24 (58.4%). Comparator group(s) – N = 24; age (yrs) 52.4 ± 7.4; duration of diabetes (yrs) 13 ± 7; exposed bone 12/24 (50%); peripheral occlusive vascular disease 9/24 (37.5%), neuropathy 6/24 (24%); blood urea nitrogen (mg%) 49.7 ± 43.2; serum creatinine (mg%) 1.4 ± 0.8; white blood cell count (cells/mm^3) 21.4 ± 7.2; ulcer area (cm^2) 198.3 ± 186.8; no. ulcers > 5 cm diameter 12/24 (50%); ulcer location: thigh 2/24 (8.3%); leg 4/24 (16.7%); foot 18/24 (75%).				
Length of follow-up [11] 3 months		Outcome(s) measured [12] healing and time to healing		
INTERNAL VALIDITY				
Allocation [13] Randomised	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] Blinded evaluation	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] 100%
Overall quality assessment (descriptive) [18] average quality study				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size	Benefits (NNT) [23] 95% CI [25]
Healed wounds	24/24 (100%)	17/24 (70.8%)	RR = 1.41 [1.13, 1.41]	NNT = 3 [3, 10]
By primary intention (split-skin grafting)	19/19 (100%)	12/12 (100%)	RR = 1.00 (not calculable)	
By secondary intention (re-epithelialisation)	5/5 (100%)	5/12 (41.7%)	RR = 2.40 [1.14, 2.40]	NNT = 2 [2, 13]
Days till healing (mean ± SD) (median)	22.5±15.4 (16)	52.0±22.7 (60)	p < 0.001	
	Clinical importance (1-4) [26] A clinically important benefit		Relevance (1-5) [27] evidence of an effect on patient relevant clinical outcome, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] not stated
EXTERNAL VALIDITY
Generalisabilty [29] likely generalisable to the target population
Applicability [30] benefits outweigh harms
Comments [31] wound dressing in sterile non medicated polyurethane foam granulated earlier and epithelised faster than wound dressing with conventional dressing nethods

STUDY DETAILS				
Reference [1] : Veves, A., P. Sheehan, et al. (2002). "A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers." Archives of surgery (Chicago, Ill. : 1960) 137(7): 822-827.				
Affiliation/source of funds [2] Joslin Beth Isreal Deaconess Foot Center, Boston and the Diabetes Foot and Ankle Centre, Hospital for Joint Diseases Orthopaedic Institute, New York, USA				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] university teaching hospitals and primary care centers, USA		
Intervention [6] Debridement performed initially and during follow up visits if necessary. Wound was cleaned and irrigated with isotonic sodium chloride solution where necessary. Surrounding tissue was dried to avoid tissue damage. Promogran (consisting of collagen and oxidesed regenerated cellulose) cut to wound size and applied as primary dressing, covered with gauze a bandage (Sof-Kling Conforming Bandage; Johnson & Johnson) and tape as secondary dressing Sample size [7] N= 138		Comparator(s) [8] Debridement performed initially and during follow up visits if necessary. Wound was cleaned and irrigated with isotonic sodium chloride solution where necessary. Surrounding tissue was dried to avoid tissue damage. Isotonic sodium chloride solution-moistened gauze as primary dressing, covert with gauze, bandage and tape as second dressing. Sample size [9] N=138		
The frequency of dressing change was according to condition of wound and amount of drainage. Heavy drainage advised to change twice daily, moderate to mild drainage change advise of once daily, otherwise change every 2 to 3 days. Wound were cleansed with isotonic sodium chloride solution				
Selection criteria: Inclusion criteria –18 years or older with a diabetic foot ulcer of at least 30 days duration, Wagner grade 1 to 2, area of at least 1cm², adequate circulation with an oscillometer reading on the limb that had the target wound of at least 1U and a wound that was debrided of necrotic/nonviable tissue. Exclusion criteria – clinical sign of infection, a target wound exposing bone, a current illness or a condition that may have interfered with wound healing (carcinoom, vasculitis, connective tissue disease or an immune system disorder); known current abuse of alcohol or other drugs or treatment with dialysis or, radiation therapy or chemotherapy, immunosuppressive agents, corticosteroids at a dose that might interfere with wound healing within 30 days before study enrolment. Know hypersensitivity to any of the dressing components, unwillingness or inability to be fitted with appropriate shoe gear or an off loading device; and multiple ulcers on the same foot.				
Patient characteristics [10] Intervention group – age mean(range) (yrs) 58 (23-85), Male 68.8% (n=95), Female 31.2% (n=43), Race; African American 10.9% (n=15), Native American 11.6% (n= 16), White 61.6% (n=85), Hispanic 15.9% (n=22), HbA1c level (range) 8.6% (5.3-14.0), Oscillometry mean (range) U 4.4 (0.9-13.0), Wound area mean (range) cm² 2.5 (0.2-27.4), Wound duration median (range) months 3 (1-84), history of foot ulcer 71% (n= 98) Comparator group(s) – age mean(range) (yrs) 59 (37-83), Male 78.3% (n=108), Female 21.7% (n=30), Race; African American 8.7% (n=12), Native American 11.6% (n= 16), White 63.8% (n=88), Hispanic 15.9% (n=22), HbA1c level (range) 8.5% (4.9-13.1), Oscillometry mean (range) U 4.3 (0.9-12.0), Wound area mean (range) cm² 3.1 (0.1- 42.4), Wound duration median (range) months 3 (1-144), history of foot ulcer 63.8% (n=88)				
Length of follow-up [11] 12 weeks		Outcome(s) measured [12] healing and time to healing		
INTERNAL VALIDITY				
Allocation [13] Randomised	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] Blinded evaluation	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] Intervention 75% Control 61%
Overall quality assessment (descriptive) [18] good quality study				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size	Benefits (NNT) [23] 95% CI [25]
Healed wounds	37% (n=51)	28.3% (n=39)	P=0.12	
Mean % reduction wound area	64.5%	63.8%		
Mean time to healing (wks)	7.0±0.4	5.8±0.4		
Group with wound duration less than 6 months				

Healed wounds	45.3% (n=43)	32.6% (n=29)	P=0.056	
Mean time to healing (wks)	6.9±0.4	6.3±0.4		
Group with wound duration greater than 6 months				
Healed wounds	18.6% (n=8)	20.4% (n=10)	P=0.83	
Group with Wagner grade1 wounds				
Healed wounds	44.6% (n=25)	31.7% (n=20)		
Group with Wagner grade 2 wounds				
Healed wounds	32.9% (n=27)	25.3% (n=19)	P=0.30	
	Clinical importance (1-4) [26] A clinically important benefit		Relevance (1-5) [27] evidence of an effect on patient relevant clinical outcome, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] 26.8% (n=37) in intervention group with non serious adverse events vs 24.6% (n=34) in control group. Serious adverse events in intervention 18.1% (n=25) vs 25.4% (n=35) in control. None were described as related to the dressing. 2 patients died in intervention group, 6 in control, which were unrelated to dressing.				
EXTERNAL VALIDITY				
Generalisabilty [29] likely generalisable to the target population				
Applicability [30] benefits outweigh harms				
Comments [31] 90% compliance. Promogran equally effective in promoting complete wound healing in the studied diabetic population compared with moistend gauze				

STUDY DETAILS				
Reference [1] : Viswanathan, V., S. Madhavan, et al. (2005). "Amputation prevention initiative in South India: positive impact of foot care education." Diabetes Care 28(5): 1019-1021.				
Affiliation/source of funds [2] M.V. Hospital of Diabetes and Diabetic Research Centre, Royapuram, Chennai, India				
Study design [3] cohort study	Level of evidence [4] III-2	Location/setting [5] speciality foot clinic M.V. Hospital for Diabetes India		
Intervention 1[6] individual counselling with family member presence, education regarding diabetes foot disease and its complications by photomaterial and regular foot examination (thought to examine foot with mirror and pedicure techniques. Futher assistance with proper fitting foot wear and routine foolow up. Sample size [7] N= 2871		Comparator(s) [8] Sample size [9] N=1766		
The frequency of dressing change was according to condition of wound and amount of drainage. Heavy drainage advised to change twice daily, moderate to mild drainage change advise of once daily, otherwise change every 2 to 3 days. Wound were cleansed with isotonic sodium chloride solution				
Selection criteria: Inclusion criteria –18 years or older with a diabetic foot ulcer of at least 30 days duration, Wagner grade 1 to 2, area of at least 1cm², adequate circulation with an oscillometer reading on the limb that had the target wound of at least 1U and a wound that was debrided of necrotic/nonviable tissue. Exclusion criteria – clinical sign of infection, a target wound exposing bone, a current illness or a condition that may have interfered with wound healing (carcinoom, vasculitis, connective tissue disease or an immune system disorder); known current abuse of alcohol or other drugs or treatment with dialysis or, radiation therapy or chemotherapy, immunosuppressive agents, corticosteroids at a dose that might interfere with wound healing within 30 days before study enrolment. Know hypersensitivity to any of the dressing components, unwillingness or inability to be fitted with appropriate shoe gear or an off loading device; and multiple ulcers on the same foot.				
Patient characteristics [10] Intervention group 1– age mean(range) (yrs) 58 (23-85), Male 68.8% (n=95), Female 31.2% (n=43), Race; African American 10.9% (n=15), Native American 11.6% (n= 16), White 61.6% (n=85), Hispanic 15.9% (n=22), HbA1c level (range) 8.6% (5.3-14.0), Oscillometry mean (range) U 4.4 (0.9-13.0), Wound area mean (range) cm² 2.5 (0.2-27.4), Wound duration median (range) months 3 (1-84), history of foot ulcer 71% (n= 98) Comparator group(s) – age mean(range) (yrs) 59 (37-83), Male 78.3% (n=108), Female 21.7% (n=30), Race; African American 8.7% (n=12), Native American 11.6% (n= 16), White 63.8% (n=88), Hispanic 15.9% (n=22), HbA1c level (range) 8.5% (4.9-13.1), Oscillometry mean (range) U 4.3 (0.9-12.0), Wound area mean (range) cm² 3.1 (0.1- 42.4), Wound duration median (range) months 3 (1-144), history of foot ulcer 63.8% (n=88)				
Length of follow-up [11] 12 weeks		Outcome(s) measured [12] healing and time to healing		
INTERNAL VALIDITY				
Allocation [13] Randomised	Comparison of study groups [14] Groups identical except for intervention	Blinding [15] Blinded evaluation	Treatment/ measurement bias [16] Both groups measured the same	Follow-up (ITT) [17] Intervention 75% Control 61%
Overall quality assessment (descriptive) [18] good quality study				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size	Benefits (NNT) [23] 95% CI [25]
Healed wounds	37% (n=51)	28.3% (n=39)	P=0.12	
Mean % reduction wound area	64.5%	63.8%		
Mean time to healing (wks)	7.0±0.4	5.8±0.4		

Group with wound duration less than 6 months				
Healed wounds	45.3% (n=43)	32.6% (n=29)	P=0.056	
Mean time to healing (wks)	6.9±0.4	6.3±0.4		
Group with wound duration greater than 6 months				
Healed wounds	18.6% (n=8)	20.4% (n=10)	P=0.83	
Group with Wagner grade1 wounds				
Healed wounds	44.6% (n=25)	31.7% (n=20)		
Group with Wagner grade 2 wounds				
Healed wounds	32.9% (n=27)	25.3% (n=19)	P=0.30	
	Clinical importance (1-4) [26] A clinically important benefit		Relevance (1-5) [27] evidence of an effect on patient relevant clinical outcome, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] 26.8% (n=37) in intervention group with non serious adverse events vs 24.6% (n=34) in control group. Serious adverse events in intervention 18.1% (n=25) vs 25.4% (n=35) in control. None were described as related to the dressing. 2 patients died in intervention group, 6 in control, which were unrelated to dressing.				
EXTERNAL VALIDITY				
Generalisabilty [29] likely generalisable to the target population				
Applicability [30] benefits outweigh harms				
Comments [31] 90% compliance. Promogran equally effective in promoting complete wound healing in the studied diabetic population compared with moistend gauze				

STUDY DETAILS

Reference [1] Akbari, A., H. Moodi, et al. (2007). "Effects of vacuum-compression therapy on healing of diabetic foot ulcers: randomized controlled trial." Journal of rehabilitation research and development 44(5): 631-636.

Affiliation/source of funds [2] Zadehan University of Medical Sciences, Zadehan, Iran. Sources of funding are not stated.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Outpatinet clinic in Zadehan University of Medical Sciences Centre, Zadehan, Iran

Intervention [6] Vacuum compression therapy (VCT) using the Vasotrain-447 set for vascular disease and delivered 75 mmHg negative pressure for 60 s, followed by 38.5 mmHg positive pressure for 30 s for 1 h/day, 4 times/week, for a total of 12 sessions + conventional wound therapy (debridement, blood glucose control, systematic antibiotics, wound cleaning with saline, offloading and daily wound dressings) Sample size [7] 9 diabetics	Comparator(s) [8] Conventional wound therapy (debridement, blood glucose control, systematic antibiotics, wound cleaning with saline, offloading and daily wound dressings) Sample size [9] 9 diabetics

Selection criteria

Inclusion criteria – Diabetic patients with a foot ulcer that corresponded with grade 2 of the University of Texas Diabetic wound classification system, no history of deep venous thrombosis, and no haemorrhage in ulcer.

Exclusion criteria – If patients had significant loss of sensation, haemorrhage, or vertigo or had not completed the therapy.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention	Control
Female %	7/9=77.8%	8/9=88.9%
Mean age (SD)	58.2 (8.07)	57.6 (8.02)
Mean surface area of ulcer (mm^2)	46.88 ± 9.28	46.62 ± 10.03

The authors provided the mean of Body mass index (23.44 ± 3.7) for both groups together.

Length of follow-up [11] The intervention comprised of 10 sessions during 3 weeks. First session was for pre-intervention evaluation and last session was post-intervention evaluation. It is not stated if the controls were also evaluated at the same time.	Outcome(s) measured [12] Change in ulcer surface area

INTERNAL VALIDITY

Allocation [13] Through a computerized randomisation schedule	Comparison of study groups [14] Similar to given characteristics	Blinding [15] Neither participants nor assessors were blinded. The technician that did the ulcer tracing was blinded. However with VCT, it is hard to have blinding since it may show on the skin and therefore the likelihood that the technician stayed blinded is small.	Treatment/ measurement bias [16] Not clear if the measurement was done in an even way or at the same time for both groups.	Follow-up (ITT) [17] 1/9=11.1% from intervention, 1/9=11.1% from control. ITT was not done.

Overall quality assessment (descriptive) [18] Of moderate quality: non blinded RCT, without ITT;

The measurement of intervention and control groups is not clear and measurement bias cannot be ruled out; Assessor bias cannot be excluded; At recruitment 20 fitted the eligibility criteria but 18 were selected and it is not stated why the other two were excluded

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23]
Decrease in ulcer surface area:	From 46.88 (9.28) to 35.09 (4.09) p=0.006	From 46.62 (10.03) to 42.89 (8.1) p=0.01	Decrease in ulcer area:	Frequency: 2.25 (1.6-112)
The frequency of ulcer improvement:	5/9=55.5 Surface area after treatment: 35.09 ± 4.09	1/9=11.1 Surface area after treatment: 42.89 ± 8.1	Intervention vs. control: For frequency of ulcer RR=5.0 (1.03-30.5) Surface area of wound: p=0.024	95% CI [25] Harms (NNH) [24] - 95% CI [25]

	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes.
Any other adverse effects [28] None reported		
EXTERNAL VALIDITY		
Generalisabilty [29] Poor generalisability; predominantly female, single centre, not very elaborated inclusion and exclusion criteria		
Applicability [30] Benefits could outweigh the harms		
Comments [31]		

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] Alvarez, O. M., R. S. Rogers, et al. (2003). "Effect of noncontact normothermic wound therapy on the healing of neuropathic (diabetic) foot ulcers: an interim analysis of 20 patients." The Journal of foot and ankle surgery : official publication of the American College of Foot and Ankle Surgeons 42(1): 30-35.</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2] University Wound Care Centres and East Tremont Health Centre, New York, USA. The study was funded by research grants from the Augustine Medical Inc. Eden Prairie, MN, USA.</td></tr>
<tr><td colspan="2">Study design [3] RCT</td><td colspan="2">Level of evidence [4] II</td><td colspan="2">Location/setting [5] University Wound Care Centres and East Tremont Health Centre, New York, USA</td></tr>
<tr><td colspan="3">Intervention [6] Heavy debridement at baseline + treatment with non-contact normothermic wound therapy (NNWT) + standard wound care + weekly light debridement to remove callus surrounding diabetic foot ulcer
Sample size [7] 25 patients</td><td colspan="3">Comparator(s) [8] Heavy debridement at baseline + standard wound care + weekly light debridement to remove callus surrounding diabetic foot ulcer
Sample size [9] 24 patients</td></tr>
<tr><td colspan="6">Selection criteria
Inclusion criteria – Diabetic patients aged between 38 and 78 years with a diabetic neuropathic foot ulcer defined as follows: An ulcer on the plantar surface of the foot in a type 1 or 2 diabetic patient. The ulcer had to be secondary to neuropathy in a patient with adequate arterial circulation (ankle brachial pressure index >0.7 and palpable pulses). The ulcer had to extend through the dermis and into subcutaneous tissue with granulation tissue present but without exposure of muscle, tendon, bone or joint capsule.
Exclusion criteria – Clinical signs of infection, osteomyelitis, cellulitis, uncontrolled diabetes and any other condition that would impair wound healing inclusive of renal, hepatic, haematological, neurological or immunological disease. Patients taking corticosteroids, chemotherapy, radiation, immunosuppressants, or chemotherapy within one month prior to entry into the study were also excluded.</td></tr>
<tr><td colspan="6">Patient characteristics [10] Intervention group – Comparator group(s) – General characteristics for <u>all</u> the patients were stated without elaborating by groups. It was stated that 57% of all patients were female, 43% were insulin-dependent diabetics, 96% had type 2 diabetes. The mean ulcer area was 320 mm^2, and 78% reported having the ulcer open for less than one year and 23% had a history of non healing wounds for 1-3 years. 72% of the ulcers were in the forefoot area. The authors stated that there were no differences between the intervention and control groups in patient demographics, baseline ulcer size nor ulcer duration.</td></tr>
<tr><td colspan="3">Length of follow-up [11] Patients were followed up till 12 weeks</td><td colspan="3">Outcome(s) measured [12] Complete wound healing</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13] Based on a computer generated randomisation schedule.</td><td>Comparison of study groups [14] No differences were found. Analysis not controlled for antibiotic treatment.</td><td>Blinding [15] Not done</td><td colspan="2">Treatment/ measurement bias [16] Similar to all, done objectively, via photographing, not blinded. Evaluation of wound was done on a weekly basis.</td><td>Follow-up (ITT) [17] All were followed up and therefore analysis was done on all patients.</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18] Moderate quality mainly because of the non-blinded nature of the study. However, since the study main outcome was objectively assessed by photographs and a complete healing of the wounds was assessed, the likelihood of assessor biased reports is minimal. A drawback in the study is the unreported characteristics of each group. Although the authors said that the groups were similar in patient demographics, ulcer duration and ulcer size.</td></tr>
<tr><td colspan="6">RESULTS
(In the result section, the number of patients seen each week dropped most probably because their wounds healed and no further follow-up was done, though this was not elaborated in the paper)</td></tr>
<tr><td>Outcome [19]
Mean % area of wound relative to baseline after:
2 weeks
4 weeks:
6 weeks:
8 weeks:
10 weeks:
12 weeks:

Number of days needed for 50% reduction in ulcer area:</td><td>Intervention group [20]

68.2%
43.3%
20.5%
14.5%
8.7%
11.0%

25 days</td><td>Control group [21]

82.5%
78.2%
53.6%
30.4%
25.3%
35.1%

43 days</td><td colspan="2">Measure of effect/effect size [22]
95% CI [25] The hazard ratio for faster healing comparing the NNWT to controls were as follows:
At 4 w: RR 1.8 (p=0.039)
At 6 w: RR 2.6 (p=0.044)
At 10 w: RR 2.9 (p=0.019)
At 12 w: RR 3.2 (p=0.011)

P value for difference in days needed for 50% reduction in ulcer area: p=0.031</td><td>Benefits (NNT) [23] could not be calculated since results are given in “mean % change relative to baseline”. Absolute numbers of patients who had healed ulcers were not provided.
95% CI [25]

Harms (NNH) [24]
-
95% CI [25]</td></tr>
<tr><td></td><td colspan="2">Clinical importance (1-4) [26] 1 A clinically important benefit for the full range of plausible estimates.</td><td colspan="3">Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes</td></tr>
</table>

Any other adverse effects [28] Slight to moderate skin maceration was observed for 40% of the NNWT group but this did not result in any serious adverse effect or discontinuation of study.
EXTERNAL VALIDITY
Generalisabilty [29] Moderate generalisability. A single centre RCT.
Applicability [30] The overall benefits may outweigh the harms.
Comments [31]

STUDY DETAILS

Reference [1] Alvarez, O. M., R. S. Rogers, et al. (2003). "Effect of noncontact normothermic wound therapy on the healing of neuropathic (diabetic) foot ulcers: an interim analysis of 20 patients." J Foot Ankle Surg 42(1): 30-35.

Affiliation/source of funds [2] University Wound Care Centre, Bronx, NY, USA. Supported by Augustine Medical Inc., Eden Prairie, MN and by the Fanwood Foundation

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] One medical centre, NY, USA

Intervention [6] Patients with diabetic neuropathic foot ulcers were treated with negative normothermic wound therapy (NNWT) after debridement of the ulcer + minor debridement to remove callus during follow-up visits. Patients were fitted with a therapeutic healing sandal with customized plastizote inserts Sample size [7] 10 patients	Comparator(s) [8] Patients with diabetic neuropathic foot ulcers were treated with saline dressings after debridement of the ulcer + minor debridement to remove callus during follow-up visits. Patients were fitted with a therapeutic healing sandal with customized plastizote inserts Sample size [9] 10 patients

Selection criteria

Inclusion criteria – Diabetics age 18 or older with neuropathic foot ulcers on the plantar surface of the foot with adequate arterial circulation (ankle-to-brachial index, >0.7 and palpable pulses). The ulcers had to extend through the dermis and into subcutaneous tissue, but without exposure of muscle, tendon, bone, or joint capsule.

Exclusion criteria – Clinical signs of infection, osteomyletis, cellulites, uncontrolled diabetes, and any other clinically significant medical condition that would impair wound healing inclusive of renal, hepatic, hematologic, neurologic, or immunologic disease. Patients taking steroids, immunosuppressive agents, radiation, or chemotherapy within 1 month before study were also excluded.

Patient characteristics [10] Intervention group – Comparator group(s) –

	NNWT (N=10)	Control (N=10)
Male sex %	60	40
Mean age, range	61 (38-75)	53 (47-78)
Mean ulcer area (mm^2)	346	216
Ulcer location: forefoot, % Other, %	70 30	80 20
More than one ulcer, %	40	10
Medical history of non-healing <1 y,% 1-3 y,%	 70 30	 90 10
Type 11 diabetes	80	90
Insulin dependent diabetes, %	50	40

Length of follow-up [11] Patients were followed every week for a period of 12 weeks	Outcome(s) measured [12] Healing of wound

INTERNAL VALIDITY

Allocation [13] based on computer randomisation schedule	Comparison of study groups [14] Differences in duration of ulcer and BMI measures were not reported	Blinding [15] Not blinded	Treatment/ measurement bias [16] Similar in both groups. Photographed wounds were weekly assessed.	Follow-up (ITT) [17] Drop outs were not reported

Overall quality assessment (descriptive) [18] Moderate quality. Non-blinded study. Duration of ulcer and BMI measures were not reported, confounding cannot be excluded.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23]
Healing of ulcer: Week 6: Week 12:	(numbers of ulcers not given) 30% of the ulcers 70% of the ulcers	 10% of the ulcers 40% of the ulcers	*p*=0.11 *p*=0.069	Cannot be calculated 95% CI [25] Harms (NNH) [24] - 95% CI [25]

	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.	Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes
Any other adverse effects [28] None reported		
EXTERNAL VALIDITY		
Generalisabilty [29] Moderate generalisability patients were treated in one medical centre. Information on all the patients who were evaluated for inclusion was not reported.		
Applicability [30] The benefits do not outweigh the harms. No significant differences were seen. A similar proportion of ulcers healed in both intervention and control groups. However, with such a small number of patient, type-II error cannot be excluded.		
Comments [31]		

STUDY DETAILS

Reference [1] Armstrong, D. G., M. A. Rosales, et al. (2005). "Efficacy of fifth metatarsal head resection for treatment of chronic diabetic foot ulceration." Journal of the American Podiatric Medical Association 95(4): 353-356.

Affiliation/source of funds [2] Department of Surgery, Southern Arizona, Veterans Affairs Medical Centre, Tucson, USA; Franklin University of Medicine and Science, Chicago, USA; Manchester Royal Infirmary, Manchester, England. Source of funding was not stated.

Study design [3]	Level of evidence [4]	Location/setting [5]
Retrospective cohort study	III - 2	Department of Surgery, Southern Arizona, Veterans Affairs Medical Centre, Tucson, USA

Intervention [6]	Comparator(s) [8]
diabetics undergoing a surgical procedure of fifth metatarsal head resection Sample size [7] 22	diabetics undergoing standard wound care that consisted of wound dressing changes, aggressive offloading, and weekly debridement Sample size [9] 18

Selection criteria

Inclusion criteria – Diagnosis of diabetes mellitus, presence of neuropathic ulceration on the plantar aspect of the fifth metatarsal head and the ability to walk unassisted. University of Texas ulcer classification of either 1A or 2A

Exclusion criteria – Infection or ischemia or ulcer probed to bone

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention group	Control group
Mean age	65 ± 9.0	64 ± 7.7
Male %	81.8	83.3
Mean wound size	2.3 ± 1.4	2.6 ± 1.6
Mean Glycosylated haemoglobin	8.3 ± 1.6	8.4 ± 1.6
Mean duration of diabetes (years)	13.7 ± 4.9	12.4 ± 5.5

Length of follow-up [11]	Outcome(s) measured [12]
6 months	Time to healing, return of ulcers

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Not randomised. Selection bias cannot be excluded.	Similar in basic characteristics.	Not done.	Done from medical reports for both groups. Information bias cannot be excluded as the data were collected retrospectively via chart review.	All were followed up from chart reviews. Lost to follow-up was not reported.

Overall quality assessment (descriptive) [18] A retrospective cohort study that recruited patients during a period of 4 years; selection bias cannot be excluded since no information is provided on the whole population from whom the patients were selected. The study relied on reported data from charts and thus information bias cannot be excluded. The results were crude and not adjusted for co-morbidity or for duration of antibiotic treatment among the groups. The quality is moderate to poor.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22]	Benefits (NNT) [23] 95% CI [25]	Harms (NNH) [24] - 95% CI [25]
Mean time to heal (weeks):	5.8 ± 2.9	8.7 ± 4.3	For re-ulceration: RR= 0.16 (0.02-0.93)	For re-ulceration: 4.3 (3.17-106.2)	
Re-ulceration:	1/22=4.5%	5/18=27.8	For amputation: RR= 0.4 (0.05 – 2.9)	For amputation: 15.2 (6.7-infinite)	
Amputation:	1/22=4.5%	2/18=11.7%	95% CI [25] Time to heal: p=0.02 Amputation: p=0.4		

Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.

Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes, though results must be viewed with caution

Any other adverse effects [28] None reported

EXTERNAL VALIDITY

Generalisabilty [29] The study group was predominantly male, thus poor generalisability for women. Overall moderate generalisability since it is not known the denominator from whom these patients were selected.
Applicability [30] The potential benefits may outweigh potential harm given that the study was properly conducted, but because of the possible flaws in study design, caution must be regarded in interpreting the results.
Comments [31]

STUDY DETAILS

Reference [1] Armstrong, D. G., K. Holtz, et al. (2005). "Can the use of a topical antifungal nail lacquer reduce risk for diabetic foot ulceration? Results from a randomised controlled pilot study." International Wound Journal 2(2): 166-170.

Affiliation/source of funds [2] Rosalind Franklin University of Medicine, Chicago, IL; Southern Arizona Veterans Affairs Medical Centre, Tucson, AZ, USA. The study was supported by Aventis / Dermik Investigator Initiated Merit Award.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] High-risk diabetic clinic, Chicago, IL, USA

Intervention [6]	Comparator(s) [8]
Diabetic patients at high risk for foot ulceration were enrolled into a preventative care program involving daily self-inspection with the possible use of a topical antifungal nail lacquer (AFL) (ciclopirox 8%) routine use of a (AFL) persons at high risk for diabetic foot ulceration Sample size [7] 34 patients	Diabetic patients at high risk for foot ulceration received only self-inspection instructions Sample size [9] 36 patients

Selection criteria

Inclusion criteria – A confirmed diagnosis of diabetes, persons with foot risk category 2 (neuropathy / deformity) or category 3 (history of ulceration or amputation).

Exclusion criteria – Patients were excluded if they were unable to ambulate without the assistance of a wheelchair or crutches; if they were sight impaired to the extent that they were legally blind and if they were unable or unwilling to give consent to participate in the study.

Patient characteristics [10] Intervention group – Comparator group(s) –

	AFL (N=34)	Controls (N=36)
Mean age, (SD)	69.5 (13.6)	70.3 (9.3)
Male %	100 %	94.4 %
Mean duration of diabetes mellitus, years (SD)	12.8 (9.0)	11.2 (8.2)
Risk category 3 %	55.9 %	58.3 %
VPT (Volts)	37.0 (17.4)	43.4 (23.4)

Length of follow-up [11]	Outcome(s) measured [12]
Patients were followed every 3 months for 12 months or until ulceration.	Ulceration, unexpected visit, missed appointments.

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Using a computerised randomisation schedule	Similar to given characteristics	Not blinded	Similar	Drops outs were not reported though ITT analysis was applied

Overall quality assessment (descriptive) [18] Of average quality

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23]
Ulceration:	2/34=5.9%	2/36=5.6 %	RR= 1.059 (0.191-5.870)	No benefits seen 95% CI [25]
Unexpected visits:	6/34=17.6%	11/36=30.6%	P value=0.208	Harms (NNH) [24]
One or more missed visits:	30.6%	26.5%	P value: 0.7	- 95% CI [25]

Clinical importance (1-4) [26]	Relevance (1-5) [27]
4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	1 Evidence of an effect on patient-relevant clinical outcomes

Any other adverse effects [28] None reported

EXTERNAL VALIDITY

Generalisabilty [29] Moderate generalisability. No information was given about screening and recruitment process

Applicability [30] No benefits were seen. Benefits may not outweigh harms.

Comments [31]

STUDY DETAILS

Reference [1] Armstrong, D. G., L. A. Lavery, et al. (2003). "Clinical Efficacy of the First Metatarsophalangeal Joint Arthroplasty as a Curative Procedure for Hallux Interphalangeal Joint Wounds in Patients with Diabetes." Diabetes Care 26(12): 3284-3287.

Affiliation/source of funds [2] Southern Arizona Veterans Affairs Medical Center, Tucson, Arizona; Texas A&M Health Science Center, Scott and White Hospital, Temple, Texas; Diabetes Research Institute, University of Miami, Miami, Florida; Department of Medicine, Manchester Royal Infirmary, Manchester, U.K. Source of funding was not stated.

Study design [3] Retrospective cohort study	Level of evidence [4] III-2	Location/setting [5] A large, referral-based diabetic foot clinic located in a teaching institution, USA.

Intervention [6] Patients treated with resectional arthroplasty + treatment with standard off-loading and wound care. Sample size [7] 21 patients	Comparator(s) [8] Control subjects received standard nonsurgical care received standard off-loading and wound care. Sample size [9] 20 patients

Selection criteria

Inclusion criteria – 1) Diagnosis of diabetes by the primary care physician, 2) presence of a single neuropathic wound of the plantar hallux interphalangeal joint, *3*) ability to ambulate freely without assistance of a wheelchair, and *4*) at least 6 months of reliable follow-up information. All wounds were classified as University of Texas Grade 1A or 2A (wounds without infection/ischemia not involving bone or joint). Data were abstracted over a 2-year period for any first metatarsophalangeal joint arthroplasty procedure performed during that period of time, yielding 21 procedures. These were compared to 20 age- and sex-matched control subjects receiving standard nonsurgical care for hallux interphalangeal joint wounds, thus yielding a 1-to-1 case-to-control ratio.

Exclusion criteria – Patients were excluded if they had a diagnosis of clinically significant vascular disease. Patients were excluded from analysis if they had a clinical diagnosis of acute soft-tissue or bone infection which included presence of purulence, advancing cellulitis, or two or more other local signs of inflammation.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Cases (N=21)	Controls (N=20)
Mean age, (SD)	70.5 (7.6)	69.8 (10.3)
Male %	90.5%	100%
GHb % (SD)	7.9 (1.4)	8.4 (1.2)
Duration of diabetes, years (SD)	14.1 (3.4)	13.7 (3.1)
Duration of wound, weeks (SD)	15.6 (6.4)	15.5 (5.9)

Length of follow-up [11] 2 months	Outcome(s) measured [12] Outcomes included time to healing, re-ulceration, infection, and amputation

INTERNAL VALIDITY

Allocation [13] Not randomised	Comparison of study groups [14] Similar	Blinding [15] Not blinded	Treatment/ measurement bias [16] Similar	Follow-up (ITT) [17] No drop outs were reported

Overall quality assessment (descriptive) [18] Of good quality

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25] / Harms (NNH) [24] 95% CI [25]
Mean days to healing:	24.2 ± 9.9 days	67.1 ± 17.1	Time to healing: P<0.001	Recurrence: 3.31 (2.62-16.27)
Recurrence of ulcers:	1/21=4.8%	7/20=35%	Recurrence: RR=0.136 (0.022-0.729)	Amputation (no benefit) 22.1 (8.02-inf)
Infection:	8/20=40%	8/21=38.1	Infection: p=0.901	
Amputation:	1/20=5%	2/21=9.5%	Amputation: RR=0.525 (0.070-3.85)	

Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.	Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes, though results must be viewed with caution

Any other adverse effects [28] No other than infection was reported

EXTERNAL VALIDITY

Generalisabilty [29] Moderate generalisability (the choice of controls was not that clear), these were matched to the cases by age and sex but it is not clear if these were selected from the same time period as the cases. The cases were selected over a period of two years. The initial recruitment process is not clear. No information is provided to how many patient charts were initially reviewed and how many were excluded, though the authors do provide a good list of inclusion and exclusion criteria. The potential of selection bias cannot be excluded.
Applicability [30] Benefits may outweigh harms
Comments [31]

STUDY DETAILS

Reference [1] Baker, L. L., R. Chambers, et al. (1997). "Effects of electrical stimulation on wound healing in patients with diabetic ulcers." Diabetes Care 20(3): 405-12.

Affiliation/source of funds [2] University of Southern California, Los Angeles, USA. The study was supported by the National Institute on Disability Rehabilitation and Research.

Study design [3] RCT | Level of evidence [4] II | Location/setting [5] Rancho Los Amigos Medical centre, LA, USA

Intervention group A[6] Diabetics with ulcers (also on distal extremities) were treated with asymmetric biphasic stimulation + standard treatment

Sample size group A [7] 21 patients with 33 ulcers

Intervention group B [6] Diabetics with ulcers (also on distal extremities) were treated with symmetric biphasic stimulation + standard treatment

Sample size group B [7] 20 patients with 28 ulcers

Intervention group MC [6] Diabetics with ulcers (also on distal extremities) were treated with micro-current stimulation + standard treatment

Sample size group MC[7] 19 patients with 28 ulcers

Comparator(s) group C (controls) [8] Diabetics with ulcers (also on distal extremities) were not exposed to any electric stimulation (though electrodes were placed on patients but no electric current was given) + standard treatment

Sample size group C (controls) [9] 20 patients with 25 ulcers

NOTE: the treatment went on for 4 weeks, but after this period those from the control or MC groups whose wounds still did not heal, were randomly allocated to either A or B groups. The treatment given was known to the therapist who also assessed the wound for healing. Then the outcome measure was the healing rate of the ulcer which took into account the time and the change in area of wound.

Selection criteria

Inclusion criteria – No clear criteria were stated. The authors said that the study targeted diabetic patients with “hard-to-heal” wounds with no other criteria.

Exclusion criteria – No criteria were provided.

Patient characteristics [10] Intervention group – Comparator group(s) –

Patient characteristics by groups:

	A N=21	B N=20	MC N=19	C N=20
Male sex %	76.2%	55%	73.7%	70%
Age years (SD)	58 (2)	50 (2)	51 (2)	52 (2)
Ethnicity				
Non Hispanic white	42.8%	30%	10.5%	10%
Hispanic	42.8%	50%	68.4%	80%
Black	9.5%	20%	15.8%	10%
Other	4.8%	0%	5.3%	0%
Diabetes onset (months) mean (SD)	158 (20)	161 (22)	188 (49)	142 (22)
Vital capacity (2000-3250)	3560 (270)	2800 (164)	2530 (246)	2910 (140)

Characteristics of wounds by groups:

	A N=33	B N=28	MC N=28	C N=25
Duration of ulcer days (SD)	109 (24)	74 (21)	54 (10)	59 (10)
Standard treatment: Betadine (numbers)	1	2	-	-
Acetic acid, wet to dry	16	16	23	18
Dry dressing	4	4	3	2
Saline, wet to dry	9	2	1	5
Other	3	4	1	-
Ulcer location: Toe / metatarsal (%)	51.5	75%	75%	84%
Heel	18.2%	21.4%	3.6%	8%
Shank	30.3%	3.6%	-	4%
Knee	-	-	3.6%	-
Other	-	-	17.8%	4%
Infected %	90.9%	96.4%	96.4%	100%
Hb (Normal 12-16 g/100)	12 (0.3)	11 (0.4)	12 (0.8)	12 (0.3)
Glucose (normal 5.6 mmol/l)	10.2 (0.7)	10.2 (1.1)	10.8 (0.9)	9.8 (0.7)
Hospital length of stay	41 (6)	45 (7)	47 (7)	36 (4)

Length of follow-up [11] Treatment was for 4 weeks or till healing (any that came first). Later follow up was done by the therapist every 2-4 weeks	Outcome(s) measured [12] Healing of wound; Mean healing rates of the wounds were calculated

INTERNAL VALIDITY

Allocation [13] Randomisation method not stated.	Comparison of study groups [14] No significant differences were found between the groups at baseline	Blinding [15] Patient blinded by not therapist (who was also assessed the wounds after the therapy)	Treatment/ measurement bias [16] Similar to all patients and was done by the non-blinded assessor	Follow-up (ITT) [17] Drop outs: 24.2% from A; 42.8% from B; 17.8% from MC; 12% from C. Not stated if ITT was used to calculate the healing rates

Overall quality assessment (descriptive) [18] Of moderate quality: not assessor blinded; groups were not mutually exclusive as after 4 weeks, those who did not heal were randomised to either A or B. MC were later joined with the controls based on the results; reasons for the drop outs are not stated; the authors did not state if ITT was used in calculating the healing rates of the wounds; randomisation method was not stated; the groups differed by the type of standard treatment they all got; most of the ulcers were infected and duration and type of antibiotic treatment were not controlled for.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22]	Benefits (NNT) [23] 95% CI [25] - No benefit was seen
Ulcers healed:	A: 15/33=45.4% B: 8/28=28.6% MC: 10/28=35.7%	C: 12/25=48%	95% CI [25] A vs. C:0.9 (0.3-2.5) B vs. C: 0.9 (0.3-2.3) MC Vs. C: 0.7 (0.4-1.4)	Harms (NNH) [24]
Healing rates (not clear if this was ITT):	A: 27 (4.0) B: 16.4 (6.1) MC: 17.2 (4.8)	C: 17.3 (4.8)		95% CI [25]
	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	

Any other adverse effects [28] not reported

EXTERNAL VALIDITY

Generalisabilty [29] Moderate to poor since we are not told the inclusion and exclusion criteria and we do not know the denominator from whom the patients were selected.

Applicability [30] No benefit was seen, given the many flaws of the study
Comments [31]

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] Birke, J. A., R. Horswell, et al. (2003). "The impact of a staged management approach to diabetes foot care in the Louisiana public hospital system." J La State Med Soc 155(1): 37-42.</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2] Louisiana State University Health Sciences Center, Diabetes Foot Program, Baton Rouge, USA. Source of funding was not stated</td></tr>
<tr><td colspan="2">Study design [3] Non randomised controlled trial</td><td colspan="2">Level of evidence [4] III-2</td><td colspan="2">Location/setting [5] The Louisiana public hospitals, USA</td></tr>
<tr><td colspan="3">Intervention [6] Patients hospitalized in Louisiana public hospitals in 1999 after the implementation of Disease Management Initiative (DMI), consisting of targeted goals for the medical management of diabetes, and a regional Diabetes Foot Program (DFP) utilizing a staged management approach to foot problems
Sample size [7] 14,097 hospitalized patients in 1999</td><td colspan="3">Comparator(s) [8] Patients hospitalized in the Louisiana public hospitals during 1998 before the implementation of DMI and the DFP
Sample size [9] 12,245 hospitalized patients in 1998</td></tr>
<tr><td colspan="6">Selection criteria
Inclusion criteria – Exclusion criteria –
Computerized data from the Louisiana State University Health care Services Division (HCSD) hospital systems were used to compare annual rates of foot related hospitalizations and lower extremity amputations among patients in 1998 and 1999. The eight facilities share a common computerized administrative system. Patients included were those who had at least one outpatient encounter carrying a diagnosis of diabetes. Eligible patients were assigned to a hospital based on their residence zip code. Medicare-defined Diagnostic related Groupings and ICD-9 diagnosis and procedure codes were used to determine which admissions were foot related. Amputation-related admissions were a subset of the foot related admissions.</td></tr>
<tr><td colspan="6">Patient characteristics [10] Intervention group – Comparator group(s) –
The authors do not state differences between the hospitalized populations in 1998 compared to 1999. They do provide patient demographics among the hospitals. However the comparison is between the two years and not the hospitals and the change was introduced in all of the hospitals. Under the assumption of steady state, one would assume that the patient population admitted to these hospitals in 1998 would not systematically differ from those admitted in 1999.</td></tr>
<tr><td colspan="3">Length of follow-up [11] Follow-up was limited to the hospitalization period</td><td colspan="3">Outcome(s) measured [12] Annual rates of hospitalization for diabetes-related foot problems and diabetes-related lower extremity amputations in diabetes patients treated for foot ulceration</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13] Not randomised</td><td>Comparison of study groups [14] Patient characteristics not stated between the two years</td><td>Blinding [15] Not blinded</td><td>Treatment/ measurement bias [16] Similar</td><td colspan="2">Follow-up (ITT) [17]
Follow-up was limited to the hospitalization period, therefore all were followed.</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18] Average quality study.</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="2">Outcome [19]

Diabetes foot-related hospitalization rates:
Diabetes related lower extremity amputation rates:</td><td>After change: [20]

1.96 per 100 person-years
0.72 per 100 person-years</td><td>Before change [21]

2.61 per 100 person-years
1.03 per 100 person-years</td><td>Measure of effect/effect size [22]
95% CI [25]
Hospitalization: p<0.001
Diabetes-related-amputation: P<0.001</td><td>Benefits (NNT) [23]
-
95% CI [25]</td><td>Harms (NNH) [24]

95% CI [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] 1 A clinically important benefit for the full range of plausible estimates.</td><td colspan="3">Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes</td></tr>
<tr><td colspan="6">Any other adverse effects [28] Not abstracted from the databases</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisabilty [29] Good generalisability</td></tr>
<tr><td colspan="6">Applicability [30] Benefits may outweigh the harms</td></tr>
<tr><td colspan="6">Comments [31]</td></tr>
</table>

STUDY DETAILS

Reference [1] Bloomgarden, Z. T., W. Karmally, et al. (1987). "Randomized, controlled trial of diabetic patient education: improved knowledge without improved metabolic status." Diabetes Care 10(3): 263-272.

Affiliation/source of funds [2] Mount Sinai School of Medicine, New York, NY, USA. The study was supported by a grants from Mount Sinai Hospital Auxiliary Board, the New York State Bureau of Health, the Centres for Disease Control, and the Alexander Foundation

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Patients belonging to Mount Sinai Medical Center Diabetes clinic

Intervention [6] Willing diabetic participants attended the diabetic clinic and at each visit with their physician a nurse reviewed medications and specific problems. In addition to this, nine education sessions were offered to each participant. The completion of the educational program lasted an average of 1.6 (0.3) years. Sample size [7] 145 participants	Comparator(s) [8] Willing diabetic participants attended the diabetic clinic and at each visit with their physician a nurse reviewed medications and specific problems. Follow –up was up to 1.5 (0.3) years. Sample size [9] 157 participants

Selection criteria

Inclusion criteria – All insulin-treated patients found on the Mount Sinai Diabetic Clinic roster as of 1 September 1979 were randomly assigned to intervention or control groups. Of the total 749 patients, 556 who attended the clinic were interviewed; of these 345 were willing to participate (163 in the intervention group, and 180 in the control group). However, only 145 (intervention) and 157 (control) managed to complete baseline assessment.

After the period of follow up, a second assessment was done for all participants.

Exclusion criteria – Not stated

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention N=127	Control N=139
Mean age, (SD)	56 (12)	59 (13)
Race,		
White %	5.5	6.5
Black	40.9	28.8
Hispanic	31.5	35.2
Type 2 diabetes %	75.6	65.5
Currently smoking %	12.6	10.1
Retinopathy %		
Background	13.4	17.3
Proliferative	3.1	3.6
HbA1c, % (SD)	6.8 (2.1)	6.6 (2.0)
Glucose (mg/dl), (SD)	223 (94)	199 (81)
Insulin dose (U/kg), (SD)	0.66 (0.63)	0.70 (0.50)
BMI (kg/m^2), (SD)	31.3 (6.2)	30.8 (6.6)
Sick days/yr, (SD)	11 (20)	10 (38)
Knowledge score, (SD)	5.3 (1.6)	5.3 (1.7)
Behaviour score, (SD)	3.4 (1.4)	3.6 (1.6)

	Intervention N=127	Control N=139
Male %	39.4	51.8
Education: none %	7.8	7.2
Did not complete high school	49.6	43.2
High school graduate	22.0	21.6
Missing (Unreported)	21.6	28.0
Hypertensive %	37.8	34.5
Duration of diabetes, Yr, (SD)	13 (8)	14 (9)
Foot lesions %		
Callus, nail dystrophy,or fungal infection	23.6	31.6
Ulcer or amputation	4.7	6.5
Abnormal renal function %	9.4	7.2
Cholesterol (mg/dl), (SD)	205 (52)	212 (48)
Triglycerides (mg/dl), (SD)	130 (77)	132 (97)
HDL cholesterol (mg/dl), (SD)	46 (14)	45 (14)
LDL cholesterol (mg/dl), (SD)	135 (45)	139 (45)
Emergency room visits/yr. (SD)	1.1 (1.7)	1.4 (2.5)
Hospitalizations / yr, (SD)	0.5 (0.8)	0.3 (0.5)
History of myocardial infarction %	7.9	5.7

Length of follow-up [11] 1.6 $\pm$ 0.3 years for the intervention group and 1.5 $\pm$ 0.3 years for the controls	Outcome(s) measured [12] Knowledge, health behaviour, HbA1c levels, Blood Glucose levels, body mass index, hospitalization rates, emergency room visits, outpatient clinic visits, foot lesions. This review will relate to the last four outcome measures

INTERNAL VALIDITY

Allocation [13] Method of randomisation was not stated	Comparison of study groups [14] Similar to most of the given characteristics. However, the controls had significantly more callus, lower blood glucose and a higher rate of past hospitalization compared with the intervention group	Blinding [15] Not blinded	Treatment/ measurement bias [16] Similar	Follow-up (ITT) [17] Drop outs: Intervention: 18/145=12.4% Controls: 18/157=11.5%. ITT was not applied

Overall quality assessment (descriptive) [18] Of moderate quality; a non-blinded RCT; around 11-12% were lost for follow up, ITT was not applied; some differences were observed between the intervention and control groups which may imply possible selection bias; these differences were not controlled for when analysing the data

<table>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td rowspan="2">Outcome [19]
Incidence of foot lesions in those free of lesions:

Incidence of severe lesions in those initially with minor lesions:

Hospitalization rates, emergency visit rates, outpatient visit rates:</td><td>Intervention group [20]
33/83=39.7%

2/37=5.4%

These rates were not reported, however, it was stated that no differences were seen between the intervention and controls groups</td><td>Control group [21]
30/63=47.6%

3/63=4.8%

These rates were not significantly different from those the intervention group</td><td>Measure of effect/effect size [22] 95% CI [25]
RR=0.8356 (0.581-1.214)

P value=0.887</td><td>Benefits (NNT) [23]
95% CI [25]
No significant difference in incidence of new lesions:
12.72 (4.22-inf)
Harms (NNH) [24]
-
95% CI [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.</td><td colspan="2">Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes</td></tr>
<tr><td colspan="5">Any other adverse effects [28] None related to study</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Low generalisability, the majority of the participants were of black or Hispanic ethnic background; inclusion and exclusion criteria were not elaborated, the exclusion criteria were not stated; selection bias cannot be excluded</td></tr>
<tr><td colspan="5">Applicability [30] The study failed to significantly demonstrate that insulin-dependent-diabetes-patient education is efficacious in preventing adverse outcomes including hospitalizations and new ulceration. Benefits may outweigh harms; however, the benefits were not statistically significant</td></tr>
<tr><td colspan="5">Comments [31]</td></tr>
</table>

STUDY DETAILS

Reference [1] Blume, P. A., J. Walters, et al. (2008). "Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial." Diabetes Care 31(4): 631-636.

Affiliation/source of funds [2] Southern Arizona Veterans Affairs Medical Centre, Tuscon, Arizona; Valley Baptist Hospital, Brownsville, Texas, and Saint Luke's Roosevelt Hospital, New York, NY, USA. The study was funded by the KCl USA Incorporated (San Antonio, TX)

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Multi-centre RCT (one Canadian and 28 US diabetic foot and wound clinics or hospitals)

Intervention [6] Debridement of diabetic ulcer + assignment to negative pressure vacuum-assisted closure therapy (NPWT) + conventional wound care + offloading therapy as deemed necessary

NPWT was via a negative pressure generating unit programmed according to the manufacturer's guidelines to deliver controlled negative pressure ranging from 50 to 200 mmHg until wound closure.

Sample size [7] 169 patients

Comparator(s) [8] Debridement of diabetic ulcer + assignment to Advanced Moist Wound Therapy (AMWT) mainly with hydrogels and alginates + conventional wound care + offloading therapy as deemed necessary

Sample size [9] 166 patients

Selection criteria

Inclusion criteria – Diabetic adults age >=18 years with a stage 2 to 3 Wagner Scale, calaneal, dorsal, or plantar foot ulcer >=2 cm^2 in area after debridement; a dorsum transcutaneous oxygen test >=30 mmHg; ankle-brachial index values >=0.7 and <=1.2 with toe pressure >=30 mmHg, or Doppler arterial waveforms that were triphasic or biphasic at the ankle of the affected leg.

Exclusion criteria – Patients with active Charcot disease, or ulcers resulting from electrical, chemical or radiation burns and those with collagen vascular disease, ulcer malignancy, untreated osteomyelitis, or cellulitis, were excluded from the study. Likewise, patients with uncontrolled hyperglycaemia (HbA_{1c} >12%) or inadequate lower extremity perfusion were also excluded. Patients who were treated with normothermic or hyperbaric oxygen therapy; concomitant medications such as corticosteroids, immunosuppressants, chemotherapy, growth factors, or use of enzymatic debridement, or dermal substitutes within 30 days from treatment were also not enrolled. Pregnant or nursing mothers were excluded.

Patient characteristics [10] Intervention group – Comparator group(s) –

Characteristics	NPWT N=169	AMWT N=166
Age years (SD)	58 (12)	59 (12)
Male %	83.4%	73.5%
Race: African American	16.6%	13.3%
Caucasian	56.2%	60.2%
Hispanic	24.3%	24.1%
Native American	1.8%	1.8%
Other	1.2%	0.6%
Weight kg (SD)	99.2 (25.2)	93.8 (25.6)
Height cm (SD)	175 (9.6)	175 (12.4)
Current smoker	20.1%	19.4%
Current use of alcohol	21.9%	27.1%
Type 2 diabetes	91.1%	91.6%
Pre-albumin (g/l) (SD)	21.1 (7.6)	19.9 (7.9)
Ankle-brachial index (mm HG) (SD)	1.0 (0.2)	1.0 (0.2)

Characteristics	NPWT N=169	AMWT N=166
Oxygen tension (mmHg) (SD)	43.2 (10.4)	43.2 (12.5)
Loss of sensation	90.4%	88.8%
Therapy received:		
NPWT	100%	-
Hydrogel	-	47.0%
Alginate	-	18.7%
Other	-	16.9%
Saline	-	10.2%
Collagen	-	6.6%
Hydrocolloid	-	0.6%
Ulcer duration (days) (SD)	198.3 (323.5)	206 (365.9)
Baseline ulcer area (cm^2) (SD)	13.5 (18.2)	11.0 (12.7)
Received offloading therapy	97.0%	97.6%
Treated for infection before study	29.6%	27.1%
A1C (SD)	8.3 (2.0)	8.1 (1.9)
Albumin (g/l) (SD)	3.4 (0.6)	3.4 (0.8)

Length of follow-up [11] Follow up till ulcer closure or till 112 days. Those whose wounds were closed were followed for at 3 and 9 months.

Outcome(s) measured [12] Complete ulcer closure; reduction in ulcer surface area, time to ulcer closure, secondary amputation

INTERNAL VALIDITY				
Allocation [13] Randomization was provided through generating random blocks of numbers provided by an external company and sealed in opaque envelopes containing black paper.	**Comparison of study groups** [14] No significant differences were seen at baseline.	**Blinding** [15] Not blinded.	**Treatment/ measurement bias** [16] All patients were similarly followed and ulcer closure was assessed via tracing, and granulation formation as judged by the clinicians. The authors did not state whether there were differences between the various centres in timing and method of outcome assessment.	**Follow-up** (ITT) [17] drop-outs: 54/169=31.9 from NPWT and 43/166=25.9% from control (AMWT). ITT analysis was applied.
Overall quality assessment (descriptive) [18] Of good quality. The differences in the centres were not reported and antibiotic treatment during study was not controlled for and this is important for healing of the wounds especially when infection was one of the side effects. Some of the withdrawal reasons are vague and one cannot know why certain were withdrawn by the treating clinician. However, ITT analysis was applied.				

RESULTS				
Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/effect size** [22] 95% CI [25]	**Benefits** (NNT) [23] 95% CI [25]
Complete ulcer closure:	73/169 =43.2%	48/166=28.9%	RR = 1.49 [1.12, 2.01]	7 [4.1, 24.9]
Surgical closure:	16/169=9.5%	14/166=8.4%	*p* = 0.740	
Total healed:	89/169=52.7%	62/166=37.3%	RR = 1.41 [1.11, 1.80]	7 [3.9, 21.4]
75% ulcer closure:	105/169=62.1%	85/166=51.2%	RR = 1.21 [1.01, 1.46]	9 [4.7, 319]
Time to healing:	96 days (CI: 75.0-114)	Not provided		
Reduction in ulcer area:	-4.32 cm^2	-2.53 cm^2	*p* = 0.021	
Secondary amputation:				**Harms** (NNH) [24] 95% CI [25]
Minor:	2/169 (1.2%)	13/166 (7.8%)	RR = 0.15 [0.04, 0.58]	15 [12, 42.4]
Major:	5/169 (3.0%)	4/166 (2.4%)	RR = 1.23 [0.36, 4.18]	
Total:	7/169 (4.1%)	17/166 (10.2%)	RR = 0.40 [0.18, 0.92]	16 [9.9, 173]
Infections:	16/169 (11.2%)	11/166 (9.0%)	RR = 1.43 [0.70, 2.96]	
Death during study:	3/169 (1.8%)	3/166 (1.8%)	*p* = 0.982	
Proportion of home care relative to acute care:	89.5%	95.3%	*p* < 0.001	
	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		**Relevance** (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	
Any other adverse effects [28] Similar rates of adverse effects were reported in both groups including oedema, wound infection, cellulites and osteomyelitis				

EXTERNAL VALIDITY
Generalisabilty [29] Good generalisability
Applicability [30] Benefits may outweigh harms, provided that the deaths were not related to the treatment. the causes of death in both groups were not stated.
Comments [31]

STUDY DETAILS

Reference [1] Bosi, E., M. Conti, et al. (2005). "Effectiveness of frequency-modulated electromagnetic neural stimulation in the treatment of painful diabetic neuropathy." Diabetologia 48(5): 817-823.

Affiliation/source of funds [2] Department of General Medicine, Vita-Salute San Raffaele University Hospital, Milan, Italy. The study was supported in part by a research grant from Lorenz Biotech (Medolla, Italy).

Study design [3] RCT cross over study	Level of evidence [4] II	Location/setting [5] Two medical centres: Milan and Perugia in Italy

Intervention [6] Sample size [7] Comparator(s) [8] Sample size [9] (A cross over study)

The treatment consisted of ten sessions of placebo followed by ten sessions of frequency-modulated electromagnetic neural stimulation (FREMS) for sequence 1; or vice versa for sequence 2, at random, separated by a wash-out period of 1 week. Each treatment session was administered at intervals of at least 24 h, and each ten-session series lasted no more than 3 weeks.
Sample size: 31 patients

Selection criteria

Inclusion criteria – Patients who met the following criteria were invited to participate in the study: (1) type 1 or type 2 diabetes according to American Diabetes Association criteria; (2) age between 18 and 70 years; (3) painful diabetic neuropathy with reduced sensory and/or MNCV (<40 m/s in at least one nerve trunk of lower limbs); and (4) vibration perception at big toe >25 V.
Exclusion criteria – Exclusion criteria were: (1) the presence of any other severe disease; (2) pregnancy; (3) renal disease with serum creatinine levels >1.77 μmol/l; (4) a history or actual presence of foot ulcers; and (5) lower limb vasculopathy as indicated by an ankle-brachial index <0.9 or a transcutaneous partial pressure of oxygen <50 mmHg.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Sequence 1 (N=15)	Sequence 2 (N=16)
Mean age, years, (SD)	63.1 (3.1)	59.2 (3.1)
Duration of diabetes, years (SD0	15.9 (3.0)	16.6 (2.7)
Type 2 diabetes %	80.0%	68.7%
Insulin managed diabtes %	33.3%	50.0%
HbA1c %	8.3 (0.4)	8.2 (0.3)
SF-36	103.5 (2.1)	103.8 (2.2)
VAS daytime pain score	32.3 (6.8)	41.4 (8.0)
VAS night-time pain score	36.3 (6.3)	45.5 (8.2)
VPT (V)	35.1 (2.3)	36.0 (2.3)
Monofilament	5.9 (1.4) For N=6	5.7 (1.1) For N=6
MNCV (m/s)	36.1 (1.4) For N=13	35.0 (2.0) For N=13
SNCV (m/s)	26.7 (3.7) For N=7	29.2 (4.6) For N=8

Length of follow-up [11] 4 months	Outcome(s) measured [12] The primary end point was the change in grading of daytime and night-time pain, as assessed using a visual analogue scale (VAS). Secondary end points were changes in: sensitivity to monofilament; vibration perception threshold, as measured by a biothesiometer; quality of life, as assessed by questionnaire; motor nerve conduction velocity (MNCV); and sensory nerve conduction velocity (SNCV). Only quality of life will be reported in this review

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias	Follow-up (ITT)
Randomisation was performed centrally (method not stated)	Similar	Double blinded	[16] Similar	[17] No drop outs

Overall quality assessment (descriptive) [18] Of good quality

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23]
SF36	Pre-treatment: 103.7 (1.5) Post treatment: 105.6 (1.3) P value=ns	Pre-treatment: 104.4 (1.5) Post treatment: 105.9 (1.5) P value=ns		95% CI [25] Harms (NNH) [24] - 95% CI [25]
	Clinical importance (1-4) [26] 1 A clinically important benefit for the full range of plausible estimates.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes including quality of life	

Results show SF36 measures for all 31 patients as a group comparing the baseline measures with those assessed 4 months later (cross over study); results are reported in means (SD)

	Baseline N=31	4-month follow up N=31	
SF36 (total)	103.6 (1.5)	107 (1.2)	<0.001
General health	4.9 (0.3)	4.9 (0.2)	ns
Physical functioning	23.1 (0.9)	25.0 (0.7)	<0.05
Role limitation due to physical and social functioning	6.1 (0.3)	6.6 (0.3)	<0.01
Social functioning	8.5 (0.4)	9.2 (0.3)	<0.05
Bodily pain	6.2 (0.4)	6.8 (0.3)	<0.05
General mental health	37.9 (0.7)	39.0 (0.5)	<0.05
Role limitation due to emotional problems	3.5 (0.2)	3.4 (0.1)	ns
Vitality and health perception	13.4 (0.3)	13.0 (0.4)	ns

Any other adverse effects [28] Patients reported slight burning sensation at the site of electrode placement during the series of treatments later revealed as FREMS, with no residual skin signs. No particular perception was recorded during placebo sessions.

EXTERNAL VALIDITY

Generalisabilty [29] Good generalisability

Applicability [30] benefits may outweigh harms

Comments [31]

STUDY DETAILS

Reference [1] Chantelau, E. and T. Schnabel (1997). "Palliative radiotherapy for acute osteoarthropathy of diabetic feet: A preliminary study." Practical Diabetes International 14(6): 154-156.

Affiliation/source of funds [2] Heinrich-Heine University of Dusseldorf, Germany. Source of funding was not stated.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Department of nutrition and metabolic diseases; Dusseldorf, Germany

Intervention [6] Standard care for diabetic osteoarthropathy with complete relief of pressure from foot plus oral antibiotics and low dose heparin + radiotherapy (6 sessions in one week) Sample size [7] 6	Comparator(s) [8] Standard care for diabetic osteoarthropathy with complete relief of pressure from foot plus oral antibiotics and low dose heparin + sham radiotherapy (6 sessions in one week) Sample size [9] 6

Selection criteria

Inclusion criteria – Diabetics with Charcot foot. The acute osteoarthropathy of the feet had a known duration of less than two months. Patients were volunteers and were recruited during a period of three years.

Exclusion criteria – Not stated

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention (n=6)	Control (n=6)
Age (years , range)	58 (24-64)	52 (43-62)
Female %	66.7%	33.3%
Type 2 diabetes	66.7%	83.3%
Duration of diabetes (years, range)	21 (10-44)	19 (10-28)
With diabetic retinopathy	100%	83.3%
Proteinuria <45 mg/L 45-500 mg/L >500 mg/L	16.7% 66.7% 16.7%	50% 50% 0%
With active foot ulcer	16.7%	16.7%
BMI >27 kg/m^2	50%	66.7%
History of osteoporotic lumbar fractures	16.7%	16.7%

Length of follow-up [11] After the 2-3 week hospitalisation the patients were followed monthly till healing occurred in all patients. No limited point in time was stated.	Outcome(s) measured [12] Time to healing of the acute Charcot foot.

INTERNAL VALIDITY

Allocation [13] Randomisation method was not stated	Comparison of study groups [14] Similar basic characteristics.	Blinding [15] Double blind RCT.	Treatment/ measurement bias [16] Similar in all patients. Clinical assessment by the attending physician.	Follow-up (ITT) [17] All were followed up.

Overall quality assessment (descriptive) [18] Moderate to good quality study. The study was based on a small number of volunteers; length of follow-up was till all patients healed and this ranged from 2.5 to 20 months. The authors do not state if patients had other therapies during this long period of time (which could have influenced the results)

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22]	Benefits (NNT) [23]
Mean healing time: mean (range)	7 (4-10)	9.7 (4-15)	95% CI [25] Healing time difference: p>0.05	none 95% CI [25] Harms (NNH) [24]- 95% CI [25]
	Clinical importance (1-4) [26] 3 The confidence interval does not include any clinically important effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	

Any other adverse effects [28] None reported

EXTERNAL VALIDITY

Generalisabilty [29] Poor, based on volunteers.

Applicability [30] No benefits were seen; both groups healed and the time to healing was not significantly different between the groups.
Comments [31] With such a small sample, type II error is possible, when it is difficult to reject the null hypothesis when the null hypothesis is wrong.

STUDY DETAILS

Reference [1] Claeys, L. G. and S. Horsch (1996). "Transcutaneous oxygen pressure as predictive parameter for ulcer healing in endstage vascular patients treated with spinal cord stimulation." International angiology : a journal of the International Union of Angiology 15(4): 344-349.

Affiliation/source of funds [2] General Hospital Cologne-Porz; Academic Teaching Hospital of the University of Cologne, Germany; Source of funding was not stated.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] General Hospital, University of Cologne, Germany.

Intervention [6]	Comparator(s) [8]
Patients with peripheral arterial occlusive disease (PAOD) Fontaine stage IV with non-healing ischemic foot ulcers or toe gangrene received 21 days of IV prostaglandin E1 therapy (80ug/day) + spinal cord stimulation (SCS) + standard wound care (debridement of dead tissue + topical disinfection with polyvidon + cleansing of ulcer with saline + dressing –changed twice daily) Sample size [7] 45 patients	Patients with PAOD Fontaine stage IV with non-healing ischemic foot ulcers or toe gangrene received 21 days of IV prostaglandin E1 therapy (80ug/day) + standard wound care (debridement of dead tissue + topical disinfection with polyvidon + cleansing of ulcer with saline + dressing – changed twice daily) Sample size [9] 41 patients

Selection criteria

Inclusion criteria – Patients with non-constructible peripheral arterial occlusive disease (PAOD), Fontaine stage IV and whose ulcers or gangrenes have been present for at least three weeks with ankle pressure less than 50 mmHg; with occluded vessels unsuitable for angioplasty or crural or pedal bypass surgery.

Exclusion criteria – Excluded were patients with mixed type of ulceration, local infection, patients suitable for reconstructive procedures, patients with short life expectancy, patients with heart failure NYHA Class III-IV, renal failure, liver disease, uncontrolled hypertension, Buergers' disease, unstable angina and neuropsychiatric diseases.

Patient characteristics [10] Intervention group – Comparator group(s) –

	SCS (N=45)	Control (N=41)
Mean age, (SD)	67.7 (11.9)	69.9 (10.2)
PAOD %	86.7	82.9
Hypertension %	75.6%	87.8%
Number of ischemic lesions: 1 2 3 +	37 (82.2%) 4 (8.9%) 4 (8.9%)	29 (70.7%) 9 (21.9%) 3 (7.3%)
Ankle brachial index, (SD)	0.287 (0.19)	0.340 (0.187)
Walking ability, meters Unable to walk < than 50 meters	 25/45=55.6% 20/45=44.4%	 32/41=78.0% 9/41=22.0%

	SCS (N=45)	Control (N=41)
Male %	57.8	56.1
PAOD + diabetes %	6 (13.3%)	7 (17.1%)
Cigarette pack years	44.4	49.4
Ankle pressure on the treated limb (mmHg): 0 20 40	 12 (26.7%) 12 (26.7%) 21 (46.7%)	 6 (14.6%) 10 (24.4%) 25 (60.9%)
$TcPO_2$ on the treated foot (mmHg)	10.0 (7.8)	11.6 (6.7)
Mean walking distance, meters	24	13

Length of follow-up [11] 1 year	Outcome(s) measured [12] Ulcer healing, level of amputation, Fontaine stage, changes in foot $TcPO_2$ and ankle brachial index. In this review only healing and amputation outcomes are reported.

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Randomisation method not stated	Similar	Not blinded	Similar	Loss due to death: SCS: 10/45=22.2%; Control: 12/41=29.2%. ITT was applied

Overall quality assessment (descriptive) [18] Good to moderate due to the non-blinding nature of the study

RESULTS

<table>
<tr><td rowspan="2">Outcome [19]

Minor amputation:
Major amputation:
Total ulcer healing among diabetics:
Patients reaching 50% healing:</td><td>Intervention group [20]
6/45= 13.3%
7/45=15.6%

3/6=50%
5/6=83.3%</td><td>Control group [21]
6/41= 14.6%
8/41= 19.5

1/7=14.3%
1/7=13.3%</td><td>Measure of effect/effect size [22] 95% CI [25]
Minor amputation: p=0.862
Major amputation: p=0.629

RR= 3.50 (0.64-22.6)
RR=5.83 (1.39-23.7)</td><td>Benefits (NNT) [23]
95% CI [25]
Complete healing:
2.80 (1.65-inf)

50% healing:
1.45 (1.09-6.56)</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.</td><td colspan="2">Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes</td><td>Harms (NNH) [24]
-
95% CI [25]</td></tr>
<tr><td colspan="5">Any other adverse effects [28] Erythema, hypotension, headache, flushing and gastrointestinal symptoms were reported. The therapy was not stopped due to adverse effects. The authors did not state between-group differences in the incidence of the side effects.</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Poor generalisability to patients with diabetics since these constituted a very small proportion of the total study group.</td></tr>
<tr><td colspan="5">Applicability [30] Benefits may outweigh the harms</td></tr>
<tr><td colspan="5">Comments [31]</td></tr>
</table>

STUDY DETAILS

Reference [1] d'Hemecourt, P. A., J. M. Smiell, et al. (1998). "Sodium carboxymethylcellulose aqueous-based gel vs. becaplermin gel in patients with nonhealing lower extremity diabetic ulcers." Wounds: A Compendium of Clinical Research & Practice 10(3): 69-75.

Affiliation/source of funds [2] The R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ, USA. Funding was not stated.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Multi-centre trial in 10 sites in NY, USA.

Intervention 1 [6] Diabetics receiving standard wound care as for control group + sodium carboxymethylcellulose (NaCMC) acqueous-based gel daily dressings Intervention 2 [6] Diabetics receiving good wound care as for control group + becaplermin gel 100 ug /g daily dressings Sample size [7] (1) N= 34 patients; (2) N = 70 patients (The NaCMC gel and the becaplermin gel were conducted in a double-blind fashion)	Comparator(s) [8] Diabetic receiving standard wound care (SWC: debridement + saline dressings [every 12 hours], off loading of pressure and systematic control of infection) alone (assessor blinded only) Sample size [9] 68 patients

Selection criteria

Inclusion criteria – Diabetic patients who had at least one full-thickness (stage 3 or 4) chronic diabetic ulcer of the lower extremity that had been present for at least 8 weeks prior to the study. The transcutaneous oxygen tension on the limb with the ulcer had to be equal or above 30 mm Hg. The target area after debridement had to be between 1.0 and 10.0 cm^2.

Exclusion criteria – If Osteomyelitis was present at site of ulcer; if post-debridement target area was under 1.0 cm^2 or over 10.0 cm^2; if patients had more than three chronic ulcers at baseline; patients with ulcers due to other reasons apart from diabetes (i.e. cancer, radiation, burn, etc.) were excluded. Patients using concomitant medications known to affect wound healing (i.e. corticosteroids) were excluded. Pregnant women or nursing mothers were excluded.

Patient characteristics [10] Intervention group – Comparator group(s) –

Characteristics of groups at baseline

	Good wound care N=68	NaCMC gel N=70	Becaplermin gel N=34
Male %	79.4	70.0	70.6
White race % Black race % Other race %	80.9 10.3 8.8	90.0 7.1 2.9	82.4 14.7 2.9
Age mean (SD)	59.6 (11.29)	56.9 (13.02)	58.5 (11.90)
Height mean (SD)	176.8 (11.07)	177.6 (10.49)	175.8 (9.27)
Weight mean (SD)	97.8 (25.84)	93.0 (21.03)	99.8 (20.94)
Ulcer area (cm^2) mean (SD)	3.5 (3.53)	3.2 (2.75)	2.4 (2.02)
Ulcer depth (cm) mean (SD)	0.4 (0.52)	0.4 (0.20)	0.3 (0.15)
Ulcer duration weeks mean (SD)	42.0 (42.00)	52.8 (60.92)	20.0 (14.39)
Location Leg Foot	 7.3% 92.7%	 4.3% 95.7%	 11.8% 88.2%
Stage, % III IV	 96% 4%	 100% 0.0%	 94% 6%
$TcpO_2$ mm Hg mean (SD)	56.5 (24.5)	57.4 (27.5)	49.4 (11.9)

Length of follow-up [11] 20 weeks	Outcome(s) measured [12] Complete wound closure; time to heal

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Patients were randomly assigned in a 2:2:1 ratio to one of three groups	No differences were seen among the three groups. Differences between the centres were not reported.	Double blind method for the two gels; assessor blinded for the control group	Apart from the study treatment, the groups were treated and measured he same	Overall 41 patients withdrew: 31% of the controls, 16% of the NaCMC and 26% of the becaplemin. ITT was applied.

Overall quality assessment (descriptive) [18] The study is of good quality, multi-centre assessor blinded RCT, with ITT analysis. Patients were similar at baseline and follow-up measures were collected equally. The analysis was also adjusted for baseline ulcer area. However, the analysis was not controlled for antibiotic treatment in the groups for infection control. Furthermore, any differences between the 10 centres were not reported.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Complete healing	Becaplermin: 15/34=44% NaCMC: 25/70=36%	SWC: 15/68=22%	Healing: Becaplermin vs SWC: RR=2.00 (1.11, 3.50) NaCMC vs SWC: RR=1.61 (0.9, 2.8) Becaplermin vs NaCMC: RR = 1.24 (0.74, 1.96)	4.5 (2.5, 31.9)
Time to heal (days)	Becaplermin: 85 days NaCMC: 98 days	SWC: 141 days	No statistically significant differences between the groups.	
Change in evaluation ulcer scores relative to baseline:	Relative change: Becaplermin: -1.26 NaCMC: -1.04	Relative change: SWC: -0.49		NaCMC: 10.4 (4.1-infinite)
Ulcer related adverse effects:	Adverse effects: Becaplermin: 7/34=20.6% NaCMC: 19/70= 27.1%	Adverse effects: SWC: 25/68=36.7%	Becaplermin vs SWC: RR = 0.5 (0.2, 1.1) NaCMC vs SWC: RR=0.7 (0.4, 1.2) Becaplermin vs NaCMC: RR = 0.76 (0.35, 1.56)	Becaplermin: 6.2 (3.2-infinite)
Median relative ulcer areas (defined as the target ulcer are at a given visit divided by the baseline target ulcer area):	NaCMC: 0.31 Becaplermin: 0.13	Control: 0.28		
	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms	

Harms (NNH) [24]

95% CI [25]

Becaplermin: 6.2 (3.2-infinite)

Any other adverse effects [28] Adverse effects were similar in all three groups. A total of 4 patients died during the study (2 from control, 1 from NaCMC group and 1 from the becaplermin group). The authors did not state the cause of death and reported that the deaths were not related to study. Non-wound-related serious adverse effects were reported in 31% in controls, 24% in NaCMC group and 32% in the becaplermin group.

EXTERNAL VALIDITY

Generalisabilty [29] A multi-centre trial with a good generalisability

Applicability [30] The reported death of 4 patients is concerning since no information was provided for reason of deaths. It is hard to decide whether the benefits may outweigh harms.

Comments [31]

<table>
<tr><td colspan="3">STUDY DETAILS</td></tr>
<tr><td colspan="3">Reference [1] Ennis, W. J., P. Foremann, et al. (2005). "Ultrasound therapy for recalcitrant diabetic foot ulcers: results of a randomized, double-blind, controlled, multicenter study." Ostomy Wound Manage 51(8): 24-39.</td></tr>
<tr><td colspan="3">Affiliation/source of funds [2] Wound Treatment Program, Advocate Christ Medical Center, Oak Lawn, IL, USA. Source of funding is not stated</td></tr>
<tr><td>Study design [3] RCT</td><td>Level of evidence [4] II</td><td>Location/setting [5] Multi centre study: 17 outpatient wound private clinics and 13 were university hospital clinics. The sites were distributed across the United States and one was in Canada</td></tr>
<tr><td colspan="2">Intervention [6] Patients with diabetic foot ulcers underwent baseline debridement to remove all callus/necrotic tissue and were treated with active ultrasound device three times per week for 4-minute treatment intervals. A full clinical assessment including wound photography, tracing, and a limited physical exam was performed once per week at each assessment visit. Debridement was performed if considered clinically necessary by the investigator at each weekly assessment; + Standard wound care (with saline-moistened gauze, covered by a layer of dry gauze, an optional layer of Vaseline gauze, and a roll gauze wrap. Complete dressing changes occurred three times a week at the clinic treatment site and on alternate days.
Sample size [7] 70 (ITT) but only 27 patients (efficacy population)</td><td>Comparator(s) [8] Patients with diabetic foot ulcers underwent baseline debridement to remove all callus/necrotic tissue and were treated with sham device three times per week for 4-minute treatment intervals. A full clinical assessment including wound photography, tracing, and a limited physical exam was performed once per week at each assessment visit. Debridement was performed if considered clinically necessary by the investigator at each weekly assessment; + Standard wound care (with saline-moistened gauze, covered by a layer of dry gauze, an optional layer of Vaseline gauze, and a roll gauze wrap. Complete dressing changes occurred three times a week at the clinic treatment site and on alternate days.

Sample size [9] 63 (ITT) but only 28 patients (efficacy population)</td></tr>
<tr><td colspan="3">Selection criteria
Inclusion criteria – Patients with diabetes (either Type 1 or Type 2) and a chronic diabetic foot ulcer (>30 days in duration) were eligible to participate if they met the additional inclusion criteria. Eligible patients had to be at least 18 years of age and have a recorded glycosylated hemoglobin value of ≤12 within 30 days of the study start date. Only Wagner grade 1 or 2 ulcers on the plantar surface of the foot without exposure of bone, muscle, ligaments or tendons were considered. The patients had no clinical signs of infection and were not taking antibiotics at the time of enrolment. An ankle brachial index (ABI) was calculated for each potential participant with a study target value between 0.65 and 1.2. In order to qualify for study participation, the toe/brachial index had to be ≥0.7. All wounds in this study by definition were required to be >1 cm^2 and <16 cm^2 in size. If the patient had multiple wounds on the foot, the largest wound, with no other wound within 2 cm, which still met all study enrolment criteria, served as the index wound. Patients were required to be ambulatory at least 75% of the time with weight bearing on the index foot.
Exclusion criteria – The patients were excluded according to the following criteria: Ulcers were secondary to non-diabetic aetiology; gangrene was located anywhere on the index foot; patient received chemotherapy or radiation within the past 6 months; any oral, intravenous, or topical antibiotic use within the past 7 days; any use of cytokine or growth factor in the past 7 days; significant medical condition (other than diabetes) that would impair healing, including liver disease, malignancy, malnutrition, anaemia, or scleroderma; patients with known or suspected osteomyelitis; wounds that would require surgical correction in order for the index ulcer to heal (e.g. bony prominence, deformed foot); use of corticosteroids or immunosuppressive drugs 7 days before the study or if anticipated that patient would require during the course of the study; patients on renal or peritoneal dialysis; history of, or current use of alcohol, or drugs; patients in whom offloading device is contraindicated or who cannot be appropriately fitted; patients with known HIV status, hepatitis, cancer, or bleeding disorder.</td></tr>
</table>

Patient characteristics [10] Intervention group – Comparator group(s) –

These baseline characteristics are of the efficacy population and not of all the ITT population

	Ultrasound (N=27)	Sham (N=28)
Mean age, (SD)	56 (11)	54 (12)
Male %	48%	68%
White race% Black race% Hispanic race%	63% 30% 7%	71% 21% 7%
Never smoked % Current smoker % Past smoker %	67% 15% 19%	68% 18% 14%
Body Mass Index (kg/m^2)	34.57 (1)	35.30 (1)
Baseline HbA1c (mean)	9.4	8.4
Mean duration of ulcer, weeks (SD) Range	35 (32) 5-104	67 (108) 4-521
Mean ulcer area, cm^2 (SD) Range	1.7 (0.8) 1.0-3.8	4.4 (4.0) 1.0-14.5
Mean granulation tissue at baseline	2.19	2.11

Length of follow-up [11]	Outcome(s) measured [12]
Until the wound healed or 12 weeks of therapy. Patients whose wounds were confirmed healed were followed monthly for 3 months to monitor their healing status and record recurrences.	Wound closure defined as complete epithelialization without drainage

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Based on a computer-generated randomization table	Similar	Double blinded study	Similar	Drop outs: Ultrasound:43/70=61% Sham: 35/63=55.6% Both efficacy and ITT analyses were done

Overall quality assessment (descriptive) [18] Of Good quality, a multi-centre, double blind RCT. However, the huge drop outs, the loss to follow up and the unclear protocol violations that resulted in a final population of 55 patients for the efficacy analysis group, all devalues the quality of this study. (It is not totally clear how the authors ended up with the final efficacy study group).

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Closure of wound: Efficacy group: ITT:	11/27=40.7% 18/70=26%	4/28=14.3% 14/63=22%	Efficacy group: RR= 2.85 (1.11-7.86) ITT: RR=1.16 (0.63-2.13)	Efficacy group: 3.78 (2.33-34.22) ITT: 28.64 (5.64-inf)
Time to heal weeks (efficacy analysis):	Mean: 9.12(±0.58) Median: 11 (±0)	Mean: 11.74(±0.22) Median: 12 (±0.82)	Log rank test=0.0144	Harms (NNH) [24] 95% CI [25] Adverse events: Mild: 4.74 (2.96-17.4) Moderate: 6.70 (3.20-inf) Severe: 13.13 (5.54-inf)
Adverse events: (ITT) Mild % Moderate % Severe%	57/70=81% 46/70=65.7% 8/70=11.4%	38/63=60.3% 32/63=50.8% 12/63=19.0%	Adverse events: Mild: RR= 1.35 (1.08-1.65) Moderate: RR= 1.29 (0.97-1.73) Severe: RR=0.60 (0.26-1.34)	
Re-ulceration of healed wounds (efficacy analysis)	1/11=9.1%	0/4=0%	P=0.533	

Clinical importance (1-4) [26]	Relevance (1-5) [27]
2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.	1 Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms

Any other adverse effects [28] Pain, erythema, ulcer enlargement and other adverse events were reported in both the ultrasound and sham treatments. Ulcer infection, additional ulceration, blistering and oedema were reported in the ultrasound group and not in the sham treatment.
EXTERNAL VALIDITY
Generalisabilty [29] Good generalisability for the ITT group
Applicability [30] Benefits do not outweigh harms. No benefits were proven in the ITT analysis and the harms of the ultrasound treatment may outweigh its benefits.
Comments [31]

STUDY DETAILS

Reference [1] "A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds." Annals of vascular surgery 17(6): 645-9.

Affiliation/source of funds [2] No financial support was provided. Affiliation: Division of vascular surgery, Medical college of Wisconsin, WI, USA.

Study design [3]	Level of evidence [4]	Location/setting [5]
Crossover randomised controlled trial; same patients were their own controls.	II	Froedtert Memorial Lutheran Hospital and the Clement J. Zablocki Veterans Affairs Medical Centre in Milwaukee, WI, USA

Intervention [6]	Comparator(s) [8]
Healing of diabetic foot wounds by using the Vacuum Assisted Closure device (VAC) according to manufacturer's instructions and subjected to -125 mmHg continuous negative pressure for 2 weeks prior to cross-over. Sample size [7] 10 diabetics (who were their own controls)	Healing of diabetic foot wounds by using conventional moist dressings with a hydrocolloid wound gel for 2 weeks. Then crossing-over to receive other treatment for another 2 weeks. Sample size [9] Same10 diabetics treated with the VAC

Selection criteria

Inclusion criteria – Diabetics from the two centres who had significant soft tissue damage and who were willing to provide informed consent.

Exclusion criteria – Previous treatment with growth factors or hyperbaric oxygen within 30 days before study, presence of malignancy or necrotic tissue in wound, osteomyelitis and health plans that do not cover VAC therapy or wound follow-up.

Patient characteristics [10]

Intervention group – Five males and 1 female; no other characteristic was given, thus a very low external validity.

Comparator group(s) –

Length of follow-up [11]	Outcome(s) measured [12]
4 weeks with weekly assessments	Wound dimensions, and surface area were determined by comparing digital photographs of the wounds.

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
A random number generator was used to allocate patients to either of the treatments. The allocation was not concealed. All subjects got both treatments each for a period of two weeks.	Patients were their own controls with no time interval between the two interventions.	The assessment of outcomes was determined in a blinded fashion.	The subjects were treated and measured the same during both sessions.	Four out of the 10 patients dropped out. Intention to treat analysis was not done.

Overall quality assessment (descriptive) [18]

A study with a rather very small sample, that started with 10 and ended up with 6 patients. The characteristics of the patients are not known. Intention to treat analysis was not performed. Although it was assessor-blinded, the study is of moderate quality.

RESULTS

Outcome [19]	Intervention group [20] Enrolment	Vs Termination	P value	Control group [21]	Measure of effect/effect size [22]	Benefits (NNT) [23]
Wound length	7.7 ± 0.6	6.9 ± 1.3	NS	-	Percent change 95% CI [25]	Overall benefit seen in reduction in depth of wound. 95% CI [25]
Width	3.5 ± 0.6	3.1 ± 0.7	NS			Harms (NNH) [24]
Depth	3.1 ± 0.9	1.2 ± 0.3	<0.05			Harm was reported for one patient. Treatment was discontinued. 95% CI [25]

Treatment type	Length % change	Width % change	Depth % change	Area % change	Volume% change
VAC	-4.3 ± 4.7	-12.9 ± 5.2	-49 ± 11.1	-16.4 ± 6.2	-59 ± 9.7
Moist dressing	6.7 ± 11.5	2.4 ± 7.5	-7.7 ± 5.2	5.9 ± 17.4	-0.1 ± 14.7
P	NS	NS	<0.05	NS	<0.005

	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.	Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes
Any other adverse effects [28] none		
EXTERNAL VALIDITY		
Generalisabilty [29] Cannot be generalised to other patients. The characteristics of the small sample are not known. The patients who could not afford the treatment (i.e. low socioeconomic class) were excluded.		
Applicability [30] The potential benefits may outweigh the potential harms		
Comments [31] Besides the points made above, the researchers had no time-gap between the two treatments and it is not possible to know if both treatments interacted together for example if they had a synergistic effect. From the study the appropriate duration of the treatment cannot be assessed.		

STUDY DETAILS

Reference [1] Etoz, A., Y. Ã–zgenel, et al. (2004). "The use of negative pressure wound therapy on diabetic foot ulcers: a preliminary controlled trial." Wounds: A Compendium of Clinical Research & Practice 16(8): 264-269.

(Etoz & Kahveci 2007) Etoz, A. and R. Kahveci (2007). "Negative pressure wound therapy on diabetic foot ulcers." Wounds-a Compendium of Clinical Research and Practice 19(9): 250-254.

Affiliation/source of funds [2] The Medical Faculty of Uludog University, Gorukle, Bursa, Turkey. Sources of funding were not stated.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] One medical centre in Bursa, Turkey.

Intervention [6] Diabetic patients with non-healing wounds of the lower extremity were assigned to Negative pressure Wound Therapy (NPWT) using a medical aspirator pump set at 125 mmHg continuous pressure, after debridement of wound. Sample size [7] 12 patients	Comparator(s) [8] Diabetic patients with non-healing wounds of the lower extremity were assigned to Saline-moisturised gauze dressings after debridement of wound. Sample size [9] 12 patients

Selection criteria

Inclusion criteria – Diabetic patients with non-healing wounds of the lower extremity, no other inclusion or exclusion criteria were provided.

Exclusion criteria – not stated

Patient characteristics [10]

Intervention group – Comparator group(s) –

	NPWT	Control	P value
Age mean (range)	66.2 (54-77)	64.7 (56-74)	0.506
Male %	83.3%	91.7%	0.537
Ulcer surface area cm^2	109	94.8	0.729
Vascular dysfunction %	25%	16.7%	0.615
Renal failure	8.3%	0%	0.307

Length of follow-up [11] Not stated. The authors said that the wounds were followed until the wound beds approached nearly total granulation	Outcome(s) measured [12] Decrease in wound surface area, length of therapy (days)

INTERNAL VALIDITY

Allocation [13] Randomisation according to odd or even number system in the hospital done by a blinded official.	Comparison of study groups [14] Similar to known baseline characteristics. All patients were treated with similar antibiotic prophylaxis protocols.	Blinding [15] Not blinded	Treatment/ measurement bias [16] The authors did not state method of measuring wound surface area. They stated that the wound was measured every 48 hours. The assessor was not blinded.	Follow-up (ITT) [17] All patients were followed until some granulation appeared. No drop outs were reported.

Overall quality assessment (descriptive) [18] Of average quality; non blinded RCT, the selection of patients was not clear and explicit inclusion and exclusion criteria were not stated; length of follow-up not clear and not even for all patients; and the assessment of the wound surface area was subjective without using a validated tool and the assessor was not blinded

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] - 95% CI [25]
Mean decrease in wound surface area (SD):	19.5 cm^2 (11.7)	9.5 cm^2 (4.11)	p=0.032	Harms (NNH) [24] - 95% CI [25]
Length of therapy time (days):	11.25 (5.5)	15.75 (2.5)	p=0.05	
Closure of ulcer by primary intention (Skin grafting):	10/12=83.3%	9/12=75%	RR = 1.11 [0.77, 1.49] p=0.615	

	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.	Relevance (1-5) [27] 2 Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention.
Any other adverse effects [28] Bleeding was reported in the treatment group. No infection was reported.		
EXTERNAL VALIDITY		
Generalisabilty [29] The groups were predominantly male, and the denominator from whom the patients were selected is unknown. The study was performed in one centre. The generalisability is poor.		
Applicability [30] No significant benefits were seen given the poor quality of the study and the non-blinded study.		
Comments [31]		

STUDY DETAILS

Reference [1] Fife, C., J. T. Mader, et al. (2007). "Thrombin peptide Chrysalin((R)) stimulates healing of diabetic foot ulcers in a placebo-controlled phase I/II study." Wound Repair and Regeneration 15(1): 23-34.

Affiliation/source of funds [2] Department of biochemistry and Molecular Biology, The University of Texas Medical Branch. Sponsoring by Chrysalis Bio Technology Inc., Galveston, TX, USA.

Study design [3] Placebo-controlled 3-arm RCT	Level of evidence [4] II	Location/setting [5] A multi-centre-study at four medical centres in Texas, USA.

First Arm: Intervention [6] Dressing of TP508 1 ug Chryssalin in saline Sample size [7] 20 Second arm: Dressing of TP508 10 ug Chryssalin in saline Sample size: 18	Third arm: Comparator(s) [8] Saline dressing alone Sample size [9] 21

Selection criteria

Inclusion criteria –Ulcers with diameters that ranged from 1 to 7cm, present for more than 8 weeks, classified as Wagner Grades I, II, or early III.

Exclusion criteria –Clinical infection, osteomyelitis, poor diabetes control, renal failure, abnormal liver function, treatment with steroids, cancer, treatment with chemotherapy or radiation, history of drug or alcohol abuse and wound oxygen tension of <20 mmHg. Pregnant or nursing women were also excluded. Ulcers with an advanced Wagner III grade (with erosion of bone or tendon) were excluded.

Patient characteristics [10]Intervention group – Comparator group(s) –

	Saline (control)	1 ug group	10ug group
Male%	71	70	78
Caucasian % Black Hispanic Other	52 29 14 5	60 20 20 0	61 11 28 0
Mean age, (SD)	55.7 (12.8)	59.3 (6.4)	53.4 (10.5)
Median age	54.7	59.6	53.7
Weight (lbs) mean (SD) Median	196.3 (77.3) 203.5	206.5 (41.8) 211.0	229.5 (58.8) 220.0
Ulcer are cm^2, (SD) Median Range	4.11 (5.99) 1.63 0.16-26.46)	3.59 (5.31) 1.21 0.27-24.36	3.15 (3.20) 2.02 0.14-13.10

Length of follow-up [11] Twice-weekly visits till 20 weeks or till ulcer healed.	Outcome(s) measured [12] Healing of ulcer assessed by digital photography; Time to 100% and 80% ulcer closure; and wound healing rate (WHR) expressed in mm/day and expresses the average closure per day excluding any area removed by debridement.

INTERNAL VALIDITY

Allocation [13] Method of randomisation is not stated.	Comparison of study groups [14] Groups seemed to have similar basic characteristics. Other differences such as co-morbidity, ulcer duration, diabetes duration and control could have affected the results if these were different between the arms.	Blinding [15] Done but not elaborated.	Treatment/ measurement bias [16] Assessor was blinded to treatment. Measurement was similar in all groups.	Follow-up (ITT) [17] The primary population was 59 patients but the trial was complete for 35 patients (35/60=58.3%). 17/39=43.5% of both intervention groups; and 8/21=38% of controls. ITT was applied.

Overall quality assessment (descriptive) [18] Of moderate quality, placebo controlled double blind RCT. Full participation was low but an ITT analysis was done. Methods of randomisation were not reported. Subset analysis was done post hoc, therefore the results must be regarded with caution.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/ effect size [22,25] 95% CI [	Benefits (NNT) [23]
Complete foot ulcer closure at 20 wks:				
<u>All ulcers:</u>				
1 µg group:	11/20 (52%)	10/21 (48%)	RR = 1.16 [0.64, 2.07]	
10 µg group:	11/18 (61%)		RR = 1.28 [0.72, 2.20	
<u>Foot ulcers:</u>				
1 µg group:	9/12 (75%)	4/13 (31%)	RR 2.44 [1.10, 4.97]	NNT = 3 [1, 20]
10 µg group:	7/10 (70%)		RR 2.28 [0.96, 4.82]	
1 µg + 10 µg	16/22		RR= 2.36 [1.15, 4.48]	NNT= 2 [1,13]
<u>Heel ulcers:</u>				
1 µg group:	3/3 (100%)	0/5 (0%)		Harms (NNH) [24] - 95% CI [25]
10 µg group:	3/4 (75%)			
1 µg + 10 µg	6/7 (86%)		RR not calculable; p < 0.03	
Median time to 100% ulcer closure				
<u>All ulcers:</u>				
1 µg group:	122 days	>140 days	p > 0.05	
10 µg group:	87 days		p > 0.05	
<u>Foot ulcers:</u>				
1 µg group:	94 days	>140 days	p > 0.05	
10 µg group:	71.5 days		p < 0.05	
Wound healing rate				
<u>Foot ulcers:</u>				
1 µg group:	0.089 mm/day	0.058 mm/day	p > 0.05l	
10 µg group:	0.104 mm/day		p < 0.05	
<u>Heel ulcers:</u>				
1 µg + 10 µg	0.106 mm/day	0.040 mm/day	p < 0.02	
	Analysis on foot ulcers revealed significant results: The WHR for foot ulcers treated with saline, 1 and 10 ug Chrysalin was 0.058, 0.089 and 0.104 mm/day, respectively. The 10-ug Chrysalin showed an increase in healing rate of 80% compared to saline. The WHR for heel ulcers treated with saline, 1 and 10 ug Chrysalin and combined was 0.04, 0.081, 0.106 and 0.095 mm/day. versus saline, 10 ug Chrysalin and combined were both significant p<0.05.			
	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes.	
Any other adverse effects [28] Erythema, edema and pain. Serious adverse events were reported in 24% of saline group, and 22% of the 10ug group, and 20% in the 1 ug group. Overall 14 patients from the primary study population due to serious side effects such as infection, osteomyelitis and other general problems. The investigators reported that none of the serious side effects seemed drug-related.				
EXTERNAL VALIDITY				
Generalisabilty [29] Good				
Applicability [30] Benefits may not outweigh harms. The findings are not statistically significant. The effect size is not big. Serious side effects were reported.				
Comments [31] The safety of the drug is questionable (although the researchers stated that it was safe), due to the relatively high proportion of patients who had serious side effects including osteomyelitis and other serious infections.				

<table>
<tr><td colspan="5">STUDY DETAILS</td></tr>
<tr><td colspan="5">Reference [1] Foster, A. V. M., M. T. Greenhill, et al. (1994). "Comparing two dressings in the treatment of diabetic foot ulcers." Journal of Wound Care 3(5): 224-228.</td></tr>
<tr><td colspan="5">Affiliation/source of funds [2] Department of Medicine, Manchester Royal Infirmary, University of Manchester, UK. Funding was provided by Wright Medical Technology, Arlington, Tenn., USA and McGhan Limited, Arkow, Ireland.</td></tr>
<tr><td colspan="2">Study design [3] RCT</td><td colspan="2">Level of evidence [4] II</td><td>Location/setting [5] Manchester Diabetes Centre, UK.</td></tr>
<tr><td colspan="3">Intervention [6] Allevyn, a hydrophilic polyurethane foam dressing used as the primary dressing with standard wound care
Sample size [7] 15</td><td colspan="2">Comparator(s) [8] Kaltostat, a calcium-sodium alginate dressing used as the primary dressing with standard wound care
Sample size [9] 15</td></tr>
<tr><td colspan="5">Selection criteria
Inclusion criteria – Age at least 18, had a clean diabetic foot ulcer and were willing to comply to study protocol.
Exclusion criteria – If ulcer was sloughy, necrotic or infected.</td></tr>
<tr><td colspan="5">Patient characteristics [10]
Intervention group – N=15, mean age 61 years, 80% male (n=12), 20% female, (n=3), 40% (n=6) insulin dependent, 60% (n=9) non-insulin dependent, mean duration of ulcer 107 days, mean area of ulcer 88mm^2,
Comparator group(s) – N=15, mean age 70 years, 53% male (n=8), 47% female (n=7), 27% (n=4) insulin dependent, 73% (n=11) non-insulin dependent, mean duration of ulcer 170 days, mean area of ulcer 79mm^2,
No significant differences were reported between study and control arms in terms of age, sex, or ulcer duration. Other characteristics such as co-morbidity, obesity and levels of haemoglobin A1c (for diabetes control) were not provided.</td></tr>
<tr><td colspan="4">Length of follow-up [11] Eight weeks or until the ulcer was totally healed, whichever occurred first Patients were followed on a weekly basis where ulcers were debrided healing was assessed.</td><td>Outcome(s) measured [12] Ulcer time to heal.</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13] Stratified randomisation by type of lesion and if caused by trauma.</td><td>Comparison of study groups [14] Bias could have been introduced by some disparities in baseline characteristics such as duration of ulcer, age and other factors. We are not told if the analysis controlled for the differences.</td><td>Blinding [15] Trial was not blinded.</td><td>Treatment/ measurement bias [16] Was similar in all patients.</td><td>Follow-up (ITT) [17] 4/15=26.7% from controls dropped out. ITT was not done.</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18]
Satisfactory to poor. No blinding was done, no adjustment for baseline characteristics, no ITT.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td rowspan="4">Outcome [19]
Number of ulcers healed and time to heal.

Number of ulcers healed by the end of the 8 week study period

Adverde events (harms)</td><td rowspan="4">Intervention group [20] Control group [21]
No differences were observed in the clinical effectiveness of the intervention dressing compared to the control. Number of ulcers healed and times to healing were similar for both groups. However, the ease of use of the intervention dressing was more than that of the control.

Total population 57% (17/30)
Intervention 60% (9/15)
Control 53% (8/15)
No data was provided concerning times to healing; just a Kaplan Meier graph showing that no difference was found in time to heal in both groups.

Intervention 0% (0/15) Control 27% (4/15)</td><td rowspan="4">Measure of effect/effect size [22]
No difference
95% CI [25]
No difference

RR 1.13 [95% CI 0.61, 2.10]

RR = 0.00 [0.00, 0.83]</td><td>Benefits (NNT) [23] -
95% CI [25]</td></tr>
<tr><td>Harms (NNH) [24] -
95% CI [25]</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td colspan="2"></td></tr>
<tr><td></td><td>Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.</td><td colspan="2">Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes</td></tr>
<tr><td colspan="5">Any other adverse effects [28]
An infection developed in one patient from the control group.</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
</table>

Generalisabilty [29] Moderate
Applicability [30] No benefit was seen.
Comments [31] Significant advantages of the intervention dressing were identified however they were not relevant to the clinical outcome criteria of this study

STUDY DETAILS

Reference [1] Ha Van, G., H. Siney, et al. (1996). "Treatment of osteomyelitis in the diabetic foot. Contribution of conservative surgery." Diabetes Care 19(11): 1257-60.

Affiliation/source of funds [2] Department of Diabetology and Metabolism, Saint Vincent-de-Paul Hospital, Paris, France. Funding is not stated.

Study design [3]	Level of evidence [4]	Location/setting [5]
Two single arm study	III -3	Saint Vincent-de-Paul Hospital, Paris, France

Intervention [6]	Comparator(s) [8]
diabetes patients with foot osteomyelitis treated with conservative orthopaedic surgery, resection of infected part of the phalanx or metatarsal bone under the wound plus antibiotic treatment, offloading, and wound care for diabetic foot ulcers Sample size [7] 32 diabetics	retrospectively diabetes patients with foot osteomyelitis treated with antibiotic treatment, offloading and wound care for diabetic foot ulcers. Sample size [9] 35 diabetics

Selection criteria

Inclusion criteria – For the intervention group: patients with diabetic ulcers and osteomyelitis treated between September 1993 and March 1995 who received a conservative surgical treatment in addition to the medical treatment. The conservative surgical treatment was defined as a limited resection of the infected part of the phalanx or the metatarsal bone under the wound, with no other resection. The controls were diabetic patients followed retrospectively with foot ulcers and osteomyelitis admitted between 1982 and 1993 and were treated without any surgery but with the same medical treatment as the intervention group.

No other selection criteria were provided.

Exclusion criteria – Patients with severe peripheral vascular disease requiring immediate peripheral vascular bypass were excluded.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention group	controls	P value
Age	60.3 ± 10	59.4 ± 10.4	ns
Men (n)	25	29	0.047
NIDDM (n)	26	23	ns
Diabetes duration	15.6 ± 11.3	18.3 ± 11.6	ns
HbA1c	7.6 ± 1.9	8.1 ± 1.6	ns
Retinopathy (n)	24	26	ns
Renal insufficiency (n)	13	9	ns
Plasma creatinine	131 ± 151	172 ± 249	ns
Ischemic heart disease (n)	6	8	ns
History of past foot leasion (n)	22	23	ns
Plantar wound (n)	14	10	ns
Toe wound (n)	21	22	ns
Neuropathy (n)	31	29	ns
Peripheral vascular disease (n)	19	15	ns

Length of follow-up [11]	Outcome(s) measured [12]
Not clear! The authors said that each ulcer was followed from onset till healing or failure (marked by surgery). However, it is not clear when follow-up ceased. What happens to a patient from the intervention group who's ulcer does not heal? The authors do not clarify the exact time that all were followed. From the Kaplan Meier graph, one could see that for both groups, follow-up ended around 500 days after onset of ulcer, though this does not clarify if a certain date was set to assess the outcomes.	Rate of healing and duration of healing

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Not randomised. Selection bias cannot be excluded.	Similar in basic characteristics except for gender ratio.	Not done.	Done from medical reports for both groups. However, one cannot exclude differences in reporting in surgical and non-surgical patients. Therefore, information bias cannot be excluded.	All were followed up from chart reviews. Lost to follow-up was not reported.

<table>
<tr><td colspan="5">Overall quality assessment (descriptive) [18] The groups were both historic and the allocation was not random. Selection bias cannot be excluded. The follow-up period was not clear. The study relied on reported data from charts and thus information bias cannot be excluded. One important thing differed between the groups: a different orthopaedic surgeon was employed for the intervention group. This implies that the physicians treating both groups were different and this was not adjusted for. Furthermore, no other adjustment was done besides sex and duration of antibiotic treatment. Given the stated reasons, the study of poor to moderate quality.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td rowspan="2">Outcome [19]

Proportions healed:
Days of healing:
Duration of antibiotic treatment (days)</td><td>Intervention group [20]
25/32=78%
181 ± 30

111 ± 121</td><td>Control group [21]

20/35=57%
462 ± 98

246.9 ± 232</td><td rowspan="2">Measure of effect/effect size [22] 95% CI [25]
RR= 1.37 (0.97-1.81)
P for days of healing: <0.008
P for days of antibiotic treatment: <0.007</td><td>Benefits (NNT) [23]
4.8 (2.5-infinite)
95% CI [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.</td><td>Harms (NNH) [24]
-
95% CI [25]</td></tr>
<tr><td colspan="5">Any other adverse effects [28] None</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] To be generalised only to patients with diabetic ulcers and with osteomyelitis and without serious peripheral vascular disease. However, it is not clear if the patients included in the study comprised all of these patients. Generalisability is moderate.</td></tr>
<tr><td colspan="5">Applicability [30] The potential benefits may outweigh potential harm given that the study was properly conducted, but because of the possible flaws in study design, caution must be regarded in interpreting the results.</td></tr>
<tr><td colspan="5">Comments [31]</td></tr>
</table>

STUDY DETAILS

Reference [1] Horswell RL, Birke JA, Patout CA Jr. A staged management diabetes foot program versus standard care: a 1-year cost and utilization comparison in a state public hospital system. Arch Phys Med Rehabil 2003;84: 1743–6.

Affiliation/source of funds [2] Department of Public Health and Preventive Medicine, Louisiana State University Health Sciences Center, Baton Rouge, LA, USA; Diabetes Foot Program, Louisiana State University Health Sciences Center, Baton Rouge, LA, USA.

Study design [3]	Level of evidence [4]	Location/setting [5]
Nonrandomized retrospective study	III - 3	Louisiana public hospital system, USA.

Intervention [6]	Comparator(s) [8]
Diabetic patients with diabetes foot ulcer who received staged management foot care: Staged management of foot ulcers consisted of devices to offload pressure; self-care education; and, after healing, custom-fabricated orthoses and footwear, and monitored progressive ambulation Sample size [7] 45 patients	Diabetic patients with diabetes foot ulcer who received standard foot care that included wound care, antibiotics, and self-care education. Offloading devices for ulcer healing, prescription footwear, and custom-fabricated orthoses were generally not available for the controls. Sample size [9] 169 patients

Selection criteria

Inclusion criteria – To be included in the intervention group a patient had to have been diagnosed with diabetes mellitus, must have visited the Diabetic Foot Program (DFP) in 1998 (in the Louisiana State University Health Care Services Division) and must have had an active foot ulcer on his/her initial visit to the DFP. No distinction was made between new or recurrent foot ulcer. For each patient, the baseline time period was defined as the 240 days before the patient's initial visit to DFP, while the follow-up period was as the 365 days immediately after that first visit. Patients also must have had a non-DFP outpatient visit at any time at any of the State hospitals in both the baseline and follow-up period.

Patients eligible for inclusion in the comparison group were those with an outpatient foot ulcer diagnosis (code 707.1 of the International Statistical Classifications of Diseases, 9th Revision, Clinical Classifications (ICD-9-CM) and a diagnosis of diabetes appearing in the administrative database at any time of the in the Louisiana State University Health Care Services Division hospitals between March and December 1998. No distinction was made between new or recurrent ulcer. Also the patient must not have visited the DFP at any time between March 1998 and December 1999. Patient's baseline year was defined as the 240 days before the diagnosis date, whereas the follow-up time period was defined as the 365 days immediately after this date. Patients also must have had a non-DFP outpatient visit at any time at any of the State hospitals in both the baseline and follow-up period.

Exclusion criteria – Not stated separately

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention N=45	Control N=169
Mean age, years	55.4	53.8
Female %	60%	53%
African American %	73%	72%
Fraction uninsured %	40%	51%
Comorbid vascular *	0.20	0.24
Comorbid neurologic *	0.11	0.14
Comorbid renal *	0.16	0.10
Comorbid eye *	0.47	0.38
Foot related hospitalizations *	0.31	0.32
Foot related inpatient days *	3.36	1.97
Foot related inpatient charges *	$3025	$3481
Amputation hospitalizations *	0.18	0.18
Emergency department visits *	0.82	0.77
Emergency department charges *	$142	$134
Outpatient visits * +	4.32	3.85
Outpatient charges * +	$781	$700
Total charges * ±	$5079	$5389

* (Rate per patient based on 8 months baseline before treatment)
+ (Includes all-cause outpatient encounters, excluding the emergency department)
± (Includes all-cause outpatient, ambulatory surgery, and foot-related inpatient charges)

Length of follow-up [11] One year	Outcome(s) measured [12] Foot-related inpatient hospitalizations, number of amputation-related hospitalizations, total number of foot-related inpatient days, total charges for foot-related inpatient hospitalizations, all-cause outpatient visits, total charges for all-cause outpatient visits, and combined outpatient and foot-related inpatient charges			
INTERNAL VALIDITY				
Allocation [13] Not randomised	Comparison of study groups [14] Similar	Blinding [15] Not blinded	Treatment/ measurement bias [16] Similar	Follow-up (ITT) [17] All were followed through chart review
Overall quality assessment (descriptive) [18] Of moderate quality; analysis was controlled for baseline characteristics of both groups. However, during a period of 1 year, the patients could have sought care outside the Louisiana State University Health Care Services Division hospitals and these visits are not included in the analysis. Another issue of concern is possible differences in the duration of ulcer between the groups: in the intervention group, the duration of ulcer was not known and follow-up time started from the initial visit to the DFP, whereas in the controls the follow-up started from the diagnosis of the ulcer. The intervention group could have had their ulcer much longer than the controls and this was not controlled for.				
RESULTS				
Outcome [19] Foot-related: Hospitalization rate: Inpatient days: Inpatient charges: Amputation-related hospitalizations: Emergency department visits: Emergency department charges: Lower total charges: Outpatient visits: Outpatient charges:	Intervention group [20] 0.09 admissions per person 0.91days per person $1321 per person 0.04 per person 0.60 visits per person $104 per person $4776 per person 24.91 per person $2169 per person	Control group [21] 0.50 admissions per person 3.97days per person $5411 per person 0.19 per person 1.22 visits per person $208 per person $9402 per person 8.04 per person $1471 per person	Measure of effect /effect size[22] 95% CI [25] Hospitalization: *P*=.0002 Inpatient days: *P*=0.0289 Charges: *P*=0.0151 Amputation –related hospitalization: *P*=0.0351 Emergency department visits: *P*=0.0043 Emergency department charges: *P*=0.0057 Total charges: *P*=0.0141 Outpatient visits: *P*<0.001 Outpatient charges: *P*<0.001	Benefits (NNT) [23] - 95% CI [25] Harms (NNH) [24] - 95% CI [25]
	Clinical importance (1-4) [26] 1 A clinically important benefit for the full range of plausible estimates.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	
Any other adverse effects [28] None stated				
EXTERNAL VALIDITY				
Generalisabilty [29] Moderate generalisability. Both the intervention and control groups were made up of predominantly black Americans.				
Applicability [30] The benefits could outweigh the harms.				
Comments [31]				

STUDY DETAILS

Reference [1] Houghton, P. E., C. B. Kincaid, et al. (2003). "Effect of electrical stimulation on chronic leg ulcer size and appearance." Physical Therapy 83(1): 17-28.

Affiliation/source of funds [2] University of Western Ontario, Ontario, Canada; University of Michigan-Flint, Flint, Mich. USA; St Joseph's Health Care London, Ontario, Canada. The study was supported by The Victoria Hospital Foundation.

Study design [3] RCT	**Level of evidence** [4] II	**Location/setting** [5] Outpatient diabetic clinic in Ontario, Canada.

Intervention [6] Patients with chronic ulcers treated with high voltage pulsed current (HVPC) for 45 minutes, 3 times weekly, for 4 weeks + standard wound care (nonadherent gauze pads, hydrogels, hydrocolloids, and absorbent foam dressings) + relief of pressure **Sample size** [7] 14 patients	**Comparator(s)** [8] Patients with chronic ulcers treated with sham treatment for 45 minutes, 3 times weekly, for 4 weeks + standard wound care (nonadherent gauze pads, hydrogels, hydrocolloids, and absorbent foam dressings) + relief of pressure **Sample size** [9] 13 patients

Selection criteria (Based on volunteer patients)

Inclusion criteria – Patients with lower leg chronic full-thickness ulcers lasting longer than 3 months; the ulcers could have been caused by diabetes, or by venous or arterial insufficiency; the subject must be under medical treatment to treat the cause of the ulcer

Exclusion criteria – If subject was receiving corticosteroids, radiation, chemotherapy for cancer; and if patients had any of the following: ventricular arrhythmia, atrial fibrillation, use of cardiac pacemaker, history of deep radiation therapy, known deep vein thrombosis or thrombophlebitis, metal implants near the area, pregnancy, or active osteomyelitis.

Patient characteristics [10] **Intervention group – Comparator group(s) –**

	HVPC	Control
Male %	64.3%	61.5%
Mean age (SD)	66.3 (4.8)	62.4 (5.6)
Duration, y (SD)	2.96 (1.4)	4.57 (2.4)
Ulcer size cm^2 (SD)	6.39 (1.85)	5.53 (1.96)
Location of ulcer		
Toe	14.3%	7.7%
Foot	14.3%	15.4%
Ankle/malleolus	42.8%	53.8%
Leg	28.6%	15.4%

	HVPC	Control
Visual analog scale pain score (SD)	1.48 (0.6)	1.16 (0.6)
Sensory impairment %	42.8%	53.8%
Infected ulcer %	57.1%	30.8%
Ankle brachial index (SD)	0.85 (0.1)	0.89 (0.1)
Blood glucose, mmol (SD)	6.53 (0.9)	8.81 (1.8)
Type of ulcer:		
Diabetic	14.3%	23.1%
Arterial	14.3%	0.0%
Venous	50.0%	46.1%
Mixed	21.4%	23.1%

Length of follow-up [11] 2 months: first month was the treatment and the second month was the follow-up	**Outcome(s) measured** [12] Decrease in wound surface area; appearance of wound

INTERNAL VALIDITY

Allocation [13] Randomisation method was not stated	**Comparison of study groups** [14] Similar basic characteristics; not controlled for duration of antibiotic treatment due to existing infection	**Blinding** [15] Double blinded trial	**Treatment/ measurement bias** [16] Similar to both groups, using validated measures of wound tracing and photographing, and Pressure Score Status Tool (PSST) to assess appearance	**Follow-up** (ITT) [17] No drop outs were reported

Overall quality assessment (descriptive) [18] Moderate quality. An ad hoc analysis was made for a sub group.

RESULTS

Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/ effect size** [22] 95% CI [25]	**Benefits** (NNT) [23]
Mean decrease of wound surface area after:				Cannot be assessed
4 weeks:	44.3% ± 8.8%	Around 22.0 %	Not stated	95% CI [25]
8 weeks:	Around 32%	16.0% ± 8.9%	Not stated	**Harms** (NNH) [24]
Total PSST score:	31.7 ± 1.55	28.8 ± 2.1	PSST: *p*=ns	-
				95% CI [25]

	Clinical importance (1-4) [26] 3 The confidence interval does not include any clinically important effects.	Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes
Any other adverse effects [28] None reported		
EXTERNAL VALIDITY		
Generalisabilty [29] Poor generalisability, based on volunteers; although most of the ulcers were in the foot area, a small proportion of these patients were diabetics		
Applicability [30] The benefits do not outweigh the harms. No benefits were seen after the follow-up period. No significant differences were observed between the two groups.		
Comments [31] I had to extract some of the data from the graph in order to have week-comparisons		

STUDY DETAILS

Reference [1] Kästenbauer, T., B. Hörnlein, et al. (2003). "Evaluation of granulocyte-colony stimulating factor (Filgrastim) in infected diabetic foot ulcers." Diabetologia 46(1): 27-30.

Affiliation/source of funds [2] Boltzmann Institute of Metabolic Diseases and Nutrition, and Department of Metabolic Diseases and Nephrology, Hospital Lainz, Vienna, Austria. The study was funded by Amgen Austria.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Diabetic Clinic outpatients, Hospital Lainz, Vienna, Austria

Intervention [6] Diabetics with infected foot ulcers (cellulitis) receiving daily subcutaneous injections of 5 ug/kg granulocyte-colony stimulating factor (G-CSF) + standard treatment of wound + intravenous antibiotics + non weight bearing therapy, [treatment lasted for 10 days]. Sample size [7] 20 patients	Comparator(s) [8] Diabetics with infected foot ulcers (cellulitis) receiving daily subcutaneous injections of placebo + standard treatment of wound + intravenous antibiotics + non weight bearing therapy, [treatment lasted for 10 days]. Sample size [9] 17 patients

Selection criteria Of the 73 patients screened, 36 were eligible

Inclusion criteria – Diabetics with a moderate sized (diameter 0.5-3 cm) infected neuropathic (abnormal 10g-monofilament test) foot ulcer of Wagner's grade 2 or 3, together with palpable foot pulses or normal Doppler ultrasound.

Exclusion criteria – If patient had gangrene, haematological diseases, pancytopenia, neoplasia, and impaired kidney/liver function, recent treatment with cytokines or immunoactive drugs.

Patient characteristics [10] Intervention group – Comparator group(s) –

	G-CSF	Control
Mean Age (SD)	60.8 (11.1)	58.2 (8.1)
Male %	75%	77%
Type 2 diabetes	95%	94%
Diabetes duration, y (SD)	14.7 (8.5)	15.5 (10.6)
Ulcer volume (ul) (SD)	203 (203)	358 (395)

	G-CSF	Control
HbA_{1c} (%)	8.9 (1.7)	9.2 (2.6)
Leukocyte count (10^9*L^{-1}) Day1	8.1 (2.6)	7.7 (1.9)
Baseline CRP ($mg*dl^{-1}$)	1.73 (2.2)	1.71 (2.31)
Wagner grade 1/2/3 (%)	0/75/25	0/82/18

Length of follow-up [11] 10 days during treatment period	Outcome(s) measured [12] Resolution of cellulitis evaluated daily and defined clinically, specified by an infection summary score (ISS)

INTERNAL VALIDITY

Allocation [13] Randomisation method not stated	Comparison of study groups [14] Similar groups at baseline	Blinding [15] Patient blinded, but not assessor blinded	Treatment/ measurement bias [16] All were assessed similarly	Follow-up (ITT) [17] 2/20=10% from G-CSF group, and 1/17=5.9% in control. ITT was applied.

Overall quality assessment (descriptive) [18] Moderate to good quality, mainly due to the assessor-unblinded nature of the study, especially when the evaluation of the outcome was based on a clinical definition.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Reduction in ISS:	From: 29.5 ±18.4 To: 6.7 ± 6.3, p<0.001	From: 26.0 ±14.2 To: 8.9 ± 7.2, p<0.01	Reduction in ISS on day 10: G-CSF vs. control, p value=0.33	No benefit was seen Harms (NNH) [24]-
Complete healing of ulcer after 10 days:	0/20=0%	0/17=0%		
Amputation:	1/20=5%	1/17=5.9%	RR=0.8 (0.09-8.0)	
	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes	

Any other adverse effects [28] Osteomyelitis (one person in control); worsened liver function and skin efflorescence (in two G-CSF patients). Oedema and local erythema were seen in both groups.

EXTERNAL VALIDITY

Generalisabilty [29] Good generalisability to patients with infected diabetic ulcers, though no benefit was found.
Applicability [30] Benefits do not outweigh harms
Comments [31]

<table>
<tr><td colspan="3">STUDY DETAILS</td></tr>
<tr><td colspan="3">Reference [1] Lavery, L. A., K. R. Higgins, et al. (2007). "Preventing diabetic foot ulcer recurrence in high-risk patients - Use of temperature monitoning as a self-assessment tool." Diabetes Care 30(1): 14-20.</td></tr>
<tr><td colspan="3">Affiliation/source of funds [2] Scott & White Hospital, Texas A & M University Health Science Centre, Temple, San Antonio, Texas, USA. Supported by the national Institute of Diabetes and Digestive and Kidney Diseases, national Institutes of Health.</td></tr>
<tr><td>Study design [3] RCT</td><td>Level of evidence [4] II</td><td>Location/setting [5] Multi-centre, San Antonio, Texas, USA</td></tr>
<tr><td colspan="2">Intervention [6] Enhanced therapy group: The patients were similar to the standard therapy group in terms of therapy, examination by a physician every 8 weeks, examination by the podiatrist on a regular basis. The patients had an education program on foot complications, and therapeutic insoles and footwear They were also taught to use a digital infrared thermometer to measure and record temperatures on each foot. If skin temperatures were elevated by 2.2^{0}C comparing with the corresponding site on the opposite foot for two consecutive days, subjects were instructed to contact the nurse and decrease their activity until temperatures normalized.

Sample size [7] 59 patients</td><td>Comparator(s) [8] Structured examination group: Patients received standard therapy in addition to training to conduct a structured foot inspection twice a day, to identify redness, swelling, discoloration and local warmth by palpation. The patients recorded their impressions in a logbook
Sample size [9] 56 patients

Standard therapy group: Patients were examined by a physician every 8 weeks, had an education program on foot complications, and therapeutic insoles and footwear. The treating podiatrist evaluated the shoes and insoles during regularly clinic visits. Patients were advised to inspect their feet daily and report to the nurse in case of any sign of concern. Then they were examined by a physician who was blinded to the group assignment. Patients were asked not to discuss the assignment details with the physician.
Sample size: 58 patients</td></tr>
<tr><td colspan="3">Selection criteria
Inclusion criteria – Diabetics ages 18 to 80 years, with a history of foot ulceration, with the ability to provide informed consent, and ankle-brachial indexes >= 0.70.
Exclusion criteria – If patients had open ulcers or open amputation sites, active osteoarthropathy, severe peripheral vascular disease, foot infection, dementia, or other conditions that would preclude active participation based on the investigator's judgement.</td></tr>
</table>

Patient characteristics [10] Intervention group – Comparator group(s) –

	Standard	Enhanced	Structured
Mean age, SD (range)	65.0 ± 9.6 (41-80)	65.4 ± 9.3 (42-80)	64.2 ± 8.6 (40-80)
Male %	53.4	55.9	51.7
Non Hispanic white %	53.4	54.2	55
Mexican American %	41.4	37.3	45
African American %	5.2	5.1	4
Type 2 diabetes %	97	93	95
Duration of diabetes, years	13.7 ± 10.3 (2-22)	12.7 ± 9.7 (4-25)	13.8 ± 11.5 (5-31)
Treatment of diabetes: Oral medication %	53.4	54.2	53.6
Insulin	22.4	25.4	17.9
Insulin and oral med	17.2	18.6	21.4
Diet	6.9	1.7	7.1
Ulcer history of location: Hallux %	12.1	6.8	14.3
Toes	50.0	59.4	53.5
Sub-metatarsal	36.2	28.8	37.5
Mid-foot	5.1	11.9	8.9
History of previous amputation	31.0	22.0	25.0
Amputation site: Toe	20.7	18.6	21.4
Toe and metatarsal	13.8	6.8	7.1
Midfoot	0	3.4	3.6
History of: lower extremity bypass surgery %	5.2	0	0
Lower extremity angioplasty	0	0	1.8
Neuropathy examination:			
Semmes-Weinstein 10-g monofilament right	5.2 ± 4.8	5.3 ± 4.7	5.2 ± 4.7
Semmes-Weinstein 10-g monofilament left	4.7 ± 4.3	4.7 ± 4.3	4.7 ± 4.3
Vibration perception threshold right	41.8 ± 9.8 (14-50)	40.6 ± 9.6 (12-50)	40.6 ± 8.6 (14-50)
Vibration perception threshold left	39.3 ± 8.6 (12-50)	38.6 ± 8.1 (11-50)	39.0 ± 8.0 (12-50)
Presence of: Hallux rigidus %	86.2	86.4	82.1
Hallux valgus	39.0	55.0	21.0
Claw toe	56.0	69.0	73.0
Ankle-brachial index right	1.1 ± 0.4 (0.7-1.5)	1.1 ± 0.4 (0.7-1.5)	1.1 ± 0.6 (0.8-2.0)
Ankle-brachial index left	1.2 ± 0.5 (0.7-1.7)	1.1 ± 0.6 (0.7-1.9)	1.2 ± 0.6 (0.7-1.9)
Activity (steps per day)	3,817 ± 3,364	3,489 ± 2,706	3,963 ± 2,363
Time prescribed shoes were worn (h) %			
<4	1.7	3.4	0
4-8	8.6	13.6	26.8
>8-12	56.9	52.5	33.9
>12	32.6	30.5	39.3

Length of follow-up [11] 15 months	Outcome(s) measured [12] Contact of research nurse; foot ulceration

INTERNAL VALIDITY

Allocation [13] Using computer generated randomisation list	Comparison of study groups [14] Similar, level of education was not reported	Blinding [15] Single blinded	Treatment/ measurement bias [16] Not similar for those who withdrew	Follow-up (ITT) [17] Standard: 6/58= 10.3%; Enhanced: 10/59= 16.9%; Structured: 6/56=10.7%. ITT analysis was applied

Overall quality assessment (descriptive) [18] Of good to moderate quality for the following reasons: 1. Neither the nurse nor the patients were blinded. This could have affected the outcome. The physician who assessed the ulceration was blinded, but the nurse who got the first report from the patients was not. 2. More patients withdrew from intervention group and these were not followed up till 15 months. The characteristics of them are also not stated. The censoring is informative.

<table>
<tr><td colspan="4">RESULTS</td></tr>
<tr><td>Outcome [19]

Contact of nurse:
Ulceration:
Withdrawal because of too much to do:</td><td>Intervention group [20] Control group [21]
<table>
<tr><td>Standard (S1)</td><td>Enhanced (E)</td><td>Structured (S2)</td></tr>
<tr><td>18/58=31.0%</td><td>31/59=52.5%</td><td>17/56=30.4%</td></tr>
<tr><td>17/58=29.3%</td><td>5/59=8.5%</td><td>17/56=30.4%</td></tr>
<tr><td>2/58=3.4%</td><td>6/59=10.2%</td><td>2/56=3.6%</td></tr>
</table>
P value for withdrawal because too much is asked from patient:
E vs.S1: p=0.272
E vs.S2: p=0.272</td><td>Measure of effect/effect size [22]
95% CI [25]
<u>Nurse contact</u>:
E vs.S1: 1.7 (1.1-2.7)
E vs.S2: 1.7 (1.1-2.7)
<u>Ulceration</u>:
E vs.S1: 0.28 (0.1-0.7)
Evs.S2: 0.27 (0.1-0.7)</td><td>Benefits (NNT) [23]
95% CI [25]
<u>Nurse contact</u>:
E vs.S1: 4.6 (2.6-27)
E vs.S2: 4.5 (2.6-24)
<u>Ulceration</u>:
E vs.S1: 4.8 (3.3-14.6)
Evs.S2: 4.6 (3.2-13.0)

Harms (NNH) [24]
-
95% CI [25]</td></tr>
<tr><td></td><td>Clinical importance (1-4) [26] 1 A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the ‘null’) rules out a clinically unimportant effect of the intervention.</td><td colspan="2">Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes</td></tr>
<tr><td colspan="4">Any other adverse effects [28] Infection and foot trauma were reported without any between groups differences. Two deaths occurred in Standard group and one in the Enhanced group.</td></tr>
<tr><td colspan="4">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="4">Generalisabilty [29] Good generalisability</td></tr>
<tr><td colspan="4">Applicability [30] The benefits could outweigh the harms</td></tr>
<tr><td colspan="4">Comments [31]</td></tr>
</table>

STUDY DETAILS

Reference [1] Lavery, L. A., K. R. Higgins, et al. (2004). "Home monitoring of foot skin temperatures to-prevent ulceration." Diabetes Care 27(11): 2642-2647.

Affiliation/source of funds [2] College of Medicine, Texas A&M Health Science Centre, Scott and White Hospital, Temple, Texas; Xilas Medical, San Antonio, Texas, USA. The study was funded by the National Institute of Health / National Institute of Diabetes (NIDDK) under the Small Business Innovation Research (SBIR) program

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] High risk diabetic foot clinic at the University of Texas Health Science Centre At San Antonio

Intervention [6]	Comparator(s) [8]
Diabetics treated with standard care consisting of therapeutic footwear, diabetic foot education, and foot evaluation by a podiatrist every 10-12 weeks + patients were instructed to use a handheld infrared skin thermometer to measure temperatures on the sole of the foot in the morning and evening on six predetermined sites and to keep a log book of their temperatures. If there was a temperature difference between the right and the corresponding left site, the patient was advised to contact a research nurse. Sample size [7] 41 patients	Diabetics treated with standard care consisting of therapeutic footwear, diabetic foot education, and foot evaluation by a podiatrist every 10-12 weeks Sample size [9] 44 patients

Selection criteria

Inclusion criteria – Diabetics with a high risk profile to develop a foot ulcer; (high risk defined as those with a history of foot ulceration or low extremity amputation, or patients with peripheral sensory neuropathy with loss of protective sensation with a foot deformity such as hallux valgus or claw toes.) Other inclusion criteria included adults age 18-80, diabetes diagnosis confirmed by the World Health Organization criteria, with 2 to 3 foot risk classification according to the International Working group on the Diabetic Foot.

Exclusion criteria – Open ulcers, open amputations site, active Charcot arthropathy, peripheral vascular disease, active foot infection, dementia, impaired cognitive function, history of drug or alcohol abuse within 1 year of the study or other conditions based on the principal investigator's clinical judgement.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Enhanced	Control
Mean age (SD)	55.0 (9.3)	54.8 (9.6)
Male gender %	48.8	52.3
Duration of diabetes, y	14.8 (11.5)	12.7 (10.0)
VPT (left foot)	35.9 (9.1)	33.8 (10.4)
VPT (right foot)	36.5 (8.6)	35.9 (11.3)

	Enhanced	Control
History of amputation %	1/41=2.4%	1/44=2.3%
Risk category %		
2	59%	59%
3	41%	41%
Mean risk category	2.41 (0.50)	2.41 (0.50)

Length of follow-up [11] 6 months	Outcome(s) measured [12] Incidence infections, Charcot fractures, functional impairment evaluated by SF-36 and amputations

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Method of randomisation not stated	Similar for the given characteristics	Physician blinded	Similar	Intervention: 3/41= 7.3%; control: 4/44= 9.1%. ITT was applied

Overall quality assessment (descriptive) [18] Of good quality. However, this is a single blinded study. The research nurse and the patients were not blinded. The physician examining the patients was blinded, but some bias could have occurred by the nurse who could have referred the patients to the physician and the physician could have received the knowledge from the patients.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23]
Foot ulceration:	1/41= 2.4%	7/44=15.9%	Ulceration: RR=0.15 (0.02-0.89)	95% CI [25]
Charcot fracture:	0/41=0%	2/44= 4.5%		Ulceration: 7.4 (5.8-91.8)
Amputation:	0/41= 0%	2/44= 4.5%		Harms (NNH) [24]
SF-36:	SF-36: No within group differences before and after the treatment	SF-36: No within group differences before and after treatment	No between groups differences in SF-36 scores before and after treatment	-
				95% CI [25]

	Clinical importance (1-4) [26] 1 A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.	Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes.
Any other adverse effects [28] Infection in the control group. No adverse effects due to intervention.		
EXTERNAL VALIDITY		
Generalisabilty [29] Moderate generalisability. No information is given on the recruitment of participants; a single-centre study.		
Applicability [30] Benefits could outweigh harms		
Comments [31]		

STUDY DETAILS

Reference [1] Lemaster, J. W., M. J. Mueller, et al. (2008). "Effect of weight-bearing activity on foot ulcer incidence in people with diabetic peripheral neuropathy: feet first randomized controlled trial." Physical Therapy 88(11): 1385-1398.

Affiliation/source of funds [2] Department of Family and Community Medicine, University of Missouri, Missouri, USA. Study was funded by the Robert Wood Johnson Foundation.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Department of Family and Community Medicine, University of Missouri, Missouri, USA

Intervention [6] Patients with diabetic neuropathy received foot care education, regular foot care, and 8 sessions with a physical therapist + leg strengthening and balance exercise that included a graduated, self monitored walking program (part 1) and motivational telephone calls every 2 weeks (part 2) Sample size [7] 41 patients	Comparator(s) [8] Patients with diabetic neuropathy received foot care education, regular foot care, and 8 sessions with a physical therapist Sample size [9] 38 patients

Selection criteria

Inclusion criteria – Patients aged 50 and older who received diabetes or foot care at primary care, endocrinology, or podiatry practices in central Missouri were invited to join the study. Patients were inactive (did not engage in intense activity more than twice per week), had type 1 or 2 diabetes ,mellitus, had absent sensation to 5.07 Semmes-Weinstein monofilament sensation on at least one point at any of 10 sites on each foot and had loss of vibratory sensation as measured by a biothesiometer.

Exclusion criteria – Patients who lacked telephone access or had medical conditions that might contraindicate exercise

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention	Control
Mean age, (SD)	66.6 (10.4)	64.8 (9.4)
Married %	67	60
Women %	47	53
Non white %	7	8
Non smoker %	95	87
Mean years of education, (SD)	14.1 (3.0)	15 (2.9)
No health insurance %	3	0
Type 2 diabetes %	95	92
Mean Duration of diabetes, years	10.8 (8.3)	11.2 (8.5)
Mean number of comorbidities	1.8 (1.5)	2.3 (1.6)
Mean No. of days performing exercise during last 7 days, (SD)	0.8 (1.5)	1.3 (1.8)

	Intervention	Control
Cardiovascular disease%	32	26
Joint pain in lower limbs %	73	71
Cancer %	19	21
Chronic bronchitis, asthma %	20	25
BMI (SD)	35.9 (8.2)	37.2 (8)
CESD depression score (>=16 indicates depression)	10.0	10.2
Mean foot ulcers in past year (SD)	0.37 (1.3)	0.6 (1.5)
Ankle brachial blood pressure index (1.0=normal) (SD)	1.05 (0.1)	1.01 (0.1)
Adequate shoes worn %	62	54
Mean foot related disability score, (SD)	25.3 (20)	25.6 (18)

Length of follow-up [11] 12 months	Outcome(s) measured [12] Foot ulcers and bout-related daily steps. The latter physical activity outcome will not be elaborated in this review

INTERNAL VALIDITY

Allocation [13] Block randomisation as used by type of clinical site	Comparison of study groups [14] Similar	Blinding [15] Assessor blinded	Treatment/ measurement bias [16] Similar: at baseline, 3, 6, and 12 months. Ulcers were photographed	Follow-up (ITT) [17] Intervention: withdrew 2/41=4.8%; Control: one death 1/38=2.6% ITT was applied

Overall quality assessment (descriptive) [18] Of good quality

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23]
Full thickness ulcer	9/41=21.9%	9/38=23.7%	RR=0.927 (0.416-2.070)	none 95% CI [25]

	As far as activity is concerned, the groups did not differ statistically in the change of total steps			Harms (NNH) [24] none 95% CI [25]
	Clinical importance (1-4) [26] 3 The confidence interval does not include any clinically important effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	
Any other adverse effects [28] One death was reported in the control group – not related to study				
EXTERNAL VALIDITY				
Generalisabilty [29] Good generalisability				
Applicability [30] No benefits were seen. Benefits do not outweigh harms.				
Comments [31]				

STUDY DETAILS

Reference [1] Lincoln, N. B., K. A. Radford, et al. (2008). "Education for secondary prevention of foot ulcers in people with diabetes: a randomised controlled trial." Diabetologia 51(11): 1954-1961.

Affiliation/source of funds [2] University of Nottingham, Nottingham, UK. Funded by a Diabetes UK grant.

Study design [3] RCT	**Level of evidence** [4] II	**Location/setting** [5] Three diabetes outpatient clinics in Nottingham, UK

Intervention [6] Diabetics with a newly healed foot ulcer were targeted to receive a targeted, one-to-one single education session **Sample size** [7] 87 patients	**Comparator(s)** [8] Diabetics with a newly healed foot ulcer were targeted to receive usual care **Sample size** [9] 85 patients

Selection criteria

Inclusion criteria – Diabetics with a recently healed foot ulcer (on or below the malleoli) who remained ulcer free for 28 days were eligible to participate.

Exclusion criteria – The patients were excluded if they lived in an institution, had a documented history of dementia, had serious medical problems, were non-English speakers or did not have an English speaking carer, lived at a distance more than 50 miles from the clinic, were in another study, or if they were members of the focus group involved in developing the education program used in the study.

Patient characteristics [10] **Intervention group – Comparator group(s) –**

	Intervention	Control		Intervention	Control
Mean age (SD)	63.5 (12.1)	64.9 (10.9)	Type 2 diabetes %	74	81
Male %	71	62	Retinopathy %	61	59
Centre 1 % 2 3	56 27 17	63 26 11	Ethnic group: UK white Other	 95 5	 96 4
Living: alone % With partner	21 79	16 84	Neuropathy %	29	22
Social class: % 1 2 3 4 5	 9 17 46 21 6	 5 22 40 24 9	Currently working %	22	29
			Site of previous ulcer: Forefoot Mid and hindfoot	 81 19	 80 20
			Previous amputation, other leg: Minor Major	7 3	6 3
10 g monofilament % All 3 stimuli felt Only 1 or 2 felt None felt	 22 31 47	 21 36 42	Previous amputation, same leg: Minor None	20 80	12 88
Neurotip: Felt % Not felt	65 35	64 36	Vibration perception: >=25 V felt % >=25 V not felt	 32 68	 38 62
Foot pulses: Both palpable 1 palpable / both diminished Neither palpable	 35 45 20	 39 33 28	Fitted footwear: % Yes	 64	 64

Length of follow-up [11] 12 months	**Outcome(s) measured** [12] 6 and 12 months incidence of ulcers, amputation, mood and quality of life at 6 and 12 months

INTERNAL VALIDITY

Allocation [13] Computer generated random allocation	**Comparison of study groups** [14] Similar	**Blinding** [15] Assessor blinded RCT	**Treatment/ measurement bias** [16] Similar	**Follow-up** (ITT) [17] drop out due to deaths: intervention group: 6.9%; and 4.7% in controls. ITT was applied
Overall quality assessment (descriptive) [18] Of good quality, an assessor blinded RCT in three medical clinics				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	**Measure of effect/effect size** [22] 95% CI [25]	**Benefits** (NNT) [23] No benefit seen. 95% CI [25]
Outcomes at 6 months: Foot ulcer: Amputation: Outcomes at 12 months: Foot ulcer: Amputation:	 26/87=29.9% 3/87=3.4% 36/87=41.4% 9/87=10.3%	 18/85=21% 0/85=0% 35/85=41% 9/85=11%	 RR=0.89 (0.75-1.06) RR=0.97 (0.93-1.00) RR=0.99 (0.78-1.28) RR=1.00 (0.90-1.11)	**Harms** (NNH) [24] - 95% CI [25]
Recommended foot care behaviours at 12 months were better in the intervention than in the control group (p=0.03), but education had no significant effect on mood, quality of life or amputation				
	Clinical importance (1-4) [26] 3. The confidence interval does not include any clinically important effects.		**Relevance** (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes.	
Any other adverse effects [28] Deaths unrelated to study were reported in both groups: 6/87=6.9% in intervention, and 4/85= 4.7% in controls.				
EXTERNAL VALIDITY				
Generalisabilty [29] Good generalisability				
Applicability [30] Benefits may outweigh harms, except no actual benefits were found by the single-educational program				
Comments [31] The intervention group received a single educational session and maybe a single session is not enough to acquire positive outcomes.				

STUDY DETAILS

Reference [1] Lundeberg, T. C., S. V. Eriksson, et al. (1992). "Electrical nerve stimulation improves healing of diabetic ulcers." Ann Plast Surg 29(4): 328-331.

Affiliation/source of funds [2] Karolinska Hospital, Stockholm, Sweden. Supported by Tore Nilsons Foundation, and RMR and Karolinska Institutet's Foundation

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Karolinska Hospital, Stockholm, Sweden

Intervention [6] Diabetics with chronic leg ulcers treated with electrical nerve stimulation (ENS) + standard treatment (paste impregnated bandage and a self adhesive elastic bandage) Sample size [7] 32 patients	Comparator(s) [8] Diabetics with chronic leg ulcers treated with sham ENS + standard treatment (paste impregnated bandage and a self adhesive elastic bandage) Sample size [9] 32 patients

Selection criteria

Inclusion criteria – Diabetic patients with chronic leg ulcers caused by venous stasis

Exclusion criteria – Skin allergies, rheumatoid arthritis, venous ulcers due to trauma, osteomyelitis, abscess or gangrene, or ankle pressure below than 75 mm Hg.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention (ENS)	Control
Mean age, (SD)	67.5 (8.6)	66 (7.9)
Male %	40.6%	40.6%
Mean ulcer area, cm^2 (SD)	24.2 (12.6)	22 (9.6)
Deep ulcer %	12.5%	18.7%

Length of follow-up [11] Healing or maximum of 12 weeks	Outcome(s) measured [12] Healing of ulcer

INTERNAL VALIDITY

Allocation [13] Permuted blocks randomisation	Comparison of study groups [14] Similar in basic characteristics; no information was given in terms of their obesity, duration of diabetes, location of ulcer. All these could have confounded the results.	Blinding [15] Patient blinded but not assessor blinded	Treatment/ measurement bias [16] Similar in both groups. A computer graphics program was used to calculate the areas of each ulcer	Follow-up (ITT) [17] drop ups: 8/32=25% ENS; 5/32=15.6% controls. ITT was applied

Overall quality assessment (descriptive) [18] Moderate quality; not assessor blinded, location of ulcer was not stated; foot ulcers could have reacted differently to those found on other parts of the leg, some unknown characteristics such as BMI, diabetes stability, duration of antibiotic treatment between the groups could have confounded the results.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Healing at week 12:	10/32=31.2%	4/32=12.5%	RR=2.5 (0.9-7.1)	No significant benefit found, though effect size is 2.5: 5.33 (3.0-inf)
				Harms (NNH) [24] - 95% CI [25]
	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	

Any other adverse effects [28] Pain and allergy were reported similarly in both groups

EXTERNAL VALIDITY

Generalisabilty [29] Poor generalisability to patients with diabetic foot ulcers since location of the lower extremity ulcer was not stated by the authors.

Applicability [30] Benefits may outweigh harms, however, no statistically significant benefits were seen.

Comments [31]

STUDY DETAILS
Reference [1] McCabe, C. J., R. C. Stevenson, et al. (1998). "Evaluation of a diabetic foot screening and protection programme." Diabetic medicine: a journal of the British Diabetic Association 15(1): 80-84.
Affiliation/source of funds [2] Sheffield Centre for Health and Related Research, University of Sheffield, Sheffield; Department of Economics, University of Liverpool, Liverpool; Department of Orthopaedic Surgery, Cappagh Hospital, Dublin. The study was funded by the British Department of Health

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Outpatient clinic in Liverpool, UK.

Intervention [6] Diabetics recruited from the clinic received a protection program. The clinic provided foot care (chiropody and hygiene maintenance), support hosiery, and protective shoes for patients in the high risk category. Patients were advised to inspect and wash their feet daily; to avoid constricting clothing and footwear; to wear prescribed footwear at all times and to contact the clinic whenever they felt it to be necessary. Sample size [7] 1001 but from these 259 patients were defined at risk after initial screening. The final number of those attending the program changed all the time and some were shifted from the control group to the intervention group. The groups were not mutually exclusive	Comparator(s) [8] Diabetics recruited from the clinic were silently tagged and these continued to attend the general out-patient clinic but received no special care Sample size [9] 1000

Selection criteria

Inclusion criteria – Exclusion criteria –

Eligible participants were recruited at a weekly general diabetes clinic. Patients found to have a significant deficit in any of the foot screening examination (Semmes-Weinstein monofilaments, the biothesiometer, and palpation of pedal pulses) were given an appointment for a second examination which repeated the original tests. In addition the ankle–brachial index was calculated, subcutaneous oxygen levels and foot pressure were measured and x-rays were taken. Patients with foot deformities, or a history of foot ulceration, or an ankle–brachial index of <=0.75 were judged to be at high risk of ulceration and were entered into the foot protection programme. Patients not meeting any of these criteria were judged to be at a lower risk level and received no further special treatment.

Patient characteristics [10] Intervention group – Not stated Comparator group(s) – Not stated

Length of follow-up [11] Follow up of 2 years	Outcome(s) measured [12] Reduction in ulceration, reduction in amputation and costs related to diabetic foot screening and protection program

INTERNAL VALIDITY

Allocation [13] Randomisation method not stated	Comparison of study groups [14] Unknown. Not stated by authors	Blinding [15] Not blinded	Treatment/ measurement bias [16] Was different for those who did not attend a follow-up examination. For these data were extracted from hospital medical records	Follow-up (ITT) [17] Not clear from paper as intervention and control groups were not mutually exclusive. Some did not respond to the invitation. ITT was not done

Overall quality assessment (descriptive) [18] Overall bad quality due to unknown details of the study. A non-blinded RCT, but groups were not mutually exclusive. At various stages of the study patients were shifted from control to intervention group, no details were given about the characteristics of the participants;

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22]	Benefits (NNT) [23]
Ulceration: Amputation: Costs:	Crude numbers only. Ulcers: 24 Amputation: 7 49,545 British Pounds (clinic costs) 29,451 British pounds (hospital costs)	Ulcers: 35 Amputation: 23 Cost were not stated for the controls	95% CI [25] Amputation: p value<0.04	95% CI [25] Harms (NNH) [24] - 95% CI [25]
	Clinical importance (1-4) [26] 3 The confidence interval does not include any clinically important effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	

Any other adverse effects [28] None stated

EXTERNAL VALIDITY

Generalisabilty [29] Poor generalisability, unknown process of patient selection

Applicability [30] Benefits may not outweigh harms

Comments [31]

STUDY DETAILS

Reference [1] McCallon, S. K., C. A. Knight, et al. (2000). "Vacuum-assisted closure versus saline-moistened gauze in the healing of postoperative diabetic foot wounds." Ostomy/wound management 46(8): 28-32, 34.

Affiliation/source of funds [2] Louisiana State University Health Science Centre, Shreveport, LA, USA. The study was partially funded by Kinetic Concepts, Inc. (KCI)

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Diabetic foot clinic at Louisiana State University Health Science, Shreveport, LA, USA

Intervention [6] Debridement of foot ulcer + treatment with Vacuum-assisted Closure (VAC) + dressings in accordance with manufacturer's protocol for chronic wounds and changes every 48 hrs. The pressure was set at continuous suction at 125 mmHg for the first 48 h, then intermittent suction at 125 mmHg. Sample size [7] 5 patients	Comparator(s) [8] Debridement of foot ulcer + treatment with saline-moistened gauze changed twice a day Sample size [9] 5 patients

Selection criteria

Inclusion criteria – Diabetics ages 18 to 75 with a non-healing foot ulcer that had been present longer than one month.

Exclusion criteria – Patients with venous disease, coagulopathy, or those with active infections not resolved by initial debridement

Patient characteristics [10] Intervention group – Comparator group(s) –

	VAC	Control
Mean age (SD)	55.4 (12.8)	50.2 (8.7)
Blood glucose (SD)	141 (37.5)	151 (51.2)

The authors also stated that the two groups were comparable in terms of their levels of haemoglobin, albumin and also in terms of wound location and the surface area of the ulcers after the initial debridement. This was not elaborated by the groups.

Length of follow-up [11] Till healing occurred, exact time was not stated.	Outcome(s) measured [12] Time to healing, change in wound surface area.

INTERNAL VALIDITY

Allocation [13] Randomisation by a flip of the coin	Comparison of study groups [14] Similar to the given characteristics, though confounding cannot be excluded due to many unknown characteristics of the patients in both groups.	Blinding [15] Not blinded	Treatment/ measurement bias [16] Ulcer measurements and photos were obtained similarly in both groups.	Follow-up (ITT) [17] All 10 patients were followed

Overall quality assessment (descriptive) [18] An average quality of study, non blinded and the study included a very small number of patients, thus the power of such study is relatively low; many of the patient characteristics (gender, BMI, co-morbidity – important due to the wide age range-, duration of ulcer, etc) were not provided thus confounding cannot be excluded.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Healing time, days (SD):	22.8 (17.4)	42.8 (32.5)	*p* = 0.26	No benefit was seen, both groups healed and ulcers closed in both groups. For primary closure: 2.5 (1.4-inf)
Change in surface area:	28.4% (± 24.3)	9.5% (± 16.9)	*p* = 0.19	
Primary closure of ulcer:	4/5=80%	2/5=40%	RR= 2.00 (0.72-3.97)	
Secondary closure:	1/5=20%	3/5=60%	*p* = 0.524 RR = 0.33 (0.06-1.64)	Harms (NNH) [24]- 95% CI [25]
	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	

Any other adverse effects [28] Pain and minor bleeding were reported in the VAC group.

EXTERNAL VALIDITY

Generalisabilty [29] Poor, very small sample of patients of unknown gender, and it is not clear how many patients were screened for eligibility and how these were selected.

Applicability [30] The benefits do not outweigh the harms. No benefits were seen since all patients in both groups eventually had healed ulcers however the time o healing was faster in the VAC group, but due to a small number of participants, the results did not reach statistical significance.
Comments [31]

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STUDY DETAILS

Reference [1] McCulloch, Joseph (03/2002). "Noncontact normothermic wound therapy and offloading in the treatment of neuropathic foot ulcers in patients with diabetes". Ostomy/wound management (0889-5899), 48 (3), p. 38.

Affiliation/source of funds [2] Minnesota, USA. This study was funded by a grant from Augustine Medical, Inc. Eden Prairie, Minn.USA

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Outpatient diabetic clinic in Minnesota, USA

Intervention [6]	Comparator(s) [8]
Patients were instructed in the application and use of a warming device. The warming system was comprised of a noncontact foam dressing, warming card, temperature control unit, and AC adapter. Subjects were told to cleanse their wounds with saline, then apply the noncontact wound cover. Treatments were conducted daily for 3 hours, 5 days per week. At the end of the 3-hour period, patients dressed their wounds with alginate and semipermeable foam dressings, or semipermeable foam dressings alone, as directed by the investigator. They applied offloading devices in the same manner as the control subjects and likewise maintained a daily glucose monitoring log. Sample size [7] 18 patients	Patients in the control group had their wounds cleansed and dressed with an appropriate moisture-retentive dressing and received an offloading device that was applied by the nursing staff. The dressings most frequently used were calcium alginates combined with thin, semipermeable foams or semipermeable foams alone, depending on wound hydration. The patient was instructed in daily wound care, including saline irrigation and dressing application. Subjects also were instructed to maintain daily blood glucose logs as directed by their physicians in the diabetic foot clinic. Sample size [9] 18 patients

Selection criteria

Inclusion criteria – Patients were selected to participate in the study based upon a history of non-healing diabetic foot ulceration. Inclusion in the study required that the participant had a wound on the leg over a bony prominence and appeared secondary to pressure.

Exclusion criteria – Patients with active cellulitis, purulence, fever, osteomyelitis, or those determined by the referring physician to have inadequate blood supply to support healing were excluded.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention	Control
Mean age, (SD)	55.5 (12.8)	52.5 (12.1)
Location of ulcer: plantar aspect of toes or metatarsal heads %	67%	78%
Ulcer surface area (cm^2)	2.02 (1.54)	2.58 (2.80)
Mean blood glucose mg/dl (SD)	139.33 (25.7)	136.55 (27.9)

Length of follow-up [11] 2 months	Outcome(s) measured [12] Healing of ulcer, rate of healing

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
First person to go to treatment was based on a toss of a coin. Then each subsequent individual referred to the study was assigned in an alternating fashion.	Similar to the given characteristics. No information was given relating to duration of ulcer, duration of diabetes, BMI and other co-morbidities.	Not blinded	Similar	No drop outs were reported

Overall quality assessment (descriptive) [18] Moderate quality due to un-blinded nature of the study, some basic characteristics were not reported including duration of ulcer, gender, BMI and other co-morbidities. It is not known if they groups varied in duration of antibiotic treatment. No drop outs are reported, no adverse effects are reported.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Mean healing rate:	0.019 $\pm$0.019 cm^2/day	0.008 $\pm$0.009 cm^2/day	P=0.049 (for healing rate)	For healing: 2.25 (1.46-8.32)
Healing:	13/18=72.2%	5/18=27.7%	RR=2.60 (1.27-5.31)	

Mean time to complete wound closure:	32.6 ± 17.1 days	27.6 ± 13.7 days	*P*= 0.57 (for time to complete closure)	Harms (NNH) [24] - 95% CI [25]
	Clinical importance (1-4) [26] 1 A clinically important benefit for the full range of plausible estimates		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	
Any other adverse effects [28] None reported				
EXTERNAL VALIDITY				
Generalisabilty [29] Moderate generalisability. Recruitment process is not revealed. The gender of the participants is also not known.				
Applicability [30] Benefits may outweigh the harms				
Comments [31]				

STUDY DETAILS

Reference [1] McMurray, S. D., G. Johnson, et al. (2002). "Diabetes education and care management significantly improve patient outcomes in the dialysis unit." Am J Kidney Dis 40(3): 566-575.

Affiliation/source of funds [2] Indiana Medical Associates, Fort Wayne, IN; Vanderbilt University, Nashville, TN; and the Renal Care Group, Nashville, TN, USA. Supported in part by the Renal Care Group and a grant from The Kidney Foundation of Indiana

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Haemodialysis or peritoneal dialysis at the Northeast Indiana Kidney Centres at Jefferson and Marion dialysis units, Nashville, TN, USA.

Intervention [6] Diabetic patients underwent a continuous quality improvement process that included self-management education, diabetes care monitoring and management, motivational coaching, eye examinations, and nutritional counselling. All patients' feet were assessed for skin condition, structural deformity, pulses, and plantar sensation. Blood tests were taken to monitor glucose and manage the patient's diabetes mellitus. Patients with loss of protective sensation had their feet inspected at a minimum of monthly or as frequently as weekly depending on the following factors: (1) compliance with home foot care, (2) presence of deformity, (3) skin cracks, (4) lesions, (5) history of ulcer, and (6) amputations. Sample size [7] 49 patients	Comparator(s) [8] After baseline assessments were completed, the control group had no further contact with the diabetes care manager until end-of-study evaluations were initiated. Although these patients were not exposed to interventions from the diabetes care manager, they received standard diabetes care prevalent at the dialysis facility as directed by their physician. This included monitoring random blood glucose and quarterly HbA1c levels. Sample size [9] 38 patients

Selection criteria

Inclusion criteria – End stage renal disease (ESRD) requiring renal replacement therapy with either Haemodialysis or peritoneal dialysis in combination with a diagnosis of a type 1 or type 2 diabetes mellitus.

Exclusion criteria – Refusal to participate in study. Apart from this, no other criterion was stated.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Control Group (n = 38)	Study Group (n = 45)	*P*
Mean age (y), ± SD	60.9 ± 11.7	63.0 ± 13.5	0.293
Male, n (%)	21 (55)	24 (53)	0.0.860
Treatment site: Jefferson, n (%) Marion, n (%)	 18 (47) 20 (53)	25 (56)	0.457
Diabetes type 2, n (%)	34 (90)	38 (84)	0.501
Mean years with diabetes ± SD	22.0 ± 11.7	20.5 ± 13.0	0.600
Haemodialysis, n (%)	33 (87)	37 (82)	0.564
Peritoneal dialysis, n (%)	5 (13)	8 (18)	
Mean months on dialysis therapy ± SD	33.2 ± 24.2	32.4 ± 22.8	0.877
Initial foot risk score	2.7	2.2	0.287
Previous amputations	10/38=26.3%	8/45=17.8%	0.347

Length of follow-up [11] 12 months	Outcome(s) measured [12] Diabetes self-knowledge; self-management health behaviours; glycaemic control; foot care and quality of life, amputations and hospital admissions. Only the last three will be reported in this review.

INTERNAL VALIDITY

Allocation [13] Randomisation was based on patient's treatment days at the dialysis units	Comparison of study groups [14] Similar	Blinding [15] Not blinded	Treatment/ measurement bias [16] Similar	Follow-up (ITT) [17] Intervention: 4/49=8%, Controls: 4/42=9.5% ITT was not applied

Overall quality assessment (descriptive) [18] Moderate quality, a non blinded RCT, with ITT

RESULTS

<table>
<tr><td>Outcome [19]

Amputation:
Hospital admission:

Quality of life: (not stated how this was measured)</td><td>Intervention group [20]

0/45=0%
1/45=2.2%

The authors stated that patients in the intervention group had a better quality of life measures than the controls (P<0.001)</td><td>Control group [21]

5/38=13.1%
10/38=26.3%</td><td>Measure of effect/effect size [22]
95% CI [25]

Hospitalization:
RR=0.084 (0.014-0.466)</td><td>Benefits (NNT) [23]
95% CI [25]
Hospitalization:4.15(3.56-10.0)
Harms (NNH) [24]
-
95% CI [25]</td></tr>
<tr><td></td><td colspan="2">Clinical importance (1-4) [26] 1 A clinically important benefit for the full range of plausible estimates</td><td colspan="2">Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes</td></tr>
<tr><td colspan="5">Any other adverse effects [28] Non reported</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Good generalisability to diabetic patients on haemodialysis or peritoneal dialysis; poor generalisability to the overall diabetic general population</td></tr>
<tr><td colspan="5">Applicability [30] Benefits may outweigh the harms</td></tr>
<tr><td colspan="5">Comments [31]</td></tr>
</table>

<table>
<tr><td colspan="5">STUDY DETAILS</td></tr>
<tr><td colspan="5">Reference [1] Malone, J. M., M. Snyder, et al. (1989). "Prevention of amputation by diabetic education." American journal of surgery 158(6): 520-523; discussion 523-524.</td></tr>
<tr><td colspan="5">Affiliation/source of funds [2] Maricopa Medical Centre, the Tucson Veterans Administration Medical Centre, University of Arizona, Tucson, Arizona, USA. Supported by the Veterans Administration, Washington, D.C.</td></tr>
<tr><td colspan="2">Study design [3] RCT</td><td colspan="2">Level of evidence [4] II</td><td>Location/setting [5] Podiatry or vascular surgery clinic at Tucson Veterans Administration Medical Centre, Tucson, Arizona, USA.</td></tr>
<tr><td colspan="3">Intervention [6] Diabetics randomised to receive a single 1-hour education session + clinical management + routine diabetic teaching with respect to diet, weight, exercise, and medication.
Sample size [7] 103 patients (203 limbs)</td><td colspan="2">Comparator(s) [8] Diabetics randomised not to receive any education session + clinical management+ routine diabetic teaching with respect to diet, weight, exercise, and medication.
Sample size [9] 100 patients (193 limbs)</td></tr>
<tr><td colspan="5">Selection criteria
Inclusion criteria – Diabetics without foot infections or prior amputations
Exclusion criteria – Patients requiring wound debridement, incision and drainage of foot infection, amputation, or vascular reconstruction.</td></tr>
<tr><td colspan="5">Patient characteristics [10] Intervention group – Comparator group(s) –
The authors do not describe any of the groups but they state generally that no differences were found between the two groups in terms of foot deformities, neuropathy, gangrene, prior amputation, prior foot ulcer, hypertonic nails, and medical management of diabetes mellitus, prior foot education, or level of distal pulses. Foot callous was significantly higher in the intervention group.</td></tr>
<tr><td colspan="3">Length of follow-up [11] Median follow-up of 12 months for the intervention group and 8 months for the controls</td><td colspan="2">Outcome(s) measured [12] Ulceration of foot, infection, amputation</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13] Randomised according to odd or even last digit of the patients' social security number</td><td>Comparison of study groups [14] The authors did not elaborate much about the characteristics of the groups in terms of age, sex, education, co-morbidities, BMI and other factors that could have confounded their findings. The analysis was not controlled for differences in the management of the groups.</td><td>Blinding [15] Not blinded</td><td>Treatment/ measurement bias [16] Both groups did not have similar follow-up periods, though during follow-up the measurements were similar in both groups</td><td>Follow-up (ITT) [17] 13/203=6.4% in intervention; 8/100= 8% from controls. ITT was not applied</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18] Moderate quality: non blinded RCT, without ITT analysis, no clear description of the baseline characteristics of each of the groups; different follow-up periods for each of the groups</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td rowspan="3">Outcome [19]
Not ITT analysis (denominator: limbs)
Infection:
Ulceration:
Amputation:
With ITT analysis:
Ulceration:
Amputation:</td><td>Intervention group [20]

2/177= 1.13%
8/177=4.5%
7/177= 3.9%

8/203=3.9%
7/203=3.4%</td><td>Control group [21]

2/177= 1.13%
26/177=14.7%
21/177= 11.9%

26/193=13.5%
21/193=10.9%</td><td>Measure of effect/effect size [22] 95% CI [25]
P=ns
RR=0.31 (0.14-0.6)
RR=0.33 (0.14-0.7)

RR=0.29 (0.14-0.6)
RR=0.3 (0.14-0.7)</td><td>Benefits (NNT) [23]95% CI [25]
Not ITT:
9.8 (6.9-24.0)
12.6 (8.5-42.7)

With ITT:
10.5 (7.5-24.2)
13.4 (9.2-41.1)</td></tr>
<tr><td colspan="3">Clinical importance (1-4) [26] 1 A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.</td><td>Harms (NNH) [24] 95% CI [25] -</td></tr>
<tr><td colspan="4">Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms</td></tr>
<tr><td colspan="5">Any other adverse effects [28] Deaths that occurred in both groups were not related to the intervention</td></tr>
</table>

EXTERNAL VALIDITY
Generalisabilty [29] Low generalisability: a single centre study, without clear description of the groups and the inclusion and exclusion criteria and also no clear description of the recruitment procedure.
Applicability [30] The benefits outweigh the harms
Comments [31]

STUDY DETAILS

Reference [1] Mars, M., Y. Desai, et al. (2008). "Compressed air massage hastens healing of the diabetic foot." Diabetes Technology & Therapeutics 10(1): 39-45.

Affiliation/source of funds [2] Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa. Funding was not stated.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] RK Khan Hospital, Durban, South Africa

Intervention	Comparator(s)
Intervention [6] Diabetics with infected non-ischemic foot ulcers treated with radical debridement + minor amputation (if necessary) + standard medical and wound care + antibiotic treatment, daily lavage of wounds with saline + 15-20 min of compressed air massage, at 1 bar pressure, daily for 5 days a week till healing was reached or patient had skin graft Sample size [7] 30 but results are reported for 28	Comparator(s) [8] Diabetics with infected non-ischemic foot ulcers treated with radical debridement + minor amputation (if necessary) + standard medical and wound care + antibiotic treatment, daily lavage of wounds with saline Sample size [9] 30 but results are reported for 29

Selection criteria

Inclusion criteria – Diabetics with infected non-ischemic foot ulcers admitted to RK Khan Hospital for surgical treatment

Exclusion criteria – Not provided

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention	Control
Initial size of ulcer, mm^2 (SD)	3,000 (3,267)	2,668 (2,172)
Mean age, (SD)	51.5 (7.6)	55.3 (9.0)
Type 1 diabetes %	8/28=28.6%	8/29=27.6%
Mean and median Wagner score	Mean:2.9 Median 3	Mean:2.6 Median 3

Furthermore, the authors stated that there were no significant differences between the groups in terms of co-morbidity such as hypertension, ischemic heart disease, and also in vibration sense, or pulse status at the affected limb.

Length of follow-up [11] Till healing or skin graft	Outcome(s) measured [12] Time to healing of wound, amputation

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Randomisation method not stated	Similar	Not blinded	Similar in both groups using photography and planimetry	2/30=6.7% intervention; 1/30=3.3% control. ITT was not applied

Overall quality assessment (descriptive) [18] Moderate quality, a non blinded RCT, without ITT analysis.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25] Only seen in mean time to heal
Days to healing:	58.1 (49.5-66.6)	82.7 (70.0-94.3)	Time to heal: p=0.001	
Split skin grafting:	9/28=32.1%	10/29=34.5%	P=0.851	Harms (NNH) [24] - 95% CI [25]
Days to skin grafting:	30.8 (18.6-43.3)	45.1 (36.4-53.8)	P=0.39	
Amputation:	14/28=50%	15/29=51.7%	P=0.896	
	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	

Any other adverse effects [28] No adverse effects were reported. One person in each group died of myocardial infarction during the trial, not related to treatment as stated by authors.

EXTERNAL VALIDITY

Generalisabilty [29] Moderate to poor generalisability. No exclusion criteria were provided plus the inclusion criteria were general and the recruitment process was not stated (how many were assessed till this number was reached and how much time did they wait till they got this number is not clear)

Applicability [30] No benefits were seen in amputation rates and the benefits were apparent only in the time to healing however this does not include the results of those who were lost to follow-up and were excluded from the analysis. Given the disadvantages in the study, the benefits may not outweigh the harms

Comments [31]

STUDY DETAILS

Reference [1] Mody, G. N., I. A. Nirmal, et al. (2008). "A blinded, prospective, randomized controlled trial of topical negative pressure wound closure in India." Ostomy Wound Management 54(12): 36-46.

Affiliation/source of funds [2] Department of Surgery, Christian Medical College, Vellore, India. Funding of study not stated

Study design [3] RCT | Level of evidence [4] II | Location/setting [5] Christian Medical College, Vellore, India

Intervention [6] Diabetics with neuropathic foot ulcers were treated topical negative pressure (TNP) following debridement of wound. TNP was applied via a wall suction canister set at 125 mmHg and a TNP timer to intermittently cycle wall suction to 2 mins on followed by 5 mins off.

Sample size [7] 15 patients

Comparator(s) [8] Diabetics with neuropathic foot ulcers were treated with saline-soaked gauze and dry gauze dressings following debridement of the wound.

Sample size [9] 33 patients

Selection criteria

Inclusion criteria – Patients admitted to general surgery, physical medicine, and rehabilitation wards of CMC and referred by the surgical consultants for care of an acute or chronic extremity, sacral, or abdominal wound that could not be treated with primary closure were eligible for study participation.

Exclusion criteria – Exclusion criteria included wounds in anatomical locations where an adequate seal around the wound site could not be obtained, ischemic wounds, wounds with exposed bowel or blood vessels, wounds with necrotic tissue that could not be debrided, wounds with communicating fistulae, osteomyelitis, or wounds with malignancy — ie, wounds contraindicated by the commercial manufacturers of TNP devices. Grafted wounds were not included. Patients receiving therapeutic anticoagulation were excluded.

Patient characteristics [10] Intervention group – Comparator group(s) –

		TNP					Control			
Type of ulcer	N	Age	% male	Duration of Ulcer (days)	Size of ulcer (cm^2)	N	Age	% male	Duration of Ulcer (days)	Size of ulcer (cm^2)
Diabetic Foot ulcer	6	53.2 (15.1)	67	8.5 (8.3)	25.7(9.7)	9	59.6 (8.5)	67	5.2 (2.3)	48.1(53.4)
Pressure ulcer	2	46.5 (12.0)	100	17.5 (4.9)	157.8(72.2)	9	41.5 (17.9)	89	19.8 (15.1)	59.6(57.5)
Cellulitis/ fasciitis	3	55.3 (3.1)	67	6.7 (1.5)	151.4(163.3)	8	64.3 (6.3)	75	6.4 (7.8)	286.6(456.3)
Other	4	58.0 (4.0)	50	9.7 (6.7)	20.9(10.7)	7	47.6 (10.2)	67	7.7 (4.6)	103.1(82.0)

Length of follow-up [11] Follow-up for an average of 26.3 days (± 18.5) in the control and 33.1 days (± 37.3) in the treatment group

Outcome(s) measured [12] Number of days to satisfactory healing, defined as complete wound closure; cost of materials used in both treatments

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Block randomisation using a computer generated table	Similar to given basic characteristics; Results not controlled for duration of antibiotic treatment	Stated as blinded but no elaboration is provided	Similar	Lost to follow up: TNP: 1/15=7% & Controls:12/33=36%. ITT was applied

Overall quality assessment (descriptive) [18] Good quality

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
<u>Days to satisfactory healing</u>:				For closure by secondary intension (diabetic foot): 18 (3.6-inf)
Foot ulcer:	107 (one person)	25.6 (21.9)	P=n/a	
Pressure ulcer:	10 ± 7.1	27.4 (10.6)	P=0.05	
Cellulitis/fasciitis:	51 ± 60.8	42 (46.7)	P=0.56	
Other:	11 ± 4.2	23 (one person)	P=n/a	

All: Closure by secondary intention: All ulcers Diabetic foot Closure by delayed primary intention: All ulcers Diabetic foot No. ulcers achieved satisfactory healing: All ulcers Diabetic foot Cost per dressing: Total material costs for reaching satisfactory closure:	35.9 ± 44.5 13.3% 2/15 16.7% 1/6 33.3% 5/15 0% 0/6 47.7% 7/15 16.7% 1/6 $2.27 $11.35	28.4 ± 18.9 6.1% 2/33 11.1% 1/9 42.4% 14/33 11.1% 1/9 48.4% 16/33 22.2% 2/9 $0.40 $22	P=0.66 RR = 2.20 [0.40, 11.96] RR = 1.50 [0.16, 13.68] RR = 0.79 [0.33, 1.63] RR = 0.00 [0.00, 5.48] RR = 0.93 [0.48, 1.69] RR = 0.75 [0.10, 4.96]	Harms (NNH) [24] - 95% CI [25]
	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	
Any other adverse effects [28] Minor wound revisions were performed and one amputation on TNP patients (not reported if these were among the diabetics); pain and cramps were also reported. Among the controls, two revisions were reported.				
EXTERNAL VALIDITY				
Generalisabilty [29] Moderate generalisability. No clear description of the recruitment process.				
Applicability [30] Benefits do not outweigh harms. No benefits were seen				
Comments [31]				

STUDY DETAILS

Reference [1] Moretti, B., A. Notarnicola, et al. (2009). "The management of neuropathic ulcers of the foot in diabetes by shock wave therapy." BMC Musculoskeletal Disorders 10(1).

Affiliation/source of funds [2] University of Bari, General Hospital, Piazza Giulio Cesare, Bari, Italy. Source of funding was not stated.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] General Hospital, University of Bari, Bari, Italy

Intervention [6] Type 1 diabetics with neuropathic foot ulcers treated with external shock wave therapy (ESWT) of three sessions every 72 hours + standard wound care (therapeutic footwear, debridement and Silvercell dressing) Sample size [7] 15 patients	Comparator(s) [8] Type 1 diabetics with neuropathic foot ulcers treated standard wound care (therapeutic footwear, debridement and Silvercell dressing) Sample size [9] 15 patients

Selection criteria

Inclusion criteria – Diabetics with neuropathic foot plantar ulceration below the malleoli for a period of at least 6 months with an area wider than 1 cm^2, age 30-70 years, a diameter of the lesion between 0.5 to 5 cm and type 1 diabetes mellitus treated with insulin for at least 5 years prior. Patients had peripheral neuropathy, with an ankle-brachial index >0.7 and palpation of the dorsalis pedis and posterior tibial arteries.

Exclusion criteria – Patients were excluded if any of the above mentioned pulses were not palpable; or if patients had peripheral vascular disease, coronary bypass, pregnancy, coagulation diseases or history of neoplasia or other conditions, based on the principal investigator's clinical judgement.

Patient characteristics [10] Intervention group – Comparator group(s) –

	ESWT	Control
Male %	9/15=60.0%	7/15=46.7%
Mean age , (SD)	56.2 (4.9)	56.8 (7.5)
Mean ulcer initial surface area, mm^2 (SD)	297.8 (129.4)	245 (100.9)

Length of follow-up [11] 20 weeks	Outcome(s) measured [12] Healing of ulcers, time to heal and re-epithelization

INTERNAL VALIDITY

Allocation [13] Randomisation method not stated	Comparison of study groups [14] Duration of ulcer, BMI not stated	Blinding [15] Not blinded	Treatment/ measurement bias [16] Similar in both groups; ulcers were photographed	Follow-up (ITT) [17] No drop outs were reported

Overall quality assessment (descriptive) [18] Moderate quality, not blinded, many of the baseline characteristics were not reported such as duration of ulcer, diabetes control, BMI

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] no significant benefit in proportion healed: 5.0 (1.9-inf) 95% CI [25]
Healing:	8/15=53.3%	5/15=33.3%	RR=1.6 (0.7-3.7)	
Time to heal:	60.8 (4.7)	82.2 (4.7)	Time to heal: $p<0.001$	
Re-epithelization:	2.97 (0.34)	1.30 (0.26)	Re-epithelization: $p<0.001$	Harms (NNH) [24]- 95% CI [25]
	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	

Any other adverse effects [28] One patient in each group developed an infection.

EXTERNAL VALIDITY

Generalisabilty [29] Good to moderate generalisability to type 1 diabetics, patients coming from one centre

Applicability [30] Benefits do not outweigh harms. The proportion healed was similar in both groups, and the study was not blinded. Time to heal was faster in the intervention group.

Comments [31]

STUDY DETAILS

Reference [1] Mueller, M. J., D. R. Sinacore, et al. (2003). "Effect of Achilles tendon lengthening on neuropathic plantar ulcers: a randomized clinical trial." Journal of Bone & Joint Surgery, American Volume 85A(8): 1436-1445.

Affiliation/source of funds [2] Washington University School of Medicine, St. Louis, Missouri, USA. Funding was not stated

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Washington University School of Medicine, St. Louis, Missouri, USA

Intervention [6] Diabetics with a recurrent or non healing ulcers underwent percutaneous Achilles tendon lengthening followed by group immobilization in a total-contact cast Sample size [7] 31 patients	Comparator(s) [8] Diabetics with a recurrent or non healing ulcers were treated with immobilization in a total-contact cast alone Sample size [9] 33 patients

Selection criteria

Inclusion criteria – Diabetics with a loss of sensation (unable to sense the 5.07 Semmes-Weinstein monofilament on at least one location on the plantar aspect of the foot), limitation of ankle dorsiflexion to <=5^0, a palpable ankle pulse, and a recurrent or non-healing ulcer with history of non healing diabetic ulcers on the forefoot (Grade II according to Wagner scale).

Exclusion criteria – If patients had neurological problem complication the rehabilitation, had a history of Charcot fractures of the hind foot, were unable to tolerate the anaesthesia required for the operation, or if it was thought that they would not benefit from the operation (if they could not walk).

Patient characteristics [10] Intervention group – Comparator group(s) –

	Surgical group	Control
Mean age (SD)	56.6 (9.2)	56.2 (10.1)
Male %	83.8%	69.7%
Type 2 diabetes %	83.8%	66.7%
Duration of diabetes, yrs (SD)	17.1 (10.8)	19.6 (12.6)
Body Mass Index	33.3 (7.8)	30.5 (6.8)
HbA1c %	8.8 (1.9)	8.8 (1.7)
Number of previous ulcers	3.7 (4.4)	3.3 (4.0)
Ulcer length, mm (SD)	14.3 (9.2)	15.1 (12.0)
Ulcer width, mm (SD)	11.3 (8.0)	12.7 (11.9)
Hammer or claw toe	71%	73%

	Surgical group	Control
Past myocardial infarction	32%	27%
Cardiac artery bypass graft	19%	15%
Congestive heart failure	16%	18%
Hypertension	58%	55%
Retinopathy	32%	33%
Lower extremity revascularization	3%	9%
Renal failure	19%	12%
Transmetararsal amputation	10%	6%
Toe and/or ray resection	29%	18%
Hallux valgus	19%	21%

Length of follow-up [11] The measurements were made before and after treatment, at the seven-month follow-up examination, and at the final follow-up evaluation (a mean of 2.1 ± 0.7 years after initial healing)	Outcome(s) measured [12] Time to healing of the ulcer, ulcer recurrence rate, and others less relevant to current review (range of dorsiflexion of the ankle, peak torque (strength) of the plantar flexor muscles, and peak plantar pressures on the forefoot). Only the results of the first two outcomes will be presented

INTERNAL VALIDITY

Allocation [13] Randomisation by a prearranged computer generated program	Comparison of study groups [14] similar to given characteristics	Blinding [15] Not blinded	Treatment/ measurement bias [16] Similar in both groups	Follow-up (ITT) [17] one death in surgical group: 1/31= 2.3%; Patients were followed till they were lost for follow up (Kaplan Meier analysis)

Overall quality assessment (descriptive) [18] Of good to moderate mainly because it is not blinded

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]

Healing of ulcers: Days to healing: Recurrence among those available for follow up during: First 6 months: Two years after:	30/30=100.0% 41 ± 28 days 4/27=14.8% 10/26=38.5%	29/33=87.8% 58 ± 47 days 16/27=59.2% 21/26=80.8%	RR = 1.14 [1.00, 1.14] P=ns RR=0.25 (0.09-0.58) RR=0.47 (0.32-0.76)	NNT = 8 [8, 1473] Harms (NNH) [24]95% CI [25] - Recurrence: 6 months: 2.25 (1.6-5.2) 2 years: 2.36 (1.6 -6.2)
	Clinical importance (1-4) [26] 1 A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] Heal ulcer was reported in 4 of the 31 surgical patients (13%); similar proportions of patients in both groups developed superficial skin abrasions because of the cast; one patient from the surgical group developed deep infection that required debridement; one death was reported among the surgical group and the cause was myocardial infarction				
EXTERNAL VALIDITY				
Generalisabilty [29] Good generalisability				
Applicability [30] The benefits may outweigh the harms; the surgical patients were significantly at less risk to developing a recurrent ulcer.				
Comments [31]				

STUDY DETAILS

Reference [1] Mueller, M. J., D. R. Sinacore, et al. (2004). "Impact of achilles tendon lengthening on functional limitations and perceived disability in people with a neuropathic plantar ulcer." Diabetes Care 27(7): 1559-1564.

Affiliation/source of funds [2] Washington University School of Medicine, St. Louis, Missouri; USA. Funding was provided by the National Centre for Medical Rehabilitation Research, and the National Institutes of Health Grant.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Washington University School of Medicine, St. Louis, Missouri; USA

Intervention [6] Patients with a history of diabetes, loss of protective sensation, limited ankle motion, and a recurrent forefoot ulcer underwent Achilles tendon-lengthening (ATL) and total contact casting (TCC) + standard wound care Sample size [7] 31patients. However, results are provided for 14	Comparator(s) [8] Patients with a history of diabetes, loss of protective sensation, limited ankle motion, and a recurrent forefoot ulcer were treated with only total contact casting (TCC) + standard wound care Sample size [9] 33. However, results are provided for 14

Selection criteria

Inclusion criteria –Inclusion criteria were a diagnosis of diabetes, inability to sense a 5.07 (10-g) Semmes Weinstein monofilament on at least one location on the plantar surface of the foot (indicating loss of protective sensation), a recurrent (i.e., two or more episodes) Wagner grade II ulcer on the plantar forefoot or toes, and ≤5° of passive dorsiflexion range of motion at the talocrural joint as measured using a goniometer with the knee extended.

Exclusion criteria – Patients were excluded from participation in the study if they were nonambulatory, had a history of rear foot Charcot fractures, had impaired circulation indicated by an ankle-arm index <0.45, or reported a history of significant health problems that rendered them medically unfit for surgery or postsurgical rehabilitation.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention (N=14)	Control (N=14)
Male %	78.6%	71.4%
Mean age (SD)	54.8 (9.5)	54.3 (9.9)
BMI (kg/m^2)	33.6 (6.0)	31.8 (6.8)
Type 2 diabetes mellitus %	78.6%	64.3%
Duration of diabetes, years, (SD)	19.9 (10.2)	17.9 (13.9)
HbA1c %	8.7 (1.8)	8.9 (2.0)

Length of follow-up [11] 8 months after primary treatment	Outcome(s) measured [12]Quality of life ,measured by SF-36

INTERNAL VALIDITY

Allocation [13] Randomisation by a prearranged computer generated program	Comparison of study groups [14] Similar to given characteristics. Nothing stated about size, depth, severity and duration of originally treated ulcer. No reporting about possible complications post surgery	Blinding [15] Not blinded	Treatment/ measurement bias [16] Similar	Follow-up (ITT) [17] 19/33=57.5% in study group; 17/31=54.8% in controls; ITT not applied

Overall quality assessment (descriptive) [18] Poor quality. A post hoc study, reporting results for a selection of the original cohort

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23]95% CI [25] No significant benefit
				Harms (NNH) [24] - 95% CI [25]
	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes, including quality of life	

Means (SD) of norm-based standardized SF-36 components for treatment (ATL) and control groups							
	ATL treatment group			Control group (TCC)			
	Before treatment	After treatment and healing	8 months after treatment and healing	Before treatment	After treatment and healing	8 months after treatment and healing	ANOVA group x test (p value) ATCvs.TCC
Physical functioning	31.8 (8.6)	27.7 (6.8)	28.1 (5.3)	31.7 (7.1)	32.8 (8.7)	38.9 (11.5)	0.015
Role physical	40.3 (10.5)	32.1 (13.7)	35.9 (9.5)	35.4 (11.5)	35.4 (11.5)	40.8 (10.4)	0.085
Bodily pain	43.9 (11.5)	44.4 (10.6)	42.9 (12.9)	45.6 (10.6)	44.9 (11.8)	49.6 (8.5)	0.64
General health	39.7 (11.8)	41.2 (11.8)	36.3 (9.6)	37.2 (11.1)	37.8 (8.5)	40.1 (11.2)	0.049
Vitality	48.1 (8.3)	48.1 (12.9)	45.8 (11.0)	45.5 (10.9)	44.4 (9.9)	47.3 (11.7)	0.45
Social functioning	42.8 (12.4)	40.2 (15.7)	38.6 (16.3)	40.8 (12.3)	42.2 (11.8)	44.9 (10.6)	0.50
Role emotional	45.9 (12.2)	43.6 (13.8)	45.1 (12.6)	46.0 (14.1)	46.0 (13.4)	49.4 (10.2)	0.88
Mental health	48.4 (11.5)	51.1 (12.0)	50.0 (9.9)	47.0 (7.5)	43.7 (11.5)	50.4 (10.1)	0.56
Physical summary score	35.5 (6.9)	31.3 (8.0)	31.0 (6.2)	33.9 (7.5)	35.0 (7.7)	39.4 (10.9)	0.035
Mental summary score	51.2 (12.3)	52.7 (15.5)	51.6 (13.0)	49.9 (11.3)	48.2 (13.3)	51.8 (11.5)	0.56

Any other adverse effects [28] Not reported

EXTERNAL VALIDITY

Generalisabilty [29] Poor generalisability, a post hoc analysis, not clear how this sub-group was selected

Applicability [30] Benefits do not outweigh harms. Re-ulceration was similar in both of these groups and quality of life measured by SF-36 showed no difference between the groups in most of the components. However, the study group had lower scores than the controls in physical functioning and physical summary at the 8-month follow-up.

Comments [31]

STUDY DETAILS

Reference [1] Peters, E. J., L. A. Lavery, et al. (2001). "Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial." Archives of Physical Medicine & Rehabilitation 82(6): 721-725.

Affiliation/source of funds [2] University of Texas Health Sciences Centre, San Antonio, TX, USA. Supported by South Texas Health Research Centre

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] One university medical centre, Texas, USA

Intervention [6]	Comparator(s) [8]
Diabetics with foot ulcers treated with an electric stimulation through microcomputer every night for 8 hours + conventional wound therapy (weekly debridements, topical hydrogels, and off-loading with removable cast walkers Sample size [7] 20 patients	Diabetics with foot ulcers received a sham treatment using similar devices as the intervention group but no current was delivered + conventional wound therapy (weekly debridements, topical hydrogels, and off-loading with removable cast walkers Sample size [9] 20 patients

Selection criteria

Inclusion criteria – Diabetics with foot ulcers classified as grade 1A-2A using the University of Texas Diabetic Wound Classification System, with transcutaneous oxygen tension of greater than 30 mmHg measured at the dorsum of the affected foot.

Exclusion criteria – If patients had soft tissue or bone infection, malignancy, or any cardiac conductivity disorder.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention	Control
Age mean (SD)	59.9 (7.0)	54.4 (12.4)
Male %	80%	95%
Mean duration of diabetes year (SD)	17.0 (7.5)	16.4 (11.6)
Ulcer duration, months (SD)	5.5 (13.0)	5.0 (6.4)
With neuropathy %	100%	100%
Wound area cm^2	3.54 (5.56)	1.63 (1.51)
Glycosylated Haemoglobin %, (SD)	9.5 (2.4)	9.2 (2.1)
Peak plantar pressure Ncm^2	81.5 (21.9)	91.1 (15.7)
Transcutaneous oxygen tension (mm Hg)	43.4 (10.6)	47.1 (13.0)
Semmes-Weinstien monofilament	1.9 (2.4)	3.2 (3.0)
Vibratory perception threshold	41.5 (12.1)	38.5 (9.6)

Length of follow-up [11]	Outcome(s) measured [12]
Till healing or maximum 12 weeks	Proportion of healed ulcers, time to heal, and compliance with use of device

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias	Follow-up (ITT) [17]
Randomisation method not stated	The two groups were similar	Double blind	[16] Similar follow ups to both groups; outcomes evaluated via VERG videometer	Drop-outs: 2/20=10% from treatment; 3/20=15% from controls. ITT was applied

Overall quality assessment (descriptive) [18] Of good quality

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23]95% CI [25] No statistic benefits seen.
Healing:	13/20=65%	7/20=35%	RR=1.86 (0.96-12.37)	3.33 (1.79-inf)
Healing among compliant patients:	10/14=71%	5/13=39%	RR (among the complaint patients):1.86 (0.922-3.65)	Harms (NNH) [24] - 95% CI [25]
Compliance %:	14/20=70%	13/20=65%	Compliance: *p*=0.736	
Time to healing:	6.8 ± 3.4 weeks	6.9 ± 2.8 weeks	Time to healing: *p*=ns	
Infection:	2/20=10%	2/10=10%	Infection: *p*=ns	

	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.	Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes
Any other adverse effects [28] Infection was reported in 2 patients in treatment group and 2 patients from the control group. One patient in the control group underwent an amputation due to osteomyelitis		
EXTERNAL VALIDITY		
Generalisabilty [29] Moderate to good generalisability; the authors do not elaborate how many patients were first assessed before including these 40 patients		
Applicability [30] The benefits do not outweigh the harms. No significant benefits were seen between the groups although the authors concluded that electrical stimulation is beneficial for wound healing.		
Comments [31]		

STUDY DETAILS

Reference [1] Petrofsky, J. S., D. Lawson, et al. (2007). "The influence of local versus global heat on the healing of chronic wounds in patients with diabetes." Diabetes Technology & Therapeutics 9(6): 535-544.

Affiliation/source of funds [2] Loma Linda University, California; University of Nevada, Reno, Nevada; Azusa Pacific University, Azusa, California, USA. Source of funding was not stated.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Wound Centre, Loma Linda University, Loma Linda, California, USA

Intervention	Comparator(s)
Intervention [6] Global heat group: Diabetics with feet ulcers received global heat in a room with temperature of 32ºC for 20 minutes + electrical stimulation provided by a computerised current-controlled Challenge 8000 powered muscle stimulator with a frequency of 30 Hz (3 times per week for 4 weeks) + standard ulcer care including debridement, cleaning, and wet dressing of all ulcers (that took place before and during study). Sample size [7] 10 patients Intervention [6] Local heat group: Diabetics with feet ulcers received local heat using an infrared heat lamp for 20 minutes+ electrical stimulation provided by a computerised current-controlled Challenge 8000 powered muscle stimulator with a frequency of 30 Hz + (3 times per week for 4 weeks) + standard ulcer care including debridement, cleaning, and wet dressing of all ulcers (that took place before and during study). Sample size [7] 9 patients	Comparator(s) [8] controls: Diabetics with feet ulcers who did not receive any heat or electrical stimulation therapy + standard ulcer care including debridement, cleaning, and wet dressing of all ulcers (that took place before and during study). Sample size [9] 10 patients

Selection criteria

Inclusion criteria – Type 2 diabetics with neuropathic feet ulcers that showed no sign of healing for at least 2 months prior to the onset of the study

Exclusion criteria – History of cardiovascular disease except for poor circulation in the feet and mild hypertension. Patients were excluded if treated with alpha or beta blockers or nitric oxide. Exclusion also included infection in the past 2 months and ankle-brachial index of less than 0.95; loss in sensation in response to a 10-g Semmes-Weinstein monofilament around the ulcer; smokers; treatment with hyperbaric oxygen, electrical stimulation, or nerve growth factor during the 2 moths prior to the study.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Global heat	Local heat	Control
Mean age, (SD)	64.7 (13.2)	62 (7.7)	63 (7.6)
Mean weight, (SD)	77.7 (11.1)	88.2 (16.9)	111.7 (24)
Mean height, (SD)	173.5 (8.6)	169.2 (9.4)	165.2 (11.3)
Ulcer size cm^2, (SD)	8.3 (1.8)	7.1 (1.6)	0.5 (0.2)
Ulcer depth cm, (SD)	0.6 (0.3)	18.9 (10.9)	9.0 (1.8)
Duration of ulcer, months (SD)	10.6 (8.1)	18.9 (10.9)	18.4 (7.7)
HbA1c %, (SD)	8.5 (2.4)	8.9 (3.4)	9.1 (4.2)
Duration of diabetes, years (SD)	11.1 (2.3)	9.6 (3.1)	10.6 (4.2)

Length of follow-up [11] 4 weeks	Outcome(s) measured [12] Blood flow in area of ulcer (a less significant outcome for our study and the results of blood flow will not be presented here); healing rate

INTERNAL VALIDITY

Allocation [13] Method of randomisation not stated	Comparison of study groups [14] Similar for the known characteristics	Blinding [15] Not blinded	Treatment/ measurement bias [16] Similar	Follow-up (ITT) [17] Drop outs were not reported

Overall quality assessment (descriptive) [18] Of good quality, though the study has a small sample in each group, and is not blinded

RESULTS

<table>
<tr><td rowspan="2">Outcome [19]
Healing rate measured as reduction in ulcer cross sectional area::</td><td>Intervention group [20]
Global heat:
70.7 ± 16.9%
Local heat:
55.3 ± 31.2%</td><td>Control group [21]
In the control group, no reduction was seen but rather the ulcer area increased: 3.7 ± 8.0%</td><td rowspan="2">Measure of effect/effect size [22]
95% CI [25]
Global heat vs. Local heat: p<0.05
Significant tests were not provided versus the controls.</td><td>Benefits (NNT) [23]
NNT cannot be calculated
95% CI [25]</td></tr>
<tr><td></td><td></td><td>Harms (NNH) [24]
95% CI [25] -</td></tr>
<tr><td></td><td colspan="2">Clinical importance (1-4) [26] 1 A clinically important benefit for the full range of plausible estimates.</td><td colspan="2">Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes</td></tr>
<tr><td colspan="5">Any other adverse effects [28] Non reported</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Moderate generalisability, the recruiting process is not clear</td></tr>
<tr><td colspan="5">Applicability [30] Benefits could outweigh the harms</td></tr>
<tr><td colspan="5">Comments [31]</td></tr>
</table>

STUDY DETAILS

Reference [1] Piaggesi, A., E. Schipani, et al. (1998). "Conservative surgical approach versus non-surgical management for diabetic neuropathic foot ulcers: a randomized trial." Diabetic medicine : a journal of the British Diabetic Association 15(5): 412-417.

Affiliation/source of funds [2] Institudo di Clinica Medica II, Universita di Pisa, Italy. Source of funding of the study is not stated.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Outpatient clinic in one medical centre in Pisa, Italy

Intervention [6]] Diabetic patients with foot ulcers underwent surgical intervention that included debridement including the removal of bone segments underlying the lesion, surgical closure and relief of weight bearing for 4 weeks + irrigation of ulcers with povidone iodine 50% and saline 50% (twice a week) Sample size [7] 21 patients with 22 ulcers	Comparator(s) [8] Diabetic patients with foot ulcers receiving conventional therapy consisting of relief of weight-bearing, and regular saline dressings (once every 24 hours) after initial debridement and irrigation of ulcers with povidone iodine 50% and saline 50% Sample size [9] 21 patients with 24 ulcers

Selection criteria (Out of the 234 patients presenting to the outpatient clinic for the first time during 1995, 53 patients (22.6%) fulfilled the inclusion and exclusion criteria. However, only 41 patients were randomised. The remaining either refused or could not comply with the treatment.)

Inclusion criteria – Diabetic patients of known diabetes not less than 5 years who presented to the clinic for the first time, with one or more painless foot neuropathic ulcers (symptomatic peripheral neuropathy assessed with the Michigan Neuropathy Screening Instrument, absence of ankle reflexes, and abnormal vibration perception threshold (VPT>25V) at malleolus and first toe).

Exclusion criteria – Exclusion criteria included the presence of symptomatic claudication or absence of foot pulses, recent ketoacidosis, and renal failure as suggested by creatinine higher than 177 umol/l, osteomyelitis and presence of infection. Patients with congenital foot deformities or diabetic neuroarthropathy, body mass index > 30 kg/m^2, clinical history of stroke, cardiac failure, cancer, HIV, or history of mental illness were also excluded. An ankle-brachial pressure index (ABPI) less than 0.9 excluded patients from the study.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention (group B)	Control (group A)
Mean age (SD)	65.5 (9.9)	63.2 (13.5)
Duration of diabetes, years (SD)	16.8 (10.6)	18.2 (8.4)
HbA_{1c}, % (SD)	8.9 (2.2)	9.5 (3.8)
Diabetes type 2, %	90.5% 19/22	80.9% 17/24
Body mass index	28.1 (13.0)	27.7 (9.4)
VPT at first toe (V)	48.4 (24.2)	46.1 (18.2)
VPT at malleolus (V)	43.2 (15.2)	40.1 (11.9)
Maximum diameter of ulcer (cm)	4.32 (1.95)	4.25 (2.35)
Maximum depth of ulcer (cm)	1.98 (1.1)	1.58 (2.2)
Duration of ulcer (days)	39.4 (18.9)	32.7 (19.3)
Location of ulcer: Plantar	59% 13/22	67% 16/24
Medial first MTF joint	23% 5/22	21% 5/24
Lateral fifth MTF joint	18% 4/22	8% 2/24
Upper side of toes	0% 0/22	4% 1/24
Wagner grade: 1	64% 14/22	67% 16/24
2	36% 8/22	33% 8/24

Length of follow-up [11] 6 months	Outcome(s) measured [12] Healing rate, healing rate, occurrence of infection, relapse of ulcer within a 6-month period and subjective discomfort

INTERNAL VALIDITY

Allocation [13] Allocation according to a table of randomisation	Comparison of study groups [14] No differences seen.	Blinding [15] Not blinded	Treatment/ measurement bias [16] Similar in both groups.	Follow-up (ITT) [17] No drop outs were reported

Overall quality assessment (descriptive) [18] The study is of moderate quality mainly because of the non blinding nature of the study. No significant benefits were seen in healing, recurrence of infections or in infection rates, though the authors reported that all their results were statistically significant!

RESULTS

<table>
<tr><td rowspan="2">Outcome [19]

Healing of ulcers:
Healing time (days):
Infections:
Recurrence of ulcers:
No. of amputations
Levels of satisfaction and lower discomfort:</td><td>Intervention group [20]
21/22 (95.5%)
46.7 ± 38.9
1/22 (4.5%)
3/22 (13.6%)
0/21 (0%)</td><td>Control group [21]
19/24 (79.2%)
128.9 ± 86.6
3/24=12.5%
8/24=33.3%
1/21 (4.8%)</td><td>Measure of effect/effect size [22] 95% CI [25]
RR= 1.21 (0.96 - 1.31)
P value for healing time:<0.001
RR = 0.36 [0.05, 2.39]
RR = 0.41 [0.13, 1.23]
RR = 0.00 [0.00, 3.78]
P values for:
p<0.01: Satisfaction p<0.05; less discomfort:: p<0.05; less restrictions</td><td>Benefits (NNT) [23]
Non significant differences; no significant benefit seen, except for time to heal, and subjective patients measures
95% CI [25]

Harms (NNH) [24]
95% CI [25]
Non significant differences in infection rates</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.</td><td colspan="2">Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms</td></tr>
<tr><td colspan="5">Any other adverse effects [28] Other than the reported infection, one patient in the control group had an amputation due to worsening in his condition.</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Moderate, since the gender of the patients was not reported.</td></tr>
<tr><td colspan="5">Applicability [30] No significant benefits were seen in those who healed in both groups although the authors reported otherwise. Cannot say that benefit will outweigh harms, since the non-surgical patients fared similarly like the surgical ones.</td></tr>
<tr><td colspan="5">Comments [31]</td></tr>
</table>

STUDY DETAILS

Reference [1] Pieber, T. R., A. Holler, et al. (1995). "Evaluation of a Structured Teaching and Treatment Program for Type-2 Diabetes in General-Practice in a Rural Area of Austria." Diabetic Medicine 12(4): 349-354.

Affiliation/source of funds [2] Department of Internal Medicine, Karl-Franzens University, Auenbruggerplatz, Graz, Austria. Sourvce of funding was not stated.

Study design [3] Controlled trial	Level of evidence [4] III-2	Location/setting [5] In a rural area in southern Austria seven general practices

Intervention [6] Participants received a structured diabetes treatment and teaching program for non-insulin treated Type 2 diabetics patients (DTTP) + routine patient care provided by the GPs. The DTTP consisted of 4 weekly teaching sessions (90-120 min each) for groups of 4 to 8 patients. Throughout the program the patients would learn the following: basic information about diabetes, self monitoring and glycosuria, about dietary measures and weight reduction, and the advantages of non-pharmacological therapy of type 2 diabetes. They would also learn about foot care, physical activity, sick day rules and late complications of diabetes Sample size [7] 53 patients	Comparator(s) [8] Controls did not receive the educational program and had only the routine patient care provided by their GPs Sample size [9] 55 patients

Selection criteria

Inclusion criteria – Patients with non-insulin-treated Type 2 diabetes without any physical or mental handicap that would prevent patients from complying with the treatment

Exclusion criteria – Patients with any physical or mental handicap that would prevent patients from complying with the treatment

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention N=45	Control N=49
Mean age, (SD)	63.9 (8.2)	65.4 (11.2)
Male %	42%	47%
Duration of diabetes, years (SD)	7.6 (5.6)	6.9 (6.1)
Height, cm (SD)	165 (9)	165 (9)
Weight, kg (SD)	82.1 (14.5)	81.8 (13.1)
Body Mass Index (kg/m^2)	30.2 (4.7)	30.2 (4.5)
HbA1c % (SD)	8.6 (1.8)	8.8 (2.1)
Initial ulcers	1/45=2.2%	2/49=4.1%
Callus at baseline	35/45=77.8%	40/49=81.6%

Length of follow-up [11] 6 months	Outcome(s) measured [12] weight reduction, difference in HbA_{1c} levels, Systolic and diastolic blood pressure, serum triglycerides, serum cholesterol, diabetes-related knowledge, reduction in costs and callus formation. Only the last two outcomes will be reported in this review. The authors also reported minimal data on amputation and healing of ulcers.

INTERNAL VALIDITY

Allocation [13] Not randomised	Comparison of study groups [14] Similar to given characteristics	Blinding [15] Not blinded	Treatment/ measurement bias [16] Similar	Follow-up (ITT) [17] Loss to follow up: intervention: 8/53=15.1%; controls: 6/55=10.9%. ITT was not applied

Overall quality assessment (descriptive) [18] of moderate quality, non blinded, non randomized trial, without ITT analysis.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] - 95% CI [25]

Callus formation: At baseline: At follow up: Interdigital cracks / fissures or mycosis: Baseline: Follow up: Healing of the ulcer: Amputation:	 35/45=77.8% 22/45=48.9% *P* value < 0.001 26/45=57.8% 22/45= 48.9% 1/1=100% 1/45=2.2%	 40/49=81.6% 40/49=81.6% 26/49=53.1% 32/49= 65.3% 1/3=33.3% 1/49=2.0%	 RR = 0.60 [0.43, 0.83] NNT 3 [2, 7] RR = 1.09 [0.76, 1.55] RR = 0.75 [0.53, 1.06]; p<0.05 p = ns RR = 1.09 [0.11, 10.34] p = 0.951	Harms (NNH) [24] - 95% CI [25]
	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	
Any other adverse effects [28] Non reported				
EXTERNAL VALIDITY				
Generalisabilty [29] Moderate generalisability. Inclusion and exclusion criteria were too broad.				
Applicability [30] Callus formation was decreased in the intervention group. The benefits may outweigh the harms; however the study has many flaws.				
Comments [31]				

STUDY DETAILS

Reference [1] Plank, J., W. Hass, et al. (2003). "Evaluation of the impact of chiropodist care in the secondary prevention of foot ulcerations in diabetic subjects." Diabetes Care 26(6): 1691-1695.

Affiliation/source of funds [2] Karl-Franzens University Hospital, Graz, and Joanneum Research, Institute of Medical Technologies and Health Management, Graz, Austria

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Diabetic foot clinic, Karl-Franzens University Hospital, Graz, Austria

Intervention [6] Patients whose foot ulcers healed got instructions how to prevent recurrence of foot ulcers, and were informed about the possible benefits from regular chiropody care. The patients were asked to see the chiropodist at least once a month for 1 year. The treatment was free of charge. Sample size [7] 47 patients	Comparator(s) [8] Patients whose foot ulcers healed got instructions how to prevent recurrence of foot ulcers, and were informed about the possible benefits from regular chiropody care. However, chiropodist treatment was not specifically recommended. The list of the chiropodists was available for them. If they decided to visit a chiropodist the treatment was not free of charge. They were asked to report their visits to the study centre. Sample size [9] 44 patients

Selection criteria

Inclusion criteria – Diabetic patients whose foot ulcers healed were invited to participate. The patients had type 1 or 2 diabetes mellitus according to the World Health Organisation criteria. Inclusion required neuropathy assessed by reduced sensitivity to vibration of a graduated 128-HZ tuning fork or absence of sensation to a 5.07 monofilament.

Exclusion criteria – Not stated

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention group (N=47)	Control group (N=44)
Mean age, (SD)	64 (10)	65 (11)
Male %	22/47=46.8%	18/44=40.9%
Caucasian ethnicity %	100%	100%
Type 1 diabetes %	6.4%	6.8%
Duration of diabetes, years (SD)	18 (11)	14 (10)
BMI (kg/m^2), (SD)	28.4 (4.5)	28.6 (4.3)
HbA1c %	8.5 (1.6)	8.4 (1.6)
RR systolic/diastolic (mmHg)	147/80	133/80
Insulin therapy %	80.8%	65.9%
Retinopathy %	59.6%	56.8%
Nephropathy %	44.7%	43.2%
Peripheral vascular disease %	46.8%	45.4%
Therapeutic shoes %	59.6%	59.1%
Past below ankle amputation %	25.5%	29.5%
Past above ankle amputation %	4.2%	6.8%

Length of follow-up [11] Median follow up of 386 days	Outcome(s) measured [12] Ulceration

INTERNAL VALIDITY

Allocation [13] Randomisation method not stated	Comparison of study groups [14] Similar to given characteristics	Blinding [15] Not blinded	Treatment/ measurement bias [16] Similar, 12 months after the study started	Follow-up (ITT) [17] No drop outs were reported

Overall quality assessment (descriptive) [18] Of moderate quality, non-blinded study, exclusion criteria were not stated; chiropodists treating the intervention group were not paid whereas those who treated patients from the control group (those who chose to visit chiropodists) were remunerated. This could have been a source of confounding. The authors do not state how many from the controls actually visited a chiropodist

RESULTS

<table>
<tr><td>Outcome [19]
<u>Intention to treat analysis</u>:
Ulceration:
Per person:
Per feet:

Amputation:</td><td>Intervention group [20]

18/47=38.3%
20/92=21.7%

2/47=4.2%</td><td>Control group [21]

25/44=56.8%
32/85=37.6%

1/44=2.3%</td><td>Measure of effect/effect size [22] 95% CI [25]

Ulceration:
Per person: RR=0.67 (0.43-1.04)
Per feet: RR= 0.59 (0.37-0.94)

Amputation: RR=1.87(0.25-14.20)</td><td>Benefits (NNT) [23] 95% CI [25]
Ulceration:
Per person: 5.39 (2.66-inf)
Per feet: 6.48 (3.59-53.3)
Harms (NNH) [24]
95% CI [25] Amputation, not statistically significant:
50.4(17.9-inf)</td></tr>
<tr><td></td><td colspan="2">Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.</td><td colspan="2">Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms</td></tr>
<tr><td colspan="5">Any other adverse effects [28] Four patients from the control group and two patients from the intervention group died from cardiovascular events, not related to study.</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Moderate generalisability, exclusion criteria were not provided</td></tr>
<tr><td colspan="5">Applicability [30] Benefits may outweigh harms</td></tr>
<tr><td colspan="5">Comments [31]</td></tr>
</table>

STUDY DETAILS

Reference [1] Rettig, B. A., D. G. Shrauger, et al. (1986). "A randomized study of the effects of a home diabetes education program." Diabetes Care 9(2): 173-178.

Affiliation/source of funds [2] Nebraska Department of Health, Lincoln, Nebraska; St Vincent's Medical Centre, Bridgeport, Connecticut; Creighton University School of Medicine, Omaha, Nebraska; and the University of Nebraska Medical Centre, Omaha, Nebraska, USA. The study was supported by the Centres for Disease Control, U.S. Public Health Service.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Nebraska, USA

Intervention [6]	Comparator(s) [8]
Enrolled diabetic patients were assigned to receive home teaching given by nurses. The instructions given were tailored to the needs of every subject. The number of visits necessary to complete a teaching program was decided by the nurse, although no more than 12 visits were allowed for the instruction of any individual subject. They were also free to participate in any type of diabetic-patient education while simultaneously receiving the home education. Sample size [7] 228 patients; results described for only 180 patients	Enrolled control diabetic patients did not receive home teaching, but these were free to participate in any type of diabetic-patient education while enrolled in the study if they so desired or if recommended by health professionals. Sample size [9] 243 patients; results described for only 193 patients

Selection criteria

Inclusion criteria – Potential subjects were required to be younger than 65 years (this was later dropped), free of terminal illness (this was not met in every case due to lack of specific criteria), a resident of the 39-county target area, and to have physician approval to participate in the study. Eligibility was not subject to economic status. Subjects were recruited from among diabetic inpatients identified by designated home health agency or county health department personnel at participating hospitals. The pool of potential subjects consisted exclusively of hospitalized diabetic individuals.

Exclusion criteria – Not stated

Patient characteristics [10] Intervention group – Comparator group(s) – (For analysis population)

	Intervention (N=180)	Control (N=193)
Mean age , (SD)	50.9 (17.2)	52.9 (17.7)
Male %	32.8	34.2
White race %	90.6	92.7
Mean year of formal education, (SD)	10.9 (2.9)	11.4 (2.7)
Mean duration of diabetes, years, (SD)	7.8 (9.2)	7.5 (9.3)
Insulin dependent diabetes mellitus, %	24.1	23.0
Previous diabetes education, %	74.3	78.4
Pre-enrolment hospitalization rates (per 1000 persons per year, (SE))		
Non-diabetes related	432.6 (83.2)	400.0 (69.5)
Non-preventable diabetes related	84.3 (28.7)	48.5 (17.6)
Preventable diabetes related	148.9 (31.1)	127.5 (20.1)
Mean length of hospital stay, days (SE)		
Non-diabetes related	7.21 (0.41)	6.44 (0.42)
Non-preventable diabetes related	7.36 (0.74)	6.36 (1.32)
Preventable diabetes related	5.46 (0.56)	5.56 (0.64)

Length of follow-up [11] 1 year	Outcome(s) measured [12] Hospitalization rates and hospital length of stay, visits to emergency department and foot appearance score (will be reported in this review); other outcomes included diabetes-related health knowledge and skills, physician visits, days inactive due to illness (these will not be reported in this review)

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Randomisation method was not stated	Similar to the given characteristics	Not blinded	Similar. All were assessed 6 months after study (nurse visit) and 1 year following via telephone interview	drop outs: Intervention: 48/228=21.0%; Controls: 50/243=20.6%. ITT was not applied

Overall quality assessment (descriptive) [18] Of moderate quality; non blinded RCT, around 20% of the original subjects were excluded before analysis and ITT was not applied, no information is given on the characteristics of those excluded or lost to follow up; selection bias of the participants cannot be excluded; Some tools used in the study (to assess knowledge and acquired skills after the intervention) lacked reliability and validity;

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] - 95% CI [25]
Post-enrolment hospitalization rates (per 1000 persons per year, (SE))			P values:	Harms (NNH) [24] - 95% CI [25]
Non-diabetes related	544.4 (81.8)	440.4 (58.2)	Ns	
Non-preventable diabetes related	66.7 (23.1)	82.9 (33.1)	Ns	
Preventable diabetes related	94.4 (35.8)	41.5 (16.1)	Ns	
Mean length of hospital stay, days (SE)				
Non-diabetes related	7.07 (0.59)	7.40 (0.62)	Ns	
Non-preventable diabetes related	14.41 (4.41)	8.06 (1.56)	Ns	
Preventable diabetes related	6.88 (1.54)	6.13 (1.17)	Ns	
Mean foot appearance score (SE) At 6 months post enrolment (the higher the better the condition of the foot)	70.2 (0.7)	68.8 (0.7)	Ns	
Diabetes related emergency room visits during 6 months after study (mean, SE)	0.06 (0.02)	0.08 (0.02)	Ns	
	Clinical importance (1-4) [26] 3 The confidence interval does not include any clinically important effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	
Any other adverse effects [28] None related to study				
EXTERNAL VALIDITY				
Generalisabilty [29] Poor generalisability; the inclusion criteria were violated, no exclusion criteria were provided, selection bias of the participants cannot be excluded;				
Applicability [30] No benefits were seen. Benefits may not outweigh harms				
Comments [31]				

STUDY DETAILS

Reference [1] Rice, B., A. J. Kalker, et al. (2001). "Effect of biofeedback-assisted relaxation training on foot ulcer healing." Journal of the American Podiatric Medical Association 91(3): 132-141.

Affiliation/source of funds [2] Epidemiology Clinical research centre, university of Minnesota; University of Wisconsin Medical school, Madison; Oregan State University, Corvallis, USA. The study was supported by grants from the University of Wisconsin Foundation, Lutheran Hospital-La Cross Foundation and La Cross community Foundation.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Outpatient clinics at the affiliated institutions

Intervention [6] Patients with non-healing lower extremity ulcers received one session of training in biofeedback-assisted relaxation, muscular relaxation, focused breathing (teaching them the underlying concepts of vascular physiology and explained the possible physical sensations associated with peripheral warming). At home, the patients would practice the relation technique using a 16-minute audiocassette tape recording of the technique for a minimum of 5 days each week. Great toe temperature was measured both before and after relaxation and recorded.

The patients also received standard wound care which included regularly scheduled biweekly office visits, with examination and debridement of the foot ulcer. Relieving pressure on the wound was addressed and if the ulcer got infected the patients were treated with topical or oral antibiotics.

Sample size [7] 16 patients

Comparator(s) [8] Patients with non-healing lower extremity ulcers were advised to relax 15 to 20 minutes daily using a self-selected method of relaxation (e.g. listening to music, watching TV, or daydreaming) while off their feet.

The patients also received standard wound care which included regularly scheduled biweekly office visits, with examination and debridement of the foot ulcer. Relieving pressure on the wound was addressed and if the ulcer got infected the patients were treated with topical or oral antibiotics.

Sample size [9] 16 patients

Selection criteria

Inclusion criteria – Patients with chronic non-healing ulcers on the extremities with or without diabetes were recruited from the affiliated institutions. Inclusion criteria: 1) ulcer duration of more than 8 weeks, 2) continuous care by a podiatric physician for more than 2 months prior to entering the study, and 3) ulcer after debridement categorised as class 2 through 6 under the Seattle Wound Classifications System. (Class 2 refers to an ulcer or abscess due to acute soft tissue infection, and class 6 refers to full-thickness ulcer covered by eschar.

Exclusion criteria – Bone involvement and osteomyelitis, or patients who needed reconstructive or vascular surgery after study or who did not meet the criteria for compliance with experimental management.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention N=16	Control N=16			Intervention N=16	Control N=16
Mean age, (SD)	57.1 (14.5)	69.1 (9.7)		Ulcer class (Seattle wound classification system)	4.31 (1.25)	3.69 (0.95)
Male %	37.5	43.7		Ulcer duration, weeks(SD)	25.0 (18.0)	20.8 (18.0)
Diabetes mellitus (DM) %	50%	50%		Skin condition(0 poor 8, bad)	2.62 (1.20)	2.12 (0.96)
Type 1 diabetic % Duration of DM, years (SD)	5/8=62.5% 29.6 (5.8)	2/8=25% 28.0 (0)		Ulcer area, mm^2 (SD) Median	233.6(343.06) 102.24	57.42 (71.50) 36.53
Type 2 diabetic % Duration of DM, years (SD)	3/8=37.5% 14.6 (4.5)	6/8=75% 13.3 (8.6)		Ulcer perimeter, mm, (SD) Median	50.30 (34.38) 44.45	27.23 (15.87) 26.07
Pedal pulses (0 none, 4 excellent)	1.94 (1.39)	0.94 (1.24)		Vibratory measure (0 severe loss, to no loss 3)	1.94 (1.00)	1.63 (1.09)
Pain level (0 none, 9 constant)	3.12 (2.42)	2.81 (2.74)		Perception of nerve fibres Coarse (Hz) Medium (Hz) Small (Hz)	 410 (202) 219 (161) 115 (113)	 442 (152) 190 (121) 76 (51)
Patient ambulation (1 mostly sitting to 4 mostly on feet)	2.75 (1.48)	2.00 (1.15)				

Length of follow-up [11] 3 months of follow up	Outcome(s) measured [12] Healing, healing rate, time to healing, ambulation and change in large peroneal nerve fibres. Only the first three outcomes will be reported in this review

INTERNAL VALIDITY

Allocation [13] Randomisation was stratified by diabetes condition status	Comparison of study groups [14] Similar to most presented characteristics. However, controls were significantly younger and with less ulcer perimeter than the intervention group.	Blinding [15] Assessors were blinded	Treatment/ measurement bias [16] Similar	Follow-up (ITT) [17] Unlikely
Overall quality assessment (descriptive) [18] Of poor quality, non blinded study				
RESULTS				
Outcome [19] Healing: All patients: Diabetic patients: Healing rate all, mm^2/day (SD) Time to healing all, days (SD)	Intervention group [20] 14/16=87.5% 7/8=87.5% 2.84 (3.45) 47.80 (23.80)	Control group [21] 7/16=43.7% 3/8=37.5% 0.56 (1.35) 64.60 (28.50)	Measure of effect/effect size [22] 95% CI [25] RR (all patients):2.0(1.18-2.74) RR (diabetics): 2.3 (1.04-3.56) *P* value=0.002 *P* value=ns	Benefits (NNT) [23]95% CI [25] Healing all: 2.29(1.63-8.95) Healing diabetics: 2.0 (1.42-38.79) Harms (NNH) [24] - 95% CI [25]
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	
Any other adverse effects [28] None reported				
EXTERNAL VALIDITY				
Generalisabilty [29] Moderate generalisability, a small sample of diabetics				
Applicability [30] Benefits may outweigh harms				
Comments [31]				

STUDY DETAILS

Reference [1] Santamaria, N., K. Carville, et al. (2004). "The effectiveness of digital imaging and remote expert wound consultation on healing rates in chronic lower leg ulcers in the Kimberley region of Western Australia (Structured abstract)." Primary Intention 12(2): 62-70.

Affiliation/source of funds [2] The Alfred Hospital Melbourne, University of Melbourne, Victoria; and Curtin University of Technology, Western Australia, Australia.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Four sites at the Kimberly region of WA, Australia

Intervention [6] Diabetic patients received standard wound care as determined by the local wound care clinician and their wounds were photographed and measured at each clinic attendance. These images and measurements were electronically transferred every 2 weeks to a wound care consultant located in Perth. These were then returned to their treating clinician with wound management advice Sample size [7] 50 patients	Comparator(s) [8] Diabetic patients received standard wound care as determined by the local wound care clinician and their wounds were photographed and measured at each clinic attendance Sample size [9] 43 patients

Selection criteria

Inclusion criteria – Documented diagnoses of chronic ulcer of the lower extremity; patient is treated as a wound care outpatient at one of the trial site hospitals; patient provided informed consent

Exclusion criteria – Under 18 years of age; Disorientation or mental impairment and unstable medical co-morbidity.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention	Control
Mean age	63.5	49.5
Male %	48%	62.8%
Wound site: n (%)		
Leg	42%	32.6%
foot	58%	67.4%
Ulcer aetiology, n (%)		
Venous	7 (14%)	1 (2.3%)
Arterial	1 (2%)	2 (4.6%)
Mixed	1 (2%)	4 (9.3%)
Diabetic	25 (50%)	11 (25.6%)
Traumatic	6 (12%)	12 (27.9%)
Surgical	5 (10%)	0 (0%)
Presure	3 (6%)	11 (25.6%)
Burn	2 (4%)	2 (4.6%)

Length of follow-up [11] 12 months	Outcome(s) measured [12] Healing rate, amputation, estimated treatment cost

INTERNAL VALIDITY

Allocation [13] The unit of randomisation was the clinic site and not the person. Method of randomisation not stated	Comparison of study groups [14] The controls were significantly younger than the intervention. Ulcer size, ulcer duration, are not reported.	Blinding [15] not blinded	Treatment/ measurement bias [16] Similar in both groups	Follow-up (ITT) [17] No drop outs were reported

Overall quality assessment (descriptive) [18] Of moderate quality, not blinded, randomisation was for the clinics and not the patients; patients visiting the various units could have differed; the controls tended to be younger and with less diabetes than the interventions group. Differences in other co-morbidities were not reported. The analysis controlled for sex and age and the significant differences in healing rate persisted between the intervention and controls.

RESULTS

<table>
<tr><td rowspan="2">Outcome [19]

Healing rate:
Amputation:
Estimated costs for similar number of patients in each group:</td><td>Intervention group [20]
6.82%
1/50=2.0%

$670,226</td><td>Control group [21]
-4.90%
6/43=13.9%

$862,161</td><td rowspan="2">Measure of effect/effect size [22] 95% CI [25]
P=0.012 for healing rate
RR=0.143 (0.023-0.856)</td><td>Benefits (NNT) [23]
95% CI [25]
Amputation: 8.36 (6.45-85.38)</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] 1 A clinically important benefit for the full range of plausible estimates.</td><td>Harms (NNH) [24]
-
95% CI [25]</td></tr>
<tr><td colspan="5">Any other adverse effects [28] Not reported</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Moderate to poor generalisability as not all ulcers were due to diabetes</td></tr>
<tr><td colspan="5">Applicability [30] Benefits could outweigh the harms</td></tr>
<tr><td colspan="5">Comments [31]</td></tr>
</table>

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] Shukrimi, A., A. R. Sulaiman, et al. (2008). "A comparative study between honey and povidone iodine as dressing solution for Wagner type II diabetic foot ulcers." The Medical journal of Malaysia 63(1): 44-6.</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2] Department of Orthopaedics, School of Medical Sciences, University Sains Malaysia; Department of Orthopaedics, Kulliyyah of Medicine, International Islamic University Malaysia. Funding is not stated.</td></tr>
<tr><td colspan="2">Study design [3]
RCT</td><td colspan="2">Level of evidence [4]
II</td><td colspan="2">Location/setting [5]
Hospital University Sains Malaysia</td></tr>
<tr><td colspan="3">Intervention [6] Honey dressing: clean non-sterile pure honey that is commercially used for food.
Sample size [7] Not reported
(It is reported that overall 30 patients participated but allocation was not indicated)</td><td colspan="3">Comparator(s) [8] Povidone iodine solution 10%

Sample size [9] Not reported</td></tr>
<tr><td colspan="6">Selection criteria
Inclusion criteria – NIDDM with Wagner grade-II ulcers; age between 35-65; transcutaneous oxygen tension of more than 30 mm Hg, and serum albumin levels of more than 35g/dl.
Exclusion criteria – Multiple medical co-morbidity, steroid therapy, neutrophil count less than 2000/mm^3.</td></tr>
<tr><td colspan="6">Patient characteristics [10]
Intervention group – Not reported. The only thing said was that both arms had equally distributed sex ratio. Both groups had infections on the start of the trial. It is not known which group had more infections or whether there were age differences or differences in ulcer sizes or duration of ulcer or if the two groups differed in terms of co-morbidity.
Comparator group(s) –same as above.</td></tr>
<tr><td colspan="3">Length of follow-up [11] Not clearly stated. The dressings were done on a daily basis and the wounds were followed till healing or a second debridement</td><td colspan="3">Outcome(s) measured [12] Wound readiness for surgical closure (healing)– not reported how this was evaluated.</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Not stated method of randomisation</td><td>Comparison of study groups [14]
Groups characteristics are not known</td><td>Blinding [15]
Assessor was blinded to intervention group.</td><td colspan="2">Treatment/ measurement bias [16] All measured by the same intervention-blinded assessor. However, easily one would know by asking the patient who was not blinded. And this could have introduced bias towards the alternative hypothesis.</td><td>Follow-up (ITT) [17]
Not stated. Unknown</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18]
Poor quality; unknown information about randomisation method, unknown baseline characteristics of the two groups; unknown number of patients in each arm; unknown detail about follow-up and ITT, bias could have also been introduced because of lack of patient blindness to treatment. The researchers do not report how many and of which intervention group had a second debridement.</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="2">Outcome [19]
Wound readiness for surgical closure</td><td>Intervention group [20]
Mean duration of 14.4 days to be ready for surgical closure</td><td>Control group [21]
Mean duration of 15.4 days to be ready for surgical closure</td><td>Measure of effect/effect size [22]
Not significant
95% CI [25] NS</td><td colspan="2">Benefits (NNT) [23] -
95% CI [25]

Harms (NNH) [24] -
95% CI [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] 4.
No significant differences were seen between the groups and no confidence intervals were reported</td><td colspan="3">Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes.</td></tr>
<tr><td colspan="6">Any other adverse effects [28] Not reported</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisabilty [29] Poor</td></tr>
<tr><td colspan="6">Applicability [30] Benefits do not outweigh harms. No benefits were seen</td></tr>
<tr><td colspan="6">Comments [31]</td></tr>
</table>

<table>
<tr><td colspan="5">STUDY DETAILS</td></tr>
<tr><td colspan="5">Reference [1] Steed, D. L., H. D. Edington, et al. (1996). "Recurrence rate of diabetic neurotrophic foot ulcers healed using topical application of growth factors released from platelets." Wound Repair & Regeneration 4(2): 230-233.</td></tr>
<tr><td colspan="5">Affiliation/source of funds [2] Department of Vascular Surgery and Wound Healing and Plastic and Reconstructive Surgery, University of Pittsburgh, PA, USA. Funding was not stated.</td></tr>
<tr><td>Study design [3]
Double-blind RCT</td><td colspan="2">Level of evidence [4]
II</td><td colspan="2">Location/setting [5] Diabetic patients from Department of Vascular Surgery and Wound Healing and Plastic and Reconstructive Surgery, University of Pittsburgh, PA, USA</td></tr>
<tr><td colspan="3">Intervention [6] Topical application of homologous platelet growth factor preparation
Sample size [7] The researcher stated that a total of 36 patients were randomised to either arm without stating method of randomisation or number of patients allocated to each arm. Of these 16 patients had healed ulcers. 14 of these belonged to the original intervention arm.
Thus for this study the intervention arm has 14 patients</td><td colspan="2">Comparator(s) [8] Application of buffered saline dressings identical in appearance to intervention dressing.
Sample size [9] It is reported that 2 of the 16 patients whose ulcers healed belonged to the control arm. The initial number of control is not stated.
The control has 2 patients.</td></tr>
<tr><td colspan="5">Selection criteria
Inclusion criteria – A transcutaneous partial pressure of oxygen (TcP02) of 30 mm Hg or greater; free of infection;
Exclusion criteria – Having more than 3 foot ulcers; presence of osteomyelitis;</td></tr>
<tr><td colspan="5">Patient characteristics [10]
Intervention group – It is generally stated that the two groups were comparable in ulcer area and duration and all subjects were outpatients.
Comparator group(s) – same as above</td></tr>
<tr><td colspan="3">Length of follow-up [11] Trial lasting for 20 weeks and average follow-up for ulcer recurrence among those whose ulcers healed was 25 months (range 24 to 30 months)</td><td colspan="2">Outcome(s) measured [12] Recurrence of ulcers among patients whose ulcers healed after intervention or placebo.</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Randomisation method was not reported</td><td>Comparison of study groups [14] Besides ulcer area and their duration, no other characteristic is provided.</td><td>Blinding [15]
Double blind</td><td>Treatment/ measurement bias [16]
Subjectively measured by blinded-to-initial treatment researcher (recurrence of wound)</td><td>Follow-up (ITT) [17]
Not reported for original study. For the occurrence of ulcers, all 16 patients were followed up.</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18] Of poor quality; Information about the intervention and placebo groups is not provided.</td></tr>
<tr><td colspan="5">RESULTS
The ulcers healed among 16 patients (44.4%) and from these11 patients' (69%) ulcers recurred. This included 10 patients</td></tr>
<tr><td rowspan="2">Outcome [19]

Recurrence:</td><td>Intervention group [20]

10/14=71.4%</td><td>Control group [21]

1/2 = 50%</td><td>Measure of effect/effect size [22]
95% CI [25]

RR: 1.4 (0.7-7.7)</td><td>Benefits (NNT) [23] - 4.6 (1.5-inf)
95% CI [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.</td><td colspan="2">Harms (NNH) [24] -
95% CI [25]
Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes</td></tr>
<tr><td colspan="5">Any other adverse effects [28] Not reported</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Poor external validity because of the unknown characteristics of the participants and about the selection of the study popul;ation</td></tr>
<tr><td colspan="5">Applicability [30] The method is not applicable because of compliance problems and no benefits were seen</td></tr>
<tr><td colspan="5">Comments [31] The dressings stayed for 12 hours and appliance to this strict protocol is difficult. Although compliance test was performed, the results were not reported.</td></tr>
</table>

STUDY DETAILS				
Reference [1] Steed, D. L., D. Donohoe, et al. (1996). "Effect of extensive debridement and treatment on the healing of diabetic foot ulcers." Journal of the American College of Surgeons 183(1): 61-64.				
Affiliation/source of funds [2] University of Pittsburgh, PA, USA, and the Robert Wood Johnson Pharmaceutical Research Institute, Raratan, NJ, USA. Source of funding was not stated.				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] 10 medical centres		
Intervention [6] Debridement plus topical treatment with recombinant human platelet-derived growth factors (rhPDGF) + repeat debridement of callus and necrotic tissue when necessary Sample size [7] Ulcer number: 279 ulcers	Comparator(s) [8] Debridement plus topical treatment with placebo + repeat debridement of callus and necrotic tissue when necessary Sample size [9] 301 ulcers			
Selection criteria Inclusion criteria – Patients were free of infection, ulcers were due to diabetic neuropathy, patients had adequate arterial oxygen supply as indicated by a transcutaneous oxygen tension of 30 mm Hg or greater; the wounds had been present for at least 8 weeks. Exclusion criteria – Poor diabetes control, renal failure, or abnormal liver function.				
Patient characteristics [10] Overall 118 patients were randomized between the intervention or control groups. The authors do not state the number of patients in each arm but rather the number of ulcers. Intervention group – Comparator group(s) – The authors state that there were no differences between the groups in terms of age, median ulcer area, duration of the ulcer, and the transcutaneous oxygen tension in the foot. No other details are provided.				
Length of follow-up [11] 20 weeks	Outcome(s) measured [12] Healing defined as 100% closure of ulcer			
INTERNAL VALIDITY				
Allocation [13] Method of randomization is not stated	Comparison of study groups [14] No differences between the groups for the stated variables. No data were provided	Blinding [15] Stated as double blind	Treatment/ measurement bias [16] Patients followed in a similar way in 10 centres.	Follow-up (ITT) [17] Lost to follow up is not stated
Overall quality assessment (descriptive) [18] Despite the double blind RCT, the authors do not report data on methods of randomization, methods of blinding, and variation between centres in terms of measuring outcome. The results were not adjusted for duration of antibiotic treatment, and for subsequent infections. Healing was achieved significantly more in the rhPDGF group compared to placebo. The authors concluded that debridement was vital adjunct in the care of diabetic foot ulcers. It is not clear how they reached such a conclusion since debridement was similar in both groups and the difference was the growth factor and not the debridement. Due to the many missing information, the trial is of moderate quality.				
RESULTS				
Outcome [19] % healing among patients: Subsequent debridements:	Intervention group [20] 48% healed 46.8%	Control group [21] 25% healed 48.0%	Measure of effect/effect size [22] Cannot be estimated (number of patients in each arm is not given) 95% CI [25] For healing difference: p=0.01 For subsequent debridement: p=0.7	Benefits (NNT) [23] - 95% CI [25] Harms (NNH) [24] - 95% CI [25]
	Clinical importance (1-4) [26] 2		Relevance (1-5) [27] 1	
Any other adverse effects [28] Not reported				
EXTERNAL VALIDITY				
Generalisabilty [29] Cannot judge due to missing information and therefore the generalizability would be poor.				
Applicability [30] Cannot judge if benefits outweigh harms because of missing information				
Comments [31]				

STUDY DETAILS		
Reference [1] Tan, J. S., N. M. Friedman, et al. (1996). "Can aggressive treatment of diabetic foot infections reduce the need for above-ankle amputation?" Clinical Infectious Diseases 23(2): 286-291.		
Affiliation/source of funds [2] North-eastern Ohio University College of Medicine, Rootstown; and the Department of Medicine and Orthopaedics, Summa Health System, Ohio, USA. Source of funding was not stated.		
Study design [3] Retrospective cohort	Level of evidence [4] III - 3	Location/setting [5] Akron City Hospital, Ohio, USA
A total of 112 patients with 164 diabetic limb infections participated. Infections were treated differently and the outcome was compared in a historic cohort study. The main outcome was above ankle amputation.		
Intervention [6] Group IIA: Patients who underwent debridement on foot ulcers within 3 days of admission + antibiotic therapy Sample size group IIA [7] 46 infections Intervention group IIB: Patients who underwent localized amputation within 3 days of admission + antibiotic therapy Sample size group IIB: 31 infections		Comparator(s) [8] Patients who received antibiotic treatment to foot infections without any surgical intervention Sample size [9] 87 infections
Selection criteria: Inclusion criteria – Patients admitted between 1982 and 1990 to Akron City Hospital and were participants in study protocols of antibiotic efficacy for serious diabetic foot infections. The initial criteria used in these antibiotic protocols are not stated and it is not clear who was recruited to the original study and who was left out. Exclusion criteria – Not provided.		
Patient characteristics [10] All patients: 50.9% male, 49.1% female; mean age of 58.7 years (ranging from 32 to 91 years); Type of infection: 19% cellulitis, 35% were subcutaneous, 7% were deep without osteomelitis, and 40% were deep with osteomyelitis. Site of infections were as follows: 68% forefoot, 12% were midfoot, 10% were hindfoot, and 10% were ankle. Intervention group – Not stated Comparator group(s) – Not stated		
Length of follow-up [11] 1 year from day of hospital admission		Outcome(s) measured [12] Below ankle amputation; length of hospital stay

INTERNAL VALIDITY				
Allocation [13] Not random.	Comparison of study groups [14] Possible confounding due to unknown severity of ulcer infection at baseline. No adjustment was done to sex, age, and co-morbidities.	Blinding [15] None	Treatment/ measurement bias [16] Measurement of outcome was done retrospectively by reviewing patients' medical charts and it was done similarly to all patients.	Follow-up (ITT) [17] Researchers did not report if any of the patients were lost to follow-up.
Overall quality assessment (descriptive) [18] Moderate. The documentation of the clinical findings and wound depth at admission were not well documented and were not consistent for all patients as reported by investigators. In such a retrospective study, the severity of wounds could not be compared at baseline, thus confounding by different severity levels cannot be excluded. The outcome (above ankle amputation) was followed for I year, and was limited to the same hospital, and to physicians' office. Missed outcomes cannot be excluded for patients who were admitted and operated in a different hospital. Follow-up was done also via phone calls but the investigators do not provide if any were lost to follow up. The results are descriptive and crude with no adjustment done to risk factors and confounders. The average LOS was higher in the non-surgical group, but this could have been confounded by the fact that these were sicker than the surgical patients and adjustment was not done.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Above ankle amputation in diabetic patients with infected ulcers.	Group II: 10/77=13.0% Group IIA: 4/46= 8.7% Group IIB: 6/31=19.3%	Control: 24/87=27.6%	Group II: 0.47 (0.24-0.90) Group IIA: 0.32 (0.79-0.12) Group IIB: 0.70 (1.46-0.31) Group IIA v Group IIB RR = 0.45 (0.14-1.39)	Group II: 6.85 (4.1-45.2) Group IIA: 5.3 (3.7-20.9) Group IIB: 12.15 (4.6-infinite)
Above ankle amputation in diabetic patients with deeply infected ulcers.	Group II: 10/50 = 20% Group IIA: 4/24= 16.7% Group IIB: 6/26= 23.1%	Control: 24/26= 92.3%	Group II: 0.22 (0.18-0.34) Group IIA: 0.18 (0.11-0.36) Group IIB: 0.25 (0.18-0.43) Group IIA v Group IIB RR = 0.72 (0.24, 2.14)	Group II: 1.38 (1.24-1.90) Group IIA: 1.32(1.16-1.91) Group IIB: 1.44(1.25-2.18)

Length of hospital stay (LOS) intervention Vs control groups	Mean LOS for surgery within 3 days of admission: group IIA: 12.2 group IIB: 9.6	Control: average 18 days		Harms (NNH) [24] 95% CI [25] -
	Clinical importance (1-4) [26] 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] none				
EXTERNAL VALIDITY				
Generalisabilty [29] Poor, as the criteria to enrol in the initial study were not stated. The characteristics of the patients by the different groups were not reported.				
Applicability [30] Cannot tell due to crude and unadjusted results.				
Comments [31]				

STUDY DETAILS				
Reference [1] Tom, W. L., D. H. Peng, et al. (2005). "The effect of short-contact tropical tretinoin therapy for Foot ulcers in patients with diabetes." Archives of Dermatology 141(11): 1373-1377.				
Affiliation/source of funds [2] Division of Dermatology, University of California and Department of Orthopaedic Surgery, Veterans Affairs Medical Centre, San Diego. Funding done by Ortho-Neutrogena.				
Study design [3] Randomized, double-blind, placebo controlled trial	Level of evidence [4] II	Location/setting [5] Outpatient clinic at a Veterans Affairs medical centre, San Diego, California, USA.		
Intervention [6] Administration of topical 0.05% tretinoin solution on foot ulcers in diabetics + standard treatment Sample size [7] 12 patients with 13 ulcers	Comparator(s) [8] treatment of Saline solution coloured the same as the tretinoin solution + standard treatment Sample size [9] 10 patients with 11 ulcers			
Selection criteria Inclusion criteria – Volunteers who were diabetic patients at the Foot Clinic at the Veterans Affairs Medical centre and who had a lower extremity ulcer. Exclusion criteria – Refused to participate; patients with a bleeding disorder; pregnant women,; patients with infected ulcers; patients with ulcers that were due to large artery disease;.				
Patient characteristics [10] Intervention group- N=13 ulcers, mean age (yrs) 58.3±1.5, mean duration of ulcer (months) 6.3±2.0, plantar surface ulcer 12, dorsum foot 1, mean ulcer baseline surface area (cm²) 0.87±0.26, mean baseline ulcer depth (cm) 0.24±0.05, mean duration of diabetes (yrs) 14.8±2.3, mean HbA1c level (%) 7.7±0.4 Comparator group(s) – N=11ulcers, mean age (yrs) 58.3±1.5, mean duration of ulcer (months) 6.3±2.0, plantar surface ulcer 12, dorsum foot 1, mean ulcer baseline surface area (cm²) 0.87±0.26, mean baseline ulcer depth (cm) 0.24±0.05, mean duration of diabetes (yrs) 14.8±2.3, mean HbA1c level (%) 7.7±0.4				
Length of follow-up [11] Treatment continued for 4 weeks and study outcomes were assessed every 2 weeks for a total of 16 weeks.	Outcome(s) measured [12] Photographs and assessment of wound size and appearance			
INTERNAL VALIDITY				
Allocation [13] Done by a third party using a computer generated random sequence	Comparison of study groups [14] Patient characteristics were similar in regard to age, duration of diabetes, haemoglobin A 1c levels, initial ulcer size and location, and duration of ulceration.	Blinding [15] Double-blinded	Treatment/ measurement bias [16] The outcome measures were assessed similarly in both groups. Ulcer surface area was measured by a computerised planimetry, and the depth of the ulcer was measured by a probe.	Follow-up (ITT) [17] 2 out of the 24 patients (8.3%) dropped out. These 2 were from the treatment group (2/12=16.6%). ITT was applied
Overall quality assessment (descriptive) [18] The quality is good, a double blind RCT, though the sample number is relatively small				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22]95% CI [25]	Benefits (NNT) [23]
Total healing of ulcers	6 ulcers (46%) 6/13=46%	2 ulcers (18%) 2/11=18%	RR=2.54(0.74-10.05)	Healing: 2.57 (1.9-inf) 95% CI [25]
50% reduction in surface area of wound	85% of 13 ulcers had 50% reduction or more	45% of 11 ulcers had 50% reduction or more	*p*<0.01 for surface area reduction;	Harms (NNH) [24] - 95% CI [25]
Change in depth	-60.1 ± 13.8%	-29.6 ± 12.6%	*p*=0.02 for change in depth	
	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	
Any other adverse effects [28] Mild to moderate pain, and burning sensation in 3 in the treatment group. Pain was also reported in 1 patient in control. Erythema and oedema were reported in one control patient. No serious adverse effects were reported.				

EXTERNAL VALIDITY
Generalisabilty [29] Moderate
Applicability [30] The potential benefits may outweigh the potential harms
Comments [31] The study results may imply that topical tretinoin in addition to standard may improve the healing of foot ulcers in diabetic patients.

STUDY DETAILS

Reference [1] Vandeputte J, G. L. (1997). "Clinical trial on the control of diabetic foot infection by an immunomodulating hydrogel containing 65% glycerine." Proceedings of the 6th European Conference on Advances in Wound Management; 1995, 21 24 November; Harrogate, UK: 50-3.

Affiliation/source of funds [2] St Joseph Hospital, Ostend, Belgium. Sources of funding are not stated.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] St Joseph Hospital, Ostend, Belgium.

Intervention [6] Treatment of ulcer with Hydrogel dressing + wound cleansing with wound cleanser Sample size [7] 15 patients	Comparator(s) [8] Treatment of ulcer with dry gauze + irrigation with chlorhexidine 0.05% Sample size [9] 14 patients

Selection criteria

Inclusion criteria – Diabetic patients with foot ulcer(s) (neuropathic or not). Patients with necrotic or infected wounds, or those with already amputated toe were not excluded

Exclusion criteria – Patients who were on systemic antibiotic treatment for infection were excluded.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Control N=14	Hydrogel N=15
Male %	6/14 (42.8%)	7/15 (46.7%)
Age mean (SD)	65.3 (14.3)	62.6 (14.7)
Completely mobile patients	11/14 (78.6%)	12/15 (80%)
Neuropathic ulcers %	9/14 (64.3%)	9/15 (60%)
Infection at baseline	1/14 (7.1%)	1/15 (6.7%)

Length of follow-up [11] Not reported	Outcome(s) measured [12] Healing of wound, incidence of infection, amputation.

INTERNAL VALIDITY

Allocation [13] Pre-prepared randomisation listing. Method not stated.	Comparison of study groups [14] Similar in characteristics provided. Authors did not state duration of ulcer or depth of wound.	Blinding [15] Not blinded	Treatment/ measurement bias [16] Wounds were photographed every four weeks and was similar for all patients.	Follow-up (ITT) [17] Authors did not report about drop outs

Overall quality assessment (descriptive) [18] A RCT of moderate quality, not assessor blinded. Ulcer severity (duration or depth) were not stated. No control was done for antibiotic treatment during trial and thus confounding cannot be excluded; unclear follow-up period. Two patients died during trial; other than infection, adverse effects were not reported.

RESULTS

	Control	Hydrogel	P value
Patient can walk with dressing on (n)	9	12	<0.01
Average time dressing can stay on wound (days)	1 day	5 days	<0.001
Infection during trial (n)	7	1	<0.01
Formation of Callus (n)	14	7	<0.05
Antibiotic treatment (systemic or local cream) (n)	14	1	<0.000
Amputation during treatment (n)	5	1	0.053

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Healed in 1 month:	2/15=13.3%	0/14=0%	-	-
Healed in 2 months:	5/15=33.3%	2/14=14.3%	RR = 2.33 [0.62, 9.78]	5.2 (2.6-inf)
Healed in 3 months:	7/15=46.7%	5/14=35.7%	RR = 1.31 [0.56, 3.18]	9.1 (2.3-inf)
Amputation:	1/15=6.7%	5/14=35.7%	RR = 0.19 [0.03, 1.02]	3.4 (2.5-inf)

Infection: (adverse events)	1/15=6.7%	7/14=50%	RR = 0.13 (0.02-0.66)	Harms (NNH) [24] 95% CI [25] Infection: 2.3 (1.8-8.9)
	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes	
Any other adverse effects [28] Besides infection, other side effects were not reported although 2 patients died during the trial.				
EXTERNAL VALIDITY				
Generalisabilty [29] Poor generalisability; patients treated in one centre, severity of ulcer at baseline was not reported, unknown denominator from whom these patients were selected for trial.				
Applicability [30] The benefits may outweigh the harms given that deaths were not related to the trial. However the benefits seen were not statistically significant.				
Comments [31]				

STUDY DETAILS

Reference [1] van Schie, C. H., A. Whalley, et al. (2000). "Efficacy of injected liquid silicone in the diabetic foot to reduce risk factors for ulceration: a randomized double-blind placebo-controlled trial." Diabetes Care 23(5): 634-638.

Affiliation/source of funds [2] Manchester Royal Infirmary, Manchester; Lancaster university, Lancaster, UK.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Manchester Diabetic Foot Clinic, Manchester, UK

Intervention [6] Patients received 6 injections of 0.2 ml liquid silicone in the plantar surface of the foot + standard care Sample size [7] 14 patients	Comparator(s) [8] Patients received 6 injections of 0.2 ml liquid placebo in the plantar surface of the foot + standard care Sample size [9] 14 patients

Selection criteria

Inclusion criteria – Established neuropathy as a vibration perception threshold (VPT) of >25 V or a neuropathy disability score (NDS) of>6 and the presence of callus under at least 1 metatarsal head.

Exclusion criteria – Patients with peripheral vascular disease (i.e. the absence of more than 1 foot pulse in both feet or an ankle-brachial pressure index of <0.9) and with an active or previous ulcer during the past 6 months were excluded.

Patient characteristics [10] Intervention group – Comparator group(s) –

	Intervention	Control
Mean age, (SD)	58.1 (12.3)	55.0 (7.8)
Male %	64.3%	78.6%
Mean duration of diabetes (range)	10.5 (9.3-17.8)	15.0 (7.3-22.0)
Type 2 diabetes %	64.3%	57.1%
History of ulceration %	57.1%	50%

	Intervention	Control
Neuropathy disability score (NDS) (V)	8.0 (7.3-9.5)	8.0 (8.0-10)
Vibration perception threshold (VPT)	29.5 (25.3-41.5)	28.0 (25.0-34.8)
ABPI	1.23 (1.0-1.28)	1.18 (1.11-1.38)

Length of follow-up [11] 12 months	Outcome(s) measured [12] Plantar tissue thickness, plantar pressure, and callus formation. Only the third outcome will be reported in this review

INTERNAL VALIDITY

Allocation [13] Randomisation according to random number sequence	Comparison of study groups [14] Similar	Blinding [15] Double blinded	Treatment/ measurement bias [16] Similar	Follow-up (ITT) [17] Loss to follow up information is given according to visits by different times. It is not possible to quantify the total missing when looking at callus formation as outcome. ITT was applied

Overall quality assessment (descriptive) [18] Good quality, though number of few patients may lower the power of finding anything significant.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] No benefits seen 95% CI [25]
Reduction in callus formation (median score for change in callus build up from baseline):	0.5 (0.0 to 1.0)	0 (-1.25 to 0.75)	P=0.3	Harms (NNH) [24] - 95% CI [25]
Ulcers (seen as adverse event 1 year after):	3/14=21.4%	4/14=28.6	RR=0.75 (0.21-2.60)	
	Clinical importance (1-4) [26] 3 The confidence interval does not include any clinically important effects		Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms	

Any other adverse effects [28] Besides the ulcers already reported in the results section, two patients in the placebo group developed unrelated conditions (CVA and cancer)

EXTERNAL VALIDITY

Generalisabilty [29] Moderate generalisability. The recruitment process is not clearly stated.

Applicability [30] Benefits do not outweigh harms.
Comments [31]

STUDY DETAILS				
Reference [1] Yesil, S., B. Akinci, et al. (2009). "Reduction of major amputations after starting a multidisciplinary diabetic foot care team: single centre experience from Turkey." Exp Clin Endocrinol Diabetes 117(7): 345-349.				
Affiliation/source of funds [2] Division of Endocrinology and Metabolism, Department of Internal Medicine, Dokuz Eylul University Medical School, Inciralti, Izmir, Turkey				
Study design [3] historical control study	Level of evidence [4] III-2	Location/setting [5] Dokuz Eylul University Medical School, Inciralti, Izmir, Turkey		
Intervention [6] Diabetic patients admitted to hospital during January 2002 and January 2008 were managed by a multidisciplinary diabetic foot care team. Treatment was managed by a multidisciplinary diabetic foot care team that included endocrinologists, orthopaedist, plastic and vascular surgeons, infectious disease specialists, radiologists, rehabilitation specialists, diabetes education, wound care nurses and a footwear technician. All patients received standard care that included wound care, bed rest, offloading, IV antibiotics and debridement or amputation when indicated. Sample size [7] 437 patients		Comparator(s) [8] Diabetic patients admitted to hospital during January 1999 and December 2001, were managed by attending physician. All patients received standard care that included wound care, bed rest, offloading, IV antibiotics and debridement or amputation when indicated. Sample size [9] 137 patients		
Selection criteria Inclusion criteria – This study included data from diabetic foot ulcer episodes which were managed in Dokuz Eylul University Hospital in Turkey between January 1999 and January 2008. Exclusion criteria – Not stated				
Patient characteristics [10] Intervention group: N = 437; age (yrs) 62.3 ± 10.3; males 306/437 (70%); duration of diabetes (yrs) 16.3 ± 9.6; type 2 diabetes 420/437 (96%); insulin use 295/437 (68%); smokers 166/437 (38%); BMI (kg/m^2) 26.6 ± 4.5; % HbA_{1c} 9.1 ± 2.3; retinopathy 278/437 (63%); nephropathy 236/437 (54%); neuropathy 360/437 (82%); limb ischaemia 250/437 (57%); ulcer located on toe 198/437 (45%), forefoot 94/437 (22%), midfoot 39/437 (9%), hindfoot 64/437 (15%), leg 42/437 (10%); Wagner: grade 1 46/437 (11%); grade 2 155/437 (36%); grade 3 125/437 (29%); grade 4 103/437 (24%); grade 5 8/437 (2%); osteomyelitis 174/437 (40%); antibiotic treatment 408/437 (93%). Comparator group: N = 137; age (yrs) 63.8 ± 11.4; males 85/137 (62%); duration of diabetes (yrs) 14.6 ± 7.8; type 2 diabetes 134/137 (98%); insulin use 81/137 (59%); smokers 69/137 (50%); BMI (kg/m^2) 26.0 ± 4.8; % HbA_{1c} 8.5 ± 1.7; retinopathy 85/137 (62%); nephropathy 66/137 (48%); neuropathy 123/137 (90%); limb ischaemia 71/137 (52%); ulcer located on toe 65/137 (47%), forefoot 35/137 (26%), midfoot 10/137 (8%), hindfoot 21/137 (15%), leg 6/137 (4%); Wagner: grade 1 12/137 (9%); grade 2 52/137 (38%); grade 3 39/137 (29%); grade 4 30/137 (22%); grade 5 4/137 (3%); osteomyelitis 56/137 (41%); antibiotic treatment 127/137 (93%).				
Length of follow-up [11] minimum follow- up of 6 months		Outcome(s) measured [12] Amputation rates, antibiotic treatment, inpatient days, healing of ulcers		
INTERNAL VALIDITY				
Allocation [13] Not randomised	Comparison of study groups [14] Similar to given characteristics	Blinding [15] Not blinded	Treatment/ measurement bias [16] Similar	Follow-up (ITT) [17] All inpatients were followed.
Overall quality assessment (descriptive) [18] Of moderate to good quality, a non randomised, non-blinded comparative study, comparing two periods that were differentiated by the treatment provided in each period				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Hospital days, mean (SD):	26.9 (21.3)	39.5 (28.3)	p<0.001	
Overall amputations:	158/437=36.2%	55/137=40.1%	RR = 0.90 [0.72, 1.15]; p=0.418	
Minor amputations:	103/437=23.6%	27/137=19.7%	RR = 1.19 [0.83, 1.76]; p=0.413	
Major amputations:	55/437=12.6%	28/137=20.4%	RR = 0.62 [0.41, 0.93]	13 [6, 100]
Ulcers healed without amputation:	220/437=50.3%	60/137=43.8%	RR = 1.15 [0.94, 1.43]; p=0.203	Harms (NNH) [24] 95% CI [25] -

	Clinical importance (1-4) [26] 2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects	Relevance (1-5) [27] 1 Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms
Any other adverse effects [28] None reported		
EXTERNAL VALIDITY		
Generalisabilty [29] Moderate generalisability to inpatient diabetic population; exclusion criteria were not provided;		
Applicability [30] Benefits may outweigh harms		
Comments [31]		

STUDY DETAILS

Reference [1] "The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomized-controlled trial (Structured abstract)." European Journal of Vascular and Endovascular Surgery 25(6): 513-518.

Affiliation/source of funds [2] academic surgical Unit, Dept. Of Diabetic Medicine, University of Hull Royal Infirmary, Hull UK, and Hull Hyperbaric Unit BUPA Hospital, Hull UK. No funding sources or conflicts of interest stated.

Study design [3]	Level of evidence [4]	Location/setting [5]
double-blind RCT	II	United Kingdom Hull Royal Infirmary

Intervention [6] Hyperbaric oxygen therapy	Comparator(s) [8] Hyperbaric air
Treatment given in a multi-place chamber at a pressure of 2.4 ATA for 90 mins daily for 5 days a week, totalling 30 sessions. Decompression time was extended to 20 min. Wound care was standardised for all patients and included off-loading, aggressive debridement and moist dressings. Antibiotics were given if there were clinical sign of infection. Sample size [7] 8	Same as for intervention, extended decompression time was to avoid giving oxygen supplements to the control group. Medical management was optimised and equivalent for both groups and patients regularly attended a multi-disciplinary clinic for 6 weeks prior, during treatment period and follow-up period. Sample size [9] 8

Selection criteria

Inclusion criteria – Diabetic patients presenting to Hull Royal Infirmary with ischaenic lower-extremity ulcers of > 1 cm and < 10 cm diameter which had not shown any signs of healing, despite optimum medical management for more than 6 weeks.

Exclusion criteria – All patients were assessed by angiography, if clinician decides vascular surgery, angioplasty or thrombolysis was required, patient was excluded.

Patient characteristics [10]

Intervention group – N = 8, Age (yrs) 72 ± 12.6, Gender (M:F) 2:1, Duration of diabetes (yrs) 13 ± 9.9, Insulin therapy 4/8 (50%), Smokers 1/8 (12.5%), BMI (kg/m^2) 26 ± 7, Biothesiometer reading (mV) 47 ± 16.2, Great toe-brachial index 0.47 ± 0.24, Foot $TcPO_2$ (mmHg) 46 ± 15, Hb (g/dl) 12.7 ± 1.2, Serum albumin (g/l) 37 ± 2.8,. Retinopathy: background 7/8 (87.5%), proliferative 1/8 (12.5%), COPD 1/8 (12.5%), Cardiac failure 2/8 (25%), Previous angioplasty 0/8 (0%), Previous by-pass surgery 2/8 (25%), Previous amputation: minor 1/8 (12.5%), major 0/8 (0%), Previous ulcer 3/8 (37.5%), Ulcer duration (months) 6 (2-18), Ulcer size (mm^2) 106 (12-823), Ulcer depth (mm) 2.3 (0.5-4), Wagner grade 1 0/8 (0%), grade 2 8/8 (100%), Signs of infection 3/8 (37.6%).

Comparator group(s) – N = 8, Age (yrs) 70 ± 6.6, Gender (M:F) 1:2, Duration of diabetes (yrs) 10 ± 6.3, Insulin therapy 5/8 (62.5%), Smokers 2/8 (25%), BMI (kg/m^2) 29 ± 4, Biothesiometer reading (mV) 55 ± 13.7, Great toe-brachial index 0.44 ± 0.3, Foot $TcPO_2$ (mmHg) 43 ± 19, Hb (g/dl) 12.5 ± 1.7, Serum albumin (g/l) 38 ± 2.6,. Retinopathy: background 8/8 (100%), proliferative 0/8 (0%), COPD 2/8 (25%), Cardiac failure 2/8 (25%), Previous angioplasty 1/8 (12.5%), Previous by-pass surgery 3/8 (37.5%), Previous amputation: minor 2/8 (25%), major 0/8 (0%), Previous ulcer 4/8 (50%), Ulcer duration (months) 9 (3-60), Ulcer size (mm^2) 78 (18-866), Ulcer depth (mm) 1.6 (0.5-4), Wagner grade 1 1/8 (12.5%), grade 2 7/8 (87.5%), Signs of infection 2/8 (25%).

Length of follow-up [11]	Outcome(s) measured [12]
after 15 treatments, 30 treatments, and at 6 weeks, 6 months and 1 year post treatment	Difference in ulcer surface area, complete healing, Quality of life: SF-36 form and HAD Scale.

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Randomisation by sealed envelopes, code known only to chamber operator.	Similar baseline characteristics except for gender. More males in intervention group but not statistically significant.	All patients, carers and medical assessors were blinded.	There was no difference in measurement between the groups	No, authors state that data analysis was on ITT basis but initially have 9 per group (loss of 1 per group during study), and analysis is on 8 per group.

Overall quality assessment (descriptive) [18] The authors have attempted to minimise both selection and information bias by randomising assignment to each group and by blinding all involved except the chamber operator. Even though this study was very small so may not have been adequately powered, the differences between treatments is probably due to the intervention. Good.

RESULTS

Outcome [19]	Intervention group [20]		Control group [21]		Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23]
Ulcers healed:	Reported	ITT	Reported	ITT	ITT	(95% CI) [25]
At 6 weeks	5/8	5/9	1/8	1/9	RR= 5.0 (1.03, 30.55), p = 0.046	2.25 (1.6, 112)
At 6 months	5/8	5/9	2/8	2/9	RR = 2.5 (0.75, 9.52)	
At 1 year	5/8	5/9	0/8	0/9	RR = 10 (1.29, 101.8), p = 0.021	2.0 (1.67, 13.0)
Reduction in ulcer size:						
At 6 weeks	100% (34-100)		52% (-29 to 100)		p = 0.027	
At 6months	100% (-206 to 100)		95% (0-100)		NS	

	Reported	ITT	Reported	ITT	ITT	Harms (NNH) [24] (95% CI) [25]
Major amputations	1/8	1/9	1/8	1/9	RR = 1 (0.11, 9.20)	
Minor amputations	1/8	1/9	0/8	0/9	RR = 2 (0.15, 26.6), $p = 0.670$	
HAD Scale Improvement:						
In depression score	Yes ($p = 0.011$)		Yes ($p = 0.023$)		Summary:	
In anxiety score	No		Yes ($p = 0.042$)		HBOT did not produce any significant improvements in QOL measures greater than those seen in the control group.	
SF-36 improvement in:						
General health	Yes ($p = 0.012$)		No			
Vitality	Yes ($p = 0.018$)		No			
Other domains	No		No			
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.				Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] None reported.						
EXTERNAL VALIDITY						
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.						
Applicability [30] There were no reported harms. As the treatment provides some benefit, treatment benefits may outweigh any harms.						
Comments [31] Hyperbaric oxygen therapy increased the healing rate and seems to prevent re-ulceration, those that healed by 6 months seemed to re-ulcerate by 1 year in the control group but not after HBOT.						

HAD scale: Hospital Anxiety and Depression Scale, (7 questions each for anxiety and depression rating 0-3 with higher score indicating greater anxiety and depression); SF-36 form: Self report questionnaire (36 questions relating to 8 domains measuring health and well-being, the higher the score the better health and vitality)

STUDY DETAILS

Reference [1] "Efficacy of topical epidermal growth factor in healing diabetic foot ulcers." Therapy 2(5): 759-765.

Affiliation/source of funds [2] Endocrinology and Metabolism Research Centre, Shariati Hospital, Tehran. Source of funding was not disclosed.

Study design [3]	Level of evidence [4]	Location/setting [5]
single-blind RCT	II	Iran In and out patients

Intervention [6]	Comparator(s) [8]
1 mg Epidermal Growth Factor (EGF) /1000 mg of 1% silver sulphadiazine in a hydrophilic base. After wound debridement and infection control patients were assigned to one of 2 groups. Wounds were washed with normal saline and dressed with sterile gauze and adhesive tape every day. EGF or placebo was applied once a day at time of wound dressing for 28 days. Ulcers were evaluated once per week for severity and size. Sample size [7] 30	Placebo - 1% silver sulphadiazine in the same hydrophilic base. Same treatment as intervention group. Sample size [9] 20

Selection criteria

Inclusion criteria – Diabetic patients with foot ulcers (Wagner grade 1 or 2) with adequate perfusion (as indicated by ankle-brachial index) were entered randomly until a total of 50 patients were recruited.

Exclusion criteria – Patients with Wagner grade 3, 4or 5 ulcers.

Patient characteristics [10]

Intervention group – N = 30, mean age (yrs) 56 ± 12.7, gender: 16/30 (53.3%) male, 14/30 (46.7%) female, duration of diabetes (yrs) 12.6 ± 7.5, smokers 12/30 (40%), BMI (kg/m^2) 24.0 ± 3.4, ankle-brachial index < 1 11/30 (46.4%), fasting blood glucose (mg/dl) 137.9 ± 53.9, HbA_{1c} (%) 10.5 ± 2.6, erythrocyte sedimentation rate (mm/h) 47.9 ± 25, leukocyte count (10^9/ml) 9405 ± 3736, creatinine (mg/dl) 1.2 ± 0.83, triglyceride (mg/dl) 184 ± 100, total cholesterol)mg/dl) 186 ± 58. Retinopathy 25/30 (83.3%), vasculopathy 13/30 (43.3%) nephropathy 23/30 (76.7%), neuropathy 28/30 (93%). Ulcer: duration (days) 42.9 ± 38.4, size (mm^2) 87.5 ± 103.2, signs of infection 21/30 (70%).

Comparator group(s) – N = 20, mean age (yrs) 59.7 ± 12.3, gender: 11/20 (55%) male, 9/20 (45%) female, duration of diabetes (yrs) 14.9 ± 7.1, smokers 9/20 (45%), BMI (kg/m^2) 22.8 ± 3.8, ankle-brachial index < 1 10/20 (50%), fasting blood glucose (mg/dl) 157.6 ± 53.2, HbA_{1c} (%) 10.9 ± 1.65, erythrocyte sedimentation rate (mm/h) 47.9 ± 22, leukocyte count (10^9/ml) 8730 ± 3093, creatinine (mg/dl) 0.99 ± 0.33, triglyceride (mg/dl) 148 ± 64, total cholesterol (mg/dl) 169 ± 48. Retinopathy 20/20 (100%), vasculopathy 8/20 (40%) nephropathy 16/20 (80%), neuropathy 20/20 (100%). Ulcer: duration (days) 59.7 ± 55.5, size (mm^2) 103.4 ± 147.8, signs of infection 12/20 (60%).

Length of follow-up [11]	Outcome(s) measured [12]
4 weeks	No. completely healed, No. partially healed, No. < 70% healed, No. > 70% healed, average hospital stay.

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Randomisation method not disclosed	Similar baseline characteristics with the exception of ulcer size (15% difference) and duration (28% difference).	Medical assessors were blinded.	There was no difference in measurement between the groups	Yes, no loss to follow-up and all patients are included in final analysis.

Overall quality assessment (descriptive) [18] The authors have attempted to minimise both selection and information bias by randomising assignment to each group and by blinding clinicians involved in examination and assessment of ulcers. It is uncertain if this study was adequately powered, but the differences between treatments were probably due to the intervention. Study is of average quality.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. completely healed	7/30 (23.3%)	2/20 (10%)	RR = 2.33 (0.63, 9.57) p = 0.3	
No. partially healed	23/30 (76.7%)	18/20 (90%)	RR = 0.85 (0.74, 1.11) p = 0.3	
No. healed > 70%	15/30 (50%)	3/20 (15%)	RR = 3.33 (1.27, 10.08) p = 0.05	2.86 (1.97, 12.1)
No. healed < 70%	15/30 (50%)	17/20 (85%)	RR = 0.59 (0.46. 0.88) p = 0.05	2.86 (1.97, 12.1)
Ave hospital stay (days)	29.6 ±20.95	28.9 ± 15.1	p = 0.9	Harms (NNH) [24] (95% CI) [25]

Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] No adverse effects to report	
EXTERNAL VALIDITY	
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.	
Applicability [30] There were no reported harms. As the treatment provides some benefit, treatment benefits may outweigh any harms.	
Comments [31] EGF does appear to increase the healing rate of ulcers in this study.	

STUDY DETAILS

Reference [1] Apelqvist, J., J. Castenfors, et al. (1990). "Ketanserin in the treatment of diabetic foot ulcer with severe peripheral vascular disease." International angiology : a journal of the International Union of Angiology 9(2): 120-124.

Affiliation/source of funds [2]. Dept. of Internal Medicine, Dept. Clinical Physiology, and Dept. of Orthopaedic Surgery, University Hospital Lund, Sweden.This study was funded by the Swedish Research Council.

Study design [3] double-blind RCT	Level of evidence [4] II	Location/setting [5] Sweden Hospital outpatient

Intervention [6] 20 mg ketanserin (seratotin antagonist – inhibition of platelet aggregation) tablets 3 times daily for 1 month, then 40 mg tablets 3 times daily for another 2 months. Also received standard wound care Sample size [7] 20	Comparator(s) [8] Placebo tablets. All patients had a 2 week run-in period on placebo tablets. Standard wound care of dressings, debridement and off-loading, as well as antibiotic therapy to treat infections and diuretics to treat oedema. Sample size [9] 20

Selection criteria

Inclusion criteria – Diabetic patients referred to the Dept. of Internal Medicine for a foot ulcer with an area of 1 cm^2 or more and severe peripheral vascular disease (a systolic toe pressure below 45 mmHg).

Exclusion criteria – severe renal or hepatic insufficiency, myocardial infarction within the last 3 months, congestive heart disease, treatment with β-blockers, inability to co-operate in a study.

Patient characteristics [10]

Intervention group – N = 20, mean age (yrs) 71 ± 10, gender: 13/20 (65%) male 7/20 (35%) female, duration of diabetes 20 ± 12, insulin treatment 15/20 (75%), smokers 1/20 (5%), ex-smokers 10/20 (50%), HbA_{1c} (%) 7.8 ± 1.9, retinopathy 7/20 (35%), systolic arm pressure (mmHg) 17 ± 32, systolic ankle pressure (mmHg) 89 ± 36, oedema 8/20 (40%), pain at rest 2/20 (10%), superficial ulcer 8/20 (40%), deep ulcer 12/20 (60%), positive bacterial culture 12/20 (60%), wound size (cm^2) 2.0 (0.8-24).

Comparator group(s) – N = 20, mean age (yrs) 67 ± 10, gender: 12/20 (60%) male 8/20 (40%) female, duration of diabetes 18 ± 12, insulin treatment 16/20 (80%), smokers 5/20 (25%), ex-smokers 6/20 (30%), HbA_{1c} (%) 7.7 ± 1.8, retinopathy 6/20 (30%), systolic arm pressure (mmHg) 157 ± 23, systolic ankle pressure (mmHg) 103 ± 40, oedema 5/20 (25%), pain at rest 5/20 (25%), superficial ulcer 7/20 (35%), deep ulcer 13/20 (65%), positive bacterial culture 11/20 (55%), wound size (cm^2) 1.5 (1.0-160).

Length of follow-up [11] 2 week run-in plus 3 month study period	Outcome(s) measured [12] No. ulcers healed, No. ulcers improved, No. unchanged or deteriorated, No. with gangrene, No. amputated.

INTERNAL VALIDITY

Allocation [13] Randomly allocated to a group according to cards in sealed envelopes.	Comparison of study groups [14] Similar baseline characteristics with the exception of smoking status (20% difference), and systolic arm pressures (90% difference).	Blinding [15] Patients and assessors were blinded.	Treatment/ measurement bias [16] There was no difference in measurement between the groups	Follow-up (ITT) [17] All patients that started treatment were included in final analysis. 5 patients were lost during 2 week run-in period that were excluded.

Overall quality assessment (descriptive) [18] The authors have attempted to minimise both selection and information bias with the double-blind study design. It is uncertain if this study was adequately powered. The lack of a difference between treatments could be due to the failure of the intervention to have an effect. Study is of good quality.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/ effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25] / Harms (NNH) [24] (95% CI) [25]
No. ulcers healed	7/20 (35%)	5/20 (25%)	RR = 1.40 (0.55, 3.68)	
No. ulcers improved	4/20 (20%)	2/20 (10%)	RR = 2.00 (0.47, 8.96)	
No. unchanged or deteriorated	6/20 (30%)	6/20 (30%)	RR = 1.00 (0.39, 2.55)	
No. with gangrene: and amputated.	2/20 (10%) [2/2] 2/20 (10%)	6/20 (30%) [4/6] 4/20 (20%)	RR = 0.33 (0.08, 1.26) RR = 0.50 (0.11, 2.13)	

Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.

Any other adverse effects [28] None reported

EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with Ischemic Foot Ulcers.
Applicability [30] As there does not seem to be a statistically significant treatment effect, any potentials harms will outweigh the benefits
Comments [31] The data in this paper did not show a statistically significant benefit for using oral ketanserin to treat diabetic foot ulcers.

STUDY DETAILS

Reference [1] Apelqvist, J. and G. R. Tennvall (1996). "Cavity foot ulcers in diabetic patients: A comparative study of cadexomer iodine ointment and standard treatment - An economic analysis alongside a clinical trial." Acta Dermato-Venereologica 76(3): 231-235.

Affiliation/source of funds [2] Dept, of Internal Medicine, University Hospital of Lund, and the Swedish Institute for Health Economics, Lund, Sweden.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Sweden Outpatient setting

Intervention [6] Topical treatment with cadexomer iodine ointment (Iodosorb) with standard treatment. All patients were treated and assessed by a multidisciplinary foot care team at inclusion, 1, 4, 8 and 12 weeks. Sample size [7] 22	Comparator(s) [8] Standard treatment with gentamicin solution, streptodornase/strepto-kinase, dry saline gauze, and special foot wear provided for off-loading when required. Sample size [9] 19

Selection criteria

Inclusion criteria – Diabetes Caucasian patients, aged over 40 years, with an exudative foot ulcer of Wagner grade 1 or 2 and > 1 cm^2 (length x width). Systolic toe pressure of > 30 mmHg or a systolic ankle pressure of > 80 mmHg.

Exclusion criteria – Patients with ulcers larger than 25 cm^2, with a deep abscess, osteomyelitis of gangrene, undergoing investigations of the thyroid gland, inability to adhere to study protocol. Patients were withdrawn from study for non-compliance, hospitalisation, ulcer grade deterioration to Wagner grade 3-4, > 100% increase in ulcer area, adverse reaction to topical treatment.

Patient characteristics [10]

Intervention group –

Comparator group(s) –

No data presented except to say there was no major differences between the two treatment groups and all patients had signs of severe neuropathy (vibratory pressure threshold > 30)

Length of follow-up [11] 12 week study duration	Outcome(s) measured [12] No. completely healed, No. Improved (reduction of >50% of initial ulcer area or improvement of Wagner grade)

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Randomisation by computer-generated list of randomly permuted blocks.	No major differences?	Size of blocks unknown to investigators during randomisation. Assessor was blinded	There was no difference in measurement between the groups	No, 2 patients were excluded due to violation of inclusion criteria, 2 were excluded due to hospitalisation (both with heart problems) and 1 patient was excluded due to non-compliance

Overall quality assessment (descriptive) [18] The patients and investigators in this study were not blinded, thus it is possible that this study is subject to information bias, although the authors attempted to minimise this by having the assessor blinded. The study was also small. Thus, the lack of a statistically significant effect may be due to the study being underpowered. This study was of average quality.

RESULTS

Outcome [19]	Intervention group [20]		Control group [21]		Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
		ITT		ITT	ITT	
No. completely healed	5/17	5/22	2/18	2/19	RR = 2.16 (0.54, 9.27)	Harms (NNH) [24] (95% CI) [25]
No. improved (reduction of >50% of initial ulcer area or improvement of Wagner grade)	12/17	12/22	13/18	13/19	RR = 0.80 (0.52, 1.30)	

Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.

Any other adverse effects [28] No adverse reactions due to the topical treatment were documented.

EXTERNAL VALIDITY

Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.

Applicability [30] As the treatment does not provide a statistically significant benefit, harms may outweigh any treatment benefits.
Comments [31] The authors have shown that there is a trend towards cadexomer iodine ointment being beneficial compared to standard wound are with topical gentamycin. As the study was small, it may have been underpowered, and a larger study may be required to obtain a definitive result.

STUDY DETAILS				
Reference [1] Armstrong, D. G., P. Salas, et al. (2005). "Maggot therapy in "lower-extremity hospice" wound care: fewer amputations and more antibiotic-free days." J Am Podiatr Med Assoc 95(3): 254-257.				
Affiliation/source of funds [2] Dept. of surgery, Podiatry Section, Southern Arizona Veterans Affairs Medical Centre, Tuscon, USA; Dept. of Medicine, Manchester Royal Infirmary, Manchester, England.				
Study design [3] retrospective cohort study	**Level of evidence** [4] III-2		**Location/setting** [5] USA Diabetic foot clinic, inpatient?	
Intervention [6] Maggot debridement therapy plus same standard wound care as control group. **Sample size** [7] 30		**Comparator(s)** [8] Standard wound care according to protocol followed in the high-risk diabetic foot clinic. **Sample size** [9] 30 age and gender matched patients		
Selection criteria **Inclusion criteria** – diabetic patients with a single foot ulcer and unable to walk without assistance, diagnosis of peripheral vascular disease without surgical intervention, at least 6 months of reliable follow-up information. Ulcers classified as University of Texas grade C or D (with ischemia, with or without infection) received maggot debridement therapy. **Exclusion criteria** – no diagnosis of clinically significant vascular disease.				
Patient characteristics [10] **Intervention group** – N = 30, age (years) 71.7 ±6.8, gender: male 26/30 (86.7%), female 4/30 (13.3%), duration of diabetes (years) 14.7 ± 8.4, wound size (cm^2) 11.8 ± 4.5, infections 24/30 (80%). **Comparator group(s)** – N = 30 age and gender matched patients, age (years) 72.7 ±6.8, gender: male 26/30 (86.7%), female 4/30 (13.3%), duration of diabetes (years) 16.3 ± 7.6, wound size (cm^2) 12.4 ± 6.7 infections 18/30 (60%).				
Length of follow-up [11] 6 months		**Outcome(s) measured** [12] No. ulcers healed, time to healing, no. amputations.		
INTERNAL VALIDITY				
Allocation [13] Non-random	**Comparison of study groups** [14] Similar baseline characteristics for limited parameters reported, with the exception of the no. of infected ulcers (20% difference).	**Blinding** [15] None	**Treatment/ measurement bias** [16] There was no difference in measurement between the groups	**Follow-up** (ITT) [17] Retrospective, so no loss to follow-up.
Overall quality assessment (descriptive) [18] No information on potential confounders such as smoking status, neuropathy, etc was provided. Study is of average quality.				
RESULTS				

Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/effect size** [22] (95% CI) [25]	**Benefits** (NNT) [23] (95% CI) [25]
No. ulcers healed	57% 17/30	33% 10/30	OR = 2.62 [0.93, 7.37] *p* = 0.07	
Time to healing (weeks)	18.5 ± 4.8	22.4 ±4.4	*p* = 0.04	
No. amputations above foot	10% 3/30	33% 10/30	OR = 0.22 (0.06, 0.86) *p* = 0.03	4.29 [2.78, 39.79]
				Harms (NNH) [24] (95% CI) [25]
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		**Relevance** (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] None reported	
EXTERNAL VALIDITY	
Generalisabilty [29] Applicable to other diabetics with ischemic foot ulcers.	

Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits may outweigh any harms.
Comments [31]. The authors have shown that maggot debridement therapy reduces the risk of subsequent amputation and shortens the time to healing for these ulcers. However, there was no statistically significant difference in the number of ulcers that healed completely.

STUDY DETAILS				
Reference [1] Armstrong, D. G., K. Holtz-Neiderer, et al. (2007). "Skin temperature monitoring reduces the risk for diabetic foot ulceration in high-risk patients." Am J Med 120(12): 1042-1046.				
Affiliation/source of funds [2] Scholl's Centre for Lower Extremity Ambulatory Resarch, Rosalind Franklin University of Medicine and Science, North Chicago, Ill; Southern Arizona Veterans Affairs Medical Centre, Tucson, Dept. of epidermology and Biostatistics, College of Public Health, University of Arizona, Tucson; Dept. of surgery, Texas A&M College of Medicine at Scott & White Memorial Hospital, Temple. Funded by Veterans Affairs HSR&D Merit Award				
Study design [3] physician-blinded RCT	**Level of evidence** [4] II		**Location/setting** [5] USA Outpatient setting	
Intervention [6] Dermal thermometry All patients were instructed to perform a structures foot inspection daily and record their findings in a logbook. Patients used an infrared skin thermometer to measure temp on 6 sites of foot twice per day. If temp difference between left and right foot > 2.2ºC, patients were to contact the study co-ordinator and reduce activity until temperatures normalised **Sample size** [7] 106?			**Comparator(s)** [8] Standard therapy Both groups received therapeutic footwear, diabetic foot education, and regular foot care. If any foot abnormalities were detected, control patients were to contact the study co-ordinator immediately. **Sample size** [9] 115?	
Selection criteria **Inclusion criteria** – patients with type 2 diabetes receiving foot care at the Southern Arizona VA Health Care System, aged 18-80 years, who fit category 2 or 3 of the International Diabetic Foot Risk Classification System. **Exclusion criteria** – Active open ulcers, amputation sites or foot infections; active Charcot arthropathy; severs peripheral vascular disease; dementia or impaired cognitive function; history of alcohol or drug abuse within 1 year of study; sight impaired; unable to walk without assistance of a wheel chair or crutches.				
Patient characteristics [10] **Intervention group** – mean age (yrs) 68.2 ± 9.6, male? 98.2%, duration of diabetes 13.6 ± 11.6, HbA_{1c} (%) 8.1 ± 1.9, non-Hispanic white 73%, African American, 4.5%, Hispanic 20.7%, Asian 0%, Native American 1.8%, retinopathy 23.4%, diabetic foot risk classification*: Risk 2 84.7%, Risk 3 15.3%. VPT (V) 42.6 ± 21.0, neuropathy with loss of sensation 100%. **Comparator group(s)** – mean age (yrs) 69.7 ± 10.4, male? 94.7%, duration of diabetes 12.6 ± 9.1, HbA_{1c} (%) 7.4 ± 1.4, non-Hispanic white 71%, African American, 8.8%, Hispanic 17.5%, Asian 1.8%, Native American 0.9%, retinopathy 34.2%, diabetic foot risk classification: Risk 2 82.5%, Risk 3 17.5%. VPT (V) 50.1 ± 85.4, neuropathy with loss of sensation 100%.				
Length of follow-up [11] 18 months			**Outcome(s) measured** [12] No. of patients developing a foot ulcer.	
INTERNAL VALIDITY				
Allocation [13] Sequentially assigned patients according to a randomised assignment list.	**Comparison of study groups** [14] Similar baseline characteristics	**Blinding** [15] The attending physician was blinded to the use of the infrared thermometer for the length of the study	**Treatment/ measurement bias** [16] There was no difference in measurement between the groups	**Follow-up** (ITT) [17] Uncertain.
Overall quality assessment (descriptive) [18] The authors have attempted to minimise both selection and information bias by randomising assignment to each group and by blinding the attending physician. This study was adequately powered and the difference in rates of ulcer formation between groups is likely to be due to the intervention. Good.				
RESULTS				
Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/effect size** [22] (95% CI) [25]	**Benefits** (NNT) [23] (95% CI) [25] 13.4 (8.1, 1663.2)
No. patients ulcerated	5/106 (4.7%)	14/115 (12.2%)	RR = 0.39 (0.15, 0.99) [OR = 3.0 (1.0, 8.5) *P* = 0.038]	**Harms** (NNH) [24] (95% CI) [25]
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		**Relevance (1-5)** [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] None reported				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with high risk of developing diabetic foot ulcers.				

Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits may outweigh any harms.
Comments [31] The authors have shown that dermal thermometry can be used to predict the formation of an ulcer and this information can be used to prevent 2/3 of these ulcers from developing.

*Diabetic foot risk classification scheme: assesses patient history, foot pulses, monofilament sensation and presence of foot deformity to determine risk of ulceration. Three risk categories 1-3 representing low to high risk groups.

STUDY DETAILS				
Reference [1] (Bahrami et al 2008) "Clinical application of oral form of ANGIPARS (TM) and in combination with topical form as a new treatment for diabetic foot ulcers: A randomized clinical trial." Daru-Journal of Faculty of Pharmacy 16: 41-48.				
Affiliation/source of funds [2] Endocrinology Research Centre, Tabriz University of Medical Sciences; and Dept. of Biotechnology, Rabe Rashidi Institute Tabriz. Dept. of Epidemiology and Biostatistics, Public Health School; Endocrinology and Metabolism Research Centre, and Rheumatology Research Centre, Tehran University of Medical Sciences; Genetic research Centre, Social Welfare and Rehabilitation Sciences University; Tehran Iran.				
Study design [3] single-blind RCT	**Level of evidence** [4] II		**Location/setting** [5] Iran Sina University Hospital, outpatients	
Intervention [6] ANGIPARS (herbal extract) Group 1: 100 mg ANGIPARS capsule twice daily for 6 weeks Group 2: 100 mg ANGIPARS capsule twice daily plus 3% ANGIPARS gel was administered topically, for 6 weeks **Sample size** [7] Group 1 N = 6; Group 2 N = 6		**Comparator(s)** [8] Standard wound care only. Standard wound care included debridement, irrigation, dressings, pressure off-loading, and antibiotic therapy. **Sample size** [9] N = 9 In addition both groups received standard wound care and visited clinic for assessment every 2 weeks.		
Selection criteria **Inclusion criteria** – Diabetic patients, aged 18-75 years, with a diabetic foot ulcer, which remained open without healing or improvement for at least 2 weeks. Be available for the 6 week study period, be able to adhere to the treatment regimen and give informed consent. **Exclusion criteria** – Not compliant with the study, foot ulcers of Wagner grade 3 or higher, evidence of systemic or local infection, erythema in the edge of the wound with 3 cm width, exposed bone at wound site, life-threatening or serious cardiac failure, sever or chronic ischemia of lower limb, simultaneous diseases which impact on healing process, cancer, hepatic or renal failure, endocrine, haematological or immunologic disorder, history of chronic or acute autoimmune disease, history of hypersensitivity to incipients, chronic alcohol or drug abuse, immunosuppressive drugs, cytotoxic agents, radiation therapy, and chemotherapy.				
Patient characteristics [10] **Intervention group:** Group 1 – N = 6, mean age (yrs) 60.7 ± 3.0, gender: 4/6 (66.7%) male, 2/6 (33.3%) female, weight (kg) 78.8 ± 3.9, type 2 diabetes 6/6 (100%). Ulcer size (mm^2) 375.0 ± 118.1, Wagner grade 2 6/6 (100%). **Intervention group:** Group 2 – N = 6, mean age (yrs) 51.0 ± 3.7, gender: 4/6 (66.7%) male, 2/6 (33.3%) female, weight (kg) 79.4 ± 12.1, type 2 diabetes 6/6 (100%). Ulcer size (mm^2) 916.7 ± 228.6, Wagner grade 2 6/6 (100%). **Comparator group(s)** – N = 9, mean age (yrs) 59.0 ± 3.7, gender: 5/9 (55.6%) male, 4/9 (44.4%) female, weight (kg) 65.4 ± 3.6, type 2 diabetes 9/9 (100%). Ulcer size (mm^2) 766.2 ± 320.2, Wagner grade 2 9/9 (100%).				
Length of follow-up [11] 6 week study period, 2 month follow-up visit		**Outcome(s) measured** [12] % reduction in ulcer size, no. completely healed (> 70% ulcer size reduction), no. improved (10-70% ulcer size reduction), no. worsened (> 10% ulcer size increase).		
INTERNAL VALIDITY				
Allocation [13] Randomised into 3 groups using a Permuted Balanced Block method	**Comparison of study groups** [14] Baseline characteristics were similar with the exception of age (15% different in group 2), weight (17% different in group 3), and ulcer size (24% larger in group 2 and 46% smaller in group 1).	**Blinding** [15] Single-blind but unclear who was blinded.	**Treatment/ measurement bias** [16] **Treatment/ measurement bias** [16] There was no difference in measurement between the groups	**Follow-up** (ITT) [17] Yes, no loss to follow-up
Overall quality assessment (descriptive) [18] This study may be subject to information bias as it is uncertain who was blinded. Also this study was very small and probably was underpowered. Study needs to be repeated to confirm results. This study was of average quality.				
RESULTS				

Outcome [19] [O = oral; T = topical]	Intervention group [20] O	O + T	Control group [21]	Measure of effect/effect size [22] RR (95% CI) [25]		Benefits (NNT) [23]
Ulcer size:	Group 1	Group 2		Group 1	Group 2	(95% CI) [25]
Week 0	375 ± 118	917 ± 229	766 ± 320			For comp healing:
Week 6	42 ± 33	138 ± 42	689 ± 329			NNT (G1 vs C)
% ulcer size reduction	87.8 ± 11	84.4 ± 3.5	25.1 ± 14.5	p = 0.002	p = 0.002	1.64 (1.2, 10.3)
O + T versus O:	Group 2: 84.4 ± 3.5		G1: 87.8 ± 11	p = 0.49		NNT (G2 vs C)
No. completely healed	5/6 (83.3%)	6/6 (100%)	2/9 (22.2%)	3.75 (1.23, 7.23)	4.5 (1.71, 4.50)	1.27 (1.27, 3.40)
O + T versus O:	Group 2		Group 1			
	6/6 (100%)		5/6 (83.3%)	RR = 1.20 [95% CI 0.84, 1.72]		
No. improved	1/6 (16.7%)	0/6 (0%)	1/9 (11.1%)	1.50 (0.16, 13.7)	0.75 (0.06, 9.62)	
No. worsened	0/6 (0%)	0/6 (0%)	1/9 (11.1%)	0.00 (0.00, 5.48)		
No.healed or improved (groups 1 + 2)	12/12 (100%)		3/9 (33%)	RR = 3.00 [1.55, 3.00]		

Clinical importance (1-4) [26]	Relevance (1-5) [27]	Harms (NNH) [24] (95% CI) [25]
1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.	1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] There were no clinical side-effects and all participants completed the study. Also no clinically meaningful changes in serum chemistry, haematology, urinalysis or vital signs.
EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] As the treatment provides a clinically and statistically significant benefit, treatment benefits may outweigh any harms.
Comments [31] The authors have shown that oral ingestion of ANGIPARS significantly increases the rate of healing for diabetic foot ulcers compared to standard wound care. Topical application of ANGIPARS did not provide any additional clinical benefits. However, this is a very small study and a larger study needs to be undertaken to confirm these results.

STUDY DETAILS				
Reference [1] (Bayram et al 2005) "The cell based dressing with living allogenic keratinocytes in the treatment of foot ulcers: a case study." British journal of plastic surgery 58(7): 988-996.				
Affiliation/source of funds [2] Dept. of Plastic and Reconstructive Surgery and Dept. of Medical Genetics, Gulhane Military Medical Academy, Ankara, Turkey.				
Study design [3] RCT	**Level of evidence** [4] II	**Location/setting** [5] Turkey Outpatient setting		
Intervention [6] Cultured keratinocyte loaded microcarriers (produced from polyethylene and silica). Following serial debridement of the wound the microcarriers (with or without loaded keratinocytes) were applied onto the wound with a single layer (~75/cm^2) and covered with petroleum jelly gauze. The dressing was renewed every three days for up to 30 days. **Sample size** [7] 20	**Comparator(s)** Placebo - microcarrier Same treatment as intervention group. **Sample size** [9] 20			
Selection criteria **Inclusion criteria** – Diabetic patients with grade 2-3 diabetic foot ulcers. **Exclusion criteria** –				
Patient characteristics [10] **Intervention group** – N = 20; ulcer area (cm^2) 10.3 ± 4.0. **Comparator group(s)** – N = 20; ulcer area (cm^2) 8.8 ± 4.0.				
Length of follow-up [11] 30 day treatment period, 1 year follow-up	**Outcome(s) measured** [12] % reduction in ulcer area in 30 days, time to healing, healing (wound score considering granulation formation, epithelisation, contraction, and amount of discharge, each scored 0-5; 20 = completely healed)			
INTERNAL VALIDITY				
Allocation [13] Randomisation method not disclosed	**Comparison of study groups** [14] No information provided except ulcer area which has a 15% difference	**Blinding** [15] Patients may have been blinded	**Treatment/ measurement bias** [16] There was no difference in treatment and measurement between the groups	**Follow-up** (ITT) [17] Yes, no loss to follow-up
Overall quality assessment (descriptive) [18] Unclear if investigators were blinded or if this study was adequately powered, therefore potential for bias. This study was of average quality.				
RESULTS				
Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/effect size** [22] (95% CI) [25]	**Benefits** (NNT) [23] (95% CI) [25]
% reduction ulcer area	92%	32%	p < 0.001	
Time to complete healing:				**Harms** (NNH) [24] (95% CI) [25]
No. dressing changes	9.2 ± 3.2	16.5 ± 2.	p < 0.001	
x 3 = no. days	27.6 ± 9.6	49.5 ± 6.0		
healing (wound score)	17.15 ± 2.7	9.05 ± 3.0	p < 0.001	
	Clinical importance (1-4) [26] 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention		**Relevance** (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] None reported				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits may outweigh any harms.				

Comments [31]. The authors have shown that the use of cultured keratinocyte loaded microcarriers improves the clinical outcomes for patients with diabetic foot ulcers by increasing the likelihood of healing and shortening the time to healing for these ulcers.

STUDY DETAILS

Reference [1] (Belcaro et al 2006) "Diabetic ulcers: microcirculatory improvement and faster healing with pycnogenol." Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 12(3): 318-323.

Affiliation/source of funds [2] Irvine2 Vasc Lab, Dept. of Biomedical Sciences, Chieti-pescara University; San Valentino Vascular Screening Project, Italy; Institute Pharmaceutical Chemistry, Westfalische Wilhelms-Universitat Munster, Germany. The study drug was supplied without conditions by Horphag Research Management SA, Geneva, Switzerland.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Italy? Outpatient setting

Intervention [6] Pycnogenol capsules	Comparator(s) [8] Standard ulcer care
Group 1: 50 mg capsule 3 times a day orally plus 100 mg powder from capsules placed on ulcerated area after cleaning. Group 2: 50 mg capsule 3 times a day orally. Group 3: 100 mg powder from capsules placed on ulcerated area after cleaning. All groups also received standard wound care. Sample size [7] Group 1 n = 8; Group 2 n = 6; Group 3 n = 8.	Exercise plan was presented to all subjects, friction-free socks were used to protect the foot and keep medications in place during the study period. Ulcers were carefully washed and cleaned daily with warm water and a mild local disinfectant. Ulcers were dried with paper tissue. [Pycnogenol powder (groups 1 and 3) was distributed as a fine layer over ulcer.] the ulcer was covered with a soft paper, nonallergic dressing and applying a layer of tensoplast elastic adhesive bandage. Sample size [9] 8

Selection criteria

Inclusion criteria – Diabetic patients, being treated with insulin, with severe microangiopathy causing foot ulceration, who had tibial arteries with flow that could be documented by Doppler and a peripheral tibial pressure exceeding 60 mmHg. Diabetic ulceration had been present for the first time and of at least 2 months duration.

Exclusion criteria – Any clinical disease requiring treatment, severe bone or joint problems or limited mobility, uncontrolled diabetes, severe hypertension, signs of systemic infections, obesity, recent thrombosis (< 6 months), presence of aneurysms or thrombi.

Patient characteristics [10]

Intervention group Group 1 – N = 8, mean age (yrs) 54.3 ± 4.4, gender: 3/8 (37.5%) male, 5/8 (62.5%) female, duration of diabetes 11.3 ± 2.6, skin perfusion pressure (mmHg) > 68 ± 5, ulcer area (mm^2) 43 ± 4.

Intervention group Group 2 – N = 6, mean age (yrs) 55.0 ± 3.0, gender: 4/6 (66.7%) male, 2/6 (33.3%) female, duration of diabetes 11.2 ± 4.0, skin perfusion pressure (mmHg) > 65 ± 6, ulcer area (mm^2) 45 ± 4.

Intervention group Group 3 – N = 8, mean age (yrs) 55.0 ± 5.0, gender: 3/8 (37.5%) male, 5/8 (62.5%) female, duration of diabetes 11.0 ± 2.4, skin perfusion pressure (mmHg) >66 ± 5, ulcer area (mm^2) 46 ± 6.

Comparator group(s) – N = 8, mean age (yrs) 52.4 ± 6.1, gender: 4/8 (50%) male, 4/8 (50%) female, duration of diabetes 12.0 ± 3.0, skin perfusion pressure (mmHg) >65 ± 7, ulcer area (mm^2) 44 ± 5.2.

Length of follow-up [11] study duration of 6 weeks	Outcome(s) measured [12] % reduction in ulcer area, % ulcers completely healed

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Randomisation method not disclosed	Baseline characteristics were similar with the exception of gender (20-30% differences)	none	There was no difference in measurement between the groups	Yes. No loss to follow-up

Overall quality assessment (descriptive) [18] It is unclear if the authors have tried to minimise bias as there was no blinding and the randomisation method was not disclosed. The study was also very small and likely to have been underpowered, However, the results look promising. This study was of average quality.

RESULTS

Outcome [19]	Intervention group [20] Group 1	Group 2	Group 3	Control group [21]	Measure of effect/effect size [22] (95% CI) [25] [vs Control:] Group 1	Group 2	Group 3	Benefits (NNT) [23] (95% CI) [25]
Ulcer size:	O + L	O	L					
At week 0	43 ± 4	45 ± 4	46 ± 6	44 ± 5.2				
At week 6	11 ± 4	30 ± 6	27 ± 7	34 ± 5				Harms (NNH) [24] (95% CI) [25]
% reduction	74.4%	33.3%	41.3%	22.7%	$p < 0.01$	$p < 0.05$	$p < 0.01$	
	(O = oral; L = local application)				(Group 1 vs Group 3: $p < 0.05$)			
% ulcers completely healed	89%	85%	84%	61%	$p < 0.05$	$p < 0.05$	$p < 0.05$	

	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] No significant local or systemic side effects were observed.		
EXTERNAL VALIDITY		
Generalisabilty [29] Applicable to other diabetics with Ischemic Foot Ulcers.		
Applicability [30] As the treatment provides a clinically and statistically significant benefit, treatment benefits may outweigh any harms.		
Comments [31] The authors have shown that oral ingestion and local application of pycnogenol significantly increases the rate of healing for diabetic foot ulcers compared to oral ingestion or local application alone. All 3 methods of administering pycnogenol are also significantly better than standard care alone. However, this is a very small study and a larger study needs to be undertaken to confirm these results.		

STUDY DETAILS				
Reference [1] (Benotmane et al 2004) "Treatment of diabetic foot lesions in hospital: Results of 2 successive five-year periods, 1918-1993 and 1994-1998." Diabetes and Metabolism 30(3 I): 245-250				
Affiliation/source of funds [2] Dept. of endocrinology and diabetologia, UIniversity Hospital of Oran, Algeria. No funding sources stated.				
Study design [3] historical control study	Level of evidence [4] III-3		Location/setting [5] Algeria University Hospital (inpatients)	
Intervention [6] Post-GP training program. An educational training program was initiated in 1994 for GPs about diabetic foot ulcer management. To assess the impact of this programme all diabetic patients with a foot ulcer admitted to the Endocrinology service from 1st January 1994 to 31st December 1998. Sample size [7] 176		Comparator(s) [8] Pre-GP training programme. All diabetic patients with a foot ulcer admitted to the Endocrinology service from 1st January 1989 to 31st December 1993. Sample size [9] 132		
Selection criteria Inclusion criteria – All diabetic patients with a foot ulcer admitted to the Endocrinology service of the University Hospital of Oran. Exclusion criteria – Patients sent to one of other 2 services that treat diabetic patients at the University Hospital of Oran.				
Patient characteristics [10] Intervention group – N = 176; N = 183 ulcers; age (yrs) 58.3 ± 13.1; gender: male 102/176 (58%), 74/176 (42%) female; local residents 131/176 (74.4%); type 2 diabetes 158/176 (89.8%); duration of hospital stay (days) 42.5 ± 34.9; Wagner: grade 1 or 2 67/183 (36.6%), grade 3 46/183 (25.1%), grade 4 or 5 70/183 (38.3%). Comparator group(s) – N = 132, N = 163 ulcers; age (yrs) 59.6 ± 17.7; gender: male 88/132 (66.7%), female 44/132 (33.3%); local residents 102/132 (77.3%); type 2 diabetes 118/132 (89.4%); duration of hospital stay (days) 44.5 ± 37.0; Wagner: grade 1 or 2 60/163 (36.8%); grade 3 28/163 (17.2%); grade 4 or 5 75/163 (46%).				
Length of follow-up [11] 6 months after hospitilisation		Outcome(s) measured [12] no. of deaths, no. of major and minor lower extremity amputations		
INTERNAL VALIDITY				
Allocation [13] Non-random. According to date period hospitalised	Comparison of study groups [14] Baseline characteristics were similar	Blinding [15] none	Treatment/ measurement bias [16] There was no difference in measurement between the groups	Follow-up (ITT) [17] Yes. Analysis of effectiveness included those lost to follow-up
Overall quality assessment (descriptive) [18] By using 2 cohorts from different time periods, spanning 10 years, it is possible that unknown confounding factors may be influencing the diabetic foot ulcer death and amputation rates and this may mask any effect the educational programme would actually have.. Average.				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] 95% CI [25]
No. of deaths	15/176 (8.5%)	12/132 (9.1%)	RR = 0.94 (0.46, 1.92)	
No. major amputations	29/176 (16.5%)	21/132 (15.9%)	RR = 1.04 (0.62, 1.73)	Harms (NNH) [24] 95% CI [25]
No. minor amputations	20/176 (11.4%)	19/132 (14.4%)	RR = 0.79 (0.44, 1.41)	
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] None stated				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As the treatment provides a clinically and statistically significant benefit, treatment benefits outweigh any harms.				

Comments [31] This study looks at the effect of educating GPs on the long-term outcomes of patients with diabetic foot ulcers and found no difference in death and amputation rates in the 5 year periods immediately pre- and post- the education programme.

STUDY DETAILS

Reference [1] (Blozik & Scherer 2008) "Skin replacement therapies for diabetic foot ulcers - Systematic review and meta-analysis." Diabetes Care 31(4): 693-694.

Affiliation/source of funds [2] Dept. of General Practice and Family Medicine, Georg-August University of Gottingen, Gottingen, Germany.

Study design [3]	Level of evidence [4]	Location/setting [5]
Systematic Review	I	Germany

Intervention [6] Skin replacement therapies	Sample size [7]	Comparator(s) [8]	Sample size [9]
(1) Gentzkow et al, 1996. *Diabetes Care* 19(4): 350-4.		Gentzkow et al, 1996.	
Dermagraft applied weekly for 8 weeks plus standard care	12	Standard wound care	13
(2) Naughton et al, 1997. *Artificial organs* 21(11): 1203-10.		Naughton et al, 1997.	
Up to 8 applications of Dermagraft plus standard care	109	Standard wound care	126
(3) Veves et al, 2001. *Diabetes Care* 24: 290-95.		Veves et al, 2001	
Graftskin applied weekly for up to 5 times	112	Standard wound care	96
(4) Caravaggi et al, 2003. *Diabetes Care* 26: 2853-9.		Caravaggi et al, 2003	
Autologous fibroblasts on Hyalograft scaffold (2nd graft if required)		Standard wound care	
7-10 days later, autologous keratinocytes grown on Laserskin	43		36
(5) Marston et al, 2003. *Diabetes Care* 26: 1701-5.		Marston et al, 2003.	
Dermagraft applied weekly for 7 weeks plus standard care	130	Standard wound care	115
	Total 406		Total 386

Selection criteria

Inclusion criteria – Randomised controlled clinical trials with participants having diabetic foot or leg ulcers, and that compared autografts (pinch, split, full thickness), cultured keratinocytes or fibroblasts, xerografts or bioengineered skin with any other intervention.

Exclusion criteria –

Patient characteristics [10]

Intervention/Comparator groups –

Gentzkow et al, 1996.	diabetic patients, full-thickness foot ulcer on the plantar surface of the forefoot or heel > 1 cm^2.
Naughton et al, 1997.	diabetic patients, full-thickness chronic foot ulcer on the plantar surface of the forefoot or heel > 1 cm^2.
Veves et al, 2001	diabetic patients, full-thickness neuropathic ulcer on the dorsum of foot, > 1 cm^2, duration > 2 weeks.
Caravaggi et al, 2003	diabetic patients, Wagner grade 1-2 foot ulcer on plantar surface or dorsum, > 2 cm^2, duration > 1 month.
Marston et al, 2003	diabetic adults, foot ulcer on the plantar surface of the forefoot or heel 1-20 cm^2, duration > 2 weeks.

Length of follow-up [11]	Outcome(s) measured [12]
	Effect estimates.

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]		Treatment/ measurement bias [16]	Follow-up (ITT) [17]
		Gentzkow et al, 1996	single-blinded		
		Naughton et al, 1997	single-blinded		
		Veves et al, 2001	unblinded		
		Caravaggi et al, 2003	unblinded		
		Marston et al, 2003	single-blinded		

Overall quality assessment (descriptive) [18] The meta-analysis in this review looks at the number of ulcers that healed completely after treatment with skin replacement therapies compared to standard wound care and compares 5 RCTs. The authors presented the data Odds Ratios but actually used Relative Risks. They also incorrectly reported the RR for Gentzkow et al as 3.86 instead of 6.5. This study was of average quality.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. ulcers healed by week 12:				
Gentzkow et al, 1996	6/12 (50%)	1/13 (8%)	RR = 6.50 [1.29, 39.71]	
Naughton et al, 1997	42/109 (39%)	40/126 (32%)	RR = 1.21 [0.86, 1.72]	
Veves et al, 2001	63/112 (56%)	36/96 (38%)	RR = 1.50 [1.11, 2.04]	
Caravaggi et al, 2003	26/43 (60%)	15/36 (42%)	RR = 1.46 [0.92, 2.29]	
Marston et al, 2003	39/130 (30%)	21/115 (18%)	RR = 1.64 [1.03, 2.62]	
Overall	176/406 (43%)	113/386 (29%)	RR = 1.46 [1.21, 1.76]	7 [5, 14]

Clinical importance (1-4) [26] 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	Harms (NNH) [24] (95% CI) [25]
Any other adverse effects [28] None reported		
EXTERNAL VALIDITY		
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.		
Applicability [30] As the treatment provides a clinically and statistically significant benefit, treatment benefits may outweigh any harms.		
Comments [31] This systematic review indicates that there are definite clinical benefits in using skin replacement therapies compared to standard wound care for the treatment of diabetic foot ulcers.		

STUDY DETAILS		
Reference [1] (Brigido et al 2004) "Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study." Orthopedics 27(1): s145-149.		
Affiliation/source of funds [2] St. Agnes Medical Centre, Philadelphia, Pa, USA.		
Study design [3] single-blind	Level of evidence [4] II	Location/setting [5] USA
Intervention [6] GraftJacket tissue matrix. Surgical application of the scaffold at day 0, then covered with a mineral oil-soaked fluff compressive dressing to maintain moist wound environment and changed on days 5, 10 and 15. After day 15 a dry sterile dressing was used. Same off-loading as control group. Sample size [7] 20	Comparator(s) [8] conventional thrapy with sharp debridement and Curasol wound gel with gauze dressings and standardised off-loading. Sample size [9] 20	
Selection criteria Inclusion criteria – Diabetic patients with a chronic, non-healing, full-thickness ulcer of the lower extremity (leg or foot), of at least 1 cm^2 in size and at least 6 weeks duration, that presented to a medical centre between April 7 2003 and June 27 2003. Exclusion criteria – None stated.		
Patient characteristics [10] N = 40; age (years) 58 (43-70); gender: male 31/40 (77.5%); female 9/40 (22.5%); insulin therapy 24/40 (60%). Intervention group – N= 20; ulcer duration (weeks) 25; ulcer length (mm) 32.5; ulcer width (mm) 21.0; ulcer area (cm^2) 9.7; ulcer depth (mm) 8.5. Comparator group – N= 20; ulcer duration (weeks) 27; ulcer length (mm) 26.7; ulcer width (mm) 18.6; ulcer area (cm^2) 5.4; ulcer depth (mm) 6.0.		
Length of follow-up [11]4 week study period	Outcome(s) measured [12] % wound reduction over 4 weeks	

INTERNAL VALIDITY				
Allocation [13] Method not disclosed	Comparison of study groups [14] Mostly unknown, however ulcer length, depth and area varied between 18% and 44%.	Blinding [15] Not clearly described, Patients were blinded?	Treatment/ measurement bias [16] There was no difference in measurement between the groups	Follow-up (ITT) [17] Yes, all patients were included in final analysis.
Overall quality assessment (descriptive) [18] This was a pilot study of short duration, the results for % reduction of wound area over the first 4 weeks look promising, but if this correlates with complete healing cannot be determined from this study. This study was of average quality.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
% wound reduction:				
Length	50.9	15.4	p = 0.001	Harms (NNH) [24] (95% CI) [25]
Width	49.6	22.9	p = 0.001	
Depth	89.1	25.0	p = 0.001	
Area	73.1	34.2	p = 0.001	
	Clinical importance (1-4) [26] 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] 5 adverse events occurred to grafted patients, 4 experienced drying of superficial portion of graft due to insufficient mineral oil-soaked compressive dressing and one patient developed a seroma which was aspirated at first post-operative visit. In all 5 patients, the graft incorporated with host tissue and was not considered a failure.				

EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.

Applicability [30] As the treatment provides a clinically and statistically significant benefit, treatment benefits outweigh any harms.
Comments [31] This was a pilot study of short duration, a longer follow-up period is required to evaluate its efficacy in complete healing of the ulcer.

<table>
<tr><td colspan="5">STUDY DETAILS</td></tr>
<tr><td colspan="5">Reference [1] (Calle-Pascual et al 2001) "Reduction in foot ulcer incidence: relation to compliance with a prophylactic foot care program." Diabetes Care 24(2): 405-407.
(Calle-Pascual et al 2002) "A preventative foot care programme for people with diabetes with different stages of neuropathy." Diabetes Res Clin Pract 57(2): 111-7.</td></tr>
<tr><td colspan="5">Affiliation/source of funds [2] Dept. of Endocrinology Metabolism and Nutrition, and Dept. of Internal Medicine, Hospital Clinico San Carlos, Madrid. Dept. of Endocrinology and Nutrition, Santiago University Hospital Complex, Santiego de Compostela, Spain. Funding source not stated.</td></tr>
<tr><td colspan="2">Study design [3] non-randomised prospective study</td><td colspan="2">Level of evidence [4] III-2</td><td>Location/setting [5] Spain
Outpatient setting</td></tr>
<tr><td colspan="3">Intervention [6] Patients that were compliant and participated in a foot programme consisting of 4 x 120 min sessions held over 1 week, covering shoes, socks and clothes, walking barefoot, foot hygiene, callus care, nail cutting, water temperature checks, use of foot warming devices, bathroom surgery, use of foot care products, methods of shoe and foot inspection. Continued foot-care teaching and treatment, including podiatry, were established. Patients were evaluated every 6 months. Data collected by questionnaire.
Sample size [7] compliant: low risk n = 94, high risk n = 126</td><td colspan="2">Comparator(s) [8] Patients that were non-compliant with the foot programme. Compliance defined as if: completed education programme, changed inadequate foot-care behaviour during first 6 months, attended podiatry regularly, attended a foot review every 6 months, and attended an annual diabetes review. Non-compliant patients received identical screening and educational programme at baseline and were followed in the same service setting.
Sample size [9] non-compliant: low risk n = 30, high risk n = 58</td></tr>
<tr><td colspan="5">Selection criteria
Both articles report data from the same study population.
Inclusion criteria – Diabetic patients attending the outpatient clinic of the endocrinology service diagnosed as having peripheral neuropathy with NDS > 6, without a history of foot ulceration. Tested for peripheral vascular disease and morphological plantar deformities, for visual and motor capability to inspect own feet, and for foot self-care.
Stratified into low risk group (VPT < 25 V) and high risk group (VPT > 25 V)
Exclusion criteria – peripheral vascular disease, presence of a diabetic foot ulcer.</td></tr>
<tr><td colspan="5">Patient characteristics [10]
2001 report:
Intervention group – N = 223, gender: 101/223 (45%) male, 122/223 (55%) female, mean age (yrs) 65.4 ± 11.6, duration of diabetes (yrs) 8.6 ± 7.9, HbA_{1c} (%) 6.4 ± 1.4, current smokers 22/223 (10%), never smoked 44/223 (20%), neuropathy disability score 6.2 ± 0.02.
Comparator group(s) – N = 95, gender: 43/95 (47%) male, 52/95 (53%) female, mean age (yrs) 70.2 ± 10.3, duration of diabetes (yrs) 9.1 ± 8.9, HbA_{1c} (%) 6.3 ± 1.3, current smokers 11/95 (12%), never smoked 18/95 (19%), neuropathy disability score 6.3 ± 0.02.
2002 report:
Intervention group – N = 220, 45% male, mean age (yrs) 65.9 ± 11.5, duration of diabetes (yrs) 8.5 ± 7.9, HbA_{1c} (%) 6.4 ± 1.4
Comparator group(s) – N = 88, 47% male, mean age (yrs) 69.9 ± 10.5, duration of diabetes (yrs) 9.0 ± 8.8, HbA_{1c} (%) 6.6 ± 1.6</td></tr>
<tr><td colspan="3">Length of follow-up [11] 3-6 years</td><td colspan="2">Outcome(s) measured [12] No. of patients with foot ulcers, no. of amputations</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Compliant and non-compliant cohorts stratified into low and high risk groups</td><td>Comparison of study groups [14]
Similar baseline characteristics</td><td>Blinding [15]
None</td><td>Treatment/ measurement bias [16] There was no difference in measurement between the groups</td><td>Follow-up (ITT) [17]
Yes for 2001 study, all 318 patients in final analysis.
No for 2002 study. only 308 of original 318 patients recruited 2-5 years earlier in final analysis.</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18] It is possible that the authors may have introduced selection bias by using non-compliant patients as the comparator. Even though the baseline characteristics of the 2 groups are similar, there may be an unknown confounder in the non-compliant group that increases or decreases their likelihood of developing diabetic foot ulcers. The second report analyses the data further by comparing ulceration and amputation rates between low risk and high risk patients. The studies were of average quality.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
</table>

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23]
2001 report: No. of patients with ulcers detected:	compliant (%) 7/223 (3.1)	non-compliant (%) 30/95 (31.6)	Compliant vs non-compliant RR = 0.10 (0.05, 0.21)	(95% CI) [25] 3.5 (3.0, 4.9)
No. patients needed amputations:	1/223 (0.5)	19/95 (20.0)	RR = 0.03 (0.00, 0.14)	
2002 report: No. of patients with ulcers detected:	5/220 (2.3)	23/88 (26.1)	RR = 0.09 (0.04, 0.21)	4.2 (3.5, 6.1)
	Low risk High risk	Low risk High risk	RR (l-r) = 0.04 (0.01, 0.23)	
	1/94 (1.1) 4/126 (3.2)	8/30(26.7) 15/58(25.9)	RR (h-r) = 0.12 (0.04, 0.33)	Harms (NNH) [24]
No. patients needed amputations:	1/220 (0.5)	16/88 (18.2)	RR = 0.03 (0.00, 0.14)	
	Low risk High risk	Low risk High risk	RR (min) = 0.04 (0.01, 0.21)	95% CI [25]
-minor	0/94 (0) 1/126 (0.8)	2/30(6.7) 9/58(15.5)	RR (maj) = 0.04 (0.00, 0.41)	
-major	0/94 (0) 0/126 (0)	0/30(0) 5/58(8.6)	RR (l-r) = 0.09 (0.01, 0.96)	
			RR (h-r) = 0.03 (0.01, 0.18)	
	Clinical importance (1-4) [26] 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] None reported				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with peripheral neuropathy.				
Applicability [30] There were no reported harms. As the treatment provides a clinically and statistically significant benefit, treatment benefits outweigh any harms.				
Comments [31] Compliance with a foot-care programme reduces the likelihood of foot ulceration in diabetic patients with neuropathy. It also decreases the likelihood of the ulcer progressing to require amputation.				

STUDY DETAILS

Reference [1] (Caravaggi et al 2003). "HYAFF 11-based autologous dermal and epidermal grafts in the treatment of noninfected diabetic plantar and dorsal foot ulcers: a prospective, multicenter, controlled, randomized clinical trial." Diabetes Care 26(10): 2853-2859.

Affiliation/source of funds [2] Centre for the Study and Treatment of diabetic Foot Pathology, Ospedale di Abbiategrasso, Milan; Policlinico Multimedica, Sesto San Giovanni, Milan; Centro per la Prevenzione e la Cura del Piede Diabetico-Fondazione Maugen, Pavia; Casa di Cura Villa Benca, Vincenza; Divisione Medicina, Ospedale San Carlo, Milan; Ospedale San Bortolo, Vincenza; Institute of Medical Statistics and Biometry, University of Milan, Milan; Italy. Funded by a grant from Fidia Advanced Biopolymers, Abano Terme, Italy.

Study design [3] RCT	**Level of evidence** [4] II	**Location/setting** [5] Italy Multicentre (6 sites),

Intervention [6] HYAFF-11-based autologous grafts.

A skin biopsy (1-2 cm^2, 0.8 mm deep) was taken and sent to the TissueTech Autograft Laboratory (Fidia Advanced Biopolymers, Abano Terme, Italy) for fibroblast and keratinocyte cell culturing. The cells were isolated and cultered for 14 days prior to seeding on two distinct biodegradable scaffolds composed of a benzylic ester of hyaluronic acid. After 8 days these sheets were ready for transplantation.

Patients first received autologous fibroblasts on Hyalograft 3D applied over ulcer after extensive debridement and cleansing. This was then covered with non-adherent paraffin gauze and a secondary dressing of sterile cotton pads and gauze, if a second graft was required, the wound was cleansed prior to application.

After 7-10 days the autologous keratinocytes grown on laserskin was applied to the ulcer, dressed and covered as before. A second graft was permitted if required.

Seconsary dressing could be changed after 3 days (earlier if needed). After 7 days the non-adherent paraffin gauze was changed every 2 days after cleansing the ulcer with physiologic solution.

Sample size [7] 43

Comparator(s) [8]

Initially subjected to extensive debridement. The ulcers were covered with non-adherent paraffin gauze and a secondary dressing of sterile cotton pads and gauze.

Visits and dressing changes were scheduled as for treatment patients.

Antibiotics prescribed if needed. All patients provided with non-removeable fibreglass cast)plantar ulcera) or therapeutic shoe (dorsal ulcers) for off-loading.

Sample size [9] 36

Selection criteria

Inclusion criteria – Diabetic patients with a Wagner grade 1-2 ulcer on the plantar surface or dorsum of foot of > 2 cm^2 and without signs of healing for 1 month and with adequate perfusion to the limb ($TcPO_2$ > 30 mmHg).

Exclusion criteria – signs of clinical infection of ulcer, exposed bone, osteomyelitis, inability to tolerate an off-loading cast, poor-prognosis disease.

Patient characteristics [10]

Intervention group – N = 43; diabetes type 1 9/43 (20.9%); diabetes type 2 34/43 (79.1%); $TcPO_2$ (mmHg) 48.0 (interquartile range 24.0); ankle-brachial index 0.7 ± 0.3; % HbA_{1c} 7.9 ± 2.13; ulcer area (cm^2) 5.3 ± 6.76; depth of ulcer (mm) 6.1 ± 5.68; duration of ulcer (months) 4.0 (interquartile range 10.0); localisation of ulcer: forefoot 31/43 (72.1%); midfoot 7/43 (16.3%); hindfoot 3/43 (7.0%); not specified 2/43 (4.7%).

Comparator group(s) – N = 36; diabetes type 1 3/36 (8.0%); diabetes type 2 33/36 (92.0%); $TcPO_2$ (mmHg) 48.5 (interquartile range 20.5); ankle-brachial index 0.7 ± 0.22, % HbA_{1c} 8.1 ± 2.25; ulcer area (cm^2) 6.2 ± 7.58; depth of ulcer (mm) 8.0 ± 5.46; duration of ulcer (months) 4.0 (interquartile range 6.0); localisation of ulcer: forefoot 24/36 (66.7%); midfoot 7/36 (19.4%); hindfoot 2/36 (5.6%); not specified 3/36 (8.3%).

Length of follow-up [11] 11 week study period	**Outcome(s) measured** [12] complete healing at 11 weeks, median time to complete healing (days), mean % reduction in ulcer size for non-healed ulcers.

INTERNAL VALIDITY

Allocation [13]	**Comparison of study groups** [14]	**Blinding** [15]	**Treatment/ measurement bias** [16]	**Follow-up** (ITT) [17]
Randomisation list was generated and held by the sponsor, allocation by telephone.	Similar characteristics with the exception of age and gender (unknown), diabetes type 1 (13% difference), ulcer size (15%), and ulcer depth (24%)	None	There was no difference in measurement between the groups	Yes, all patients that started treatment are in final analysis.

Overall quality assessment (descriptive) [18] This study was powered for α = 0.05, β = 95% with 70% healing in intervention group and 30% healing in control group. However, the differences between the intervention and control groups were smaller than expected and did not reach significance for complete healing of all ulcers. This study was of average quality.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. ulcers completely healed:				
Plantar	12/22 (55%)	10/20 (50%)	RR = 1.09 [0.62, 1.95]	
Dorsal	14/21 (66.7%)	5/16 (31.3%)	OR = 4.44 [1.09, 17.7]	
			RR = 2.04 [1.00, 4.50]	3 [2, 533]
Total	26/43 (60.5%)	15/36 (41.7%)	*RR = 1.45 [0.94, 2.28] *included in Meta-analysis by Blozik and Scherer (2008)	
				Harms (NNH) [24] (95% CI) [25]
Median time to complete healing (days):				
Plantar	57	58.5		
Dorsal	63	77		
Total	57	77		
Mean % reduction in ulcer size for non-healed ulcers:				
Plantar	61.1 ± 26.0	64.7 ± 34.7	*p* = 0.823	
Dorsal	68.0 ± 37.3	32.9 ± 35.1	*p* = 0.072	
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] 22 adverse events equally distributed between the two groups. 8/22 were rated as severe, 6/22 as moderate and 8/22 as low. None were determined to be related to any products used in the study. Most common adverse events included infection, inflammation and worsening of ischemia.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other Diabetic patients with diabetic foot ulcers.				
Applicability [30] As the treatment does not provide a clinically significant benefit, any harms may outweigh treatment benefits.				
Comments [31] The results in this study do not show a clinical benefit for using HYAFF-11-based autologous grafts compared to standard wound care for treating diabetic foot ulcers.				

STUDY DETAILS

Reference [1] (Chin et al 2003) "Treatment of chronic ulcers in diabetic patients with a topical metalloproteinase inhibitor, doxycycline." Wounds-a Compendium of Clinical Research and Practice 15(10): 315-323.

Affiliation/source of funds [2] Dept. of Surgery, Malcolm Randall Veterans Administration Medical Centre, Gainesville, Florida; Dept. of Surgery, and Dept. of Obstetrics and Gynecology, University of Florida, Gainesville, Florida, USA. Funded in part by Veterans administration Merit Type II grant.

Study design [3] double-blind RCT	Level of evidence [4] II	Location/setting [5] USA

Intervention [6] Once-daily topical application of 1% doxycycline hydrogel and standardised wound care. Hydrogel spreas to 2 mm thickness over wound, covered with dry gauze pads and secured with soft outer wrap. Patients were then fitted with offloading shoe. Sample size [7] 4	Comparator(s) [8] Same treatment using vehicle hydrogel. Treatment continued until ulcer healed or for 20 weeks. Then, if not healed after 20 weeks patient could elect to receive doxycycline for 12 weeks of open-label use. Sample size [9] 3

Selection criteria

Inclusion criteria – Diabetic patients with full-thickness, lower extremity ulcers of duration between 4 weeks and 2 years, sized between 1.7 and 12 cm^2, with a bacterial count from punch biopsy of < 1 x 10^6/gm of tissue, $TcPO_2$ > 30 mmHg, ankle-brachial index > 0.8, HbA_{1c} < 6%, blood analysis within normal limits.

Exclusion criteria – None stated.

Patient characteristics [10]

Intervention group – N = 4, mean age (yrs) 56.75 (46-68), gender: 3/4 (75%) male, 1/4 (25%) female, duration of diabetes (yrs) 10.25 (5-20), smoking 1/4 (25%). Co-morbidities: hypertension 4/4 (100%), coronary artery disease 2/4 (50%), cerebral vascular disease 1/4 (25%), congestive heart failure 1/4 (25%), chronic obstructive pulmonary disease 1/4 (25%), end-stage renal disease 0/4 (0%), atrial fibrillation 1/4 (25%), hyperlipidemia 0/4 (0%), obesity 1/4 (25%), previous amputation 0/4 (0%). Ulcer: size (cm^2) 5.33 ± 4.59, duration (months) 3 (2-5).

Comparator group(s) – N = 3, mean age (yrs) 69.67 (64-78), gender: 3/3 (100%) male, 0/3 (0%) female, duration of diabetes (yrs) 10.67 (6-19), smoking 1/3 (33.3%). Co-morbidities: hypertension 2/3 (66.7%), coronary artery disease 1/3 (33.3%), cerebral vascular disease 0/3 (0%), congestive heart failure 1/3 (33.3%), chronic obstructive pulmonary disease 0/3 (0%), end-stage renal disease 1/3 (33.3%), atrial fibrillation 0/3 (0%), hyperlipidemia 1/3 (33.3%), obesity 1/3 (33.3%), previous amputation 2/3 (66.7%). Ulcer: size (cm^2) 3.47 ± 3.48, duration (months) 12.3 (5-24).

Length of follow-up [11] 20 weeks treatment period	Outcome(s) measured [12] No. healed, time to healing,

INTERNAL VALIDITY

Allocation [13] Randomly assigned by pharmacy.	Comparison of study groups [14] Similar baseline characteristics with the exception of age (19% difference), previous amputation (67% difference), ulcer size (35% difference) and ulcer duration (76% difference).	Blinding [15] Patients and investigators were blinded	Treatment/ measurement bias [16] There was no difference in measurement between the groups	Follow-up (ITT) [17] Yes, all patients in final analysis.

Overall quality assessment (descriptive) [18] This pilot study was very small and almost certainly underpowered. Therefore, this study needs to be repeated on a larger scale to show a statistically significant effect. This pilot study was of average quality.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. ulcers healed	100% (4/4)	33.3% (1/3)	RR = 3.00 (0.99, 3.00)	
Mean time to healing (weeks)	16.25	>22.67	p = 0.05	Harms (NNH) [24] (95% CI) [25]
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect		.Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] No adverse events observed that were attributable to doxycycline or the vehicle gel.

EXTERNAL VALIDITY

Generalisabilty [29] Applicable to other Diabetic patients with diabetic foot ulcers.

Applicability [30] There were no reported harms. As the treatment may provide a clinically significant benefit, treatment benefits may outweigh any harms.
Comments [31] The results in this pilot study show a promising trend. The patients treated with doxycycline healed faster than the control group. However, this study was underpowered and needs to be repeated on a larger scale to show a statistically significant effect.

STUDY DETAILS				
Reference [1] (Chow et al 2008) "Management and prevention of diabetic foot ulcers and infections: A health economic review." PharmacoEconomics 26(12): 1019-1035.				
Affiliation/source of funds [2] Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada; Universidad nacional de Colombia, Bogota DC, Colombia.				
Study design [3] systematic review	Level of evidence [4] I	Location/setting [5] Canada and Columbia.		
Intervention [6] Sample size [7]	Comparator(s) [8] Sample size [9]			
Cost-effectiveness analysis:				
Becaplermin plus standard wound care (5 studies)	Standard wound care			
Bioengineered living skin equivalents plus standard wound care (3 studies)	Standard wound care			
Promogran plus standard wound care (1 study)	Standard wound care			
Cost-utility analysis:				
Hyperbaric oxygen therapy plus standard wound care (1 study)	Standard wound care			
Selection criteria Inclusion criteria – English-language, peer-reviewed, health economic evaluations (cost-effectiveness, cost-minimisation, cost-utility and cost-benefit studies) of a variety of different prevention, diagnostic and treatment strategies for diabetic foot ulcers and infections. Exclusion criteria –				
Patient characteristics [10] Intervention group – Comparator group(s) – 20 studies included: 10 studies investigated interventions that have been identified as effective, and were recommended Becaplermin plus standard wound care – diabetic patients with full-thickness foot ulcers Ghatnekar et al (2001) - used Markov model for diabetic lower extremity ulcers – France, Sweden, Switzerland, UK [Pharmacoeconomics 19(7):767-778.] Kantor and Margolis (2001) - efficacy data from phase III trial by Weiman (1998) [Am J Surg 176(2A Suppl): 74s-79s] - USA Persson et al (2000) - used Markov model for diabetic lower extremity ulcers - Sweden Sibbald et al (2003) - efficacy data from phase III trial by Weiman et al (1998) – Canada Ghatnekar et al (2000) - used Markov model for diabetic lower extremity ulcers – UK Bioengineered living skin equivalents plus standard wound care – diabetic patients with chronic full-thickness foot ulcers Steinberg et al (2002) - efficacy data from Veves at al (2001) - USA Redekop et al (2003) - efficacy data from Veves at al (2001) - Netherlands Allenet et al (2000) - efficacy data from Naughton et al (1997) and Pollak et al (1997) - France Promogran plus standard wound care – diabetic patients with deep foot ulcers Ghatnekar et al (2002) [J Wound Care 11:70-74.] Hyperbaric oxygen therapy plus standard wound care – diabetic patients with severe foot ulcers (Wagner grade 3 or more) Guo et al (2003) [Intl J Technol Assess Health Care 19:731-737.]				
Length of follow-up [11] N/A	Outcome(s) measured [12] Incremental cost-effectiveness ratio (ICER), cost per QALY.			
INTERNAL VALIDITY				
Allocation [13] N/A	Comparison of study groups [14] N/A	Blinding [15] N/A	Treatment/ measurement bias [16] N/A	Follow-up (ITT) [17] N/A
Overall quality assessment (descriptive) [18] Quality scores for included studies ranged from 70.8% (fair) to 87.5% (good). Good quality review.				
EXTERNAL VALIDITY				
Generalisabilty [29] Analysis for UK, western European countries, USA, and Canada. Generalisable to other countries with similar healthcare for patients with diabetic foot ulcers.				
Applicability [30]				
Comments [31] All studies used condition-specific measures of benefits (ulcer-free months gained, additional healed weeks, ulcer days averted, additional % of ulcers healed, and ulcer months avoided) that do not allow for a meaningful comparisons.				
RESULTS				

Study	Cost-effectiveness analysis: Incremental cost-effectiveness ratio (ICER)
	Becaplermin plus standard wound care
Ghatnekar et al (2001)	The cost of becaplermin vs SWC for the number of ulcer-free months gained was estimated to be net cost saving in the UK, Sweden and Switzerland, but a higher cost in France.
	Sensitivity analysis: cost lower for less persistent ulcers but higher for more persistent ulcers.
	- for less persistent ulcers: considered to be cost-effective in all 4 countries.
	- for more persistent ulcers: cost savings occurred in all countries except France. ICER = US$142
Kantor and Margolis (2001)	Total costs for SWC were US$1759, for becaplermin plus SWC US$2202
	Sensitivity analysis: changes in medication costs and number of office visits did not significantly affect the relative cost-effectiveness of the treatments
Persson et al (2000)	Based on amputation rates and costs associated with treatment, becaplermin plus SWC was the dominant therapy.
	Sensitivity analysis: relatively insensitive to changes in most parameters
	- becaplermin was not cost saving when improvements in monthly healing rates was only 24%
	- becaplermin was not cost neutral when improvements in monthly healing rates was 34%
	- becaplermin was only cost-effective when improvements in monthly healing rates > 34%
Sibbald et al (2003)	The average cost per patient treated was slightly lower with SWC than with becaplermin plus SWC
	Sensitivity analysis: the results were sensitive to becaplermin efficacy, cost of home care and rates of healing with SWC.
Ghatnekar et al (2000)	Sensitivity analysis: the results were not sensitive to changes in SWC healing rates, time horizon, and duration of one becaplermin tube.
	- becaplermin plus SWC costs were slightly higher than SWC alone when efficacy was only 24%
	Bioengineered living skin equivalents plus standard wound care
Steinberg et al (2002)	Significantly higher mean total costs seen in the Apligraf group than the SWC group (US$7366 vs US$2020; $p < 0.001$)
	Major driver is cost of Apligraf applications – contributes 76% to total costs
	Mean costs for severe adverse event: lower for Apligraf than SWC (US$1232 vs US$1335; $p = 0.136$)
	Sensitivity analysis: number of apligraf applications and the cost of Apligraf impacted on the ICER
Redekop et al (2003)	- after 4 weeks the cost of treatment with Apligraf plus SWC was 253% higher than for SWC alone
	- after 24 weeks the cost of treatment with Apligraf plus SWC was 1% lower (€3828 vs €3853)
	- after 52 weeks the cost of treatment with Apligraf plus SWC was 12% lower
	Sensitivity analysis: cost difference was sensitive to the number of Apligraf applications
Allenet et al (2000)	The incremental cost of Dermagraft vs SWC per additional ulcer healed = FF38,784 (€5,913)
	Average annual treatment cost per patient was higher for Dermagraft plus SWC than SWC alone
	Average cost per ulcer healed was lower for Dermagraft plus SWC than for SWC alone
	Sensitivity analysis: variations in the number of Dermagraft applications, weekly cost for healed state, the number of amputations and rehabilitation time post-amputation did not affect cost-effectiveness of Dermagraft
	Promogran plus standard wound care
Ghatnekar et al (2002)	Total treatment costs per healed ulcer were higher for SWC than for Promogran plus SWC in France, Germany, Switzerland and the UK
	Sensitivity analysis: the results were relatively sensitive to healing rates and number of dressing changes
	- increasing dressing changes to 5X per week: reduced cost savings in Switzerland and the UK; increased costs in Germany and France
	- decreasing dressing changes to 3X per week: greater increase in cost savings in all countries
	Cost-utility analysis:
	Hyperbaric oxygen therapy plus standard wound care
Guo et al (2003)	The incremental cost of HBO_2 therapy vs SWC per additional quality-adjusted life year (QALY) gained = US$27,310 at year 1, US$5,166 at year 5, and$2,255 at year 12.
	The study results indicate that HBO_2 therapy plus SWC in the treatment of diabetic ulcers is cost effective for long-term treatment
	Sensitivity analysis: efficacy probabilities, number of HBO_2 treatments per case, costs of HBO_2 treatment and costs of major and minor lower-extremity amputations had a significant impact on cost-effectiveness ratios.

STUDY DETAILS

Reference [1] (Colagiuri et al 1995) "The use of orthotic devices to correct plantar callus in people with diabetes." Diabetes research and clinical practice 28(1): 29-34.

Affiliation/source of funds [2] Diabetes Centre, Prince of Wales Hospital, Randwick, NSW, Australia. Funded by a grant from Rebecca L Cooper Medical Research Foundation Ltd.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Australia Diabetes Centre (outpatient)

Intervention [6]	Comparator(s) [8]
Treatment with a custom made rigid orthotic device, made from thermal pliable plastic pressed over a plaster cast of foot. The orthotic device is light, extends from heel to behind the metatarsal heads, does not interfere with toe movement during walking, and fits well into sport shoes. Patients were asked to wear it for at least 7 hours each day. Sample size [7] 9	Traditional treatment of callus by podiatrist at three-monthly intervals, timed for soon after the study assessment visit. All patients were assessed every three months for 12 months. Sample size [9] 11

Selection criteria

Inclusion criteria – Diabetic patients with plantar callus (grade 1-3) without past history of foot ulceration. Assessed by podiatrist to grade callus, assess lower limb biomechanics and gait analysis and measurement of vibration sensation.

Exclusion criteria – Patients with grade 4-6 callus

Patient characteristics [10]

Intervention group – N = 9, mean age (yrs) 63 ± 10, gender: 4/9 (44.4%) male, 5/9 (55.6%) female, duration of diabetes (yrs) 10.7 ± 7.6, weight (kg) 74.1 ± 6.5, treatment: diet 1/9 (11.1%), oral 4/9 (44.4%), insulin 4/9 (44.4%), biothesiometer reading (mV) 23.7 ± 12.1, peripheral vascular disease 0/9 (0%), palpable pulses in feet 9/9 (100%), mild pronation of feet 9/9 (100%), evidence of neuropathy: 3/9 (33.3%), severe neuropathy 0/9 (0%),.no. of calluses 2.4 ± 1.0, mean callus grade 1.9.

Comparator group(s) – N = 11, mean age (yrs) 69 ± 6, gender: 1/11 (9%) male, 10/11 (91%) female, duration of diabetes (yrs) 7.9 ± 6.6, weight (kg) 76.2 ± 13.9, treatment: diet 1/11 (9.1%), oral 5/11 (45.5%), insulin 5/11 (45.5%), biothesiometer reading (mV) 24.6 ± 8.7, peripheral vascular disease 0/11 (0%), palpable pulses in feet 11/11 (100%), mild pronation of feet 11/11 (100%), evidence of neuropathy: 5/11 (45.5%), severe neuropathy 1/11 (9%),.no. of calluses 2.9 ± 1.4, mean callus grade 1.6.

Length of follow-up [11] 12 months	Outcome(s) measured [12] number of calluses, mean callus grade*, number of calluses improved, same or worsened.

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Randomisation method not disclosed	Baseline characteristics were similar with the exception of gender (35% difference), duration of diabetes (26% difference)	Callus grade was assessed by consensus of three authors, blinded to identity of subject, date of photograph and treatment mode.	There was no difference in measurement between the groups	Yes. There was no loss to follow-up.

Overall quality assessment (descriptive) [18] The authors have attempted to minimise both selection and information bias by randomisation of patients into the 2 groups and by blinding the assessors. Average.

RESULTS

Outcome [19]	Intervention group [20] initial	Intervention group [20] after 12 months	Control group [21] initial	Control group [21] 12 months	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. of calluses	22	20	32	32		
-Improved	16/22 (73%)		2/32 (6.3%)		RR = 11.6 (2.97, 45.61)	1 (1, 2)
-Same	6/22 (27%)		23/32 (71.9%)			
-Worsened	0/22 (0%)		7/32 (21.9%)			Harms (NNH) [24] 95% CI [25]
Mean callus grade (thickness)	1.9	1.2	1.6	1.7	*P*<0.02 Fischer exact test	

Clinical importance (1-4) [26]	Relevance (1-5) [27]
1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.	2. Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention.

Any other adverse effects [28] None stated

EXTERNAL VALIDITY

Generalisabilty [29] Applicable to other Diabetic patients with plantar callus.

Applicability [30] There were no reported harms. As the treatment provides a clinically and statistically significant benefit, treatment benefits may outweigh any harms.
Comments [31] The orthotic insole reduced the number and severity of calluses over a 12 month period in this small study. Callus severity of grade 5 is associated with an ulcer.

Classification of plantar callus: Grade 1, distinct area with minimal thickening of keratin layer; Grade 2, moderate thickening of keratin layer; Grade 3, marked thickening of keratin layer; Grade 4, callus with haematoma; Grade 5, callus with ulcer; Grade 6, callus with infected ulcer.

STUDY DETAILS		
Reference [1] (de Lalla et al 2001) "Randomized prospective controlled trial of recombinant granulocyte colony-stimulating factor as adjunctive therapy for limb-threatening diabetic foot infection." Antimicrobial agents and chemotherapy 45(4): 1094-1098.		
Affiliation/source of funds [2] Dept. of Infectious Diseases, Diabetes Centre, and Dept. of Plastic Surgery, San Bortolo Hospital, Vicenza, Italy.		
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Italy
Intervention [6] same as control plus glycosylated recombinant human G-CSF (lenograstin) administered subcutaneously at a dosage of 263 μg daily for 21 days. If neutrophil count exceeded 35,000 cells/mm^3, the dose was temporarily dropped to 175 μg, and it was discontinued if count was over 50,000 cells/mm^3. Sample size [7] 20	Comparator(s) [8] local treatment plus systemic antibiotics Local treatment consisted of careful debridement at enrolment, daily inspections, cleaning with sterile water, disinfection with povidone iodine, further debridement as needed, occlusive dressing of foot lesions. Empiric antibiotic treatment with ciprofloxacin and clindamycin, according to consensus standard. Intravenous therapy was administered for more serious infections. Sample size [9] 20	
Selection criteria Inclusion criteria – Adult diabetic patients admitted to the diabetes Centre between September 1996 and January 1998, for severe, limb-threatening foot infection. Exclusion criteria – Treatment with antibiotics during the 2 weeks prior to patient recruitment, superficial infection, refusal of consent, immediate risk of above ankle amputation for ischaemia, any critical condition with immediate risk of death, renal impairment, history of allergic reaction to ciprofloxacin or clindamycin, any other contra-indication for G-CSF administration such as myeloid leukaemia.		
Patient characteristics [10] Intervention group – N = 20, age (yrs) 56.6 ± 8.6, gender males 16/20 (80%), females 4/20 (20%), duration of diabetes (yrs) 15.6 ± 8.6, ankle-brachial index 0.96 ± 0.34, vibration perception threshold (V) 35.8 ± 14.6, mean neutrophil count (cells/mm^3) 7,800 ± 3,500, WBC count > 10,000/mm^3 1/20 (5%), erythrocyte sedimentation rate > 70 mm/h 11/20 (55%), positive blood cultures 0/20 (0%), life-threatening infection 0/20 (0%), osteomyelitis 20/20 (100%). Ulcer type: neuropathic 13/20 (65%), ischemic 2/20 (10%), mixed 5/20 (25%), Wagner grade 3 13/20 (65%), grade 4 7/20 (35%),.> 1 ulcer 6/20 (30%), ulcers/patient 1.4 ± 0.6, isolates/patient 2.05 ±1.2, polymicrobial infection 14/20 (70%), cellulitis >2 cm diameter 10/20 (50%), probing to bone 20/20 (100%), abscess 1/20 (5%), ulcer > 2 cm diameter 13/20 (65%). Comparator group(s) – N = 20, age (yrs) 59.8 ± 9.6, gender males 14/20 (70%), females 6/20 (30%), duration of diabetes (yrs) 18.5 ± 8.6, ankle-brachial index 1.29 ± 0.5, vibration perception threshold (V) 43.2 ± 0.47, mean neutrophil count (cells/mm^3) 8,300 ± 3,500, WBC count > 10,000/mm^3 5/20 (25%), erythrocyte sedimentation rate > 70 mm/h 13/20 (65%), positive blood cultures 2/20 (10%), life-threatening infection 2/20 (10%), osteomyelitis 20/20 (100%). Ulcer type: neuropathic 14/20 (70%), ischemic 0/20 (0%), mixed 6/20 (30%), Wagner grade 3 14/20 (70%), grade 4 6/20 (30%),.> 1 ulcer 5/20 (25%), ulcers/patient 1.4 ± 1.0, isolates/patient 2.30 ±1.6, polymicrobial infection 10/20 (50%), cellulitis >2 cm diameter 15/20 (75%), probing to bone 20/20 (100%), abscess 3/20 (15%), ulcer > 2 cm diameter 11/20 (55%).		
Length of follow-up [11] 6 months	Outcome(s) measured [12] no. completely healed, no. improved, and no. amputated after 3 weeks and after 9 weeks. Cured or stable at 6 months, worsened at 6 months	

INTERNAL VALIDITY				
Allocation [13] Randomised, method not disclosed	Comparison of study groups [14] Similar baseline characteristics with the exception of WBC count > 10,000/mm^3 (20% difference), and vibrator perception threshold (25% difference).	Blinding [15] Assessors were blinded	Treatment/ measurement bias [16] There was no difference in measurement between the groups	Follow-up (ITT) [17] Yes. Analysis of effectiveness was done according to ITT
Overall quality assessment (descriptive) [18] Only assessors were blinded, thus there is potential for bias. Additionally, the study may not have been adequately powered leading to a type 2 error. The study was of a average quality.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. completely healed:				
After 3 weeks	0/20 (0%)	0/20 (0%)	RR = 1.00	
After 9 weeks	7/20 (35%)	7/20 (35%)	RR = 1.00 (0.43, 2.31)	

No. improved:				
After 3 weeks	12/20 (60%)	9/20 (45%)	RR = 1.33 (0.74, 2.38)	
After 9 weeks	8/20 (40%)	4/20 (20%)	RR = 2.00 (0.76, 5.61)	
No. amputated				
After 3 weeks	1/20 (5%)	5/20 (25%)	RR = 0.20 (0.03, 1.15)	
After 9 weeks	3/20 (15%)	9/20 (45%)	RR = 0.33 (0.11, 1.05), $p = 0.038$	3.33 (2.06, 62.3)
At 6 months:				Harms (NNH) [24] (95% CI) [25]
Cured or stable	13/20 (65%)	15/20 (75%)	RR = 0.87 (0.61, 1.29)	
Worsened	3/20 (15%)	5/20 (25%)	RR = 0.60 (0.17, 2.03)	
Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.			Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] No side effects were recorded.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with infected diabetic foot ulcers.				
Applicability [30] There were no reported harms. However, the treatment provides little benefit in this study, so any rare adverse effects may outweigh any benefits.				
Comments [31] Glycosylated recombinant human G-CSF does not appear to offer any clinical benefits above standard care plus antibiotic therapy for osteomyelitis in this study.				

STUDY DETAILS				
Reference [1] (Doctor et al 1992) "Hyperbaric oxygen therapy in diabetic foot." Journal of postgraduate medicine 38(3): 112-4, 111				
Affiliation/source of funds [2] No conflicts of interest stated				
Study design [3] randomised control trial	Level of evidence [4] II	Location/setting [5] India Hospital setting.		
Intervention [6] Hyperbaric oxygen therapy Given a complete course of HBOT as an adjunct to the comparator treatment. The HBOT was given in a monoplace hyperbaric oxygen chamber at 3 atmospheres pressure for a period of 45 minutes in four separate sittings over a period of 2 weeks. The HBOT was administered using Vickers clinical hyperbaric system. The patient slides completely into the chamber and the oxygen flow is started for 2 - 3 minutes till high oxygen concentration is achieved. The chamber pressure is gradually raised to 3 atmospheric pressures, after the therapy, the chamber pressure is gradually reduced to normal. Assessment of local wound occurred daily. Sample size [7] 15		Comparator(s) [8] Standard wound care All diabetics patients with chronic foot lesions were admitted. All patients received regular surgical treatment consisting of incision and drainage of abscesses and debridement of wound. Locally, the wounds were dressed with eusof (1.25% w/v boric acid and 1.25% w/v of bleaching powder) and/or glycerine acriflavine. In those patients in whom the gangrene/infection ascended above the ankle, amputation was performed to limit the spread of infection and resulting toxaemia. Major amputation was defined as an amputation done, above the ankle joint. All others were considered as minor amputations. Antibiotics were administered according to sensitivity patterns along with metronidazole for 3 days. Sample size [9] 15		
Selection criteria Inclusion criteria – All diabetics patients with chronic foot lesions Exclusion criteria – none?				
Patient characteristics [10] Intervention group – mean age (yrs) 56.2 (range 45-70), gender (M:F) 3:1, duration of diabetes (yrs) 9.8, insulin dependent 15%, neuropathy 17%, distal pulses absent 13%. Comparator group(s) – mean age (yrs) 59.8 (range 48-70), gender (M:F) 2:1, duration of diabetes (yrs) 10.9, insulin dependent 20%, neuropathy 21%, distal pulses absent 21%.				
Length of follow-up [11] over a period of 2 years		Outcome(s) measured [12] length of hospital stay, need for amputation.		
INTERNAL VALIDITY				
Allocation [13] Method not disclosed	Comparison of study groups [14] Baseline characteristics were similar	Blinding [15] none	Treatment/ measurement bias [16] There was no difference in measurement between the groups	Follow-up (ITT) [17] Yes. Analysis of effectiveness was done according to ITT
Overall quality assessment (descriptive) [18] It is highly likely that this study was underpowered due to the small sample size. The result showing a statistically significant reduction in no. of amputations suggests that this treatment may be of benefit in treating diabetic foot ulcers. Average.				
RESULTS				
Outcome [19]	Intervention grp [20]	Control grp [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] 95% CI [25]
Length of hospital stay in days (range)	40.6 (23-65)	47 (20-68)	*p* = NS	
No. amputations: minor major total	4/15 (26.7%) 2/15 (13.3%) 6/15	2/15 (13.3%) 7/15 (46.7%) 9/15	RR = 0.5 (0.11, 2.06), *p* = 0.36 RR = 0.29 (0.07, 0.98), *p* = 0.05 RR = 0.67 (0.33, 1.36), *p* = 0.27	Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] None stated				

EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] There were no reported harms. As the treatment provides some benefit, treatment benefits may outweigh any harms.
Comments [31] Hyperbaric oxygen therapy reduced the need for major (above the ankle) amputation in this small study.

STUDY DETAILS				
Reference [1] (Donaghue et al 1998) "Evaluation of a collagen-alginate wound dressing in the management of diabetic foot ulcers." Advances in Wound Care 11(3): 114-119.				
Affiliation/source of funds [2] Johnson & Johnson Medical. Tac., Arlington, TX.				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] USA, Medical Centre, Harvard Medical School.		
Intervention [6] Intervention patients were treated the same as the control group except that they were provided with FIBRACOL Collagen-Alginate wound dressing and given explicit dressing change instructions and told to change it as often as required. Patients were seen on a weekly basis as outpatients, at each visit the ulcer was extensively re-evaluated. Sample size [7] 50		Comparator(s) [8] Initial patient visit included an extensive evaluation of the ulceration assessing: size, location, duration, and stage according to Wagner classification. The patients then receive standard treatment as recommended by the American Diabetes Association which includes: extensive wound debridement, frequent saline-moistened gauze dressing changes, appropriate use of antibiotics, periods of non-weight bearing (applying a self-adhesive felted foam dressing to the foot with a window at ulcer site and the use of healing sandals). Patients were seen the same as the intervention group. Sample size [9] 25		
Selection criteria Inclusion criteria – at least 21 years of age, adequate nutritional intake as indicated by serum albumin of >2.5 g/dl, adequate blood flow to lower extremities as indicated by palpable pulses and/or normal non-invasive tests, and foot ulceration of at least 1 cm^2 in size after initial debridement. Exclusion criteria – severe renal or liver impairment as indicated by creatinine levels and liver function tests 2x higher than normal, presence of any serious medical disorder that could interfere with wound healing, evidence of osteomyelitis as diagnosed by deep probing or radiographic findings, clinical signs of infection, and a history of alcohol or drug abuse.				
Patient characteristics [10] Intervention group – N=50, mean age 59 years (range 30-81), duration of diabetes 19 years (range 4-47), gender: 66% (n=33) male, 34% (n=17) female, Wagner Ulcer grade I 16% (n=8), grade II 72% (n=36), grade III 12% (n=6), duration of ulcer in days 146±73 (range 1-365), ulcer size 2.6 ± 0.50cm^2, mean weight 195 ± 45 pounds, presence of retinopathy 55% (n=28), mean creatinine level 1.2 ± 0.6 mg/dl, mean serum albumin level 3.72 ± 0.07 grams/dl, 12% (n= 6) did not complete the study. Comparator group(s) – N=25, mean age 60 (range 33-79), duration of diabetes 17 years (range2-25), gender: 84% (n=21) male, 16% (n=4) female, Wagner Ulcer grade I 4% (n=1), grade II 80% (n=20), grade III 16% (n=4), duration of ulcer in days 225±104 (range 1-1,825), ulcer size 2.99 ± 0.62cm^2, mean weight 214 ± 49 pounds, presence of retinopathy 76% (n=19), mean creatinine level 1.14 ± 0.06, mean albumin level 3.79 ± 0.11grams/dl, 32% (n=8) did not complete the study.				
Length of follow-up [11] up to 8 weeks		Outcome(s) measured [12] mean % reduction of wound area, complete healing, time to healing,		
INTERNAL VALIDITY				
Allocation [13] Assigned randomly in a 2:1 ratio open-label design to intervention or control group.	Comparison of study groups [14] Similar baseline characteristics with the exception of gender(18% difference) Wagner grade 1 ulcer (12%), duration of ulcer (35%), retinopathy (21%).	Blinding [15] None	Treatment/ measurement bias [16] Possible for bias in ulcer evaluation between groups	Follow-up (ITT) [17] Yes, analysis done on number enrolled in trial
Overall quality assessment (descriptive) [18] paper provides little detail on how ulcer evaluations were conducted to minimise bias. Assuming that there is no significant information bias, I find the results to be reliable. However, multivariate analysis, when wound size was averaged over the 8 week study period and factoring in duration of ulcer, indicated that the overall treatment effect was significantly in favour of the intervention (df = 1, p = 0.0049). Average.				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Mean % reduction in ulcer area	80.6% ± 6%	61.1% ± 26%	p = 0.47	

Mean time to complete healing (weeks)	6.2 ± 0.4	5.8 ± 0.4	*p* = 0.001	Harms (NNH) [24] 95% CI [25]
Median time to 75% healing (weeks)	2	4	*p* = 0.26	
No. Patients that achieved >75% wound area reduction	39/50 (78%)	15/25 (60%)	RR = 1.3 (0.96, 1.84) *p* = 0.1737	
Complete healing	24/50 (48%)	9/25 (36%)	RR = 1.3 (0.77, 2.50) *p* = 0.39	
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] 6 patients experienced adverse events but no details given.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As there does not seem to be a statistically significant treatment effect, any potentials harms will outweigh the benefits				
Comments [31] The authors claim that if both wound size and duration are taken into account, the collagen-alginate dressing offered a statistically significant benefit compared to gauze dressings. However, it is unclear if the study was adequately powered, a larger study many have found the No. of patients that achieved >75% wound area reduction in the intervention group to be statistically significant compared to the control group.				

STUDY DETAILS

Reference [1] (Driver et al 2006) "A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers." Ostomy/wound management 52(6): 68-70, 72, 74 passim.

Affiliation/source of funds [2]Centre for Lower Extremity Ambulaory Research, Dr. William M. Scholl College of Podiatric Medicine, Rosalind Franklin University of Medicine, National Centre for Limb Preservation, Advocate Lutheran General Hospital, Niles, Ill; Doctor's Research Network, South Miami, Fla, Cytomedix Inc. Rockville, MD.

Study design [3] double-blind RCT	Level of evidence [4] II	Location/setting [5] USA Multicentre (14 sites), outpatients

Intervention [6] Platelet-rich plasma gel.	Comparator(s) [8] Normal saline.
Up to 20 ml (depending on size of ulcer) blood was drawn from patient and spun in a small portable centrifuge to separate the platelet-rich plasma (PRP) from the whole blood. The PRP was extracted and reagents to activate the platelets were added, and reagents to achieve proper gel consistency, gel was then immediately applied to the wound and covered with a contact dressing. This was covered with the absorbent side of a foam dressing and secured. For protection barrier cream was placed on the skin surrounding the wound. Sample size [7] 40	Initial 7-day screening period for all patients, including surgical debridement, baseline measurements and evaluation, treated with control saline gauze and used fixed ankle-foot orthoses with crutches or walker. Blood drawn to maintain blinding. Normal saline was applied to the wound and then covered as for intervention patients. Treatment was continued twice weekly until ulcer healed or the end of the 12 week study period. Sample size [9] 32

Selection criteria

Inclusion criteria – Diabetic patients, aged 18-95 years, with an ulcer of at least 4 weeks duration if they met additional criteria: HbA1c < 12%, index foot ulcer located on plantar, medial or lateral aspects of foot, wound area (length x width) between 0.5 and 20 cm^2, wounds under Charcot deformity free of acute changes and undergone appropriate structural consolidation, no clinical signs of infection, full-thickness without exposure of bone, muscle, ligaments or tendons (University of Texas Diabetic Foot classification System grade 1A). Post-debridement the ulcer was comprised of healthy vascularised tissue, at least 4 cm from any additional wound, and with adequate perfusion. Signed, informed consent.

Exclusion criteria –Pregnancy or lactation, refusal to use birth control during study and for 6 months afterwards, currently enrolled in another investigational trial, ulcer area decreased > 50% in 7-day screening period, non-diabetic ulcers. Acute Charcot foot, evidence of infection, gangrene, osteomyelitis, radiation or chemotherapy within 3 months, antibiotic use within last 2 days, received growth factor therapy within 7 days of randomisation, serum albumin level < 2.5 g/dl, haemoglobin < 10.5 mg/dl, platelet count < 100 x 10^9/l, known platelet disorder, liver disease, active cancer, rheumatic disease, bleeding disorders, renal dialysis, immune insufficiency, peripheral vascular repair within 30 days of randomisation, surgical correction required for ulcer to heal, psychological, developmental, physical, emotional, or social disorder that may interfere with compliance, history of alcohol or drug abuse, inadequate venous access for blood draw, religious or cultural conflict with use of platelet gel treatment..

Patient characteristics [10]

Intervention group – N=40, mean age (yrs) 56.4 ± 10.2, gender: 32/40 (80%) male, 8/40 (20%) female, HbA_{1c} (%), 8.1 ± 1.8, race: Caucasian 26/40 (65%), Hispanic 8/40 (20%), Black 5/40 (12.5%), other 1/40 (2.5%). Ulcer: location: toes 13/40 (32.5%), heel 18/40 (45%), area (cm^2) 4.0 ± 5.3, volume (cm^3) 1.7 ± 4.1.

Comparator group(s) – N=32, mean age (yrs) 57.5 ± 9.1, gender: 27/32 (84.4%) male, 5/32 (15.6%) female, HbA_{1c} (%) 8.0 ± 1.8, race: Caucasian 18/32 (56.25%), Hispanic 9/32 (28.13%), Black 3/32 (9.38%), other 2/32 (6.25%). Ulcer: location: toes 14/32 (43.75%), heel 10/32 (31.25%), area (cm^2) 3.2 ± 3.5, volume (cm^3) 0.9 ± 1.2.

Length of follow-up [11] 12 week study period, 12 week follow-up for patients with healed ulcers.	Outcome(s) measured [12] complete healing after 12 weeks, time to healing and recurrent ulcers.

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias	Follow-up (ITT) [17]
Randomisation schedule was electronically generated, blocked per investigational centre	Similar baseline characteristics with the exception of ulcer size (20% difference), and ulcer volume (47% difference).	One un-blinded person per site to treat patient. Patients, investigators/ assessors, site staff were blinded.	[16] There was no difference in treatment and measurement between the groups	All patients included in complete healing analysis. Mostly used PP (per protocol analysis which excluded patients which were non-compliant, did not complete study or those where a protocol violation occurred.

Overall quality assessment (descriptive) [18] Study seemed adequately powered for main outcomes, and designed to minimise bias. Therefore data reported in this study is likely to be due to the difference between the efficacy of the intervention and the control treatments. This study was of good quality.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
ITT dataset				
Complete healing at 12 weeks	13/40 (32.5%)	9/32 (28.1%)	RR = 1.16 (0.58, 2.38), $p = 0.79$	
Excluded due to non-compliance, non-completion or protocol violation:	21/40 (52.5%)	11/32 (34.4%)		
PP (per protocol) dataset				
Complete healing at 12 weeks	13/19 (68.4%)	9/21 (42.9%)	RR = 1.60 (0.91, 2.68), $p = 0.125$	
Median time to healing (days)	45	85	$p = 0.126$	
Recurrent ulcers	1/13 (7.7%)	0/9 (0%)	RR = 1.39 (0.11, 18.5), $p = 0.572$	
PP dataset Standardised for ulcer size				
Complete healing at 12 weeks	13/16 (81.3%)	8/19 (42.1%)	RR = 1.93 (1.12, 2.85), $p = 0.036$	2.56 (1.66, 14.85)
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	Harms (NNH) [24] (95% CI) [25]
Any other adverse effects [28] 127 adverse events occurred: 60 (49%) were in the intervention group and 62 (51%) in the control group. Only 2 of these were identified as related to the treatment, one case of contact dermatitis in the interventions group and one case of maceration in the control group.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As there does not seem to be a statistically significant treatment effect, any potentials harms will outweigh the benefits				
Comments [31] The authors can only obtain a statistically significant benefit for using PRP gel compared to saline dressings by taking both wound size and number of patients that completed the study into account.				

STUDY DETAILS				
Reference [1] (Duzgun et al 2008) "Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers." Journal of Foot & Ankle Surgery 47(6): 515-519.				
Affiliation/source of funds [2] No conflicts of interest stated				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Turkey Hospital – Emergency Surgery Dept.		
Intervention [6] Standard wound care plus hyperbaric oxygen therapy administered at 2-3 ATA for 90 mins (2 sessions per day, followed by 1 session next day, alternating throughout course of therapy – 20-30 days) Sample size [7] 50		Comparator(s) [8] Standard wound care: local debridement, dressing changes, infection control. Sample size [9] 50		
Selection criteria Inclusion criteria – Diabetic patients at least 18 years old, foot ulcer present for at least 4 weeks despite local and systemic wound care, and suitable for hyperbaric oxygen therapy Exclusion criteria – contraindicated for hyperbaric oxygen therapy due to untreated pneumothorax; obstructive pulmonary disease; history of otic surgery; upper respiratory tract infection; febrile state; history of idiopathic convulsion; hypoglycaemia; current corticosteroid, amphetamine, catecholamine or thyroid hormone use				
Patient characteristics [10] Intervention group – N = 50, mean age (yrs) 58.1 ± 11.0, gender: 74% male, 26% female, duration of diabetes (yrs) 16.9 ± 6.2, insulin dependent 82%, hypertension 64%, BMI > 30 kg/m^2 80%, current smoker 72%, high lipid-lipoprotein level 62%, glycosylated Hb (mg/dl) 8.0 ± 1.9, Wagner grade: W2 12%, W3 38%, W4 50%. Comparator group(s) – N = 50, mean age (yrs) 63.3 ± 9.2, gender: 54% male, 46% female, duration of diabetes (yrs) 15.9 ± 5.6, insulin dependent 90%, hypertension 56%, BMI > 30 kg/m^2 46%, current smoker 40%, high lipid-lipoprotein level 54%, glycosylated Hb (mg/dl) 8.7 ± 2.9, Wagner grade: W2 24%, W3 36%, W4 40%.				
Length of follow-up [11] mean duration 92 ± 12 weeks		Outcome(s) measured [12]healing without surgical intervention, no. requiring amputation, extent of amputation		
INTERNAL VALIDITY				
Allocation [13] Assigned using a random number table according to a predetermined sequence.	Comparison of study groups [14] Similar baseline characteristics with the exception of gender (20% difference), BMI (34% difference), and smoking status (32% difference).	Blinding [15] none	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, all randomised patients were included in the analysis.
Overall quality assessment (descriptive) [18] There are two potential confounders (obesity and smoking) that could affect the rate of wound healing, and would predict that the clinical outcomes for the intervention group should be worse than the control group. However, the outcomes show a statistically significant benefit with the intervention, suggesting that the intervention has a true effect. Average.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/ effect size 95% CI	Benefits (NNT) [23] (95% CI) [25]
No. healed without surgery:				Healed without surgery
Ulcer grade 2	6/6 (100%)	0/12 (0%)	RR = 24 (4.03, 24.0)	1.54 (1.50, 1.92)
Ulcer grade 3	13/19 (68%)	0/18 (0%)	RR = 24.6 (3.3, 240.9)	1.52 (1.42, 2.59)
Ulcer grade 4	14/25 (56%)	0/20 (0%)	RR = 22.4 (2.9, 219.4)	1.87 (1.74, 3.40)
Total	33/50 (66%)	0/50 (0%) [0.5/50 for RR calc.]	RR = 66 (8.1, 638)	1.54 (1.50, 1.92)
No. requiring amputation:				
Distal amputation:				
Ulcer grade 2	0/6 (0%)	4/12 (33.3%)	RR = 0.0 (0.0, 1.45)	
Ulcer grade 3	1/19 (5%)	17/18 (94%)	RR = 0.06 (0.02, 0.21)	1.12 (1.03, 1.55)
Ulcer grade 4	3/25 (12%)	3/20 (15%)	RR = 0.8 (0.196, 3.27)	
Total	4/50 (8%)	24/50 (48%)	RR = 0.17 (0.06, 0.41)	2.50 (2.03, 4.22)

Proximal amputation: Ulcer grade 2 Ulcer grade 3 Ulcer grade 4 Total All amputations	 0/6 (0%) 0/19 (0%) 0/25 (0%) 0/50 (0%) 4/50 (8%)	 0/12 (0%) 0/18 (0%) 17/20 (85%) 17/50 (34%) 41/50 (82%)	 RR = 0.0 (0.00, 0.12) RR = 0.0 (0.00, 0.20) RR = 0.01 (0.04, 0.20)	 1.18 (1.18, 1.55) 2.94 (2.94, 4.43) 1.35 (1.21, 1.71)
				Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26] 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] None reported				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits might outweigh any harms. The safety of this treatment should be assessed further.				
Comments [31] The authors have provided evidence that hyperbaric oxygen therapy improves the clinical outcomes of severe diabetic foot ulcers.				

STUDY DETAILS		
Reference [1] (Edmonds et al 2009) "Apligraf in the treatment of neuropathic diabetic foot ulcers." The international journal of lower extremity wounds 8(1): 11-8.		
Affiliation/source of funds [2] Diabetic Foot Clinic, King's college Hospital, Denmark Hill, London, UK. Funded by Organogenesis Inc (manufacturer of Apligraf)		
Study design [3] multicentre, open-labelled RCT	Level of evidence [4] II	Location/setting [5] European Union and Australia. Clinical outpatient setting.
Intervention [6] Ulcer care as for control and Apligraf was placed directly on bed of target ulcer, then Mepitel (a porous wound contact layer consisting of a flexible polyamide) was applied as a primary non-adherant dressing. Secondary dressings were then applied (saline-moistened gauze, dry gauze, and bandage to hold in place). Additional applications of Apligraf at 4 and 8 weeks if the wound was judged to be not healing. Sample size [7] 33	Comparator(s) [8] Ulcer care consistent with international guidelines: sharp debridement, saline-moistened dressings, a non-weight bearing regime. The same primary and secondary dressings were used as for intervention group. Ulcers were assessed at weekly visits and treated as necessary including debridement. Both groups had the same off-loading requirements. Sample size [9] 39	
Selection criteria Inclusion criteria – diabetic patients between ages 18 and 80 years, given written informed consent, have a neuropathic ulcer limited to the plantar region of the forefoot, through the dermis but without sinus tract, tendon, capsule or bone exposure, present at least 2 weeks with a surface area of 1-16 cm^2, no more than 2 ulcers on foot, adequate vascular supply to target extremity, able to tolerate extensive debridement, can follow strict off-loading recommendations. Exclusion criteria – >40% reduction in area of ulcer during 14 day screening period, active Charcot foot, have osteomyelitis or other infections in target ulcer, have skin cancer near ulcer site, clinically significant medical conditions which would impair wound healing (renal, hepatic or immunocompromised), pregnancy, receiving immunosuppressive treatments (corticosteroids, chemotherapy, radiation therapy), history of graft at target site within 12 weeks, history of drug or alcohol abuse, noncompliant.		
Patient characteristics [10] Intervention group – N=33; age (yrs) 56.4 ± 11.6; Gender: male 29/33 (87.9%); female 4/33 (12.1%); weight (kg) 98.1 (63-145); height (cm) 177.9 ± 7.7; duration of diabetes (yrs) 15.7 ± 9.2; type 1 16/33 (48.5%); duration of ulcer (yrs) 2.0 ± 2.3; ulcer size (cm^2) 3.0 ± 2.1. Comparator group(s) – N=39; age (yrs) 60.6 ± 9.8; Gender: male 33/39 (84.6%); female 6/39 (15.4%); weight (kg) 97.9 (65-173); height (cm) 177.5 ± 10.0; duration of diabetes (yrs) 16.0 ± 9.1; type 1 13/39 (33.3%); duration of ulcer (yrs) 1.7 ± 1.8; ulcer size (cm^2) 3.0 ± 2.1.		
Length of follow-up [11] the 12 week study duration and then to 24 weeks. Patients whose ulcers healed had additional visits during this period.	Outcome(s) measured [12] time to complete healing, incidence of healing, recurrence of ulceration	

INTERNAL VALIDITY				
Allocation [13] Randomised 1:1 by sealed allocation cards 3-5 days before baseline treatment	Comparison of study groups [14] Similar baseline characteristics with the exception of type 1 diabetes (15% difference).	Blinding [15] none	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Of 82 randomised subjects, 72 were treated and comprised the ITT population
Overall quality assessment (descriptive) [18] Assuming that there is no bias between the intervention and control groups due to open-label study design, I find the results to be reliable. Even though it is a small study, a statistically significant result was achieved for the secondary outcome. Average.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] (95% CI) [25]
Median time to healing (days)	84	ND (<50% healed)	Kaplan-Meier curve (p = 0.059, log-rank test)	
No. completely healed by 12 weeks	17/33 (51.5%)	10/39 (25.6%)	RR = 2.01 [1.1, 3.73]	4 (2, 29)
Recurrence of ulceration at 12 weeks after healing	1/15 (7%)	1/10 (10%)	RR = 0.67 [0.07, 6.23] (p = 1.000)	Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] 1 intervention patient suffered a fatal myocardial infarction, 4 intervention patients and 5 control patients suffered a nonfatal serious adverse event. None of these events were attributed to the study treatment. Three serious advers events occurred at the target ulcer site: 1 intervention patient had a localised foot infection, 1 control patient had osteitis resulting in amputation, another had squamous cell carcinoma at the target ulcer site. None were due to the study treatment.
EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits will probably outweigh any harms.
Comments [31] The authors have demonstrated that the application of Apligraf improves the healing time of diabetic foot ulcers

STUDY DETAILS		
Reference [1] (Edwards & Stapley 2010) "Debridement of diabetic foot ulcers." Cochrane Database Syst Rev.		
Affiliation/source of funds [2] Dept. of Health and Social Care, Trafford College, Altrincham; Health Sciences, University of York, York , UK. Published as a Cochrane Review.		
Study design [3] Systematic Review	Level of evidence [4] I	Location/setting [5] UK

Intervention [6] Surgical debridement	Sample size [7]	Comparator(s) [8]	Sample size [9]
(1) (Piaggesi et al 1998)		(Piaggesi et al 1998)	
Conic ulcerectomy, debridement and surgical closure of wound	22/46	Standard wound care	24/46
Hydrogels			
(2) (d'Hemecourt et al 1998)		(d'Hemecourt et al 1998)	
Sodium carboxymethylcellulose (NaCMC) aqueous-based gel	70/170	Saline dressings	68/170
		Becaplermin gel 100 µg/g	34/170
(3) (Jensen et al 1998)		(Jensen et al 1998)	
Carrasyn (Acemannan) Hydrogel	14/31	Saline guaze	17/31
(4) (Vandeputte & Gryson 1997)		(Vandeputte & Gryson 1997)	
Hydrogel (Elasto-gel) with 65% glycerine	15/29	Dry gauze	14/29
This review also included 2 studies that were excluded from our analysis because they are unpublished conferences reports (Markevich et al 2000; Whalley et al 2001).			
	Total 121		Total 123

Selection criteria

Inclusion criteria – RCTs (published or unpublished) that measured the effects of one or more methods or debridement on ulcer healing in the treatment of diabetic foot ulcers. Debridement methods could include mechanical or non-mechanical methods.

Exclusion criteria –

Patient characteristics [10]

Intervention/Comparator groups –

Piaggesi et al (1998)	diabetic patients with neuropathy and a foot lesion of Wagner grade 1 or 2.
d'Hemecourt, et al, (1998)	diabetic patients with a full-thickness chronic diabetic foot ulcer (stage 3 or 4), > 8 weeks duration.
Jensen et al, (1998)	diabetic patients with Wagner grade 2 foot ulcer of at least 1 cm diameter and adequate perfusion
Vandeputte et al, (1997)	any diabetic patient with a foot ulcer.

Length of follow-up [11]	Outcome(s) measured [12] No. of ulcers completely healed, no. of adverse events reported.

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
		Piaggesi et al (1998) not blinded d'Hemecourt, et al, (1998) assessor blinded Jensen et al, (1998) not blinded Vandeputte et al, (1997) not blinded		

Overall quality assessment (descriptive) [18] The meta-analysis is quite small as only 3 studies were compared. The combined results of the 3 studies for both no. of ulcers healed and no. of adverse events were statistically significant. Good quality review.

RESULTS

Outcome [19] Meta-analysis for studies 2-4.		Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. of ulcers completely healed	(2)	(2) 25/70 (36%)	15/68 (22%)	RR = 1.62 (0.94, 2.80)	
	(3)	12/14 (86%)	6/17 (35%)	RR = 2.43 (1.23, 4.79)	
	(4)	14/15 (93%)	7/14 (50%)	RR = 1.87 (1.09, 3.21)	
	Total:	51/99 (52%)	28/99 (28%)	RR = 1.84 (1.30, 2.61)	4.30 (2.80, 10.34)
					Harms (NNH) [24] (95% CI) [25]
No. of adverse events reported.	(2)	19/70 (10%)	25/68 (37%)	RR = 0.74 (0.45, 1.21)	
	(3)	2/14 (14%)	4/17 (24%)	RR = 0.61 (0.13, 2.84)	
	(4)	1/15 (7%)	7/14 (50%)	RR = 0.13 (0.02, 0.95)	
	Total:	22/99 (22%)	36/99 (36%)	RR = 0.60 (0.38, 0.95)	7.00 (3.87, 68.20)

Clinical importance (1-4) [26] No. ulcers healed: 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention. No. adverse events: 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] 22% of intervention patients and 36% of control patients reported an adverse event	
EXTERNAL VALIDITY	
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.	
Applicability [30] As the treatment has a clinically significant effect on healing of diabetic foot ulcers and the intervention groups reported less advers events than the control groups, treatment benefits should outweigh any harms.	
Comments [31] This systematic review indicates that there are definite benefits for treating diabetic foot ulcers with hydrogels compared to standard wound care using saline or dry gauze dressings.	

STUDY DETAILS

Reference [1] (Eneroth et al 2004) "Nutritional supplementation for diabetic foot ulcers: the first RCT." Journal of Wound Care 13(6): 230-234

Affiliation/source of funds [2] Dept. of Orthopaedics; Dept. of Internal Medicine, Foot Care Unit, Lund University Hospital and Dept. of Endocrinology, Malmo University Hospital, Sweden. Funded by Nutricia ABB, Netherlands.

Study design [3]	Level of evidence [4]	Location/setting [5]
double-blind RCT	II	Sweden Lund University Hospital - outpatients.

Intervention [6]	Comparator(s) [8]
to take 400 ml Fortimel between meals everyday for 6 months Standard wound care. Sample size [7] 26	take 400 ml placebo (similar taste and appearance) between meals every day for 6 months Standard wound care. Sample size [9] 27

Selection criteria

Diabetic patients referred to the diabetic foot care team at the Dept. Of Internal Medicine, Lund University Hospital

Inclusion criteria – aged over 60 years, Wagner grade I or II foot ulcer of at least 4 weeks duration, distal BP measured in last 3 months, agree to participate (informed consent).

Exclusion criteria – active chronic inflammatory intestinal disease, malignancy, immunosuppressive treatment, decreased kidney function, severe heart disease, psychiatric, addictive or other disorder compromising ability to participate.

Patient characteristics [10]

Intervention group – N = 26, Age 74 (59-88), Gender: male 19/26 (73%), female 7/26 (27%), Duration of diabetes (yrs) 16 (1-51), Insulin use 18/26 (69%), Smoking history 12/23 (52%), Neuropathy 23/23 (100%), Retinopathy 13/23 (56%), Nephropathy 7/24 (29%), Hypertension 20/26 (80%), Ischaemic heart disease 12/26 (46%), Cardiac failure 6/26 (23%), Cerebrovascular lesion 4/26 (15%), Palpable pulses (foot) 3/26 (12%), Ulcer duration (weeks) 25 (4-100), Ulcer area (cm^2) 3.3 ± 5.8. Group wound size: < 1 cm^2 10/26 (38%), 1-3 cm^2 8/26 (31%), > 3 cm^2 8/26 (31%). Ulcer site: toes 15/26 (58%), mid/hindfoot 4/26 (15%), plantar metatarsal 7/26 (27%). Ulcer characteristics: oedema 12/25 (48%), rest pain 8/19 ((42%), increased temperature 7/23 (30%), secretion 9/25 (36%), necrosis 10/25 (40%), granulation 14/25 (56%), hyperkeratosis 4/25 (16%).

Comparator group(s) – N = 27, Age 75 (61-85), Gender: male 21/27 (77.8%), female 6/27 (22.2%), Duration of diabetes (yrs) 15 (1-41), Insulin use 22/27 (81.5%), Smoking history 10/27 (37%), Neuropathy 24/26 (92%), Retinopathy 16/26 (62%), Nephropathy 11/26 (42%), Hypertension 17/27 (63%), Ischaemic heart disease 11/27 (41%), Cardiac failure 5/27 (19%), Cerebrovascular lesion 7/27 (26%), Palpable pulses (foot) 10/27 (37%), Ulcer duration (weeks) 22 (4-105), Ulcer area (cm^2) 4.7 ± 6.7. Group wound size: < 1 cm^2 6/27 (22%), 1-3 cm^2 10/27 (37%), > 3 cm^2 11/27 (41%). Ulcer site: toes 9/27 (33%), mid/hindfoot 11/27 (41%), plantar metatarsal 7/27 (26%). Ulcer characteristics: oedema 15/27 (56%), rest pain 7/22 (32%), increased temperature 5/27 (19%), secretion 14/27 (52%), necrosis 5/27 (19%), granulation 16/27 (59%), hyperkeratosis 7/20 (35%).

Length of follow-up [11]	Outcome(s) measured [12]
monthly for 6 months then at 1 and 2 years after inclusion.	no. wounds healed at 6 months

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Randomisation method not disclosed	Similar baseline characteristics with the exception of smoking status (15% difference), nephropathy (13%), hypertension (17%), palpable foot pulses (25%), ulcer size (30%), mid/hindfoot ulcers (26%), ulcer secretion (16%), necrosis (21%), and hyperkeratosis (19%).	Both patients and investigators were blinded	There was no difference in treatment and measurement between the groups	Yes, those that did not complete the study were included in some analyses

Overall quality assessment (descriptive) [18] Assuming that there is little or no bias between the intervention and control groups, I find the results to be reliable, showing that the intervention has no benefit for ulcer healing in this study. Good.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/ effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25] / Harms (NNH) [24] 95% CI [25]
No. wounds healed at 6 months	12/26	10/27	RR = 1.25 (0.66, 2.36)	

Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.

Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.

Any other adverse effects [28] 7 intervention patients withdrew, 4 did not like the taste, 3 experienced nausea, vomiting and diarrhoea. 2 patients from the control group withdrew because they did not like the beverage.

EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] As there does not seem to be an treatment effect, any potentials harms will outweigh the benefits
Comments [31] This nutritional supplement does not appear to have had any effect in this study. It also had no beneficial effect on the number of patients in the intervention group defined as having protein-energy malnutrition, increasing from 5 to 7 patients..

STUDY DETAILS

Reference [1] (Faglia et al 1996) "Adjunctive systemic hyperbaric oxygen therapy in treatment of diabetic foot ulcer A randomized study." Proceedings of the International Joint Meeting on Hyperbaric and Underwater Medicine; 1996; Grafica Victoria, Bologna: 391-9.

Affiliation/source of funds [2] Niguarda Hospital, Dept of Anesthesia and Hyperbaric Medicine, Galezzi Institute, Milan University, Milan, Italy.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Italy Niguarda Hospital

Intervention [6] Hyperbaric oxygen therapy plus standard wound care. Patients breathed pure oxygen in a multi-place chamber, pressurized with air, with a soft helmet. In the first phase, treatment was daily, pressurised to 2.5 ATA, for 90 mins each session, for 30 sessions. In the second phase, 2.4-2.2 ATA were applied for 90 mins for 5 days each week. Sample size [7] 36	Comparator(s) [8] Standard wound care only. Aggressive debridement was performed and the wound was cleaned with antimicrobial agents and wadded with occlusive dressing. This was carried out at least twice per day when necrosis or exudates were present, daily when ulcer was clean, and every 2 days during granulation period. All patients were given broad-spectrum antibiotics, modified if necessary and continued until culture exam was negative. Metabolic control of blood sugar levels was also optimised. Sample size [9] 34

Selection criteria

Inclusion criteria – Diabetic patients, consecutively hospitalised in the diabetologic unit for foot ulcer, underwent the diagnostic and therapeutic protocol and gave their informed consent were randomised for HBOT treatment.

Exclusion criteria – none stated

Patient characteristics [10]

Intervention group – N = 35, mean age (yrs) 61.7 ± 10.4, gender: 27/35 (77%) male, 8/35 (23%) female, duration of diabetes (yrs) 16 ± 10, insulin therapy 60%, smokers 31.4%, obesity 25.7%, HbA_{1c} (%) 9.3 ± 2.5, ankle-brachial index 0.65 ± 0.28, $TcPO_2$ (mmHg) 23.25 ± 10.6, microalbuminuria 34.2%, proteinuria 22.8%, impaired vibration sense 85.7%, Neuropathy: sensorimotor 100%, autonomic 73.9%, Retinopathy: background 34.2%, proliferative 37.1%, renal impairment 11.4%, hypertension 54.2%, hyperlipidaemia 31.4%, coronary artery disease 40%, prior stroke 8.6%, infection 91.4%, peripheral angiography 88.5%, bone lysis 31.4%, osteopenia 42.8%, monckeberg sclerosis 60%,), Wagner grade 2 11.5%, grade 3 25.7%, grade 4 62.8%, previous amputation: minor 17.1%, major 0%, previous ulcer 25.7%.

Comparator group(s) – N = 33, mean age (yrs) 65.6 ± 9.1, gender: 21/33 (63.6%) male, 12/33 (36.4%) female, duration of diabetes (yrs) 19 ± 9, insulin therapy 66.7%, smokers 36.4%, obesity 27.3%, HbA_{1c} (%) 8.5 ± 2.3, ankle-brachial index 0.64 ± 0.25, $TcPO_2$ (mmHg) 21.29 ± 10.7, microalbuminuria 27.3%, proteinuria 21.2%, impaired vibration sense 85.2%, Neuropathy: sensorimotor 93.9%, autonomic 71.4%, Retinopathy: background 39.4%, proliferative 27.3%, renal impairment 27.3%, hypertension 51.6%, hyperlipidaemia 24.2%, coronary artery disease 45.4%, prior stroke 12.1%, infection 84.8%, peripheral angiography 78.8%, bone lysis 27.3%, osteopenia 63.6%, monckeberg sclerosis 60.6%, Wagner grade 2 15.2%, grade 3 24.2%, grade 4 60.6%, previous amputation: minor 30.3%, major 0%, previous ulcer 36.4%.

Length of follow-up [11] Not stated.	Outcome(s) measured [12] No. amputations, time to amputation, duration of hospital stay

INTERNAL VALIDITY

Allocation [13] Randomisation method not disclosed	Comparison of study groups [14] Similar baseline characteristics with the exception of gender (13% difference), renal impairment (15%), osteopenia (21%), previous minor amputation (13%)	Blinding [15] None	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] No. 2 patients lost during study period not included in final analysis.

Overall quality assessment (descriptive) [18] The study was adequately powered to determine the major outcome and indeed the number of major amputations decreases after HBOT. Assuming there is little information bias, the results should be reliable. Average quality.

RESULTS

Outcome [19]	Intervention group [20]		Control group [21]		Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
	Reported	ITT	Reported	ITT	ITT	
Major amputations:	3/35 (8.6%)	3/36	11/33 (33.3%)	11/34	RR = 0.26 (0.08, 0.77)	4.2 (2.87, 18.68)
Wagner grade 2	0/4 (0%)		0/5 (0%)		RR = 1.00	
Wagner grade 3	1/4 (25%)		0/8 (0%)		RR = 4.0 (0.32, 52.6)	
Wagner grade 4	2/22 (9.1)		11/20 (55%)		RR = 0.17 (0.04, 0.54)	
Minor amputations:	21/35 (60%)	21/36	12/33 (36.4%)	12/34	RR = 1.65 (0.99, 2.79)	4.34 (2.28, infinite)
Forefoot	5/35 (14.3)		4/33 (12.1)		RR = 1.18 (0.37, 3.86)	
Toe	16/35 (45.7)		8/33 (24.2)		RR = 1.89 (0.97, 3.83)	Harms (NNH) [24] (95% CI) [25]
Time to major amputation (days)	57.6 ± 24 (range 31-78)		72.8 ± 59 (range 26-176)			
Length of hospital stay (days)	43.2 ± 31		50.8 ± 32		*p* = 0.37	
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.				Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] 2 patients showed symptoms of barotraumatic otitis, which did not interrupt their treatment.						
EXTERNAL VALIDITY						
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.						
Applicability [30] As there does seem to be a treatment benefit in preventing major amputations, benefits may outweigh the harms.						
Comments [31] The authors have shown that HBOT can prevent major amputations in this study. However, no data on wound healing was provided.						

STUDY DETAILS

Reference [1] (Fernández Montequín et al 2007) "Intralesional injections of Citoprot-P (recombinant human epidermal growth factor) in advanced diabetic foot ulcers with risk of amputation." International Wound Journal 4(4): 333-43.

Affiliation/source of funds [2] Heber Biotec, Havana, Cuba

Study design [3] double-blind RCT	**Level of evidence** [4] II	**Location/setting** [5] Cuba 5 hospitals

Intervention [6]	**Comparator(s)** [8]
Identical vials containing lyophilised powder and either 75 µg (intervention) or 25 µg (control) rhEGF Receive intralesion injections of 75 µg rhEGF in 5 ml saline, three times per week on alternate days until complete response or for 5 weeks. If partial response observed treatment continued for an additional 3 weeks. Also treated with a standardised good wound care regimen as for control. **Sample size** [7] 23	Receive intralesion injections of 25 µg rhEGF in 5 ml saline, same as for intervention group. Also treated with a standardised good wound care regimen. Ulcers were subjected to sharp debridement whenever necessary, dressed with saline-moistened gauze, pressure was off-loaded, broad spectrum antibiotics used to manage infections, and metabolic control was strictly followed. **Sample size** [9] 18

Selection criteria

Inclusion criteria – Diabetic patients over 18 years of age with Wagner grade 3 or 4 foot ulcer, with high risk of amputation.

Exclusion criteria – Foot ulcer area < 1cm^2, Hb < 100 g/L, uncontrolled chronic disease (coronary, renal failure, ketoacidosis, oligoanuria), malignancies, psychiatric or neurological disease that could impair reasoning, pregnancy and breast feeding.

Patient characteristics [10]

Intervention group – N = 23, mean age 63.0 ± 12.0, male 52.2%, Caucasian 65.2%, duration of diabetes (yrs) 20.1 ± 8.5, type 1 diabetes 8.7%, history of heart disease 26.1%, ankle brachial index > 0.8 30.4%, median ulcer duration (months) 1.0 ±1.5, ulcer area (cm^2) 22.5 ± 35.0. Ulcer: neuropathic 26.1%, ischemic 74.9%, Wagner grade 3 78.3%, grade 4 21.7%. Ulcer location: toes 65.2%, internal edge 4.3%, external edge 13%, dorsum 17.4%, sole 21.7%, transmetatarsal 13%, ankle 13%.

Comparator group(s) – N = 18, mean age 67.5 ± 19.5, male 55.6%, Caucasian 72.2%, duration of diabetes (yrs) 17.5 ± 10.1, type 1 diabetes 11.1%, history of heart disease 16.7%, ankle brachial index > 0.8 22.2%, median ulcer duration (months) 1.0 ±1.5, ulcer area (cm^2) 25.0 ± 10.9. Ulcer: neuropathic 44.4%, ischemic 55.6%, Wagner grade 3 100%, grade 4 0%. Ulcer location: toes 66.7%, internal edge 0%, external edge 22.2%, dorsum 11.1%, sole 22.2%, transmetatarsal 11.1%, ankle 11.1%.

Length of follow-up [11] 12 months	**Outcome(s) measured** [12] no. complete healing, % healing, time to healing, no. amputations, time to amputations.

INTERNAL VALIDITY

Allocation [13]	**Comparison of study groups** [14]	**Blinding** [15]	**Treatment/ measurement bias** [16]	**Follow-up** (ITT) [17]
Randomised according to a computer-generated random list, stratified by investigation site.	Similar baseline characteristics with the exception of neuropathic and ischemic ulcers (19% difference), and ulcer grade (20%).	Both patients and investigators were blinded	There was no difference in treatment and measurement between the groups	Yes, those that did not complete the study were included in the analysis

Overall quality assessment (descriptive) [18] It is highly likely that the lack of a statistically significant result is due to the small sample size. The study is underpowered. Good.

RESULTS

Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/ effect size**, 95% CI	**Benefits** (NNT) [23] 95% CI [25]
No. completely healed	13/23 (56.5%)	9/18 (50%)	RR = 1.13 (0.65, 2.05)	
75-100% healing (5 w)	17/23 (73.9%)	9/18 (50%)	RR = 1.48 (0.92, 2.38)	
Time to healing (weeks)	20.6 (95% CI 17.0, 24.2)	19.5 (16.3, 22.7)	*p* = 0.65	
No. amputations	8/23 (34.8%)	6/18 (33.3%)	RR = 1.04 (0.46, 2.5)	
-Above knee	3/8 (37.5%)	1/6 (16.7%)	RR = 2.25 (0.41, 14.9)	**Harms** (NNH) [24] 95% CI [25]
-Below knee	2/8 (25%)	4/6 (66.7%)	RR = 0.38 (0.12, 1.28)	
-Transmetatarsian	2/8 (25%)	1/6 (16.7%)	RR = 1.5 (0.23, 10.9)	
-Toes	1/8 (12.5%)	0/6 (0%)	RR = 1.5 (0.12, 19.9)	
Time to amputation (months)	15.6 (95% CI 11.9, 19.3)	13.9 (9.3, 18.5)	*p* = 0.49	

	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] sepsis (5/23 intervention, 3/18 control), burning sensation (5/23, 2/18), local pain (4/23, 3/18), tremors (5/23, 1/18), chills (4/23, 1/18), fever (3/23, 1/18), anaemia (1/23, 0/18), enterocolitis (2/23, 0/18), chest pain (1/23, 1/18), facial paralysis (1/23, 0/18)		
EXTERNAL VALIDITY		
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.		
Applicability [30] As there does not seem to be any treatment effect, any potentials harms will outweigh the benefits		
Comments [31] It is unclear if the study was adequately powered, the RR 75-100% healing results may have been statistically significant with a larger sample size.		

<table>
<tr><td colspan="5">STUDY DETAILS</td></tr>
<tr><td colspan="5">Reference [1] (Gentzkow et al 1996) "Use of dermagraft, a cultured human dermis, to treat diabetic root ulcers." Diabetes Care 19(4): 350-354.</td></tr>
<tr><td colspan="5">Affiliation/source of funds [2] Advanced Tissue Sciences, Inc., La Jolla; Endocrine-Metabolic Associates, Atherton, Californis;Diabetes ans Metabolic Centre of Florida, Orlando, Florida; Millard Filmore Hospital, Buffalo; North Shore Diabetes and Endocrine Association, New Hyde Park, New York; Allentown Medical Centre, Allentown, Pennsylvania. Supported by Advanced Tissue Sciences, Inc., La Jolla.</td></tr>
<tr><td colspan="2">Study design [3] single-blinded RCT</td><td colspan="2">Level of evidence [4] II</td><td>Location/setting [5] USA
Multicentre, (5 sites),</td></tr>
<tr><td colspan="2">Intervention [6] Dermagraft skin replacement therapy.
All ulcer underwent sharp debridement to remove all necrotic tissue and callous, and received treatment as for standard wound care but with Dermagraft as the innermost layer.
Group A:1 piece of Dermagraft applied weekly, total of 8 pieces
Group B: 2 pieces of Dermagraft applied 2-weekly, total of 8.
Group C: 1 piece of Dermagraft applied 2-weekly, total of 4.
Sample size [7] A: 12; B: 14; C: 11.</td><td colspan="3">Comparator(s) [8] Group D: Standard wound care which included sharp debridement to remove all necrotic tissue and callous, covered with a non-adherent interface, then with saline-soaked gauze, and secured with an adhesive covering. Patients were provided with high-quality therapeutic shoes for off-loading.
Sample size [9] 13</td></tr>
<tr><td colspan="5">Selection criteria
Inclusion criteria – diabetic patients under reasonable glycaemic control, with diabetic ulcers of the plantar surface or heel, of full-thickness and have an area > 1 cm^2, with adequate perfusion. At randomisation the wound had to be suitable for a skin graft, free of necrotic tissue with no exposed bone, tendon or joint, with no tunnels or sinus tracts that could not be debrided. Ability to complete a 12-week trial.
Exclusion criteria – ulcers of non-diabetic origin, ulcers not suitable for a skin graft, patients taking medications known to interfere with healing, such as corticosteroids, immune-suppressives and cytotoxic agents, pregnancy.</td></tr>
<tr><td colspan="5">Patient characteristics [10]
Intervention group A – N = 12; age (yrs) 62.7; gender: male 8/12 (75%); female 4/12 (25%); insulin dependent 7/12 (58%); % HbA_{1c} 8.0; ankle-arm index 1.0; area of ulcer (cm^2) 2.2; duration of ulcer (weeks) 50.4.
Intervention group B – N = 14; age (yrs) 66.2; gender: male 11/14 (79%); female 3/14 (21%); insulin dependent 9/14 (64%); % HbA_{1c} 8.2; ankle-arm index 1.1; area of ulcer (cm^2) 2.3; duration of ulcer (weeks) 40.7.
Intervention group C – N = 11; age (yrs) 62.7; gender: male 7/11 (64%); female 4/11 (36%); insulin dependent 9/11 (82%); % HbA_{1c} 8.4; ankle-arm index 0.9; area of ulcer (cm^2) 3.3; duration of ulcer (weeks) 43.2.
Comparator group D – N = 13; age (yrs) 53.8; gender: male 9/13 (69%); female 4/13 (31%); insulin dependent 10/13 (77%); % HbA_{1c} 9.1; ankle-arm index 1.0; area of ulcer (cm^2) 1.9; duration of ulcer (weeks) 87.0.</td></tr>
<tr><td colspan="2">Length of follow-up [11] 12 weeks, with follow-up as long as possible for recurrence</td><td colspan="3">Outcome(s) measured [12] no. of ulcers healed completely, no. ulcers 50% healed, median time (wks) to complete closure and to 50% closure, median % decrease in wound volume, no. of infections (harms)</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Assigned to 1 of 4 groups via sealed randomisation envelopes</td><td>Comparison of study groups [14]
Similar baseline characteristics with the exception of age (up to 19% difference), insulin dependent (up to 24% difference), HbA_{1c} (up to 12% difference), (up to 42% difference), ulcer duration (up to 53% difference).</td><td>Blinding [15]
Patients were blinded</td><td>Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups</td><td>Follow-up (ITT) [17] Yes, all patients enrolled in study included in analysis</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18] Study may be subject to information bias as investigators were not blinded Study was of average quality.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
</table>

Outcome [19]	Intervention group [20] A	B	C	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits [23] NNT(95% CI)
No of ulcers with complete closure	6/12 50%	3/14 21.4%	2/11 18.2%	1/13 7.7%	*RR (A:D) = 6.50 [1.29, 39.71]* RR (B:D) = 2.79 [0.44, 18.00] RR (C:D) = 2.36 [0.33, 17.56] *included in Meta-analysis by Blozik and Scherer (2008)	2 [2, 14]
No. ulcers with 50% closure	9/12 75%	7/14 50%	2/11 18.2%	3/13 23.1%	RR (A:D) = 3.25 [1.31, 7.96] RR (B:D) = 2.17 [0.78, 6.69] RR (C:D) = 0.79 [0.17, 3.48]	2 [1, 8]
	A	B	C			Harms (NNH) [24]
Median time (wks) to:						
Complete closure	12	> 12	> 12	> 12	*p* = 0.056	(95% CI) [25]
50% closure	2.5			> 12	*p* = 0.0047	
Median % decrease in wound volume	88.9%			0%	*p* = 0.017	
Infections (harms)	2/12 17%	4/14 29%	3/11 27%	3/13 23%	RR (A:D) = 0.72 [0.16, 3.22] RR (B:D) = 1.24 [0.36, 4.43] RR (C:D) = 1.18 [0.31, 4.49]	
	Clinical importance (1-4) [26] 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.				Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] None reported.
EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits will probably outweigh any harms.
Comments [31] The authors have demonstrated that the application of Dermagraft improves the healing outcomes for diabetic foot ulcers

STUDY DETAILS		
Reference [1] (Goretti et al 2007) "Clinical outcomes of wide postsurgical lesions in the infected diabetic foot managed with 2 different local treatment regimes compared using a quasi-experimental study design: a preliminary communication." Int J Low Extrem Wounds 6(1): 22-7.		
Affiliation/source of funds [2] Diabetic Foot section, Dept. of Endocrinology and Metabolism, University of Pisa, Italy. No funding source stated.		
Study design [3] historical control study	Level of evidence [4] III-3	Location/setting [5] Italy Hospital, inpatient, then outpatient
Intervention [6] foot lesions were measured from a tracing with polyurethane film and were then photographed. Next the wound underwent surgical debridement and was dressed with sterile gauze soaked in Dermacyn Wound Care which was renewed daily with a catheter to keep the gauze soaked with DWC. The foot was then bandaged and off-loaded by either bed rest or a wheelchair. The inner gauze dressing was changed every three days until discharge and the weekly where the foot lesions were measured Sample size [7] 18	Comparator(s) [8] had been previously treated with diluted povidone iodine, and standard wound care Sample size [9] 15	
Selection criteria Intervention Group: Inclusion criteria – patients with diabetes who underwent surgical debridement or drainage to treat foot ulcers between June and December, 2004, and with a post-surgical lesion wider than 5 cm^2, transcutaneous oxygen tension > 50 mmHg distal to the ankle, presence of infection confirmed by microbiological investigations. Patients who underwent lower limb revascularization were admitted if transcutaneous oxygen tension > 50 mmHg on the dorsal of foot after procedure. Exclusion criteria – bilateral ulceration, active or previous Charcot's foot, peripheral arterial disease not amenable to revascularization, and a life expectancy of > 1 year. Control group: patients that had been previously treated with diluted povidone iodine.		
Patient characteristics [10] Intervention group – N = 18, mean age (yrs) 62.4 ± 9.7, duration of diabetes (yrs) 21.7 ± 10.3, type 1 4/18 ((22%), HbA_{1c} (%) 8.2 ± 1.1, area of ulcer (cm^2) 25.8 ± 10.4, duration of ulcer (days) 95.7 ± 52.4. Comparator group(s) – N = 15, mean age (yrs) 63.7 ± 12.2, duration of diabetes (yrs) 19.8 ± 9.1, type 1 3/15 (20%), HbA_{1c} (%) 8.8 ± 1.9, area of ulcer (cm^2) 20.2 ± 12.3, duration of ulcer (days) 78.3 ± 65.8.		
Length of follow-up [11] 6 months	Outcome(s) measured [12] frequency of minor amputations, time to healing, the proportion of patients healed.	

INTERNAL VALIDITY				
Allocation [13] Consecutive patients	Comparison of study groups [14] Similar baseline characteristics with the exception of ulcer duration (18% difference)	Blinding [15] None	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, all patients enrolled in study included in analysis
Overall quality assessment (descriptive) [18] Assuming that there is little or no bias between the intervention and control groups, I find the results to be reliable, showing that the intervention has a statistically significant benefit. Average.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/ [22] effect size (95% CI) [25]	Benefits (NNT) [23] [95% CI) [25]
Time to healing (mean no. days ± 1 SD	144 ± 39.2 (95% CI 125.1, 163.6)	212.3 ±67.8 (95% CI 178.6, 246.9)	p = 0.00361	
No. patients healed in 6 months	16/18 (87.5%)	8/15 (51.4%)	RR = 1.67 (1.07, 2.19) (p = 0.00827)	2.8 (1.9, 20.1)
No. minor amputations	9	18	p < 0.01	Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] no adverse effects for patients in the intervention group, 1 patient in the control group withdrew due to topical dermatitis.
EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits will probably outweigh any harms.
Comments [31] The authors have demonstrated that the application dressings with Dermacyn Wound Care improves the time to healing of diabetic foot ulcers

STUDY DETAILS		
Reference [1] (Gough et al 1997) "Randomised placebo-controlled trial of granulocyte-colony stimulating factor in diabetic foot infection." Lancet 350(9081): 855-859.		
Affiliation/source of funds [2] Amgen Ltd, CA, USA		
Study design [3] RCT (double-blind)	Level of evidence [4] II	Location/setting [5] England Hospital inpatients
Intervention [6] Subcutaneous injection of G-CSF was administered daily for 7 days. Initial dose at 5 μg/kg, after 2 doses: lowered to 2.5 μg/kg if absolute neutrophil count higher than 25 x 10^9/L, if count remained high, given on alternate days. Also given standard wound care. Sample size [7] 20	Comparator(s) [8] given a saline injection in same way as intervention group in addition to standard wound care. Sample size [9] 20	
Selection criteria Inclusion criteria – Diabetic patients aged over 18 years with extensive cellulitis, Exclusion criteria – absolute neutrophil count of < 1 x 10^9/L or > 50 x 10^9/L, a history of malignant disorders, blood dyscrasia. HIV infection, serum creatinine > 250 μmol/L, renal or hepatic disease, immunosuppressive disorder or therapy, pregnancy or lactation, septicaemia, critical leg ischemia.		
Patient characteristics [10] Intervention group – N = 20, mean age (yrs) 65 (range 30-86), gender: 14/20 (70%) male, 6/20 (30%) female, Caucasian 18/20 (90%), BMI (kg/m^2) 28.4 (range 21.0-40.8), current smokers 3/20 (15%), duration of diabetes (yrs) 18.5 (range 0.1-50), diabetes type 1 6/20 (30%), insulin use 13/20 (65%), HbA_{1c} (%) 9.25 (range 5.5-13.7), ankle brachial index 1.00 (range 0.53-1.28), vibration threshold (V) 35.7 (range 18.3-50.0), nephropathy 5/20 (25%), retinopathy 12/20 (60%), history of coronary/cerebrovascular disease 7/20 (35%), previous minor amputation or debridement 9/20 (45%). Comparator group(s) – N = 20, mean age (yrs) 66 (range 58-81), gender: 15/20 (75%) male, 5/20 (25%) female, Caucasian 15/20 (75%), BMI (kg/m^2) 24.9 (range 21.1-40.7), current smokers 2/20 (10%), duration of diabetes (yrs) 19 (range 1-44), diabetes type 1 4/20 (20%), insulin use 15/20 (75%), HbA_{1c} (%) 8.70 (range 5.5-12.9), ankle brachial index 0.99 (range 0.65-1.50), vibration threshold (V) 37.4 (range 8.3-50.0), nephropathy 5/20 (25%), retinopathy 13/20 (65%), history of coronary/cerebrovascular disease 10/20 (50%), previous minor amputation or debridement 13/20 (65%).		
Length of follow-up [11] 7 day treatment period, plus 18 month study duration.	Outcome(s) measured [12]length of hospital stay, no. required surgery (debridement and/or ray amputation), no. ulcers healed at day 7	

INTERNAL VALIDITY				
Allocation [13] randomisation list generated and patients allocated by pharmacist.	Comparison of study groups [14] Similar baseline characteristics with the exception of Caucasian race (15% difference), history of coronary/cerebrovascular disease (15%), previous minor amputation or debridement (20%).	Blinding [15] Both patients and investigators were blinded.	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, all patients enrolled in study included in analysis
Overall quality assessment (descriptive) [18] Assuming that there is little or no bias between the intervention and control groups due to the double-blind study design, I find the results to be reliable, showing that the intervention has a statistically significant benefit. Good.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] 95% CI [25] Harms (NNH) [24] 95% CI [25]
Median (range) in days to hospital discharge	10 (7-31)	12 (5-93)	p = 0.02	
No. required surgery	0/20 (0%)	4/20 (20%)	p = 0.114 RR = 0.00 (0.00, 0.87)	
No. healed at day 7	4/20 (20%)	0/20 (0%)	p = 0.09 RR = 8.0 (0.84, 83.98)	
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] None reported.
EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits will probably outweigh any harms.
Comments [31] The authors have shown that G-CSF can shorten the hospital stay of patients with diabetic foot ulcers. The study only looked at healing after 7 days. Another study could be undertaken to investigate if shortened healing times may be another benefit of this treatment.

STUDY DETAILS		
Reference [1] (Ha Van et al 2003) "Nonremovable, windowed, fiberglass cast boot in the treatment of diabetic plantar ulcers: efficacy, safety, and compliance." Diabetes Care 26(10): 2848-2852.		
Affiliation/source of funds [2] Dept. of diabetology and Metabolism, Pitie-Salpetriere Teaching Hospital, and the Computer Sciences Dept., Saint-Vincent-de-Paul Teaching Hospital, Paris, France. No funding source stated.		
Study design [3] prospective nonrandomised study	Level of evidence [4] III-2	Location/setting [5] France Diabetic Foot clinic
Intervention [6] Standard wound care plus off-loading by a non-removable fibreglass cast boot with a window cut over the ulcer. Daily care at home by nurse (cleansing with saline, petroleum jelly saturated gauze), fortnightly clinic examinations for monitoring, and wound debridement. Treatment stopped when healed or treatment failed. Sample size [7] 42	Comparator(s) [8] Standard wound care plus off-loading with either the Barouk half shoe for patients with ulcers under the forefoot or the Sanital heel-relief shoe for patients with ulcers under the hindfoot. Daily care and clinic examinations as for intervention group. Sample size [9] 51	
Selection criteria Inclusion criteria – patients with diabetic neuropathy (insensitivity to the 10 g Semmes-Weinstein 5.07 monofilament at the plantar aspects of the toes and metatarsal heads) and a University of Texas grade 1A plantar ulcer. Exclusion criteria – severe peripheral arterial disease (presence of critical ischemia or a wound with gangrene or necrosis, $TcPO_2$ <20 mmHg or failure of arterial Doppler ultrasonography to detect a major leg artery, severe arterial lesions by arteriography), cellulitis, clinical or radiological evidence of infection or osteomyelitis.		
Patient characteristics [10] Intervention group – N = 42, mean age 58 ± 11, male 90.5%, duration of diabetes (yrs) 17 ± 11, type 1 diabetes 14.3%, BMI 28.55 ± 3.42, retinopathy 74%, peripheral arterial disease 55%, neuropathy 100%, HbA_{1c} (%) 7.85 ± 2.7, creatinine (µmol/L) 119 ± 205, duration of ulcer (days) 395 ± 560, duration > 6 months 48%. Ulcer size (mm): length 20.43 ± 12.06, width 13.8 ± 7.71, depth 5.42 ± 5.35, under forefoot 83%, under midfoot (Charcot) 10%, under hindfoot 7%. Comparator group(s) – N = 51, mean age 62 ± 7, male 78.4%, duration of diabetes (yrs) 15 ± 10, type 1 diabetes 23.5%, BMI 29.06 ± 4.76, retinopathy 73%, peripheral arterial disease 43%, neuropathy 96%, HbA_{1c} (%) 8.18 ± 1.6, creatinine (µmol/L) 163 ± 200, duration of ulcer (days) 134 ± 272, duration > 6 months 18%. Ulcer size (mm): length 15.61 ± 12.31, width 10.21 ± 9.12, depth 3.37 ± 3.16, under forefoot 96%, under midfoot (Charcot) 0%, under hindfoot 4%.		
Length of follow-up [11] followed until healing , failure or end of study (at least 4 months)	Outcome(s) measured [12] time to healing, healing rate.	

INTERNAL VALIDITY				
Allocation [13] Allocated on basis of duration of ulcer and refusal to use either boot or shoe	Comparison of study groups [14] Similar baseline characteristics with the exception of gender (13% difference), peripheral arterial disease (12%), creatinine levels (27% difference), ulcer duration (30-66%), forefoot location (13%), and ulcer size (24-38%).	Blinding [15] None	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes. No loss to follow-up, all failures included
Overall quality assessment (descriptive) [18] Authors attempted to correct for potential selection bias using the Cox model to account for other prognostic factors. The patient's age was included in the analysis as it was the only factor that was statistically prognostic of healing. I find the results to be reliable. Average quality.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25] Harms (NNH) [24] 95% CI [25]
Mean time to healing	68.6 ± 35.1	134.2 ±133.0	*p* = 0.017	
Healing rate	34/42 (80.9%)	36/51 (70.6%)	RR = 1.15 (0.91, 1.39) Age-adjusted hazard ratio healing (cast boot) = 1.68 (95% CI 1.04, 2.7)	
Secondary osteomyelitis	7% (n=3)	25% (n=13)	RR=0.37 [0.013, 0.88] p=0.03	

	Clinical importance (1-4) [26] 3. The confidence interval does not include any clinically important effects.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] 3 intervention and 13 control patients developed osteomyelitis, 5 intervention patients developed a new ulcer due to fibreglass boot due to secondary oedema (detected and treated promptly).		
EXTERNAL VALIDITY		
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.		
Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits will probably outweigh any harms.		
Comments [31] the authors have demonstrated that the non-removable cast boot offers advantages over the removable therapeutic shoe. The faster healing rate may be due to the huge difference in compliance of using the boot compared to the shoe.		

STUDY DETAILS

Reference [1] (Han et al 2009) "Efficacy and safety of fresh fibroblast allografts in the treatment of diabetic foot ulcers." Dermatol Surg 35(9): 1342-8.

Affiliation/source of funds [2] Dept. of Plastic surgery, Korea University College of Medicine, Seoul, Korea. No funding source stated.

Study design [3] non-randomised study	Level of evidence [4] III-2	Location/setting [5] Korea Outpatient setting

Intervention [6] Patients underwent debridement as necessary and the ulcer area was determined using the Visitrak Digital Wound Measurement system. Fresh cultured fibroblasts were then dispersed over the wound and sealed with thrombin. Tegaderm was applied to the graft site and changed 5 days later. Patients returned every 3-7 days to have the dressings (were kept moist) changed and the wound examined. Pressure from ulcer site was off-loaded using foam dressings with a hole at ulcer site and appropriate footwear. Sample size [7] 37	Comparator(s) [8] Treatment and wound management was the same as for the intervention group except that only fibrinogen and thrombin without cells was applied to the wound. Sample size [9] 18

Selection criteria

Inclusion criteria – Patients with type 1 or 2 diabetes and a foot ulcer that has not displayed signs of healing for 1 month.

Exclusion criteria – Significant lower extremity ischemia as determined by a transcutaneous O_2 pressure of <30 mmHg or an ankle brachial pressure index of <0.5 mmHg, presence of cellulitis, osteomyelitis diagnosed by MRI and microbiological culture, chronic renal insufficiency (serum creatinine >265 μM), uncontrolled hyperglycaemia (Hb Alc > 9%)

Patient characteristics [10]

Intervention group – N=37, mean age (yrs) 63.9 ± 8.2, gender: 20/37 (54%) male, 17/37 (46%) female, mean ulcer size (cm^2) 4.6 ± 1.7, duration of ulcer (weeks) 13.2 ± 5.5, ulcer with exposed bone 20/37 (54%). Dorsal ulcers 19/37 (51%): forefoot 8/19 (42%), heel 2/19 (11%), toe 9/19 (47%). Plantar ulcers 18/37 (49%): forefoot 9/18 (50%), heel 5/18 (28%), toe 4/18 (22%).

Comparator group(s) – N=18, mean age (yrs) 59.8 ± 5.8, gender: 11/18 (61%) male, 7/18 (39%) female, mean ulcer size (cm^2) 4.3 ± 1.9, duration of ulcer (weeks) 12.4 ± 5.1, ulcer with exposed bone 8/18 (44%). Dorsal ulcers 9/18 (50%): forefoot 5/9 (56%), heel 0/9 (0%), toe 4/9 (44%). Plantar ulcers 9/18 (50%): forefoot 5/9 (56%), heel 1/9 (11%), toe 3/9 (33%).

Length of follow-up [11] 8-week study period with up to 40 months follow-up.	Outcome(s) measured [12] % complete healing, time to healing

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Eligible patients that agreed to intervention, remainder formed control group	Similar baseline characteristics with the exception of dorsal forefoot ulcers (15% difference), plantar heel ulcers (17%).	None	There was no difference in treatment and measurement between the groups	Yes, analysis done on number enrolled in trial

Overall quality assessment (descriptive) [18] Assuming that there is little or no selection bias between the intervention and control groups, I find the results to be reliable, showing that the intervention has a statistically significant benefit. Average quality.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/ [22] effect size 95% CI [25]	Benefits (NNT) [23] (95% CI) [25]
No. (%) patients healed	31/37 (83.8%)	9/18 (50%)	RR = 1.68 (1.12, 2.56)	3 (2, 12)
Mean time to healing	30.9 ± 10.1 days	47.2 ± 7.8 days	$p < 0.05$	Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] infection: 3 intervention and 2 control patients during the study period and 1 intervention patient during the follow-up period, developed infections. Successfully treated with debridement and antimicrobial therapy.

EXTERNAL VALIDITY

Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.

Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits will outweigh any harms.
Comments [31] The authors have demonstrated that fresh fibroblast allografts do improve the clinical outcomes of diabetic foot ulcers

STUDY DETAILS		
Reference [1] (Hanft & Surprenant 2002) "Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis." Journal of Foot & Ankle Surgery 41(5): 291-9.		
Affiliation/source of funds [2] The Foot and Ankle Institute of South Florida, South Miami, FL. Funded by Advanced Tissue Sciences, Inc., Smith & Nephew plc.		
Study design [3] single-blind RCT	**Level of evidence** [4] II	**Location/setting** [5] USA Foot and ankle Institute, Florida
Intervention [6] Treatment for both groups were the same, except intervention patients received an application of Dermagraft after sharp debridement at day 0 and up to 7 additional applications over course of study. **Sample size** [7] 24. For ulcers > 6 week duration N = 14	**Comparator(s)** [8] Standard wound care included sharp debridement, non-adherent interface, saline-moistened gauze, dry gauze, and adhesive tape, and prescribed orthotics to avoid weight-bearing. **Sample size** [9] 22. For ulcers > 6 week duration N = 14	
Selection criteria **Inclusion criteria** – diabetic patient aged 18 years or over, plantar foot ulcer present for at least 2 weeks prior and >1 cm^2 on day of randomisation, ulcer extends through dermis into subcutaneous tissue without exposure of muscle, tendon, bone or joint capsule, exhibits no sign of clinical infection, adequate circulation to the foot (palpable pulse), using birth control (if could get pregnant), informed consent given. **Exclusion criteria** – pregnancy, clinical evidence of gangrene, ulcer over Charcot deformity, ulcer due to non-diabetic etiology, ulcer has sinus tracts that cannot be debrided, ulcer is greater than 20 cm^2, ulcer increased or decreased in size by >50% during screening period, has a medical condition that affects wound healing (renal, hepatic, immune), has a malignant disease, severe malnutrition, history of alcohol or drug abuse, uncontrolled diabetes (>450 mg/dl), ketoacidosis, immunosuppressive treatment, known bleeding disorder, elective osseous procedure 30 days prior to screening visit, previous dermagraft treatment, clinical infection of ulcer including osteomyelitis and cellulitis.		
Patient characteristics [10] Baseline characteristics of patients with ulcers of >6 week duration. **Intervention group** – N = 14; age (yrs) 54.1 ± 15.6; male 92.9%; Caucasian 57.1%; smoker 28.6%; alcohol use 28.6%; type 1 diabetes 7.1%; BMI (kg/m^2) 29.95 ± 7.35; $\%HbA_{1c}$ 7.95 ± 2.5; albumin (g/dl) 3.99 ± 0.41; ankle-arm index 1.07 ± 0.2; duration of ulcer (weeks) 21.0 ± 18.2; ulcer area (cm^2) 1.56 ± 0.83; ulcer location: forefoot or toe 71.4%; heel 28.6%. **Comparator group(s)** – N = 14; age (yrs) 58.2 ± 10.8; male 92.9%; Caucasian 57.1%; smoker 14.3%; alcohol use 42.9%; type 1 diabetes 21.4%; BMI (kg/m^2) 32.64 ± 9.21; $\%HbA_{1c}$ 7.96 ± 1.9; albumin (g/dl) 3.88 ± 0.35; ankle-arm index 1.10 ± 0.27; duration of ulcer (weeks) 80.8 ± 188.9; ulcer area (cm^2) 1.54 ± 0.81; ulcer location: forefoot or toe 92.9%; heel 7.1%.		
Length of follow-up [11] 12 week study period	**Outcome(s) measured** [12] no. wound healed, % reduction in wound size	

INTERNAL VALIDITY				
Allocation [13] Stratified into 2 groups: ulcers >1cm^2 and < 2 cm^2, and ulcers > 2 cm^2 and < 20 cm^2 to ensure proportional representation, then randomised into intervention and control groups. Method undisclosed except that a block size of 4 was used.	**Comparison of study groups** [14] Similar baseline characteristics with the exception of smoking status (15% difference), alcohol use (14%), type I diabetes (14% difference), duration of ulcer (74%), and ulcer location (22%).	**Blinding** [15] Single-blind. Patients were unaware of the treatment group they belonged to.	**Treatment/ measurement bias** [16] There was no difference in treatment and measurement between the groups	**Follow-up** (ITT) [17] Yes, analysis done on number enrolled in trial
Overall quality assessment (descriptive) [18] Assuming that there is little or no information bias between the intervention and control groups due to investigators not being blinded, I find the results to be reliable, showing that the intervention has a statistically significant benefit. Average.				

RESULTS				
Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/effect size** [22] 95% CI [25]	**Benefits** (NNT) [23] (95% CI) [25]
Total no. wounds healed by week 12	15/24 (62.5%)	6/22 (27.3%)	RR = 2.29 (1.15, 4.77)	3 (2, 15)
No. forefoot or toe ulcers healed by week 12	7/10 (70%)	2/13 (15%)	RR = 4.55 (1.45, 15.64)	2 (1, 7)
No. >6 week duration ulcer closure by wk 12	10/14 (71.4%)	2/14 (14.3%)	RR = 5.0 (1.67, 17.6)	2 (1, 5)
Mean % wound closure by wk 12 (>6 week duration)	98% ± 5.2%	48.2% ± 93%	*p* = 0.002	**Harms** (NNH) [24] 95% CI [25]

	Clinical importance (1-4) [26] 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] 1 intervention and 4 control patients suffered non-fatal adverse events, mostly osteomyelitis requiring surgery. No adverse effects associated with the use of Dermagraft.		
EXTERNAL VALIDITY		
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.		
Applicability [30] There were no reported harms. As the treatment provides a statistically significant benefit, treatment benefits will outweigh any harms.		
Comments [31] The authors have demonstrated that the application of Dermagraft improves the healing rates of diabetic foot ulcers		

STUDY DETAILS

Reference [1] (Hanft et al 2008) "Phase I trial on the safety of topical rhVEGF on chronic neuropathic diabetic foot ulcers." Journal of Wound Care 17(1): 30-37.

Affiliation/source of funds [2] Doctor's Research Network, South Miami, Florida; San Antonio Podiatry Associates, San Antonio, Texas; Dept. of Surgery, Sinai Hospital, John Hopkins University, Baltimore, Maryland; Dixie Regional Medical Centre, St. George, Utah; SARcode Corporation, San Francisco, and Genentech, South San Francisco, California.

Study design [3]	Level of evidence [4]	Location/setting [5]
double-blind RCT	II	USA Multicentre (9 sites), outpatients

Intervention [6]	Comparator(s) [8]
72 mg/cm^2 topical telbermin (recombinant human cascular endothelial growth factor [rhVEGF]) gel Clinicians administered the study drug or placebo evenly over the surface of the ulcer 3 times per week for up to 6 weeks. The ulcer was then covered with a sterile semi-permeable barrier and then wrapped in cotton gauze. The ulcer was assessed at each visit. Sample size [7] 29	placebo - the methylcellulose gel only. Concurrently, all patients received good ulcer care including periodic sharp debridement as required and off-loading. Weekly photographs were taken and the ulcer surface area was measured using planimetric tracings of the ulcer perimeter. Sample size [9] 26

Selection criteria

Inclusion criteria – Diabetic patients, aged 18-80 years, with a University of Texas diabetic wound classification grade 1A ulcer, of at least a 4 week duration but less than 6 months, ulcer area following sharp debridement of 1-4 cm^2, glycosylated Hb (HbA1c) of < 12%, ankle-brachial pressure index of 0.6-1.2.

Exclusion criteria – non-diabetic ulcers, active ulcer infection, cellulitis, osteomyelitis, caused by Charcot foot deformity, use of investigational drug/therapy within past month, previous use of platelet-derived of other growth factors on study ulcer in past 3 months, immunosuppressive treatment, history of neoplasia, proliferative retinopathy, connective tissue disease, pregnancy or lactation, refusal to use contraception if could become pregnant, multiple ulcers on study foot, renal failure, poor nutritional status, known hypersensitivity to any ingredients of gel or vehicle, known prior inability to complete study visits during treatment period.

Patient characteristics [10]

Intervention group – N = 29, mean age 59.5 (42-74), gender: 19/29 (66%) male, 10/29 (34%) female, race: 18/29 (62%) Caucasian, 3/29 (10%) black, 7/29 (24%) Hispanic, 1/29 (3%) Native American or Alaskan, mean weight (kg) 101.8 (59-208), mean glucose at screening (mg/dl) 179.1 (29-593), HbA_{1c} (%) 8.3 (5.6-13.6). Ulcer location: plantar 23/29 (79%), dorsal 2/29 (7%), lateral 2/29 (7%), medial 2/29 (7%). Ulcer debridement at screening: yes 27/29 (93%), no 2/29 (7%). Ulcer area (cm^2): length x width (at screening) 1.92 (0.96-4.08), planimetry (at day 1) 1.35 (0.59-3.51).

Comparator group(s) – N = 26, mean age 59.3 (38-81), gender: 18/26 (69%) male, 8/26 (31%) female, race: 17/26 (65%) Caucasian, 5/26 (19%) black, 4/26 (15%) Hispanic, 0/29 (0%) Native American or Alaskan, mean weight (kg) 105.9 (59-177), mean glucose at screening (mg/dl) 225.8 (77-463), HbA_{1c} (%) 8.4 (5.5-13.6). Ulcer location: plantar 21/26 (81%), dorsal 2/26 (8%), lateral 2/26 (8%), medial 1/26 (4%). Ulcer debridement at screening: yes 21/26 (81%), no 5/26 (19%). Ulcer area (cm^2): length x width (at screening) 1.85 (1.08-2.90), planimetry (at day 1) 1.05 (0.62-2.34).

Length of follow-up [11]	Outcome(s) measured [12]
up to 12 weeks	% reduction in ulcer surface area and no. ulcers healed at days 29, 43 and 84, for healed ulcers: no. ulcer recurred, incidence of increased ulcer size and progression of ulcer stage.

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Randomisation was stratified by study site and ulcer surface area.	Similar baseline characteristics with the exception of glucose level at screening (21% difference)	Patients and investigators were blinded.	There was no difference in measurement between the groups	Yes, all patients were used in the analysis

Overall quality assessment (descriptive) [18] The randomised, double-blind study design should also minimise bias. The sample size was calculated for the study to be powered at 80%. I find the results to be sufficiently reliable to find that there is little benefit in using rhVEGF gel to reduce the healing time of diabetic foot ulcers. Study was of good quality.

RESULTS

Outcome [19]	Intervention group [20]		Control group [21]		Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
% reduction in ulcer surface area at:	median	mean ± SD	median	mean ± SD		
Day 29	87.0	59.4 ± 53.7	79.3	67.9 ± 35.9	$p = 0.80$	
Day 43	94.5	65.0 ± 52.0	85.3	67.4 ±47.0	$p = 0.67$	
Day 84	100	64.7 ± 55.5	92.1	66.9 ± 54.0	$p = 0.49$	

No. ulcers healed at: Day 29 Day 43 Day 84 No. healed ulcers that recurred: No. ulcers increased in size by >15% No. ulcers that progressed in stage.	 7/29 (24.1%) 12/29 (41.4%) 15/29 (51.7%) 4/15 (27%) 6/29 (20.7%) 2/29 (6.9%)	 3/26 (11.5%) 7/26 (26.9%) 9/26 (34.6%) 3/9 (33%) 2/26 (7.7%) 1/26 (3.9%)	 RR = 2.09 (0.66, 7.08), p = 0.30 RR = 1.54 (0.74, 3.34), p = 0.39 RR = 1.49 (0.81, 2.83), p = 0.28 RR = 0.80 (0.25, 2.82), p = 0.57 RR = 2.69 (0.68, 11.32) RR = 1.79 (0.24, 13.54)	Harms (NNH) [24] (95% CI) [25]
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] No clinically significant cases of hypotension followed administration of drug, no clinically significant differences in systolic or diastolic blood pressure was observed during the entire study period. Adverse events that occurred (% intervention, % control): nausea (4%, 7%), vomiting (4%, 3%), fatigue (0%, 7%), pyrexia (4%, 3%), infected skin ulcer (0%, 10%), cellulitis (4%, 3%), urinary tract infection (8%, 3%), contusion (4%, 3%), limb injury (8%, 0%), pain in the extremities (0%, 10%), arthralgia (4%, 3%), headache (4%, 7%), cough (8%, 0%), skin ulcer (4%, 7%), erythemia (4%, 3%).				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As there does not seem to be a statistically significant treatment effect, any potentials harms will outweigh the benefits				
Comments [31] The data in this paper did not show a statistically significant benefit for using topical rhVEGF gel to treat diabetic foot ulcers.				

STUDY DETAILS

Reference [1] (Hardikar et al 2005) "Efficacy of recombinant human platelet-derived growth factor (rhPDGF) based gel in diabetic foot ulcers: a randomized, multicenter, double-blind, placebo-controlled study in India." Wounds: A Compendium of Clinical Research & Practice 17(6): 141-152.

Affiliation/source of funds [2] Seth GS Medical College, KEM Hospital, Nair Charitable Hospital, and TN Medical College, Mumbai. Amrutha Diabetic Centre, Hariprasad Memorial Trust Hospital, and Kamineni Hos[pital, Hyderabad. Amrita Institute of Medical Sciences and Research Centre, Cochin. King George Hospital and Andhra Medical College, Vishakapatnam. Jain Institute of Vascular Sciences, Bangalore, India. Study was funded by the Research and Development Department, Virchow Biotech [P] Ltd, Hyderabad, India.

Study design [3] multi-centre, double-blind RCT. Phase III trial.	**Level of evidence** [4] II	**Location/setting** [5] India Multicentre (8 sites) Outpatient setting

Intervention [6] Recombinant human platelet-derived growth factor homodimer-BB (rhPDGF-BB). A 0.01% gel containing 100 µg of rhPDGF-BB/g. After randomisation, assessment and evaluation patients were placed on a standard wound care regimen for 1 week. Then the rhPDGF-BB gel or placebo were applied when dressing the wound for a period of up to 20 weeks. The wound was covered with a 1.5 mm layer of gel and covered with moist saline gauze. **Sample size** [7] 55	**Comparator(s)** [8] Placebo the same low bioburden topical gel formulated with sodium carboxymethylcellulose and other ingredients but no rhPDGF-BB. Standard care regimen consisted of sharp surgical debridement, daily ulcer cleaning and dressing and off-loading (crutches, wheelchair or bed rest). Patients were examined once a week for the first 8 weeks and then fortnightly to the study end. The regular use of antidiabetic medication and appropriate use of systemic antibiotics was advised during the treatment period. **Sample size** [9] 58

Selection criteria

Inclusion criteria – Diabetic patients aged between 18 and 80 years, with at least 1 but less than 3 full-thickness chronic neuropathic ulcers of at least 4 weeks duration on lower extremity and categorised as stage III or IV (as defined by the Wound, Ostomy, and Continence Society) and with infection control (as determined by a wound evaluation score). If multiple ulcers present the largest ulcer was taken as the target ulcer. Size of ulcer was restricted to 1-40 cm^2 (as measured by width and length multiplied together) post-debridement. Adequate perfusion of foot as measured by Doppler Ultrasonography or ankle-brachial index.

Exclusion criteria – Patients with arterial venous ulcers, osteomyelitis, ulcers caused by burns, poor nutritional status (serum protein < 6.5 g/dl), persistent infection, life-threatening concomitant diseases, deformities such as Charcot foot, chronic renal insufficiency,, uncontrolled hypoglycaemia, history of corticosteroid or immunosuppressant use, any known hypersensitivity to gel components. Pregnant and nursing women, and women of child-bearing age not willing to use contraceptives.

Patient characteristics [10]

Intervention group – N = 55, mean age (yrs) 54.7 ± 9.0, gender: 40/55 (73%) male, 15/55 (27%) female, duration of diabetes (yrs) 11.5 ± 6.7, mean HbA_{1c} 7.8 ± 1.7, fasting plasma glucose (mg/dl) 154.0 ± 65.0, 2 hr post-prandial plasma glucose (mg/dl) 215.8 ± 91.5, total serum protein (g/dl) 7.1 ± 0.6, serum creatinine (mg/dl) 0.90 ± 0.29, ankle brachial index 1.07 ± 0.16. Ulcer characteristics: surface area (cm^2) 11.9 ± 9.9, wound evaluation score 0.114 ± 0.200, duration of ulcer (weeks) 25.5 ± 31.9.

Comparator group(s) – N = 58, mean age (yrs) 54.5 ± 9.9, gender: 40/58 (69%) male, 18/58 (31%) female, duration of diabetes (yrs) 11.5 ± 6.5, mean HbA_{1c} 7.2 ± 1.3, fasting plasma glucose (mg/dl) 143.4 ± 59.3, 2 hr post-prandial plasma glucose (mg/dl) 191.7 ± 83.9, total serum protein (g/dl) 7.0 ± 0.6, serum creatinine (mg/dl) 0.95 ± 0.30, ankle brachial index 1.05 ± 0.14. Ulcer characteristics: surface area (cm^2) 13.7 ± 11.2, wound evaluation score 0.115 ± 0.216, duration of ulcer (weeks) 19.8 ± 39.8.

Length of follow-up [11] 20 weeks	**Outcome(s) measured** [12] No. completely healed at 10 weeks and at 20 weeks, time to healing, % reduction in ulcer size

INTERNAL VALIDITY

Allocation [13] Randomisation method not disclosed	**Comparison of study groups** [14] Similar baseline characteristics	**Blinding** [15] All patients, carers and medical assessors were blinded.	**Treatment/ measurement bias** [16] There was no difference in measurement between the groups	**Follow-up** (ITT) [17] Yes, all patients who met criteria, took at least 1 dose of treatment and had post-baseline efficacy data was used for most of the parameters.

Overall quality assessment (descriptive) [18] Study should be large enough to be adequately powered. The randomised, double-blind study design should also minimise bias. I find the results to be sufficiently reliable to find that there is some benefit in using rhPDGF-BB gel to reduce the healing time of diabetic foot ulcers. Study was of good quality.

RESULTS

<table>
<tr><td rowspan="4">Outcome [19]
No. completely healed:
At 10 weeks
At 20 weeks
Average Time to healing (days)
Average % reduction in ulcer size</td><td>Intervention group [20]
39/55 (71%)
47/55 (85%)
46
58%</td><td>Control group [21]
18/58 (31%)
31/58 (53%)
61
26%</td><td>Measure of effect/effect size [22] (95% CI) [25]
RR = 2.29 (1.55, 3.44) $p < 0.001$
RR = 1.60 (1.25, 1.94) $p < 0.05$
$p < 0.001$
$p < 0.001$</td><td>Benefits (NNT) [23] (95% CI) [25]
2.51 (1.81, 4.57)
3.12 (2.25, 6.48)
Harms (NNH) [24] (95% CI) [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the ‘null’) rules out a clinically unimportant effect of the intervention.</td><td colspan="2">Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.</td></tr>
<tr><td colspan="5">Any other adverse effects [28] None reported</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.</td></tr>
<tr><td colspan="5">Applicability [30] As the treatment provides a statistically significant benefit in this study, treatment benefits may outweigh any harms.</td></tr>
<tr><td colspan="5">Comments [31] The data in this paper shows that rhPDGF-BB increases the healing rate of ulcers and thus has a statistically significant benefit over standard wound care.</td></tr>
</table>

STUDY DETAILS		
Reference [1] (Heng et al 2000) "Angiogenesis in necrotic ulcers treated with hyperbaric oxygen." Ostomy/wound management 46(9): 18-28, 30-12.		
Affiliation/source of funds [2] Dept. of Medicine, Dept. of Pathology and Nursing Home Unit, VA Greater Los Angeles Healthcare System, Sepulveda, UCLA San Fernando Valley Program. Funded by the Veteran Administration.		
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] USA Inpatients in long-term care facility
Intervention [6] Topical hyperbaric oxygen therapy (THOT) and standard care as for control group. THOT was administered via an 84-inch by 48-inch pleated polyethylene bag. The open end is taped around the chest, using pressures validated by instruments designed to measure low pressures, intrabag pressures were maintained within a narrow range (1.004 to 1.013 atmospheres) at all times, ensuring a 15 L/min flow rate. The wounds were treated for 4 h/day, 4 days/week for 4 weeks and assessed weekly. Sample size [7] N = 13, diabetic ulcers 7/13	Comparator(s) [8] Standard wound care according to the recommendations of the National Pressure Ulcer Advisory board. All ulcers underwent initial sharp debridement, antibiotics were prescribed as needed, wet to dry local dressings, and pressure relief. Sample size [9] N = 27, diabetic ulcers 8/27	
Selection criteria Inclusion criteria – All non-ambulatory residents of the long-term care facility of the Veterans Affairs Greater Los Angeles Healthcare system in Sepulveda, California, plus all new consecutive non-ambulatory admissions within a stipulated 12-month period with a necrotic/gangrenous ulcer. Exclusion criteria –Presence of life-threatening gangrene, uncontrolled diabetes, and untreated sepsis.		
Patient characteristics [10] Intervention group – N = 13, mean age (yrs) 73.8 ± 6.4, gender: 13/13 (100%) male, 0/13 (0%) female, systemic infection 9/13 (70%), osteomyelitis 3/13 (23%),renal dialysis 2/13 (15%), CHD PVD CVA 10/13 (77%), malignancy 4/13 (31%), multiple sclerosis 2/13 (15%), smokers 0/13 (0%),HbA1c < 12% 8/13 (62%), haematocrit < 36% 8/13 (62%). Ulcer duration > 2 weeks 7/28 (25%), < 2 weeks 22/28 (75%). Stage II ulcers 16/28 (57%), ulcer area (cm^2) 7.13 ± 6.21. Stage III ulcers 6/28 (21%), ulcer area (cm^2) 11.05 ± 6.9. Stage IV ulcers 6/28 (21%), ulcer area (cm^2) 20.92 ± 12.0. Diabetic patients: N = 7, diabetes mellitus patients 7/13 (54%), diabetic ulcers 21/28 (75%), diabetic foot ulcers 10/21 (34.5%), Stage II ulcers 15/21 (71%), lower limb 9/15 (60%), ulcer area (cm^2) 7.4 ± 6.3. Stage III ulcers 4/21 (19%), lower limb 2/4 (50%), ulcer area (cm^2) 10.2 ± 7.6. Stage IV ulcers 2/21 (10%), lower limb 2/2 (100%), ulcer area (cm^2) 23.8 ± 4.4. Comparator group(s) – N = 27, mean age (yrs) 75.5 ± 8.0, gender: 26/27 (96%) male, 1/27 (4%) female, systemic infection 13/27 (48%), osteomyelitis 5/27 (19%),renal dialysis 1/27 (4%), CHD PVD CVA 20/27 (74%), malignancy 4/27 (15%), multiple sclerosis 1/27 (4%), smokers 0/27 (0%),HbA1c < 12% 14/27 (52%), haematocrit < 36% 14/27 (52%). Ulcer duration > 2 weeks 7/50 (14%), < 2 weeks 43/50 (86%). Stage II ulcers 31/50 (62%), ulcer area (cm^2) 5.68 ± 7.4. Stage III ulcers 8/50 (16%), ulcer area (cm^2) 7.78 ± 7.0. Stage IV ulcers 11/50 (22%), ulcer area (cm^2) 16.35 ± 12.82. Diabetic patients: N = 8, diabetes mellitus patients 8/27 (30%), diabetic ulcers 16/50 (32%), diabetic foot ulcers 10/16 (62.5%), Stage II ulcers 8/16 (50%), lower limb 4/8 (50%), ulcer area (cm^2) 10.6 ± 12.9. Stage III ulcers 4/16 (25%), lower limb 2/4 (50%), ulcer area (cm^2) 10.4 ± 9.7. Stage IV ulcers 4/16 (25%), lower limb 4/4 (100%), ulcer area (cm^2) 14.5 ± 14.5.		
Length of follow-up [11] 4 week treatment period, up to 12 month study duration.	Outcome(s) measured [12] % reduction in diabetic ulcer area, logistic regression analysis of healed ulcers at 4 weeks.	

INTERNAL VALIDITY				
Allocation [13] Random allocation by drawing lots, but due to limitations (only able to treat 2 THOT patients at any one time) 14 "overflow" inpatients randomised to THOT were treated as controls.	Comparison of study groups [14] Similar baseline characteristics for whole groups with the exception of diabetes mellitus (24% difference), systeminc infection (22%), malignancy (16%), ulcer size (20-30%).	Blinding [15] None	Treatment/ measurement bias [16] There was no difference in measurement between the groups	Follow-up (ITT) [17] Yes, all patients that participated in the study were included in the analysis.
Overall quality assessment (descriptive) [18] This study may be subject to information bias as patients and investigators were not blinded. This study includes non-diabetic patients with ulcers of various aetiologies and patients with diabetic foot ulcers represent only 37.5% of all patients. Therefore, the study was probably not adequately powered for outcomes relating to diabetic patients only. This study was of average quality.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
% reduction in area for all ulcers:				
(N = 28 + 50 = 78 ulcers)				
Stage II ulcers	99.4%	-52.8%	$p < 0.05$	
Stage III ulcers	75.4%	-36.9%	$p < 0.05$	
Stage IV ulcers	46.2%	-37.4%	$p < 0.05$	
% reduction in diabetic ulcer area for:				
(N = 21 + 16 = 37 ulcers)				
Stage II ulcers	100%	-46.2%	$p < 0.05$	
Stage III ulcers	73.5%	-58.7%	$p < 0.05$	
Stage IV ulcers	45.4%	-44%	$p < 0.05$	
No. ulcers healed:				
all ulcers (within 4 weeks)	18/28 (64%)	3/50 (6%)	RR = 10.71 (4.02, 31.70)	1.72 (1.45, 2.56)
all ulcers (during study period)	26/28 (93%)	11/50 (22%)	RR = 4.22 (2.79, 5.11)	1.41 (1.27, 1.93)
diabetic ulcers (within 4 wks)	16/21 (76%)	3/16 (19%)	RR = 4.06 (1.71, 10.92)	1.74 (1.30, 3.84)
No. stage II ulcers healed:				
all ulcers (during study period)	16/16 (100%)	8/31 (26%)	RR = 3.88 (2.50, 3.88)	1.35 (1.35, 1.98)
diabetic ulcers (within 4 wks)	15/15 (100%)	3/8 (37.5%)	RR = 2.67 (1.45, 2.67)	1.60 (1.60, 3.65)
No. Stage III ulcers healed:				
all ulcers (during study period)	6/6 (100%)	3/8 (37.5%)	RR = 2.67 (1.22, 2.67)	1.60 (1.60, 7.65)
diabetic ulcers (within 4 wks)	1/4 (25%)	0/4 (0%)	RR = 2.00 (0.16, 26.13)	
No. Stage IV ulcers healed:				
all ulcers (during study period)	4/6 (67%)	0/11 (0%)	RR = 14.67 (1.85, 149.85)	1.90 (1.59, 9.09
diabetic ulcers (within 4 wks)	0/2 (0%)	0/4 (0%)	p = NS	
				Harms (NNH) [24] (95% CI) [25]
Clinical importance (1-4) [26] 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.			Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] None reported				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As the treatment provides a statistically significant benefit over standard care alone, any treatment benefits may outweigh potential harms.				
Comments [31] There was a statistically significant improvement in all diabetic ulcers over the 4 week study period for the THOT group, whereas only the Stage II ulcers in the control group improved, the Stage III and IV ulcers worsened. Even though all the ulcers in the THOT group improved, only the least severe (Stage II) ulcers healed completely (no Stage IV ulcers healed completely). This may be due to the short 4 week study period. Thus, topical hyperbaric oxygen therapy offers a significant clinical benefit of improved rate of wound healing compared to standard wound care in this study.				

*Ulcer severity scale: determined by wound team consensus, modified version of severity staging of pressure ulcers and diabetic ulcers. Stage II: ulcers with necrotic tissue, which after debridement revealed a depth of up to 3 mm; Stage III: ulcers infected and/or undermined with necrotic tissue involving the subcutaneous tissue to deep facia; Stage IV: deep ulcers infected and undermined with necrotic tissue involving muscle, tendons and/or bones.

<table>
<tr><td colspan="5">STUDY DETAILS</td></tr>
<tr><td colspan="5">Reference [1] (Holloway et al 1993) "A Randomized, Controlled, Multicenter, Dose Response Trial of Activated Platelet Supernatent, Topical CT-102 in Chronic, Nonhealing, Diabetic Wounds." WOUNDS 5(4): 198-206.</td></tr>
<tr><td colspan="5">Affiliation/source of funds [2] Dept. of surgery, Maricopa Medical Centre, Phoenix, AZ; Dept. of Surgery, University of Pittsburgh, Pittsburgh, PA; Dept. of Podiatry, UMDN/Saint Michael's Medical Centre, Newark, NJ; Dept. of surgery and Dept. of Humanities and Biometrics, Hahnemann University, Philidephia, PA, USA. Funded by Curative Technologies, Inc.</td></tr>
<tr><td colspan="2">Study design [3] double-blind RCT</td><td colspan="2">Level of evidence [4] II</td><td>Location/setting [5] USA
Multicentre (4 sites), outpatient setting.</td></tr>
<tr><td colspan="2">Intervention [6] activated platelet supernatant CT-102 prepared from single apheresis donors and standardised to a β-thromboglobulin level of 24 mg/ml.
Group 1: 0.01 dilution of CT-102
Group 2: 0.033 dilution of CT-102
Group 3: 0.1 dilution of CT-102
Treatment for both groups was identical.
Sample size [7] G1: N = 15, G2: N = 13, G3: N = 21</td><td colspan="3">Comparator(s) [8] Placebo – isotonic platelet buffer containing N-2-hydroxyethyl piperazine-N-2-ethanesulphonic acid (HEPES), glucose, sodium chloride, and potassium chloride (pH = 6.6).
After debridement and assessment, patients were instructed on proper use of medication. They were assessed weekly for the first 2 weeks, then bi-weekly until 20 weeks or wound healing.
Sample size [9] 21</td></tr>
<tr><td colspan="5">Selection criteria
Inclusion criteria – Diabetic patients with at least 1 chronic, non-healing, diabetic ulcer of at least 8 weeks duration and 500-50,000 mm^2 in area. Supine periwound $TcPO_2$ > 30 mmHg with no signs of systemic wound infection.
Exclusion criteria – malignancy in ulcer area, pre-existing disease or condition such as connective tissue disease or terminal disease, pregnant and nursing women, women of child-bearing potential.</td></tr>
<tr><td colspan="5">Patient characteristics [10]
Intervention group 1 – N = 15, mean age (yrs) 60.7 ± 13.5, gender: 11/15 (73%) male, 4/15 (27%) female. Race: White 9/15 (60%), Black 2/15 (13%), Other 4/15 (27%). HbA_{1c} (%) 6.6 ± 1.3, $TcPO_2$ 51 ± 8, Wound grade*: grade 2 11/15 (73%), grade 3 4/15 (27%); grade 4 0/15 (0%), grade 5 0/15 (0%). Median ulcer duration (months) 15.7 (2-60), mean wound severity score 37.7 ± 8.7, ulcer volume (mm^3) 5460 ± 5454, ulcer area (mm^2) 756 ± 633.
Intervention group 2 – N = 13, mean age (yrs) 59.4 ± 13.8, gender: 10/13 (77%) male, 3/13 (23%) female. Race: White 12/13 (92%), Black 0/13 (0%), Other 1/13 (8%). HbA_{1c} (%) 7.0 ± 1.2, $TcPO_2$ 50 ± 8, Wound grade*: grade 2 9/13 (69%), grade 3 3/13 (23%); grade 4 1/13 (8%), grade 5 0/15 (0%). Median ulcer duration (months) 17.6 (2-60), mean wound severity score 32.2 ± 7.3, ulcer volume (mm^3) 4500 ± 4800, ulcer area (mm^2) 600 ± 441.
Intervention group 3 – N = 21, mean age (yrs) 62.6 ± 8.6, gender: 17/21 (81%) male, 4/21 (19%) female. Race: White 16/21 (76%), Black 5/21 (24%), Other 0/21 (0%). HbA_{1c} (%) 6.5 ± 1.3, $TcPO_2$ 47 ± 17, Wound grade*: grade 2 15/21 (71%), grade 3 4/21 (19%); grade 4 1/21 (5%), grade 5 1/21 (5%). Median ulcer duration (months) 11.7 (2-108), mean wound severity score 29.2 ± 6.0, ulcer volume (mm^3) 5788 ± 1163, ulcer area (mm^2) 603 ± 742.
Comparator group – N = 21, mean age (yrs) 60.4 ± 9.6, gender: 14/21 (67%) male, 7/21 (33%) female. Race: White 17/21 (81%), Black 1/21 (5%), Other 3/21 (14%). HbA_{1c} (%) 6.7 ± 1.3, $TcPO_2$ 48 ± 9, Wound grade*: grade 2 18/21 (86%), grade 3 2/21 (9%); grade 4 1/21 (5%), grade 5 0/21 (0%). Median ulcer duration (months) 25.3 (2-120), mean wound severity score 35.9 ± 7.7, ulcer volume (mm^3) 3236 ± 2592, ulcer area (mm^2) 507 ± 609.</td></tr>
<tr><td colspan="2">Length of follow-up [11] 20 weeks treatment period</td><td colspan="3">Outcome(s) measured [12] No. ulcers healed (functional healing rating** 3 and 4) at 20 weeks, mean % reduction in ulcer area and ulcer volume.</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Randomisation via a computer-generated list of random numbers.</td><td>Comparison of study groups [14]
Similar baseline characteristics with the exception of race (11-30% difference), grade 2 ulcers (13-17% difference), grade 3 ulcers (10-18% difference), ulcer duration (31-54% difference), and ulcer area (21-67% difference)</td><td>Blinding [15]
Patients and investigators were blinded</td><td>Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups</td><td>Follow-up (ITT) [17]
No, started with 97 patients, 16 patients excluded as they did not meet entrance criteria, 11 excluded due to non-compliance with protocol.</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18] The randomised, double-blind study design should minimise bias. Thus, the results should be sufficiently reliable to find that there is some benefit in using CT-102 to reduce the healing time of diabetic foot ulcers. Study was of good quality.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
</table>

Outcome [19]	Intervention group [20] Group 1 0.01	2 0.033	3 0.1	Control group [21]	Measure of effect/effect size [22] (95% CI) [25] Group vs placebo	Benefits (NNT) [23] (95% CI) [25]
No, ulcers healed	12/15 (80%)	8/13 (62%)	11/21 (52%)	6/21 (29%)	RR (1) = 2.8 (1.45, 4.59) RR (2) = 2.15 (0.98, 4.37) RR (3) = 1.83 (0.87, 4.02)	1.94 (1.39, 5.28)
	p = 0.01	0.08	0.21			
G1 + G2 + G3		31/49 (63%)			RR(Ave)=2.21(1.20,4.62)	2.88 (1.85, 10.84)
Mean % decrease in ulcer area:	95.7	87.8	94.3			Harms (NNH) [24] (95% CI) [25]
Ave for G1 + G2 + G3		93.0 ± 14.4		77.1 ± 25.7	*p* = 0.002	
Mean % decrease in ulcer volume	96.9	90.7	96.0			
Ave for G1 + G2 + G3		94.9 ± 12.0		82.7 ±21.5	*p* = 0.005	
	Clinical importance (1-4) [26] 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.				Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] Rates of adverse events (cellulitis, wound worsening, burning sensation) were similar between CT-102 treted groups (46%) and the placebo group (42%). No events were considered to be definitely realted to study drug.						
EXTERNAL VALIDITY						
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.						
Applicability [30] As the treatment provides a statistically significant benefit in this study, treatment benefits may outweigh any harms.						
Comments [31] The data in this paper shows that treating diabetic foot ulcers with CT-102 in conjunction with standard wound care has a statistically significant benefit over standard wound care.						

*Wounds Graded as follows: Grade 1: partial thickness ulcer involving only dermis and epidermis; Grade 2: full thickness ulcer involving subcutaneous tissue only; Grade 3: full thickness ulcer involving tendon, bone, ligament, and/or joint and includes an abscess and/or osteomyelitis; Grade 5: full thickness ulcer involving tendon, bone, ligament, and/or joint and has necrotic tissue/gangrene in the wound; Grade 6: full thickness ulcer involving tendon, bone, ligament, and/or joint and has gangrene in the wound and surrounding tissue.
**Functional Healing Assessment as follows: Rating 1: less than 100% epithelised, has drainage, needs a dressing; Rating 2: 100% epithelised, has drainage, needs a dressing; Rating 3: 100% epithelised, maturing skin with a small amount of drainage, requires protective dressing only; Rating 4: 100% epithelised, 100% mature functional skin, no dressing required.

STUDY DETAILS		
Reference [1] (Huang et al 2005) "Autologous transplantation of granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cells improves critical limb ischemia in diabetes." Diabetes Care 28(9): 2155-2160.		
Affiliation/source of funds [2] National Research Centre for Stem Cell Engineering and Technology, State Key Laboratory of Experimental Haematology, Institute of Haematology and Hospital of Blood Diseases, Chinese Academy of Medical Sciences and Peking Union of Medical College; & the TEDA Centre of Life Science and Technology, Tianjin, China		
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] China Hospital, initially inpatient setting
Intervention [6] Transplantation of granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood mononuclear cells (PBMNCs) plus Standard wound care. Treatment consisted of subcutaneous injection of 600 µg/day recombinant human G-CSF for 5 days and a perfusion of 10,000 units/day heparin (to avoid risk of embolism). The 300 ml blood containing increased numbers of blood circulating PBMNCs was collected through a blood-cell separator and concentrated to 1 x 10^8 MNCs/ml and excess cells were frozen in liquid nitrogen, 3 hours later each diseased lower limb was intramuscularly injected (40 sites 3 x 3 cm distance, 1-1.5 cm deep, 7.5 x 10^8 PBMNCs/site) into thigh and leg with a total of 3 x 10^9 PBMNCs. 40 days later, the severely diseased lower limb was given an additional transplantation with the same number of frozen PBMNCs. Sample size [7] 14	Comparator(s) [8] IV injection of 90-200 µg/day prostaglandin E1 plus Standard wound care. Standard wound care consisted of: debridement as necessary, wound dressing, pressure relief, broad spectrum antibiotics if needed. Sample size [9] 14	
Selection criteria Inclusion criteria – Diabetic patients admitted to the Hospital of Blood diseases between February 2003 and June 2004, with critical limb ischemia and at least one foot ulcer, and gave informed consent. Exclusion criteria – critical limb ischemia with hypercoagulable states, gangrene above the ankle, severe coronary, cerebral or renal vascular disease.		
Patient characteristics [10] Intervention group – N = 14, mean age (yrs) 71.1 ± 5.9, gender: 9/14 (64.3%) male, 5/14 (35.7%) female, duration of diabetes (yrs) 12.9 ± 8.9, type 1 diabetics 4/14 (28.6%), ankle-brachial index (ABI) 0.50 ± 0.21, lower limbs with ABI < 0.9 23/28 (82.1%), lower limbs with ulcers 18/28 (64.3%). Patients with: ischemic ulcers 6/14 (42.9%), neuroischemic ulcers 8/14 (57.1%), ulcer on forefoot 10/14 (71.4%), midfoot 3/14 (21.4%), hindfoot 1/14 (7.1%), University of Texas grade 1: stage C 4/14 (28.6%), stage D 5/14 (35.7%); grade 2: stage C 2/14 (14.3%), stage D 2/14 (28.3%); grade 3: stage C 0/14 (0%), stage D 1/14 (7.1%). Ulcer size (cm^2) 2.71 ± 1.32. Comparator group(s) – N = 14, mean age (yrs) 70.9 ± 6.0, gender: 9/14 (64.3%) male, 5/14 (35.7%) female, duration of diabetes (yrs) 11.6 ± 8.0, type 1 diabetics 4/14 (28.6%), ankle-brachial index (ABI) 0.49 ± 0.25, lower limbs with ABI < 0.9 24/28 (85.7%), lower limbs with ulcers 18/28 (64.3%). Patients with: ischemic ulcers 5/14 (35.7%), neuroischemic ulcers 9/14 (64.3%), ulcer on forefoot 9/14 (64.3%), midfoot 4/14 (28.6%), hindfoot 1/14 (7.1%), University of Texas grade 1: stage C 5/14 (35.7%), stage D 4/14 (28.6%); grade 2: stage C 2/14 (14.3%), stage D 2/14 (28.3%); grade 3: stage C 0/14 (0%), stage D 1/14 (7.1%). Ulcer size (cm^2) 2.39 ± 1.15.		
Length of follow-up [11] 3 months	Outcome(s) measured [12] No. of ulcers healed, no. of lower limb amputation, pain-free walking distance, no. recovered normal sleep	

INTERNAL VALIDITY				
Allocation [13] Randomisation method not disclosed	Comparison of study groups [14] Similar baseline characteristics	Blinding [15] None	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, analysis done on number enrolled in trial
Overall quality assessment (descriptive) [18] This study may be subject to information bias as there was no blinding. I find the results are probably sufficiently reliable to find that there is some benefit in transplantation of G-CSF mobilized PBMNCs into ischemic limbs with diabetic foot ulcers. Study was of good quality.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. of ulcers healed	78% (14/18)	39% (7/18)	RR = 2.00 (1.12, 3.29)	2.57 (1.61, 14.78)
No. of amputations	0% (0/23)	21% (5/24)	RR = 0.00 (0.00, 0.72)	4.8 (4.8, 28.9)

<table>
<tr><td rowspan="2">Pain-free walking distance (m):
At treatment
After 3 months
No. recovered normal sleep</td><td>
0.0 ± 0.0
306.4 ± 289.1
79% (11/14)</td><td>
0.0 ± 0.0
78.6 ± 142.3
43% (6/14)</td><td>
Int. group Cont group
p = 0.001 p = 0.059
RR = 1.83 (0.99, 3.02)</td><td>Harms (NNH) [24]
(95% CI) [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.</td><td colspan="2">Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.</td></tr>
<tr><td colspan="5">Any other adverse effects [28] No side-effects specifically due to transplantation were observed by measurement of ECG, ultrasound, cardiogram, liver or kidney function, routine blood and urine parameters, during a 12 week follow-up period.</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Applicable to other diabetics with Ischemic Foot Ulcers.</td></tr>
<tr><td colspan="5">Applicability [30] As the treatment provides a statistically significant benefit in this study, treatment benefits may outweigh any harms.</td></tr>
<tr><td colspan="5">Comments [31] The data in this paper shows that transplantation of G-CSF mobilized PBMNCs into ischemic limbs with foot ulcers has a statistically significant benefit over standard wound care.</td></tr>
</table>

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] (Jacobs & Tomczak 2008) "Evaluation of Bensal HP for the treatment of diabetic foot ulcers." Advances in Skin & Wound Care 21(10): 461-465.</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2] A private practice in St. Louis, MO, USA. Caribbean Medical University, Piscadera Bay, Curacao, Netherlands Antilles.</td></tr>
<tr><td colspan="2">Study design [3] RCT</td><td colspan="2">Level of evidence [4] II</td><td colspan="2">Location/setting [5] Netherlands Antilles
Outpatient setting</td></tr>
<tr><td colspan="3">Intervention [6] Topical treatment with Bensal HP [6% benzoic acid and 3% salicylic acid in a polyethylene glycol and 3% Quercus rubra bark extract (QRB7)] as an adjunctive treatment.
All patients in both groups underwent debridement prior to assessment of ulcer. Ulcers were assessed at entry and at weeks 2, 4 and 6.
Sample size [7] 20</td><td colspan="3">Comparator(s) [8] Topical application of silver sulphadiazine cream as an adjunctive treatment.

In both groups, topical treatments were applied every 12 h and covered with gauze dressings. All patients were treated by off-loading.
Sample size [9] 20</td></tr>
<tr><td colspan="6">Selection criteria
Inclusion criteria – Diabetic patients with a Wagner grade 1 or 2 ulceration of 3 cm diameter or less on the plantar aspect of the foot.
Exclusion criteria – HbA1c > 10%, clinical evidence of local sepsis.
Additional co-morbidities were not evaluated in this study.</td></tr>
<tr><td colspan="6">Patient characteristics [10]
Intervention group – N = 20, ulcer diameter (cm) 1.9 ± 0.76, Wagner: grade 1 6/20 (30%), grade 2 14/20 (70%).
Comparator group(s) – N = 20, ulcer diameter (cm) 1.6 ± 0.78, Wagner: grade 1 11/20 (55%), grade 2 9/20 (45%).</td></tr>
<tr><td colspan="3">Length of follow-up [11] 6 week treatment period</td><td colspan="3">Outcome(s) measured [12] No. ulcers resolved, % reduction in ulcer diameter.</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Randomly assigned by a research coordinator</td><td colspan="2">Comparison of study groups [14]
Unclear, data for most characteristics not provided. There is 16% difference in ulcer diameter and 25% difference in ulcer grade.</td><td>Blinding [15]
None</td><td>Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups</td><td>Follow-up (ITT) [17]
Yes, no loss to follow-up.</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18] The results in this study may be subject to both selection bias (almost no information about the participants has been provided) and information bias (there was no blinding). It is also unclear if the study was large enough to be adequately powered. This study is of poor quality.</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td>Outcome [19]

No. ulcers resolved:
After 4 weeks
After 6 weeks
% reduction in ulcer diameter</td><td>Intervention group [20]

15% (3/20)
40% (8/20)

72.5%</td><td>Control group [21]

20% (4/20)
30% (6/20)

54.7%</td><td>Measure of effect/effect size [22] (95% CI) [25]

RR = 0.75 (0.20, 2.73)
RR = 1.33 (0.58, 3.15)

p = 0.016</td><td colspan="2">Benefits (NNT) [23] (95% CI) [25]

Harms (NNH) [24] (95% CI) [25]</td></tr>
<tr><td></td><td colspan="2">Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.</td><td colspan="3">Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.</td></tr>
<tr><td colspan="6">Any other adverse effects [28] No patient developed any apparent adverse reactions to either topical treatment.</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.</td></tr>
<tr><td colspan="6">Applicability [30] As the treatment provides some statistically significant benefit in this study, treatment benefits may outweigh any harms.</td></tr>
</table>

Comments [31] The data in this paper shows that topical application of Bensal HP resulted in a faster rate of wound healing than topical application of silver sulphadiazine cream. Even so, this did not result in a significantly greater number of ulcers completely healed after 6 weeks in this group. These results need to be repeated in a larger study to determine if Bensal HP is clinically beneficial for treating diabetic foot ulcers.

STUDY DETAILS		
Reference [1] (Jeffcoate et al 2009) "Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes." Health Technol Assess 13(54): 1-86, iii-iv.		
Affiliation/source of funds [2] Nottingham University Hospitals Trust, Nottingham; Dept. of wound Healing, School of medicine, Cardiff University; Institute of Health research, Swansea University; Leeds General Infirmary, Leeds; Kings College Hospital, London; Royal Gwent Hospital, Newport; Southmead Hospital, Bristol; East Lancashire Hospitals NHS trust, Blackburn; Hull Royal Infirmary, Hull; Singleton and Morriston Hospitals Swansea; Ipswich Hospital, Ipswich; UK.		
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] UK Multicentre, (9 centres) clinic outpatient setting.
Intervention 1 [6] Inadine – iodine-impregnated dressing Intervention 2 Aquacel – a carboxymethyl-cellulose hydrocolloid dressing Sample size [7] Inadine: 108; Aquacel: 103	Comparator(s) [8] a simple non-adherent (N-A), knitted, viscose filament gauze dressing All patients received the same care. All ulcers underwent initial debridement, dressings were changed daily, on alternate days or three times a week depending on need and/or availability of professional staff. Sample size [9] 106	
Selection criteria Inclusion criteria – diabetic patients, over 18 years, with chronic (at least 6 weeks duration) full-thickness foot ulcer on or below the malleoli, not penetrating to tendon, bone or peristeum, and with an area of 25-2500 mm^2. Exclusion criteria – known allergy to any of the trial preparations, any ulcer on either foot extending to tendon, peristeum or bone, infection of bone, soft tissue infection requiring systemic antibiotic therapy, ulcer on limb being considered for revascularisation, non-removeable cast without a dressing window, gangrene on affected foot, eschar which was not removeable by clinical debridement, evidence of a sinus or deep tract, hallux amputation of affected side, ankle-brachial index of < 0.7 or toe systolic pressure < 50 mmHg, non-diabetic ulcer, patients with other serious disease likely to compromise outcome of trial, critical renal disease, taking immuno-suppressants, corticosteroids or other considered to be interfering, those with no easy access to the clinic, withheld consent.		
Patient characteristics [10] Intervention group 1 – N = 108, mean age (yrs) 58.8 ± 13.2, gender: male 81/108 (75%), female 27/108 (25%), duration of diabetes (yrs) 15.3 ± 9.8, type 1 diabetes 25/108 (23%), insulin treatment 44/108 (41%), oral hypoglycaemic agents 33/108 (31%), smokers 17/108 (16%), cerebrovascular disease 7/108 (6%), cardiovascular disease 40/108 (37%), retinopathy 62/108 (57%), nephropathy 19/108 (18%), first ulcer 35/108 (32%), previous ulcer at same site 21/108 (19%), previous amputation 21/108 (19%), peripheral arterial disease: dorsalis pedis felt 93/108 (86%), posterior tibial felt 86/108 (80%), loss of sensation: under 1st metatarsal head 87/108 (81%), under 5th metatarsal head 81/108 (75%), plantar hallux 85/108 (79%), plantar heel 74/108 (69%), location of ulcer toe 45/108 (42%), forefoot 38/108 (35%), hindfoot 23/108 (21%), malleolus 2/108 (2%), ulcer area: 25-100 mm^2 48/108 (44%), 101-250 mm^2 36/108 (33%), 251-2500 mm^2 24/108 (22%). Intervention group 2 – N = 103, mean age (yrs) 59.5 ± 11.5, gender: male 81/103 (77%), female 22/103 (23%), duration of diabetes (yrs) 16.0 ± 11.4, type 1 diabetes 22/103 (21%), insulin treatment 43/103 (42%), oral hypoglycaemic agents 35/103 (34%), smokers 15/103 (15%), cerebrovascular disease 8/103 (8%), cardiovascular disease 37/103 (36%), retinopathy 62/103 (60%), nephropathy 22/103 (21%), first ulcer 35/103 (34%), previous ulcer at same site 27/103 (26%), previous amputation 27/103 (26%), peripheral arterial disease: dorsalis pedis felt 89/103 (86%), posterior tibial felt 84/103 (82%), loss of sensation: under 1st metatarsal head 85/103 (83%), under 5th metatarsal head 68/103 (66%), plantar hallux 71/103 (69%), plantar heel 57/103 (55%), location of ulcer toe 38/103 (37%), forefoot 44/103 (43%), hindfoot 18/103 (17%), malleolus 3/103 (3%), ulcer area: 25-100 mm^2 53/103 (51%), 101-250 mm^2 34/103 (33%), 251-2500 mm^2 16/103 (16%). Comparator group – N = 106, mean age (yrs) 61.9 ± 12.8, gender: male 78/106 (74%), female 27/106 (26%), duration of diabetes (yrs) 15.8 ± 11.4, type 1 diabetes 21/106 (20%), insulin treatment 35/106 (33%), oral hypoglycaemic agents 36/106 (34%), smokers 22/106 (21%), cerebrovascular disease 9/106 (8%), cardiovascular disease 46/106 (43%), retinopathy 58/106 (55%), nephropathy 26/106 (25%), first ulcer 44/106 (42%), previous ulcer at same site 13/106 (12%), previous amputation 15/106 (14%), peripheral arterial disease: dorsalis pedis felt 90/106 (85%), posterior tibial felt 84/106 (79%), loss of sensation: under 1st metatarsal head 82/106 (77%), under 5th metatarsal head 71/106 (67%), plantar hallux 77/106 (73%), plantar heel 66/106 (62%), location of ulcer toe 37/106 (35%), forefoot 44/106 (42%), hindfoot 22/106 (21%), malleolus 3/106 (3%), ulcer area: 25-100 mm^2 50/106 (47%), 101-250 mm^2 34/106 (32%), 251-2500 mm^2 22/106 (21%).		
Length of follow-up [11] healed ulcers:" follow-up 12 weeks after healing, non-healed ulcers: 24 weeks, final assessment at 36 weeks	Outcome(s) measured [12] No. of ulcers healed in 24 weeks	

INTERNAL VALIDITY				
Allocation [13] Stratified by centre and ulcer size (3 groups), randomisation lists created using SPSS using blinded dressing codes, phoned to get designated number.	Comparison of study groups [14] Similar baseline characteristics with the exception of previous ulcer at same site (up to 14% difference), previous amputation (up to 12% difference), ulcer located on plantar heel (up to 14% difference).	Blinding [15] The observer was blinded	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, patients that were lost were included in the analysis.

Overall quality assessment (descriptive) [18] Potential for information bias as there was no blinding of patients. Study was powered (to 80%) to detect a 20% difference in healing, with $\alpha = 0.05$. The lack of effect suggests that there was little difference in the efficacy of the three different dressings. This study was of good quality.

RESULTS

Outcome [19]	**Intervention group** [20] Inadine	 Aquacel	**Control group** [21]	**Measure of effect/ effect size** (95% CI) [22]	**Benefits** (NNT) [23] (95% CI) [25]
<u>No. ulcers healed at 12 weeks</u>					**Harms** (NNH) [24] (95% CI) [25]
Total	32/108 30%		27/106 25%	RR = 1.16 [0.75, 1.80]	
		29/103 28%		RR = 1.11 [0.71, 1.73]	
(Inadine v Aquacel)				RR = 1.05 [0.69, 1.61]	
For ulcers 25-100 mm^2	19/48 40%		16/50 32%	RR = 1.24 [0.73, 2.11]	
		14/53 26%		RR = 0.82 [0.45, 1.50]	
(Inadine v Aquacel)				RR = 1.50 [0.86, 2.65]	
For ulcers > 100 mm^2	13/60 22%		11/56 20%	RR = 1.10 [0.55, 2.25]	
		15/50 30%		RR = 1.53 [0.79, 3.01]	
(Inadine v Aquacel)				RR = 0.72 [0.38, 1.36]	
<u>No. ulcers healed at 24 weeks</u>					
Total	48/108 44%		41/106 39%	RR = 1.15 [0.84, 1.58]	
		46/103 45%		RR = 1.16 [0.84, 1.59]	
(Inadine v Aquacel)				RR = 0.99 [0.74, 1.35]	
For ulcers 25-100 mm^2	26/48 54%		24/50 48%	RR = 1.13 [0.77, 1.66]	
		23/53 43%		RR = 0.90 [0.60, 1.38]	
(Inadine v Aquacel)				RR = 1.25 [0.84, 1.85]	
For ulcers > 100 mm^2	22/60 35%		17/56 30%	RR = 1.21 [0.73, 2.03]	
		23/50 46%		RR = 1.52 [0.93, 2.48]	
(Inadine v Aquacel)				RR = 0.80 [0.51, 1.25]	
<u>Time to healing (days)</u>	77.6 ± 45.3		71.7 ± 37.3	*p* = 0.51	
		73.6 ± 45.3		*p* = 0.83	
(Inadine v Aquacel)				*p* = 0.52	
<u>SF36 scores:</u>	39.7 ± 29.7		40.4 ± 27.9	*p* = NS	
Physical function at 24 weeks		44.8 ± 32.1		*p* = NS	
	43.4 ± 22.3		44.2 ± 22.7	*p* = NS	
General health at 24 weeks		44.5 ± 24.7		*p* = NS	
<u>Incremental Cost Effectiveness Ratio (ICER):</u>					
Inadine v N-A				£8.48	
Aquacel v N-A				£8.36	
Inadine v Aquacel				£7.73	
				Per 1% likelihood increase in healing	

Clinical importance (1-4) [26]	**Relevance** (1-5) [27]
4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.

Any other adverse effects [28] There were 10 infections related to index ulcer for Inadine, 7 for aquacel, and 7 non-adherent dressing .

EXTERNAL VALIDITY

Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.

Applicability [30] As the treatment does not provide a statistically significant benefit in this study, any harms may outweigh treatment benefits.

Comments [31] The data in this paper did not show a statistically significant difference between the three different wound dressings when used to treat diabetic foot ulcers.

STUDY DETAILS

Reference [1] (Jensen et al 1998) "A controlled, randomized comparison of two moist wound healing protocols: Carrasyn Hydrogel Wound dressing and wet-to-moist saline gauze (Provisional abstract)." Advances in Wound Care 11(7 Supplement): 1-4.

Affiliation/source of funds [2] Diabetic Foot and Wound Centre, Denver, CO, USA. Supported by an Educational grant from Carrington Laboratories, Inc.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] USA Outpatient clinic

Intervention [6] Carrasyn hydrogel wound dressing (CHWD) After initial debridement, ulcer cleansed with UltraKlenz wound cleanser, covered with 1/8 to 1/4-inch layer of CHWD, covered with gauze pad, wrapped in Kling bandage and secured with tape and given custom-made healing sandals for off-loading with instructions for use. Dressings were changed daily. Ulcers were evaluated weekly for up to 16 weeks or until ulcer closure. Sample size [7] 14	Comparator(s) [8] standard wet-to-moist saline dressing After initial debridement, ulcer cleansed with UltraKlenz wound cleanser, dressed with gauze pad soaked in sterile saline, wrapped in Kling bandage and secured with tape and given custom-made healing sandals for off-loading with instructions for use. Dressings were changed daily. Sample size [9] 17

Selection criteria

Inclusion criteria – Diabetic patients with Wagner grade 2 foot ulcers measuring at least 1 cm diameter, with no evidence of infection and adequate perfusion (palpable foot pulses) and willingness and ability to comply with protocol instructions.

Exclusion criteria – None reported

Patient characteristics [10]

Intervention group – Ulcer duration (months) 8.9

Comparator group(s) – Ulcer duration (months 3.0

No data provided

Length of follow-up [11] 16 weeks plus 4 week follow-up period	Outcome(s) measured [12] No. ulcers closed, Average time to healing, No. adverse events

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias	Follow-up (ITT) [17]
Randomisation method not disclosed	No data presented for comparison	None	[16] There was no difference in treatment and measurement between the groups	No. patients that did not complete the study were excluded from analysis

Overall quality assessment (descriptive) [18] This study is subject to information bias as there was no blinding of patients or investigators. Additionally, no information about the baseline characteristics of the patients was provided so the potential for selection bias cannot be excluded. The study may also have been underpowered due to its small size. This study was of poor quality.

RESULTS

Outcome [19]	Intervention group [20] ITT	Control group [21] ITT	Measure of effect/ effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. ulcers healed	11/13 (84.6%)	6/13 (46.1%)	RR = 1.83 [1.03, 2.68]	2.6 [1.7, 52.7]
	11/14 (78.6%)	6/17 (35.3%)	RR = 2.23 [1.16, 3.68]	2.3 [1.5, 12.1]
No. of amputations	0/14 (0%)	1/17 (5.8%)	RR = 0.00 [0.00, 4.56]	
No. adverse events	2/14 (14.3%)	4/17 (23.5%)	RR = 0.61 [0.14, 2.50]	Harms (NNH) [24] (95% CI)
Time to healing (weeks)	10.30	11.69		

Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.

Any other adverse effects [28] CHWD group: 2 patients developed cellulitis which was successfully treated with antibiotics and they finished the trial, 1 patient was hospitalised for non-study related dehydration but completed the study. Saline control group: 1 patient worsened and required partial amputation and did not finish the study, 2 patients had increased eschar formation and 1 was referred to a vascular specialist, 1 patient developed cellulitis requiring hospitalisation and alternate therapy.

EXTERNAL VALIDITY

Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] As the treatment provides a statistically significant benefit in this study, treatment benefits may outweigh any harms.
Comments [31] Debridement of ulcers using Carrasyn hydrogel wound dressing provides some clinical benefits in treating diabetic foot ulcers compared to standard wound care with saline dressings.

STUDY DETAILS

Reference [1] (Kakagia et al 2007) "Synergistic action of protease-modulating matrix and autologous growth factors in healing of diabetic foot ulcers. A prospective randomized trial." Journal of diabetes and its complications 21(6): 387-391.

Affiliation/source of funds [2] Depts. of Surgery, Orthopaedics, Vascular Surgery, and Medical statistics, Democritus University Hospital, Alexandroupolis, Greece. Funding source not disclosed.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Greece Outpatient?

Intervention [6]	Comparator(s) [8]
Group A: biomaterial consisting of 45% oxidised regenerated cellulose (ORC) and 55% collagen (Promogran) applied to the wound Group C: combination of platelet derived growth factors applied to the wound and covered with ORC/ collagen biomaterial Sample size [7] 17 patients in both groups	Group B: autologous platelet derived growth factors applied directly to the wound. All ulcers in all groups were covered with vapour-permeable film and assessed weekly. Sample size [9] 17

Selection criteria

Inclusion criteria – Diabetic patients that attended the clinic from December 2004 to December 2006, with significant soft tissue defects of the foot that had been present for at least 3 months. All patients had undergone debridement of the ulcer, followed by standard moist gauze treatment for at least 4 weeks, resulting in no more than 15% reduction in ulcer dimensions. All ulcers had to be> 2.5 cm in at least one dimension after debridement.

Exclusion criteria – Previous treatment with vacuum, hyperbaric oxygen, corticosteroid, immunosuppressive agents, radiation, or growth factors, presence of anaemia, cellulitis, osteomyelitis, or malignancy in wound, venous stasis, inadequate perfusion, patient's inability to attend clinics for follow-up.

Patient characteristics [10]

Total 51 patients: male 22/51 (43%), female 29/51 (57%).

Intervention group A – N = 17, mean age (yrs) 58 ± 10, leukocyte count (M/μl) 7.7 ± 1.9, haemoglobin (g/dl) 13.4 ± 1.9, Hb (g/dl) 8.9 ± 3.1, platelet count (K/μl) 289 ± 63.5, sodium (mmol/l) 140 ± 1.6, potassium (mmol/l) 4.4 ± 0.4, glucose (mg/dl) 129 ± 69, creatinine (mg/dl) 1.6 ± 0.9, albumin (g/dl) 3.7 ± 0.7. Ulcer: duration (weeks) 17 ± 11, size (mm^2) 25.8 ± 15.2.

Intervention group C – N = 17, mean age (yrs) 61 ± 9, leukocyte count (M/μl) 8.1 ± 1.3, haemoglobin (g/dl) 14.2 ± 1.5, Hb (g/dl) 8.5 ± 4.0, platelet count (K/μl) 269 ± 96, sodium (mmol/l) 139 ± 2.2, potassium (mmol/l) 4.6 ± 0.3, glucose (mg/dl) 134 ± 72, creatinine (mg/dl) 2.0 ± 1.1, albumin (g/dl) 3.7 ± 0.6. Ulcer: duration (weeks) 19 ± 8, size (mm^2) 27.6 ± 17.5.

Comparator group B – N = 17, mean age (yrs) 57 ± 12, leukocyte count (M/μl) 7.9 ± 1.7, haemoglobin (g/dl) 13.9 ± 1.2, Hb (g/dl) 8.1 ± 2.8, platelet count (K/μl) 270 ± 101, sodium (mmol/l) 140 ± 1.7, potassium (mmol/l) 4.3 ± 0.6, glucose (mg/dl) 140 ± 67, creatinine (mg/dl) 1.3 ± 0.7, albumin (g/dl) 3.6 ± 0.9. Ulcer: duration (weeks) 20 ± 6, size (mm^2) 28.4 ± 13.6.

Length of follow-up [11] 8 week treatment period	Outcome(s) measured [12] % change in ulcer dimensions, no. ulcers completely healed.

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Randomly assigned to 1 of 4 groups via a random number generator	Similar baseline characteristics with the exception of creatinine level (19-35% difference).	Assessment of wounds was in a blinded fashion.	There was no difference in treatment and measurement between the groups	No, 3 patients that did not complete the protocol were excluded from the analysis.

Overall quality assessment (descriptive) [18] This study could be subject to information bias as there was no blinding of patients or investigators. However, to minimise this bias, the assessors were blinded. Also, as this is a small study, it may not have been adequately powered to determine a difference between the two individual treatments. This study was of average quality.

RESULTS

Outcome [19]	Intervention group [20]		Control group [21]	Measure of effect/effect size [22] (95% CI) [25]		Benefits (NNT) [23] (95% CI) [25]
% change in ulcer dimensions:	Group A	Group C	Group B	Group A vs B	Group C vs A or B	
Length	-18.6±10.4	-33.8±14.7	-14.3±7.1	$p = 0.507$	$p < 0.001$	
Width	-23.9±10.8	-46.1±13.1	-17.4±8.0	$p = 0.194$	$p < 0.001$	Harms (NNH) [24] (95% CI) [25]
Depth	-35.6±10.6	-55.1±10.8	-34.9±9.9	$p = 0.979$	$p < 0.001$	
No. ulcers completely healed.	11.8% (2/17)	11.8% (2/17)	11.8% (2/17)	RR = 1.00 (0.19, 5.40)		

Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] No complications or side effects were recorded during the follow-up period.	
EXTERNAL VALIDITY	
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.	
Applicability [30] As the treatment provides a statistically significant benefit in this study, treatment benefits may outweigh any harms.	
Comments [31] The data in this paper did not show a statistically significant difference in using either Promogran or PDGFs as an adjunct to standard wound care. However, using both together resulted in faster wound healing than for either treatment alone. Even so, this did not result in a greater number of ulcers completely healed after 8 weeks compared to the other 2 groups.	

STUDY DETAILS				
Reference [1] (Kalani et al 2003) "Effect of dalteparin on healing of chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease: A prospective, randomized, double-blind, placebo-controlled study." Diabetes Care 26(9): 2575-2580.				
Affiliation/source of funds [2] Dept. of Cardiology, Dept. of Surgical Sciences/Coagulation Research, Dept. of Internal medicine, Karolinska Hospital, Karolinska Institute, Stockholm; the Atherosclerosis Research Unit, King Gustaf V Research Institute, Karolinska Hospital, Karolinska Institute, Stockholm; Dept. of Endocrinology, University Hospital in Malmo, University of Lund, Malmo; Dept. of Internal Medicine, University Hospital in Lund, University of Lund, Lund; the Diabetes Centre, Sahlgrenska University Hospital, Goteborg; Dept. of Medicine, University Hospital of Umea, Umea; Sweden.				
Study design [3] double-blind RCT	**Level of evidence** [4] II		**Location/setting** [5] Sweden Multicentre (4 sites), outpatient setting	
Intervention [6] subcutaneous injection of 0.2 ml dalteparin (25,000 units/ml) daily until ulcer healing or a maximum of 6 months. Also stopped if ulcer increased more than 50% in area or amputation was needed.. Patients also received same standard care as control group. **Sample size** [7] 44 (1 drop out after 2 weeks) N = 43		**Comparator(s)** [8] subcutaneous injection of 0.2 ml normal saline All patients treated by a foot care team, standard treatment included debridement, dressings, off-loading, antibiotic therapy as needed. Treatment with aspirin was continued in all patients during the study period. **Sample size** [9] 43 (1 drop out before 1st injection) N = 42		
Selection criteria **Inclusion criteria** – Diabetic patient with chronic Wagner stage 1 or 2 foot ulcers of at least 2 month duration and Peripheral Arterial Occlusive Disease enrolled in the study from June 1997 to February 2001, toe/arm blood pressure index < 0.6, treatment with a daily dose of 75 mg aspirin for at least 4 weeks before randomisation. **Exclusion criteria** – Vascular reconstruction of angioplasty less than 3 months before randomisation, renal insufficiency (serum creatinine level > 200 μM, treatment with anticoagulants.				
Patient characteristics [10] **Intervention group** – N = 43, mean age (yrs) 73 ± 8, gender: 29/43 (67.4%) male, 14/43 (32.6%) female, BMI (kg/m^2) 27 ± 5, diabetes type 1 5/43 (11.6%), diabetes duration (yrs) 20 ± 13, smokers 5/43 (11.6%), ex-smokers 10/43 (23.3%), insulin therapy 33/43 (76.7%), previous amputation 10/43 (23.3%), previous myocardial infarction and/or stroke 20/43 (46.5%), previous vascular reconstruction and/or angioplasty 8/43 (18.6%), peripheral neuropathy 43/43 (100%), treatment with aspirin 43/43 (100%), toe blood pressure (mmHg) 53 ± 23, toe/arm blood pressure index 0.33 ± 0.14. Ulcer surface area (length x width: mm^2) 413 ± 820. **Comparator group(s)** – N = 42, mean age (yrs) 72 ± 11, gender: 31/42 (73.8%) male, 11/42 (26.2%) female, BMI (kg/m^2) 26 ± 4, diabetes type 1 7/42 (16.7%), diabetes duration (yrs) 21 ± 14, smokers 6/42 (14.3%), ex-smokers 17/42 (40.5%), insulin therapy 33/42 (78.6%), previous amputation 11/42 (26.2%), previous myocardial infarction and/or stroke 20/42 (47.6%), previous vascular reconstruction and/or angioplasty 11/42 (26.2%), peripheral neuropathy 42/42 (100%), treatment with aspirin 42/42 (100%), toe blood pressure (mmHg) 53 ± 20, toe/arm blood pressure index 0.35 ± 0.12. Ulcer surface area (length x width: mm^2) 535 ± 1086.				
Length of follow-up [11] 6 months		**Outcome(s) measured** [12] No. ulcers healed, no. ulcers improved, no. amputations		
INTERNAL VALIDITY				
Allocation [13] Computer-generated random numbers list prepared by independent statistician for each treatment, which were assigned using a central stratified randomisation scheme designed to provide equal numbers in each group. Stratified according to systolic toe blood pressure and Wagner classification of ulcer.	**Comparison of study groups** [14] Similar baseline characteristics with the exception of ulcer size (13% difference)	**Blinding** [15] Patients and investigators were blinded	**Treatment/ measurement bias** [16] There was no difference in treatment and measurement between the groups	**Follow-up** (ITT) [17] No, 1 early dropout in each group were omitted from analysis
Overall quality assessment (descriptive) [18] Study should be large enough to be adequately powered. The randomised, double-blind study design should also minimise bias. There appears to be some benefit in using dalteparin to reduce the amputation rate of diabetic patients with Peripheral Arterial Occlusive Disease and foot ulcers. Study was of good quality.				
RESULTS				

Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/effect size** [22] (95% CI) [25]	**Benefits** (NNT) [23] (95% CI) [25]
No. ulcers healed	33% (14/43)	21% (9/42)	RR = 1.52 (0.75, 3.14)	
No. ulcers > 50% improved	35% (15/43)	26% (11/42)	RR = 1.33 (0.70, 2.56)	
Total improved or healed	67.4% (29/43)	47.6% (20/42)	RR = 1.42 (0.98, 2.03)	

Total No. amputations: Above ankle Below ankle	4.7% (2/43) 100% (2/2) 0% (0/2)	19% (8/42) 50% (4/8) 50% (4/8)	RR = 0.24 (0.06, 0.94) (p = 0.039) RR = 2.00 (0.61, 2.00) RR = 0.00 (0.00, 1.73)	6.95 (4.74, 143.27) Harms (NNH) [24] (95% CI) [25]
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] 1 patient receiving dalteparin developed a retinal haemorrhage after 9 weeks and treatment was discontinued. 1 patient receiving placebo developed superficial skin necrosis at the site of subcutaneous injections on the belly (also site of twice daily insulin injections).				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with Ischemic Foot Ulcers.				
Applicability [30] As the treatment provides some statistically significant benefit in this study, treatment benefits may outweigh any harms.				
Comments [31] The data in this paper suggests that dalteparin may reduce the amputation rate in diabetic patients with Peripheral Arterial Occlusive Disease and chronic foot ulcers. However it did not seem to have a statistically significant effect on ulcer healing rates.				

STUDY DETAILS		
Reference [1] (Kästenbauer et al 2003) "Evaluation of granulocyte-colony stimulating factor (Filgrastim) in infected diabetic foot ulcers." Diabetologia 46(1): 27-30.		
Affiliation/source of funds [2] Boltzmann Institute of Metabolic Diseases and Nutrition & Med. Dept. for Metabolic Disease and Nephrology, Hospital Lainz, Vienna, Austria.		
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Austria Hospital inpatient setting
Intervention [6] granulocyte-colony stimulating factor (G-CSF), 5 µg/kg body weight, injected subcutaneously daily in addition to standard wound care. Neutrophil and leukocyte counts were measured daily. Treatment was stopped if neutrophil count was > 50,000/L and leukocyte count was > 75,000/L, and restarted if counts dropped below 30,000 and 50,000, respectively. Cellulitis, infection summary score, ulcer volume (using syringe) and Wagner grade were evaluated daily. Sample size [7] 20	Comparator(s) [8] placebo, 0.9% sterile saline injected subcutaneously Both groups had a 10 day in-hospital stay to ensure same standard of wound care, including debridement and total bed rest, for all patients. All patients were treated with iv antibiotics until inflammation had visibly improved, oral antibiotics, thereafter. Sample size [9] 17	
Selection criteria Inclusion criteria – Diabetic patients with a moderate-sized (o.5-3 cm diameter) infected neuropathic ulcer of Wagner grade 2 or 3, with cellulitis and adequate foot pulses. Exclusion criteria – Gangrene, haematological disorders, pancytopenia, neoplasia, impaired kidney or liver function, recent treatment with cytokines or immune-active drugs.		
Patient characteristics [10] Intervention group – N = 20, mean age (yrs) 60.8 ± 11.1, gender: 15/20 (75%) male, 5/20 (25%) female, duration of diabetes (yrs) 14.7 ± 8.5, type 1 diabetes 19/20 (95%), HbA_{1c} (%) 8.9 ± 1.7, leukocyte count (10^9/L) 8.1 ± 2.6, baseline C-reactive protein (mg/dl) 1.73 ± 2.2, Wagner grade 2 15/20 (75%), grade 3 5/20 (25%), ulcer volume (µl) 203 ± 203. Comparator group(s) – N = 17, mean age (yrs) 58.2 ± 8.1, gender: 13/17 (77%) male, 4/17 (23%) female, duration of diabetes (yrs) 15.5 ± 10.6, type 1 diabetes 16/17 (94%), HbA_{1c} (%) 9.2 ± 2.6, leukocyte count (10^9/L) 7.7 ± 1.9, baseline C-reactive protein (mg/dl) 1.71 ± 2.31, Wagner grade 2 14/17 (82%), grade 3 3/17 (18%), ulcer volume (µl) 358 ± 395.		
Length of follow-up [11] 10 days	Outcome(s) measured [12] Resolution of cellulitis using the % improvement in Infection Summary Score (ISS).	

INTERNAL VALIDITY				
Allocation [13] Randomisation method not disclosed	Comparison of study groups [14] Similar baseline characteristics with the exception of ulcer volume (63% difference)	Blinding [15] Patients were blinded.	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, analysis done on number enrolled in trial
Overall quality assessment (descriptive) [18] The study is quite small and may not have been adequately powered to obtain a clear outcome for ulcer healing. Additionally the study duration of 10 days was also too short for definitive ulcer healing outcomes. This study was of good quality.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
ISS: day 1	29.5 ± 18.4	26.0 ± 14.2	*p* = 0.83	
ISS: day 10	6.7 ± 6.3	8.9 ± 7.2	*p* = 0.33	
% improvement in ISS	77.3%	65.8%		
Resolution of cellulitis (days)	7	12		
Length of hospital stay (days)	10	17.5		Harms (NNH) [24] (95% CI) [25]
Ulcer volume (µl): day 1	203 ± 203	358 ± 395	*p* = 0.20	
day 10	83 ± 140	233 ± 235	*p* = 0.07	
% reduction ulcer vol.	59%	35%	*p* = 0.0005	
No. ulcers improved by 1 grade	8/20 (40%)	4/17 (24%)	RR = 1.70 (0.66, 4.73)	
No. amputations	1/20 (5%)	1/17 (5.9%)	RR = 0.85 (0.09, 8.01)	

Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] 2 intervention patients dropped out due to treatment related adverse events (worsened liver function, skin efflorescence).	
EXTERNAL VALIDITY	
Generalisabilty [29] Applicable to other diabetics with infected diabetic foot ulcers.	
Applicability [30] As the treatment provides some statistically significant benefit in this study, treatment benefits may outweigh any harms.	
Comments [31] The data in this paper suggests G-CSF can speed up the resolution time of infections in neuropathic ulcers and reduce the time spent in hospital. However it did not seem to have a statistically significant effect on ulcer healing rates.	

*ISS is based on absolute CRP values, erythrocyte sedimentation scores, presence of erythema (local, dorsal and lower leg) and lymphangitis. Time for resolution of cellulitis, length of hospital stay, ulcer volume (% reduction), no. ulcers improved by 1 grade.

STUDY DETAILS				
Reference [1] (Kessler et al 2003) "Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study." Diabetes Care 26(8): 2378-82.				
Affiliation/source of funds [2] Dept, of endocrinology and Diabetology, Dept. Of Cardiovascular Disease and Medical Intensive Care and Regional Hyperbaric Oxygenation Centre University Hospital, Strasbourg, France. Funded by The Centre European d'Etude du Diabete.				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] France Hospital inpatient (2 weeks) then outpatient		
Intervention [6] All patients initially hospitalised for 2 weeks for conventional treatment. The patients underwent 2 90-min daily sessions of 100% oxygen breathing in a multi-place hyperbaric chamber pressurized at 2.5 ATA for five days, for the 2 weeks. They were then followed as outpatients for 2 weeks. The patients also received the same standard care as the controls. Sample size [7] 14	Comparator(s) [8] All patients initially hospitalised for 2 weeks for conventional treatment. They were then followed as outpatients for 2 weeks. Standard care was provided for this entire period. Each patient was provided with an orthopaedic device. Sample size [9] 13			
Selection criteria Inclusion criteria – Diabetic patients consecutively admitted to the ward for chronic foot ulcers (Wagner grade 1, 2 or 3). Their ulcers (depth < 2mm) have not shown significant healing in the past 3 months despite stabilised glycaemia, the absence of local infection and satisfactory off-loading measures. Exclusion criteria – septic or gangrenous ulcer, severe arteriopathy ($TcPO_2$ < 30 mmHg) contraindications for HBO therapy (emphysema, proliferating retinopathy, claustrophobia)				
Patient characteristics [10] Intervention group – N = 14, mean age (yrs) 60.2 ± 9.7, gender: 10/14 (71.4%) male, 4/14 (28.6%) female, BMI (kg/m^2) 29.9 ± 3.1, diabetes type 1 2/14 (14.3%), duration of diabetes (yrs) 18.2 ± 13.2, insulin therapy 13/14 (92.8%), mean HbA_{1c} 9.4 ± 2.4, $TcPO_2$ (mmHg) foot dorsum 45.6 ± 18.1, sensorimotor neuropathy 14/14 (100%), stabilised retinopathy 10/14 (71%), renal impairment 5/14 (35.7%), coronary artery disease 2/14 (14.2%), carotid arteriopathy 1/14 (7.1%), antibiotic therapy 8/14 (57.1%), bone lysis 4/14 (50%). Ulcer surface area (cm^2) 2.31 ± 2.18. Comparator group(s) – N = 13, mean age (yrs) 67.6 ± 10.5, gender: 9/13 (69.2%) male, 4/13 (30.8%) female, BMI (kg/m^2) 29.1 ± 5.9, diabetes type 1 2/13 (15.4%), duration of diabetes (yrs) 22.1 ± 13.1, insulin therapy 12/13 (92.8%), mean HbA_{1c} 8.1 ± 1.4, $TcPO_2$ (mmHg) foot dorsum 45.2 ± 24.2, sensorimotor neuropathy 13/13 (100%), stabilised retinopathy 11/13 (84.6%), renal impairment 6/13 (46.1%), coronary artery disease 4/13 (30.8%), carotid arteriopathy 1/13 (7.6%), antibiotic therapy 9/13 (69.2%), bone lysis 6/13 (46.1%). Ulcer surface area (cm^2) 2.82 ± 2.43.				
Length of follow-up [11] 4 weeks	Outcome(s) measured [12] % reduction in ulcer size, complete healing			

INTERNAL VALIDITY				
Allocation [13] Randomised according to a randomisation table.	Comparison of study groups [14] Similar baseline characteristics with the exception of duration of diabetes (18% difference), HbA_{1c} (14%), coronary artery disease (17%), ulcer surface area (18%).	Blinding [15] None	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, analysis done on number enrolled in trial
Overall quality assessment (descriptive) [18] Study is quite small and may not have been adequately powered to obtain a clear outcome. Average.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
% reduction in ulcer surface area:				
After 2 weeks	41.8% (SD 25.5%)	21.7% (SD 16.9%)	p = 0.037	Harms (NNH) [24] (95% CI) [25]
After 4 weeks	61.9% (SD 23.3%)	55.1% (SD 21.5%)	p = 0.4	
Complete healing	2/14 (14.3%)	0/13 (0%)	RR = 3.71 (0.34, 42.5)	
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] One patient developed barotraumatic otitis.
EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] As the treatment does not provide a statistically significant benefit in this study, treatment benefits may outweigh any harms.
Comments [31] The data in this paper suggests that HBOT can speed up the healing time of ulcers, as immediately after 2 weeks of HBOT, ulcers had healed at twice the rate of the control group. However in the next 2 weeks, the control group caught up and overall % reduction in ulcer size was the same in both groups..

STUDY DETAILS

Reference [1] (Krupski et al 1991) "A prospective randomized trial of autologous platelet-derived wound healing factors for treatment of chronic nonhealing wounds: a preliminary report." J Vasc Surg 14(4): 526-532; discussion 532-526.

Affiliation/source of funds [2] Dept. of surgery, University of California, and the Dept. of Veteran Affairs Medical Centre, San Francisco, USA. Supported by the Dept. of Veteran Affairs Research Service and Curative Technologies Inc, Setauker, NY.

Study design [3] RCT	**Level of evidence** [4] II	**Location/setting** [5] USA Outpatients and/or inpatients

Intervention [6] Platelet-derived wound healing factor (PDWHF). Prepared from patient's own blood by Curative Technologies Inc and supplied frozen in 10 ml aliquots. Each aliquot was thawed as needed and used for 1 dressing change. **Sample size** [7] 10 patients with 17 wounds	**Comparator(s)** [8] Physiological saline – identical to PDWHF in appearance. All patients also received standard surgical and supportive care. Patients applied PDWHF or placebo every 12 hours, after rinsing wound with saline. Standard 4 x 4 gauze was then placed over the wound followed by a layer of petroleum-impregnated gauze and gauze-wrap dressings. **Sample size** [9] 8 patients with 9 wounds

Selection criteria

Inclusion criteria – Patients referred to the San Francisco Dept. of veteran Affairs Medical Centre for treatment of at least one chronic, non-healing, cutaneous lower extremity wound of 8 weeks duration or longer.

Exclusion criteria – Platelet count < 100,000/mm^2; periwound $TcPO_2$ < 20 mmHg; local or systemic signs of ongoing infection; wounds caused by burns, irradiation, connective tissue disease, or containing malignant cells; history of uncooperative, noncompliant or unreliable behaviour; inability to remain non-weight bearing on the involved extremity; terminal disease; wounds exceeding 100 cm^2 in area or 50,000 mm^3 in volume; more than 3 chronic non-healing wounds; hypersensitivity to peptide-like drugs or multiple drug allergies; treatment with any other investigational agent within 30 days of admission.

Patient characteristics [10]

Intervention group – N = 10 patients, n = 17 wounds, mean age (yrs) 66.0 ± 5.0, gender: 10/10 (100%) male, smokers 3/10 (30%), ankle-brachial index 1.04 ± 0.56, $TcPO_2$ (mmHg) 37.1 ± 9.1, previous arterial revascularisation 2/10 (20%), platelets (x $10^8/mm^3$) 354 ± 215, Hb (gm/dl) 13.3 ± 1.9, leukocytes (x $10^8/mm^3$) 9.5 ± 3.2, sodium (meq/l) 137 ± 5.4, potassium (meq/l) 4.5 ± 0.5, glucose (mg/dl) 189 ± 97, blood urea nitrogen (mg/dl) 23.0 ± 11.9, creatinine (mg/dl) 1.2 ± 0.4, albumin (gm/l) 4.0 ± 3.1. Wound aetiology: diabetes 8/10 (80%), peripheral vascular disease 8/10 (80%), venous disease 3/10 (30%). Ulcer: duration (months) 6.2 ± 4.4, wound score 2.29 ± 0.85, area (cm^2) 13.0 ± 14.4, volume (cm^3) 1.4 ± 3.6.

Comparator group(s) – N = 8 patients, n = 9 wounds, mean age (yrs) 67.0 ± 4.5, gender: 8/8 (100%) male, smokers 2/8 (25%), ankle-brachial index 0.93 ± 0.54, $TcPO_2$ (mmHg) 37.8 ± 11.9, previous arterial revascularisation 4/8 (50%), platelets (x $10^8/mm^3$) 327 ± 189, Hb (gm/dl) 12.0 ± 1.7, leukocytes (x $10^8/mm^3$) 8.5 ± 3.3, sodium (meq/l) 138 ± 4.7, potassium (meq/l) 4.7 ± 0.5, glucose (mg/dl) 245 ± 127, blood urea nitrogen (mg/dl) 23.9 ± 20, creatinine (mg/dl) 1.7 ± 0.7, albumin (gm/l) 3.9 ± 0.4. Wound aetiology: diabetes 6/8 (75%), peripheral vascular disease 5/8 (63%), venous disease 2/8 (25%). Ulcer: duration (months) 4.3 ± 4.1, wound score 2.11 ± 0.33, area (cm^2) 28.9 ± 45.2, volume (cm^3) 2.0 ± 3.4.

Length of follow-up [11] 12 weeks	**Outcome(s) measured** [12] Rate of wound healing area, rate of wound healing volume, No. healed.

INTERNAL VALIDITY

Allocation [13]	**Comparison of study groups** [14]	**Blinding** [15]	**Treatment/ measurement bias** [16]	**Follow-up** (ITT) [17]
Via a blinded card process by means of computer-generated numbers	Similar baseline characteristics with the exception of previous arterial revascularisation (30% difference), blood glucose (23%), creatinine levels (30%), peripheral vascular disease (17%), ulcer duration (30%), ulcer size (50%).	Patients and care providers were blinded	There was no difference in treatment and measurement between the groups	Yes, no loss to follow-up.

Overall quality assessment (descriptive) [18] This study is very small and may not have been adequately powered. This could explain the lack of a statistically significant outcome. This study was of a good quality.

RESULTS

Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/effect size** [22] (95% CI) [25]	**Benefits** (NNT) [23] (95% CI) [25]
Initial area (cm^2)	13.0 ± 14.4	28.9 ± 45.2		
Final area (cm^2)	43.5 ± 87.4	8.7 ± 12.9		
Rate of wound healing area (cm^2/week)	-4.3 ± 12.2	1.9 ± 2.7	$p > 0.05$	

Initial volume (cm^3) Final volume (cm^3) Rate of wound healing volume (cm^3/week) No. healed: Patients Ulcers	1.4 ± 3.6 2.6 ± 4.6 -0.1 ± 0.7 30% (3/10) 24% (4/17)	2.0 ± 3.4 0.4 ± 0.5 0.1 ± 0.2 25% (2/8) 33% (3/9)	 $p > 0.05$ RR = 1.20 (0.29, 5.40) RR = 0.57 (0.18, 2.06)	Harms (NNH) [24] (95% CI) [25]
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] No complications were encountered.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers, with caution. Only 78% of patients in this study were diabetic.				
Applicability [30] As the treatment does not provide a statistically significant benefit, any potential harms will probably outweigh treatment benefits.				
Comments [31] This study does not show any clinical benefit for using platelet-derived growth factors as an adjunct to standard wound care. This contrasts to other studies that do show a benefit.				

STUDY DETAILS				
Reference [1] (Kurd et al 2009) "Evaluation of the use of prognostic information for the care of individuals with venous leg ulcers or diabetic neuropathic foot ulcers." Wound Repair & Regeneration 17(3): 318-325.				
Affiliation/source of funds [2] Dept. of Dermatology, Centre for Clinical Epidemiology and Biostatistics, Dept. of Biostatistics and epidemiology, University of Pennsylvania, Philadelphia, PA, USA. Funded in part by a National Research Service award from the National Institute of Health.				
Study design [3] cluster RCT	**Level of evidence** [4] II	**Location/setting** [5] USA 74 treatment centres		
Intervention [6] Provision of prognostic information by using a pre-existing electronic database from Curative Health Services, that was common to all of the wound care centres to calculate baseline and week 4 algorithms. Baseline algorithm based on wound duration wound size and anatomic depth (or grade) of ulcer. Week 4 algorithm based on % change in area, log healing rate, and log area ratio. **Sample size** [7] 1. Baseline prognosis: N= 19 centres; N = 424 patients 2. Week 4 prognosis: N= 17 centres; N = 366 patients 3. Baseline and week 4 prognosis: N= 18 centres; N = 499 patients		**Comparator(s)** [8] No prognostic information provided. (participating centres were randomised into 4 groups) **Sample size** [9] N= 20 centres; N = 521 patients		
Selection criteria **Inclusion criteria** – patients with diabetic neuropathic foot ulcers that attended centres that agreed to participate in this trial. **Exclusion criteria** – none stated.				
Patient characteristics [10] **Intervention group 1** – N= 19 centres; N = 424 patients; age (yrs) 64.1 ± 14.3; males 230/424 (54.2%); ulcer area (cm^2) 4.9 ± 13.4; duration of ulcer (months) 4.3 ± 15.2; ulcer grade > 2 84/424 (19.8%). **Intervention group 2** – N= 17 centres; N = 366 patients; age (yrs) 63.0 ± 14.2; males 211/366 (57.6%); ulcer area (cm^2) 6.8 ± 22.7; duration of ulcer (months) 4.0 ± 15.6; ulcer grade > 2 86/366 (23.5%). **Intervention group 3** – N= 18 centres; N = 499 patients; age (yrs) 63.1 ± 14.4; males 251/499 (50.5%); ulcer area (cm^2) 6.4 ± 28.7; duration of ulcer (months) 6.7 ± 16.1; ulcer grade > 2 96/499 (19.2%). **Comparator group** – N= 20 centres; N = 521 patients; age (yrs) 61.6 ± 14.1; males 281/521 (53.9%); ulcer area (cm^2) 6.2 ± 33.8; duration of ulcer (months) 3.2 ± 11.7; ulcer grade > 2 101/521 (19.4%).				
Length of follow-up [11] 20 weeks		**Outcome(s) measured** [12] complete healing by week 20		

INTERNAL VALIDITY				
Allocation [13] Centres were randomised based on a simple randomisation procedure	**Comparison of study groups** [14] Similar baseline characteristics for age, gender and ulcer grade. Group 1 ulcers are 21-28% smaller, up to 53% difference in ulcer duration.	**Blinding** [15] Centres blinded. They knew that they might receive different information compared to usual, they did not know different centres would receive different information.	**Treatment/ measurement bias** [16] centre were not provided with any educational information about prognostic models.	**Follow-up** (ITT) [17] Yes, any individual lost to follow-up with an open wound was considered unhealed at week 20.
Overall quality assessment (descriptive) [18] This study was of average quality.				

RESULTS				
Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/effect size** [22] (95% CI) [25]	**Benefits** (NNT) [23] (95% CI) [25]
No. healed by week 20.	(1) 221/424 (52.1%) (2) 213/366 (58.2%) (3) 265/499 (53.1%)	255/521 (48.9%)	OR = 1.14 [0.81, 1.58] OR* = 1.18 [0.80, 1.73] RR = 1.07 [0.94, 1.21] OR = 1.45 [1.04, 2.02] OR* = 1.50 [1.05, 2.14] RR = 1.19 [1.05, 1.34] OR = 1.18 [0.81, 1.58] OR* = 1.18 [0.85, 1.63] RR = 1.09 [0.96, 1.22]	*OR adjusted for age, gender, ulcer area and ulcer duration 11 [6, 39]

				Harms (NNH) [24] (95% CI) [25]
Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.			Relevance (1-5) [27] 2. Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention.	
Any other adverse effects [28] None reported.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with neuropathic foot ulcers.				
Applicability [30] As the week 4 prognostic information provides a statistically significant benefit, treatment benefits will outweigh any potential harms.				
Comments [31] This study shows that providing 4 week prognostic data to the treating physician increases the number of ulcers that heal compared to those treated by physicians not provided with this information.				

Wound grade = a progressive scale used in the Curative Health Services as described by: wound grade I, a partial thickness wound involving only dermis and epidermis; wound grade 2, a full thickness wound that may extend into subcutaneous tissues; wound grade 3, all those that have exposed tendons, ligament and/or joint; wound grade 4, the subset of wound grade 3 that have an abscess and/or osteomyelitis; wound grade .5, the subset of wound grade 3 that are covered by necrotic tissue; and wound grade 6, all wounds that contain gangrene in the wound and surrounding tissue.

STUDY DETAILS

Reference [1] (Kusumanto et al 2006) "Treatment with intramuscular vascular endothelial growth factor gene compared with placebo for patients with diabetes mellitus and critical limb ischemia: a double-blind randomized trial." Human gene therapy 17(6): 683-691.

Affiliation/source of funds [2] Depts. of Internal Medicine, Medical Oncology, Vascular Surgery, Opthalmology, Cardiology Pathology and Laboratory Medicine, Endocrinology, University of Groningen and University Medical Centre, Groningen; Dept. of Vascular surgery, Leiden University Medical Centre and Gaubius Laboratory, Leiden, The Netherlands.

Study design [3]	Level of evidence [4]	Location/setting [5]
double-blind RCT	II	Netherlands Two centres, outpatient setting

Intervention [6]	Comparator(s) [8]
2000 µg plasmid DNA containing the vascular endothelial growth factor gene (phVEGF) injected intramuscularly into the thigh and calf muscles on day 0 and day 28. Follow-up evaluations were on days 7, 14, 35, 42, 72 and 100. Sample size [7] 27	Normal saline placebo injections as for intervention group. All patients received the same standard care. Sample size [9] 27

Selection criteria

Inclusion criteria – Diabetic patients with evidence of critical limb ischemia including, rest pain and/or ulcers that had not healed for a minimum of 2 weeks. Patients with compressible vessels had to have a resting ankle systolic blood pressure < 50 mmHg or toe systolic blood pressure of < 30 mmHg. Patients had to be unsuitable for surgical or percutaneous revascularisation. Written informed consent.

Exclusion criteria – Active proliferative diabetic retinopathy, history of malignancy, severe co-morbidity and/or compromising co-medication.

Patient characteristics [10]

Intervention group – N = 27, mean age (yrs) 68.7 (45-85), gender: 16/27 (59.3%) male, 11/27 (40.7%) female, diabetes type 1 5/27 (18.5%), duration of diabetes (yrs) 17.0 (0.08-14), insulin dependent 8/27 (29.6%), mean HbA_{1c} 8.1 (6.4-12.2), pain 24/27 (88.9%), ulcer 21/27 (77.8%), duration of ulcer (months) 3.0 (1-12), hypertension 15/27 (55.6%), hypercholesterolemia 9/27 (33.3%), coronary artery disease 12/27 (44.4%), duration of leg ischemia (months) 8.6 (1-30),prior vascular reconstruction/ percutaneous angioplasty 10/27 (37.0%), prior amputation 3/27 (11.1%).

Comparator group(s) – N = 27, mean age (yrs) 68.4 (40-84), gender: 15/27 (55.6%) male, 12/27 (44.4%) female, diabetes type 1 4/27 (14.8%), duration of diabetes (yrs) 14.2 (0.67-55), insulin dependent 10/27 (37.0%), mean HbA_{1c} 8.0 (5.8-9.8), pain 23/27 (85.2%), ulcer 17/27 (63.0%), duration of ulcer (months) 5.0 (1-12), hypertension 18/27 (66.7%), hypercholesterolemia 8/27 (29.6%), coronary artery disease 9/27 (33.3%), duration of leg ischemia (months) 9.5 (1-48),prior vascular reconstruction/ percutaneous angioplasty 10/27 (37.0%), prior amputation 3/27 (11.1%).

Length of follow-up [11]	Outcome(s) measured [12]
100 days.	No. ulcers improved, No. amputations, mean time to amputation, No. responders (hemodynamic, ulcer and/or pain improvement).

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Computerised block randomisation without stratification or matching.	Similar baseline characteristics with the exception of duration of diabetes (16% difference), ulcer duration (40%).	Both patients and investigators were blinded.	There was no difference in treatment and measurement between the groups	Yes, no loss to follow-up.

Overall quality assessment (descriptive) [18] The study was designed to minimise bias and be adequately powered for amputation outcomes. The study was of good quality.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]	Harms (NNH) [24] (95% CI) [25]
No. ulcers improved	33% (7/21)	0% (0/17)	RR = not calculcable	3.3 (2.9, 18.4)	
No. amputations	11% (3/27)	22% (6/27)	RR = 0.50 (0.14, 1.66)		
No. responders	52% (14/27)	11% (3/27)	RR = 4.67 (1.72, 14.20)	2.46 (1.83, 6.01)	
Mean time to amputation (days)	78	25.5	p = 0.11		

Clinical importance (1-4) [26]	Relevance (1-5) [27]
1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.	1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.

Any other adverse effects [28] phVEGF was well tolerated. There were no adverse events attributed to the intervention. New episodes of oedema, teleangiectasias, hypoglycaemia, microalbuminuria occurred in both groups. There were 4 deaths in the follow-up period of 100 days, not related to the treatment. No progression to proliferative diabetic retinopathy was seen.
EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with ischemia and diabetic foot ulcers.
Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits will probably outweigh any potential harms.
Comments [31] This study shows that treatment of ischemic limbs with intramuscular injections with phVEGF increases the number of ulcers that heal.

STUDY DETAILS		
Reference [1] (Landsman et al 2008) "Living cells or collagen matrix: which is more beneficial in the treatment of diabetic foot ulcers?" Wounds: A Compendium of Clinical Research & Practice 20(5): 111-116.		
Affiliation/source of funds [2] Weil foot and Ankle Institute, Des Plaines, Ill; Coastal Podiatry Inc, Virginia Beach, Va; Ocean County Foot and ankle surgical Associates, Toms River, NJ; the Foot and Ankle Institute of south Florida, South Miami, Fla; USA.		
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] USA Multicentre (4 sites),
Intervention [6] OASIS Wound Matrix (acellular collagen-based bioactive) as an adjunct to standard wound care. Applied to wound, could be reapplied if not adhering to the wound (up to 8 times) Standard wound care consisted of debridement, and the use of saline-moistened gauze dressings. Sample size [7] 13	Comparator(s) [8] Dermagraft replacement skin therapy as an adjunct to standard wound care. Applied directly to wound, could be reapplied twice more. All wounds were debrided prior to study commencement. Off-loading via well-padded fixed ankle removable boot to be worn at all times. Sample size [9] 13	
Selection criteria Inclusion criteria – Diabetic patients, over 18 years, with a full-thickness ulcer that does not extend to bone or tendons, has a viable wound bed with granulation tissue, ulcer is 1-16 cm^2, and of at least 4 weeks duration. Exclusion criteria – Malnourishment (albumin < 2,5 g/dl), known allergy to porcine-derived products, dextran, EDTA, or gelatine, known hypersensitivity to the components of Dermagraft, severe arterial disease (ABI < 0.65), history of radiation therapy to ulcer site, use of corticosteroids, use of any immunosuppressant, immune-compromised patients, ulcers of non-diabetic aetiology, vasculitis, severe rheumatoid arthritis, other collagen vascular disease, erythema or purulence associated with a severe infection of ulcer, signs of cellulitis, osteomyelitis, necrotic or avascular ulcer beds, undergoing haemodialysis, uncontrolled diabetes (HbA_{1c} > 12%), active Charcot's neuropathy, sickle cell disease, exposed bone, tendon or fascia.		
Patient characteristics [10] Intervention group – N = 13; age (yrs) 62.2 ± 12.2; Gender: male 10/13 (77%); female 3/13 (23%); ulcer area (cm^2) 1.85 ± 1.83. Comparator group – N = 13; age (yrs) 63.4 ± 9.84; Gender: male 8/13 (62%); female 5/13 (38%); ulcer area (cm^2) 1.88 ± 1.39.		
Length of follow-up [11] 12 week study period, follow-up at 16 and 20 weeks.	Outcome(s) measured [12] complete healing,	

INTERNAL VALIDITY				
Allocation [13] Randomisation was achieved by contacting an independent site	Comparison of study groups [14] Similar baseline characteristics for age and ulcer area. There is a 15% difference in gender between groups	Blinding [15] None.	Treatment/ measurement bias [16] Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] No. only those that completed study were included in analysis.
Overall quality assessment (descriptive) [18] This is a small study so may not be sufficiently powered to detect a difference between the groups. The authors predicted that there would be no difference between the two groups. This study also has the potential for bias as there was no blinding. This was an average quality study.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. ulcers healed	10/13 (80%)	11/13 (85%)	RR = 0.91 [0.70, 1.27]	Harms (NNH) [24] (95% CI) [25]
Time to healing (days)	35.67 ± 41.47	40.90 ± 32.32	*p* = 0.73	
	Clinical importance (1-4) [26]		Relevance (1-5) [27]	
Any other adverse effects [28] None reported.				

EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.

Applicability [30] There is no statistically significant difference in the clinical outcomes for these two treatments in addition to standard wound care, as Dermagraft has been shown to be clinically effective in other studies, potential benefits will probably outweigh any potential harms form treatment with OASIS wound Matrix.
Comments [31] This study shows that OASIS Wound Matrix is as effective in treating diabetic foot ulcers as Dermagraft skin replacement therapy.

STUDY DETAILS		
Reference [1] (Langer & Rogowski 2009) "Systematic review of economic evaluations of human cell-derived wound care products for the treatment of venous leg and diabetic foot ulcers." BMC health services research 9.		
Affiliation/source of funds [2] Institute of Health Economics and Health Care Management, Munich school of Management, Ludwig-Maximilians University, Munich; Institute of Health Economics and Health Care Management Helmholtz Zentrum Munchen, German Research Centre for environmental Health, Neuherberg; Germany.		
Study design [3] systematic review	Level of evidence [4] I	Location/setting [5] Germany

Intervention [6] Sample size [7]	Comparator(s) [8] Sample size [9]
Steinberg et al (2002)	
Apligraf plus standard wound care	Standard wound care
Segal and John (2002)	
Dermagraft plus standard wound care	Standard wound care
Ghatnekar et al (2000)	
Becaplermin plus standard wound care	Standard wound care
Ghatnekar et al (2001) [Pharmacoeconomics 19(7):767-778.]	
Becaplermin plus standard wound care	Standard wound care
Kantor and Margolis (2001)	
Becaplermin plus standard wound care	Standard wound care
Persson et al (2000)	
Becaplermin plus standard wound care	Standard wound care
Sibbald et al (2003)	
Becaplermin plus standard wound care	Standard wound care
Overview of studies included in Ho et al (2005)	
Redekop et al (2003)	
Apligraf plus standard wound care	Standard wound care
Allenet et al (2000)	
Dermagraft plus standard wound care	Standard wound care

Selection criteria

Inclusion criteria – Only full health economic evaluations (cost-minimisation, cost-utility or cost-benefit analysis) of topical growth factors and bioengineered skin products for the treatment of therapy-resistant chronic wounds (venous leg ulcers and diabetic foot ulcers), in English, French or German.

Exclusion criteria – Publications outside the above categories, economic evaluations included in systematic review by Ho et al (2005) were excluded to avoid duplication [Ho et al (2005) was excluded from Baker IDI diabetic foot ulcer guidelines due to unreliable evidence]

Patient characteristics [10] – diabetic patients a full-thickness chronic ulcer of the lower extremities

Studies included for diabetic foot ulcer:

Steinberg et al (2002)

efficacy data from Veves at al (2001) - USA

Segal and John (2002)

efficacy data from Naughton et al (1997) and Pollak et al (1997) - Australia

Ghatnekar et al (2000)

used Markov model for diabetic lower extremity ulcers – UK

Ghatnekar et al (2001)

used Markov model for diabetic lower extremity ulcers – France, Sweden, Switzerland, UK

Kantor and Margolis (2001)

efficacy data from phase III trial by Weiman et al (1998) - USA

Persson et al (2000)

used Markov model for diabetic lower extremity ulcers - Sweden

Sibbald et al (2003)

efficacy data from phase III trial by Weiman et al (1998) – Canada

Overview of studies included in Ho et al (2005)

Redekop et al (2003)

efficacy data from Veves at al (2001) - Netherlands

Allenet et al (2000)

efficacy data from Naughton et al (1997) and Pollak et al (1997) - France

Length of follow-up [11] N/A	Outcome(s) measured [12] Cost-effectiveness analysis, Incremental cost-effectiveness ratio

INTERNAL VALIDITY

Allocation [13] N/A	Comparison of study groups [14] N/A	Blinding [15] N/A	Treatment/ measurement bias [16] N/A	Follow-up (ITT) [17] N/A

Overall quality assessment (descriptive) [18] The quality of evidence for Apligraft and Dermagraft was considered to be limited. The quality of the evidence on becaplermin was considered to be high. Good quality review.

RESULTS

Study	Cost-effectiveness analysis: Incremental cost-effectiveness ratio (ICER)
Steinberg et al (2002) Price year = 2000	The incremental cost of Apligraf vs SWC per ulcer-free month gained = US$6,683 per amputation or resection avoided = US$86,226
Segal and John (2002) Price year = 2000	The incremental cost of Dermagraft vs SWC per additional healed week = A$383 (US$292) Average cost to treat ulcer prior to dermagraft treatment = A$12,500 Average cost after starting Dermagraft treatment = A$4,682
Ghatnekar et al (2000)	The cost of becaplermin vs SWC for the number of ulcer days averted was found to be cost saving in the UK Average cost to treat ulcer with SWC = £10,880 Average cost for becaplermin plus SWC = £10,403
Ghatnekar et al (2001) Price year = 1999	The incremental cost of becaplermin vs SWC per ulcer-free month gained = US$19 in France The cost of becaplermin vs SWC for the number of ulcer-free months gained was found to be cost saving in the UK, Sweden and Switzerland. France / Sweden / Switzerland / UK Average cost to treat ulcer with SWC = US$11,993 / US$11,783 / US$13,832 / US$17,133 Average cost for becaplermin plus SWC = US$11,977 / US$12,168 / US$14,112 / US$17,601
Kantor and Margolis (2001) Price year = 1999	The incremental cost of becaplermin vs SWC per additional 1% of ulcers healed = US$36.59 The incremental cost of becaplermin vs specialised multidisciplinary wound care per additional 1% of ulcers healed = US$70.86
Persson et al (2000) Price year = 1999	The cost of becaplermin vs SWC for the number of ulcer months avoided was found to be cost saving, in Sweden. Average cost to treat ulcer with SWC = US$12,078 Average cost for becaplermin plus SWC = US$11,708
Sibbald et al (2003) Price year = 1998 Updated to 2002	The incremental cost of becaplermin vs SWC per number of ulcer days averted = Can$6 (US$5)
Redekop et al (2003)	The cost of Apligraf vs SWC for the number of ulcer-free months gained was found to be cost saving in the Netherlands.
Allenet et al (2000)	The incremental cost of Dermagraft vs SWC per additional ulcer healed = FF38,784 (€5,913)

Any other adverse effects [28] N/A

EXTERNAL VALIDITY

Generalisabilty [29] Analysis for UK, Australia, other western European countries, USA, and Canada. Generalisable to other countries with similar healthcare for patients with diabetic foot ulcers.

Applicability [30]

Comments [31] All studies used condition-specific measures of benefits (ulcer-free months gained, additional healed weeks, ulcer days averted, additional % of ulcers healed, and ulcer months avoided) that do not allow for a meaningful comparisons.

STUDY DETAILS				
Reference [1] (Larijani et al 2008) "Effects of intravenous Semelil (ANGIPARS[trademark]) on diabetic foot ulcers healing: a multicenter clinical trial." Daru 16(Suppl 1): 35-40.				
Affiliation/source of funds [2] Endocrinology and Metabolism Research Centre, Dept. of Epidemiology and Biostatistics, Public Health School, Rheumatology Research centre, Tehran University of medical Science, Tehran; Endocrinology Research centre, Tabriz University of Medical Sciences, Tabriz; Endocrine and Metabolism Research Centre, Shiraz University of Medical Sciences, Shiraz; ENT – Head and Neck Surgery Dept. and Research Centre, Iran University of Medical Sciences, Dept. of Biotechnology, Rabe Rashidi Institute, Tabriz, Iran. Internal Diseases Ward, Iranians' Hospital, Dubai, UAE. Funded by ParsRoos Co.				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Iran/United Arab Emirates Multicentre (3 sites: in Tehran, Tabriz and Dubai)		
Intervention [6] Combination of the herbal extract, Semelil (ANGIPARS), and conventional therapy. Intravenous administration of 4 cc ANGIPARS daily for 28 days, the drug was diluted in 50-100 cc normal saline and infused during 30-60 mins. Sample size [7] 16		Comparator(s) [8] Conventional therapy. This included: wound debridement, betadine baths, dressings, antibiotic therapy, pressure decompression, foot deformity correction, as required. Sample size [9] 9		
Selection criteria Inclusion criteria – Diabetic patients (on oral medication or insulin), aged 18-75 years, with chronic non-healing diabetic foot ulcer for at least 2 weeks without improvement. Informed written consent. Exclusion criteria – Patients with severe heart failure, showing symptoms of chronic and severe ischemia with pulse-less lower limbs, other disease that impairs ulcer improvement, malignancy, alcohol and drug abuse, chronic renal failure, progressive liver failure, corticosteroid use, immune-suppressive therapy, radiotherapy, chemotherapy, known hypersensitivity to study drug.				
Patient characteristics [10] Intervention group – N = 16, mean age (yrs) 50.6 ± 12.7, gender: 13/16 (81.3%) male, 3/16 (18.7%) female, weight (kg) 73.1 ± 18.2, diabetes type 2 14/16 (87.5%), duration of diabetes (yrs) 10.6 ± 4.8, fasting blood glucose 182.9 ± 74.4. Ulcer surface area (mm^2) 479.9 ± 379.8. Comparator group(s) – N = 9, mean age (yrs) 59.0 ± 11.0, gender: 5/9 (55.6%) male, 4/9 (44.4%) female, weight (kg) 65.4 ± 9.4, diabetes type 2 9/9 (100%), duration of diabetes (yrs) 14.8 ± 9.6, fasting blood glucose 155.0 ± 35.4. Ulcer surface area (mm^2) 766.2 ± 960.5.				
Length of follow-up [11] 28 days study duration		Outcome(s) measured [12] % reduction in ulcer area,		
INTERNAL VALIDITY				
Allocation [13] Randomisation using permuted balanced block method in each study centre.	Comparison of study groups [14] Similar baseline characteristics with the exception of age (14% difference), gender (32%), weight (11%), duration of diabetes (28%), fasting blood glucose (15%), and ulcer size (37%).	Blinding [15] None	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, no loss to follow-up.
Overall quality assessment (descriptive) [18] This study may be subject to information bias as there was no blinding. I find the results are probably sufficiently reliable to find that there is some treatment benefit. Study was of average quality.				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
Ulcer size:				
Before treatment	479.93 ± 379.75	766.22 ± 960.50		Harms (NNH) [24] (95% CI) [25]
After treatment	198.93 ± 143.75	689.11 ± 846.74		
% reduction	64%	25%	p = 0.015	
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 2. Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention.	
Any other adverse effects [28] No adverse effects were observed.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				

Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits will probably outweigh any potential harms.
Comments [31] This study shows that treatment with intravenous ANGIPARS increases the rate of wound healing. However, this is a small study and a larger trail needs to be undertaken for a longer time-frame to determine if this treatment will ultimately completely heal the diabetic foot ulcers.

STUDY DETAILS		
Reference [1] (Leslie et al 1988) "Randomized controlled trial of topical hyperbaric oxygen for treatment of diabetic foot ulcers." Diabetes Care 11(2): 111-115.		
Affiliation/source of funds [2] School of Medicine, University of Southern California, Los Angeles, the Ortho-Diabetes Service, Dept. of Medicine, and the Regional Spinal Cord Injury Care System of Southern California, Rancho Los Amigo Medical Centre, Downey California. Funded in part by Topox Corporation, Jersey City, New Jersey.		
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] USA Hospital inpatient setting
Intervention [6] Topical hyperbaric oxygen therapy (THOT) THOT was administered in two daily 90-min sessions with the topical hyperbaric leg chamber which provided humidified 100% oxygen at pressures that cycled between 0 and 30 mmHg every 20 seconds. Wounds were assessed after 7 and 14 days of treatment. Sample size [7] 12	Comparator(s) [8] Standard wound care All ulcers underwent initial debridement, then all patients were treated for 2 weeks with intravenous antibiotics, wet to dry local dressings and bed rest. Sample size [9] 16	
Selection criteria Inclusion criteria – Diabetic patients admitted to the Rancho Los Amigos Medical Centre Ortho-Diabetes Service between April 1983 and July 1985 for treatment of foot ulcers. A well-demarcated foot ulcer, circular or elliptical (amenable to measurement with a simple ruler), located at or below the ankle, with no visible bone exposure, considered to be a candidate for a 2-week conservative trial. Exclusion criteria – Did not require an urgent amputation. Presence of gangrene, crepitation, severe ischemia, or persistent fever.		
Patient characteristics [10] N = 28. Race: Hispanic 16/28 (57%), Black 7/28 (25%), White 5/28 (18%). Intervention group – N = 12, mean age (yrs) 52.8 ± 8.6, gender: 6/12 (50%) male, 6/12 (50%) female, diabetes type 2 12/12 (100%), duration of diabetes (yrs) 11.4 ± 7.6, ankle/brachial index <0.5 or >1.5 1/10 (10%), abnormal X-ray or bone scan 6/12 (50%), white blood cell count >12,000/mm^3 0/12 (0%), erythrocyte sedimentation rate (mm/h, Westergren method) 72 ± 31, previous amputations 7/12 (58%). Ulcer characteristics: duration (weeks) 6.4 ± 6.2, surface area (mm^2) 551.8 ± 546.7, ulcer depth (mm) 8.1 ± 4.5. Comparator group(s) – N = 16, mean age (yrs) 46.2 ± 8.5, gender: 10/16 (62.5%) male, 6/16 (37.5%) female, diabetes type 2 12/16 (75%), duration of diabetes (yrs) 13.2 ± 8.0, ankle/brachial index <0.5 or >1.5 2/14 (14.3%), abnormal X-ray or bone scan 5/16 (31.3%), white blood cell count >12,000/mm^3 2/16 (12.5%), erythrocyte sedimentation rate (mm/h, Westergren method) 66 ± 40, previous amputations 5/16 (31.3%). Ulcer characteristics: duration (weeks) 6.2 ± 7.8, surface area (mm^2) 319.6 ± 255.7, ulcer depth (mm) 4.8 ± 3.3.		
Length of follow-up [11] 2 weeks	Outcome(s) measured [12] % reduction in ulcer area, % reduction in ulcer depth.	

INTERNAL VALIDITY				
Allocation [13] Random assignment by independent collaborator with the aid of a random numbers table	Comparison of study groups [14] Similar baseline characteristics with the exception of age (12% difference), gender (13%), diabetes type (25%), abnormal X-ray (19%), previous amputations (27%), ulcer size (42%).	Blinding [15] None	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, all patients were included in analysis
Overall quality assessment (descriptive) [18] This study could be subject to information bias as there was no blinding. The study was also small and may not have been adequately powered. However, there is no obvious difference in % improvement between the two groups suggesting that THOT therapy has no effect. This study was of average quality.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
% reduction in ulcer area at:				
Day 7	32.9 ± 18.3	30.4 ± 34.5	$p = 0.8$	
Day 14	54.4 ± 23.4 $p = 0.02$	64.4 ± 23 $p = 0.003$	$p = 0.27$	

<table>
<tr><td>% reduction in ulcer depth at:
Day 7
Day 14</td><td>
4.1 ± 9.1
24.2 ± 23.4
p = 0.011</td><td>
10.5 ± 29.2
32.7 ± 23.5
p = 0.024</td><td>
p = 0.47
p = 0.35</td><td>Harms (NNH) [24]
(95% CI) [25]</td></tr>
<tr><td></td><td colspan="2">Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.</td><td colspan="2">Relevance (1-5) [27] 2. Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention.</td></tr>
<tr><td colspan="5">Any other adverse effects [28] None reported.</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.</td></tr>
<tr><td colspan="5">Applicability [30] As the treatment does not provide a statistically significant benefit over standard care alone, any potential harms may outweigh treatment benefits.</td></tr>
<tr><td colspan="5">Comments [31] Even though there was a statistically significant improvement in the ulcers over the 2 week study period, there was no difference in the rate of improvement between the two groups. Thus, topical hyperbaric therapy does not offer any clinical benefit compared to standard wound care in this study.</td></tr>
</table>

STUDY DETAILS

Reference [1] (Leung et al 2008). "Limb salvage in extensive diabetic foot ulceration: An extended study using a herbal supplement." Hong Kong Medical Journal 14(1): 29-33.

Affiliation/source of funds [2] Institute of Chinese Medicine, The Chinese University of Hong Kong; Dept. of Orthopaedics and Traumatology, Prince of Wales Hospital; Dept. of Orthopaedics and Traumatology, Kwong Wah Hospital, Shatin, Hong Kong.

Study design [3] double-blind RCT	Level of evidence [4] II	Location/setting [5] Hong Kong Orthopaedic units of 2 hospitals,

Intervention [6] twice daily consumption of a herbal drink and standard wound care Herbal drink consisted of 12 herbs: Radix astragali, Rhizoma atractylodis marcocephalae, Radix stephaniae tetrandrae, Radix polygoni multiflora, Radix rehmanniae, Radix smilax china, Fructus corni, Rhizoma dioscoreae, Cortex moutan, Rhizoma alismatis, Rhizoma smilacis glabrae, and Fructus schisandrae. Sample size [7] 40	Comparator(s) [8] twice daily starch placebo drink and standard wound care which consisted of antibiotic treatment as required, daily cleaning with antiseptics and dressing of ulcer, de-sloughing performed at the same time. If deterioration or no improvement after 4 weeks patients were crossed-over to herbal supplement Sample size [9] 40

Selection criteria

Inclusion criteria –Diabetic patients being treated for chronic foot ulcers, of 7-25 week duration, and in receipt of regular antidiabetic treatment admitted to the orthopaedic units of 2 general hospitals in Hong Kong.

Exclusion criteria – Patients suffering from serious cardiac and renal deficiencies.

Inclusion/exclusion criteria same as in preliminary study published in 2001.

Patient characteristics [10]

Intervention group – N = 40, mean age (yrs) 66.3 ± 12.6, gender: 25/40 (62.5%) male, 15/40 (37.5%) female, diabetes type 2 35/40 (88%), duration of diabetes (yrs) 8.4 ± 7.6, insulin therapy 7/40 (18%), oral hypoglycaemic 28/40 (70%), diet control 5/40 (13%), diabetes control (blood check): good (steady) 19/37 (51%), fair (occasionally fluctuating) 14/37 (38%), poor (fluctuating) 4/37 (8%), smoker 13/40 (33%), body weight (kg) 59.1 ± 12.3, serum albumin level (g/L) 31.7 ± 4.5. Ulcer characteristics: duration (weeks) 7.8 ± 8.2, surface area (cm^2) 28.7 ± 31.3, ulcer bed: infected with slough 28/35 (80%), oedematous with patchy necrosis 6/35 (17%), relatively clean 1/35 (3%), gangrenous tissue: dry 12/38 (32%), wet 19/38 (50%), none 7/38 (18%).

Comparator group(s) – N = 40, mean age (yrs) 68.5 ± 11.1, gender: 22/40 (55%) male, 18/40 (45%) female, diabetes type 2 30/39 (77%), duration of diabetes (yrs) 12.4 ± 8.8, insulin therapy 8/40 (20%), oral hypoglycaemic 26/40 (65%), diet control 6/40 (15%), diabetes control (blood check): good (steady) 17/35 (49%), fair (occasionally fluctuating) 17/35 (49%), poor (fluctuating) 1/35 (3%), smoker 16/40 (40%), body weight (kg) 61.2 ± 12.3, serum albumin level (g/L) 32.2 ± 4.2. Ulcer characteristics: duration (weeks) 12.9 ± 24.6, surface area (cm^2) 26.7 ± 27.3, ulcer bed: infected with slough 30/36 (83%), oedematous with patchy necrosis 4/36 (11%), relatively clean 2/36 (6%), gangrenous tissue: dry 8/31 (26%), wet 12/31 (39%), none 11/31 (35%).

Length of follow-up [11] 24 week study period	Outcome(s) measured [12] Time to healing, No. ulcers improved, No. amputations.

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Randomised using blocked randomisation scheme	Similar baseline characteristics with the exception of duration of diabetes (32% difference), duration of ulcer (40%), ulcer with/without gangrene (17%).	Clinicians and patients blinded for 4 weeks, then non-responders were unblended and crossed-over to herbal supplement if on placebo	There was no difference in treatment and measurement between the groups	Yes, all patients were included in analysis

Overall quality assessment (descriptive) [18] This study was powered to detect a 30% difference and was designed to minimise bias by blinding both the patients and the clinicians. The lack of statistical significance for the trend towards healing that is seen suggests that the effect of the herbal drink is small. This was a good quality study.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
Time to healing (weeks)	5.9 ± 1.4	9.2 ± 1.9	*p* = 0.147	Harms (NNH) [24] (95% CI) [25]
No. ulcers improved	31/40 (77.5%)	25/40 (62.5%)	RR = 1.24 (0.93, 1.61)	
No. amputations in first 4 weeks	3/40 (7.5%)	3/40 (7.5%)	RR = 1	
Total no. of amputation	3/40 (7.5%)	9/40 (22.5%)	RR = 0.33 (0.10, 1.04) *p* = 0.057	

	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] Some self-limiting adverse events (epigastric pain, dry mouth, and diarrhoea) were experienced. Liver and renal function were not affected.		
EXTERNAL VALIDITY		
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.		
Applicability [30] As the treatment does not provide a statistically significant benefit, any potential harms may outweigh treatment benefits.		
Comments [31] Even though it was not statistically significant, this study shows a trend towards shorter healing times when taking the herbal drink. However, this study was powered to detect a difference of 30% between the two groups, thus the effect of this herbal drink is very modest, and requires a much larger study to determine any significant differences.		

STUDY DETAILS		
Reference [1] (Lipkin et al 2003) "Effectiveness of bilayered cellular matrix in healing of neuropathic diabetic foot ulcers: results of a multicenter pilot trial." Wounds: A Compendium of Clinical Research & Practice 15(7): 230-236.		
Affiliation/source of funds [2] Dept. of Surgery, Lehigh Valley Hospital, Allentown, Pennsylvania; Dept. of Surgery, Emory University, Atlanta, Georgia; North Shore Diabetes and Endocrine Research, New Hyde Park, New York; Baptist Integris Burn and Wound Care Centre, Oklahoma City, Oklahoma; USA. Supported by a grant from Ortec International, New York, New York, USA		
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] USA. Multicentre (8 sites),
Intervention [6] Bilayered cellular matrix (BCM) is a porous collagen sponge containing co-cultured allogenic keratinocytes and fibroblasts harvested from human neonatal foreskin. After initial 2-week screening period with standard wound care, BCM was applied to ulcer and covered with a non-adherent dressing and gauze wrap. The gauze wrap was changed every 2-3 days, as required. The BCM was applied weekly for up to six total applications, then standard care alone was given. Sample size [7] 20	Comparator(s) [8] Standard wound care Consists of sharp debridement, covering with moist saline gauze, then a layer of transparent adhesive dressing and gauze wrap. This dressing was changed twice daily. Provided with a pressure relief walker and encouraged to limit mobility. Continued for 12 weeks, or until ulcer healed. Sample size [9] 20	
Selection criteria Inclusion criteria – Diabetic patients between 18 and 85 years, with peripheral neuropathy (absence of protective sensation) and a University of Texas grade 1A (superficial, not involving bone or tendon, without infection or ischemia) ulcer on the plantar surface of the foot, between 1 and 12 cm^2 in size, and present for at least 30 days. Diabetes must be controlled (HbA_{1c} < 12%), and limb adequately perfused (ABI > 0.7 and great toe pressure > 0.6), study ulcer must be at least 2 cm away from any other ulcer and not healed more than 30% during 2-week screening period. Exclusion criteria – Pregnancy or nursing mothers, presence of immunocomprimising disease or other disease or treatment that would interfere with the study treatment, osteomyelitis,		
Patient characteristics [10] Intervention group – N = 20; age (yrs) 57.4 ± 10.6; Gender: male 18/20 (90%); female 2/20 (10%); Race: Caucasian 15/20 (75%); African-American 3/20 (15%); other 2/20 (10%); % HbA_{1c} 8.39 ± 1.4; ulcer duration (months) 12.2 ± 10.8; ulcer area (cm^2) 6.0 ± 7.6; ulcers < 6 cm^2 15/20 (75%); ulcers < 6 cm^2 area (cm^2) 2.8 ±1.5; ulcers > 6 cm^2 5/20 (25%); ulcers > 6 cm^2 area (cm^2) 15.7 ±10.4. Comparator group(s) – N = 20, Age (yrs) 59.0 ± 12.7, Gender: male 14/20 (70%), female 6/20 (30%), Race: Caucasian 17/20 (85%), African-American 2/20 (10%), Other 1/20 (5%), % HbA_{1c} 8.97 ± 2.08, Ulcer duration (months) 11.9 ± 11.8, Ulcer area (cm^2) 5.5 ± 4.3, Ulcers < 6 cm^2 13/20 (65%), ulcers < 6 cm^2 area (cm^2) 2.9 ±1.5, Ulcers > 6 cm^2 7/20 (35%), ulcers > 6 cm^2 area (cm^2) 10.3 ±3.6.		
Length of follow-up [11] up to 12 weeks	Outcome(s) measured [12] No. of ulcers healed, rate of wound closure, No. of infections (harms)	

INTERNAL VALIDITY				
Allocation [13] Randomisation according to a computer-generated randomisation code.	Comparison of study groups [14] Similar baseline characteristics with the exception of gender (20% difference), and ulcer > 6 cm^2 area (34%).	Blinding [15] None	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, all patients were included in analysis
Overall quality assessment (descriptive) [18] This study has the potential for information bias as there was no blinding. Also, the lack of statistical significance for no. of ulcers healed may be due to a lack of power, the study was designed as a pilot trial. This study was of good quality.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. of ulcers healed:				
Total	7/20 (35%)	4/20 (20%)	RR = 1.75 [0.64, 5.05]	
Ulcers < 6 cm^2	7/15 (47%)	3/13 (23%)	RR = 2.02 [0.72, 6.33]	
Ulcers > 6 cm^2	0/5 (0%)	1/7 (14.3%)	RR = not calculable	
Rate of wound closure (%/day):				Harms (NNH) [24] (95% CI) [25]
Total	1.8 ± 2.5	1.1 ± 1.9	p = 0.0087	
Ulcers < 6 cm^2	2.2 ± 2.81	1.1 ± 2.03	p = 0.001	
Ulcers > 6 cm^2	0.8 ± 1.19	1.2 ± 1.61	p = 0.248	
No of infections (harms)	2/20 (10%)	4/20 (20%)	RR = 0.5 [0.11, 2.13]	

	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] There were no treatment related adverse events. 2 patients from intervention group withdrew prior to end of treatment, one due to unrelated adverse event, the other due to treatment failure. One of the infections in standard care group became serious.		
EXTERNAL VALIDITY		
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.		
Applicability [30] As the treatment provides some statistically significant benefit, treatment benefits may outweigh any potential harms.		
Comments [31] This study shows that treatment with BCM has a statistically significant effect on the rate of wound healing. However, no statistically significant effect was seen for the number of ulcers that healed after BCM treatment compared to standard wound care.		

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] (Lishner et al 1985) "Treatment of diabetic perforating ulcers (mal perforant) with local dimethylsulfoxide." Journal of the American Geriatrics Society 33(1): 41-43.</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2] Dept. of Medicine, Meir Hospital, Kfar Saba; and the Sackler School of Medicine, Tel Aviv University, Israel.</td></tr>
<tr><td colspan="2">Study design [3] pseudo-randomised controlled trial</td><td colspan="2">Level of evidence [4] III-1</td><td colspan="2">Location/setting [5] Israel.
Hospital, 3-5 days inpatient, then outpatient</td></tr>
<tr><td colspan="3">Intervention [6] Dimethylsulphoxide (DMSO) treatment.
Received standard treatment except that the affected foot was soaked in 500 ml of 25% solution of DMSO in normal saline for 20 mins every day. If ulcers were infected, 80 mg garamycin was added to the solution. A fresh solution was prepared every 3 days. If progress of healing seemed unsatisfactory the concentration of DMSO was raised to 50% from the 6th week onwards. Therapy continued for 20 weeks.
Sample size [7] 20</td><td colspan="3">Comparator(s) [8] Standard treatment.
Foot ulcers underwent debridement, any slough was removed with a chlorinated lime (1.25%) and boric acid (1.25%) solution in water, dry dressings were applied, and broad-spectrum antibiotics were given systemically when cellulitis was present.
The patients were instructed to wear soft shoes, cut out if necessary, to minimise pressure.
Sample size [9] 20</td></tr>
<tr><td colspan="6">Selection criteria
Inclusion criteria – Diabetic patients with neuropathy and perforating ulcers that had failed to heal after 4 months of conventional treatment.
Exclusion criteria – None stated.</td></tr>
<tr><td colspan="6">Patient characteristics [10]
Intervention group – N = 20, mean age (yrs) 67, gender: 12/20 (60%) male, 8/20 (40%) female, duration of diabetes (yrs) 14, insulin therapy 12/20 (60%), nephropathy 11/20 (55%), neuropathy 20/20 (100%), retinopathy 20/20 (100%), peripheral vascular disease 14/20 (70%), duration of ulcer (months) 16.
Comparator group(s) – N = 20, mean age (yrs) 64, gender: 10/20 (50%) male, 10/20 (50%) female, duration of diabetes (yrs) 15.5, insulin therapy 14/20 (70%), nephropathy 14/20 (70%), neuropathy 20/20 (100%), retinopathy 20/20 (100%), peripheral vascular disease 12/20 (60%), duration of ulcer (months) 14.</td></tr>
<tr><td colspan="3">Length of follow-up [11] 20 weeks study period.</td><td colspan="3">Outcome(s) measured [12] No. ulcers completely healed, No. ulcers improved.</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Every second patient allocated to treatment group</td><td>Comparison of study groups [14]
Similar baseline characteristics with the exception of nephropathy (15% difference).</td><td>Blinding [15]
None.</td><td colspan="2">Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups</td><td>Follow-up (ITT) [17]
Yes, all patients were included in analysis</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18] There is potential for information bias in this study as there was no blinding. Study may also not have been adequately powered even though a statistically significant result was obtained. This study was of average quality.</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td>Outcome [19]</td><td>Intervention group [20]</td><td>Control group [21]</td><td colspan="2">Measure of effect/effect size [22] (95% CI) [25]</td><td>Benefits (NNT) [23] (95% CI) [25]</td></tr>
<tr><td>No. ulcers healed</td><td>70% (14/20)</td><td>10% (2/20)</td><td colspan="2">RR = 7.00 (2.30, 25.35)</td><td>1.67 (1.35, 3.17)</td></tr>
<tr><td>No. ulcers improved</td><td>90% (18/20)</td><td>35% (7/20)</td><td colspan="2">RR = 2.57 (1.54, 3.46)</td><td>1.82 (1.45, 3.78)</td></tr>
<tr><td></td><td></td><td></td><td colspan="2"></td><td>Harms (NNH) [24] (95% CI) [25]</td></tr>
<tr><td></td><td colspan="3">Clinical importance (1-4) [26] 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.</td><td colspan="2">Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.</td></tr>
<tr><td colspan="6">Any other adverse effects [28] No untoward systemic reaction to DMSO in any patient. Locally, the 25% solution was well tolerated, but the 50% solution caused local irritation of the skin and a burning sensation that occasionally necessitated the temporary interruption of DMSO application for 2-4 days.</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
</table>

Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits will probably outweigh any potential harms.
Comments [31] This study shows that treatment with DMSO has a statistically significant clinical effect on wound healing. However, this is a small study and a larger trail should be undertaken to demonstrate that this result can be duplicated.

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] (Lobmann et al 2006) "Expression of matrix metalloproteinases and growth factors in diabetic foot wounds treated with a protease absorbent dressing." Journal of diabetes and its complications 20(5): 329-335.</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2] Dept. of Endocrinology and Metabolism, Magdeburg University Medical School, Magdeburg; Diabetic Foot Outpatient Clinic, Wanzleben, Germany.</td></tr>
<tr><td colspan="2">Study design [3] RCT</td><td colspan="2">Level of evidence [4] II</td><td colspan="2">Location/setting [5] Germany
Out[patient setting</td></tr>
<tr><td colspan="3">Intervention [6] treated with Promogran matrix (protease inhibitor) in addition to standard good wound care.
Sample size [7] 18</td><td colspan="3">Comparator(s) [8] Standard good wound care
Sample size [9] 15</td></tr>
<tr><td colspan="6">Selection criteria
Inclusion criteria – Diabetic patients with chronic diabetic foot lesions (University of Texas wound classification stage 2a).
Exclusion criteria – None stated</td></tr>
<tr><td colspan="6">Patient characteristics [10]
Intervention group – N = 18, mean age (yrs) 64 ± 11, duration of diabetes (yrs) 15 ± 11, HbA_{1c} (%) 7.4 ± 1.1, mean ulcer area (mm^2) 1237 (25-7200).
Comparator group(s) – N = 15, mean age (yrs) 62 ± 12, duration of diabetes (yrs) 16 ± 11, HbA_{1c} (%) 7.7 ± 1.9, mean ulcer area (mm^2) 1132 (360-3600).</td></tr>
<tr><td colspan="3">Length of follow-up [11] 8 days</td><td colspan="3">Outcome(s) measured [12] % reduction in wound area</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Not disclosed</td><td>Comparison of study groups [14]
Similar baseline characteristics</td><td>Blinding [15]
Single blind, but uncertain who was blinded</td><td>Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups</td><td colspan="2">Follow-up (ITT) [17]
Yes, all patients were included in analysis</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18] This study may be subject to information bias as it was unclear who was blinded. This study may also not have been adequately powered and the 8 day treatment period was too short for definitive healing outcomes. The study was of average quality.</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="2">Outcome [19]

% reduction in wound area</td><td>Intervention group [20]

16%</td><td>Control group [21]

1.6%</td><td>Measure of effect/effect size [22] (95% CI) [25]

$p = 0.045$</td><td>Benefits (NNT) [23] (95% CI) [25]</td><td>Harms (NNH) [24] (95% CI) [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.</td><td colspan="3">Relevance (1-5) [27] 2. Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention.</td></tr>
<tr><td colspan="6">Any other adverse effects [28] None stated.</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.</td></tr>
<tr><td colspan="6">Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits will probably outweigh any potential harms.</td></tr>
<tr><td colspan="6">Comments [31] This study shows that treatment with Promogran has a statistically significant clinical effect on wound healing. However, this is a small study of short duration and a larger trail should be undertaken to determine the longer term effects of Promogran on wound healing.</td></tr>
</table>

STUDY DETAILS

Reference [1] (Lund et al 1999) "Intravenous hydroxyethylrutosides combined with long-term oral anticoagulation in atherosclerotic nonreconstructable critical leg ischemia: a retrospective study." Angiology 50(6): 433-445.

Affiliation/source of funds [2] Depts. of Clinical Physiology, Karolinska Hospital and Sodersjukhuset; and Clinical Reserach Centre Sodersjukhuset, Stockholm, Sweden.

Study design [3]	Level of evidence [4]	Location/setting [5]
historical control study	III-3	Sweden Multicentre (3 sites) hospital in- and outpatient setting?

Intervention [6]	Comparator(s) [8]
standard treatment plus treatment with two slow (30 min) daily IV hydroxyethylrutosides (HR) infusions of 1.5 g each for a mean period of 3.6 weeks in combination with oral anticoagulant warfarin, which was continued until the end of the 24 month study period. [HR inhibits red cell aggregation, powerful antioxidant, inhibits permeability of endothelial cell barrier] Sample size [7] 42 patients in total, 19 diabetic patients, 23 CLI diabetic legs	Standard care Patients did not receive HR treatment but 11 patients received warfarin alone, a few had low-dose aspirin, 2 received subcutaneous low-molecular-weight heparin, and 1 received an IV prostacyclin analogue. This classifies as standard treatment. This included local treatment of lesions, control of diabetes, coronary heart disease, congestive heart failure, and infection if required. Sample size [9] 28 patients in total, 18 diabetic patients, 20 CLI diabetic legs

Selection criteria

Inclusion criteria – Patients fulfilled the inclusion/exclusion criteria defined in the Second European Consensus Documents on chronic leg ischemia of 1991.

Exclusion criteria – wide-spread gangrene on a greater part of foot

Patient characteristics [10]

Intervention group – N = 42; n = 52 CLI legs, diabetics 19/42 (45%); previous leg amputation 5/42 (11.9%); smokers~25%; rest pain with ischaemic cyanotic discolouration but without trophic lesions ~6%.

N = 19 diabetic patients, n = 23 CLI legs, mean age 71.7 ± 6.6, mean toe blood pressure in CLI legs (mmHg) 7.4. N = 42 patients in total, previous leg amputation 5/42 (11.9%), smokers ~25%, rest pain with ischemic cyanotic discolouration but without trophic lesions ~6%.

Comparator group(s) – N = 28; n = 34 CLI legs, diabetics 18/28 (64%) previous leg amputation 4/28 (14.3%); smokers~25%; rest pain with ischemic cyanotic discolouration but without trophic lesions ~9%.

N = 18 diabetic patients, n = 20 CLI legs, mean age 70.4 ± 8.7, mean toe blood pressure in CLI legs (mmHg) 8.0. N = 28 patients in total, previous leg amputation 4/28 (14.3%), smokers ~25%, rest pain with ischemic cyanotic discolouration but without trophic lesions ~9%.

Patients in control group fulfilled same inclusion/exclusion criteria as treatment group, had similar prevalence of gender, arterial reconstruction, angina pectoris, myocardial infarction, congestive heart failure, and cerebrovascular disease. The number of more advanced ischemic lesions was also comparable.

Length of follow-up [11]	Outcome(s) measured [12]
up to 24 months	For Diabetic patients only: Survival rate, No. amputations

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Non-random	Similar baseline characteristics for limited data provided	None.	There was no difference in treatment and measurement between the groups	No, 3 patients that reacted to HR treatment were excluded. All other patients were included in analysis

Overall quality assessment (descriptive) [18] This study is potentially subject to bias as no blinding occurred. The authors attempted to minimise selection bias by ensuring that they were comparable in factors such as age, gender and smoking status. This study was of average quality.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
All patients:				
No. deaths after:				
1 month	0/42 (0%)	1/28 (4%)	RR = 0.00 [0.00, 2.54]	
3 months	2/42 (5%)	5/28 (18%)	RR = 0.27 [0.06, 1.12]	
6 months	2/42 (5%)	9/28 (32%)	RR = 0.15 [0.04, 0.55]	
12 months	6/42 (14%)	10/28 (36%)	RR = 0.40 [0.17, 0.95]	
24 months	17/42 (40%)	11/28 (39%)	RR = 1.03 [0.59, 1.89]	

No. amputations after:				Harms (NNH) [24] (95% CI) [25]
1 month	3/52 (6%)	4/34 (12%)	RR = 0.49 [0.13, 1.88]	
3 months	17/52 (33%)	13/34 (38%)	RR = 0.86 [0.49, 1.54]	
6 months	20/52 (38%)	15/34 (44%)	RR = 0.97 [0.53, 1.47]	
12 months	23/52 (44%)	17/34 (50%)	RR = 0.89 [0.58, 1.41]	
24 months	27/52 (52%)	20/34 (59%)	RR = 0.88 [0.62, 1.32]	
Diabetic patients:				
No. deaths after:				
1 month	0% (0/19)	0% (0/18)	RR = 1.00	
3 months	10.5% (2/19)	22.2% (4/18)	RR = 0.47 (0.11, 2.00)	
6 months	10.5% (2/19)	33.3% (6/18)	RR = 0.32 (0.01, 1.18)	
12 months	15.8% (3/19)	33.3% (6/18)	RR = 0.47 (0.14, 1.49)	
24 months	31.6% (6/19)	33.3% (6/18)	RR = 0.95 (0.38, 2.38)	
No. amputations after:				
1 month	4.3% (1/23)	10% (2/20)	RR = 0.44 (0.06, 3.20)	
3 months	30.4% (7/23)	40% (8/20)	RR = 0.76 (0.34, 1.71)	
6 months	34.8% (8/23)	45% (9/20)	RR = 0.77 (0.37, 1.61)	
12 months	43.5% (10/23)	55% (11/20)	RR = 0.79 (0.44, 1.46)	
24 months	56.5% (13/23)	65% (13/20)	RR = 0.87 (0.56, 1.41)	
No. patients surviving without amputations or ulcer healing outcomes could not be extracted from total data.	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] 3 patients developed exanthema soon after starting IV HR treatment and were excluded from the study. No hypotensive reactions occurred due to slow infusion technique. There was no anticoagulant bleeding of clinical significance during the observation period.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with critical limb ischemic with or without diabetic foot ulcers.				
Applicability [30] As the treatment does not provide a statistically significant benefit, any potential harms will probably outweigh any treatment benefits.				
Comments [31] The authors have stated that treatment with IV HR increases the average survival time of these patients. The mean survival time for all patients were 16.2 months for the intervention group compared to 3.7 months for the control group but this data was not available for the diabetic cohort only.				

STUDY DETAILS

Reference [1] (Lyons et al 2007) "Talactoferrin alfa, a recombinant human lactoferrin promotes healing of diabetic neuropathic ulcers: a phase 1/2 clinical study." American journal of surgery 193(1): 49-54.

Affiliation/source of funds [2] BethIsrael Deaconess Medical Centre, Harvard Medical School, Boston, MA; The Wound Healing Centre, Terre House, IN; Penn North Centres for Advanced Wound Care, Warren, PA; New York University School of Medicine Hospital for Joint diseases, New York, NY; Scott and White Hospital, Temple, TX; University of Miami School of Medicine, Miami, FL; Scholl's centre for Lower Extremity Ambulatory Reseasrch, Rosalind Franklin University of Medicine and Science, Chicago, IL; Agennix Inc, Houston, TX. Funded by Agennix Inc and the National Institute of Arthritis and Muscoskeletal and Skin Diseases of the National Institute of Health.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] USA Multicentre (7 sites), outpatient setting

Intervention [6] 2.5% and 8.5% talactoferrin gel (recombinant lactoferrin - iron-binding glycoprotein) After sharp debridement the gel was applied topically twice daily for 12 weeks with standard care. Sample size [7] 2.5% gel, n = 15; 8.5% gel, n = 15	Comparator(s) [8] Placebo gel. Standard care consisted of periodic sharp debridement, as needed, twice daily saline dressing changes, off-loading using standardised devices, and systemic control of infection. Sample size [9] 16

Selection criteria

Inclusion criteria – Diabetic patients, aged > 18 years, with HbA_{1c} of 6-13%, and had a neuropathic foot ulcer at or below the ankle that had not decreased in size by > 30% within 4 weeks prior to assessment. The ulcer was required to be full thickness but without tendon, muscle, joint capsule or bone exposure, and without sinus tracts, with a post-debridement size of 0.5-10 cm^2. Patients also required adequate perfusion with $TcPO_2$ > 30 mmHg or ankle-brachial index of > 7. Informed consent.

Exclusion criteria – Non-diabetic ulcers, clinical signs of infection including cellulitis, osteomyelitis, gangrene, active Charcot's foot ulcer on the limb under study, prior treatment of target ulcer with Regranex within the last 14 days, autologous or allogeneic graft to target ulcer within the last 4 weeks.

Patient characteristics [10]

Intervention group 2.5% gel– N = 15, mean age 58 ± 10, gender: 14/15 (93%) male, 1/15 (7%) female, race: 14/15 (93%) Caucasian, 1/15 (7%) African-American, 0/15 (0%) Hispanic, type 1 diabetes 4/15 (27%), mean BMI 37.8 ± 9.0, HbA_{1c} (%) 8.2 ± 1.9, ulcer duration (months) 9.7 ± 8.4, mean ulcer area (cm^2) 2.6 ± 1.8.

Intervention group 8.5% gel– N = 15, mean age 53 ± 15, gender: 12/15 (80%) male, 3/15 (20%) female, race: 10/15 (67%) Caucasian, 4/15 (27%) African-American, 1/15 (7%) Hispanic, type 1 diabetes 3/15 (20%), mean BMI 33.0 ± 7.6, HbA_{1c} (%) 8.7 ± 1.6, ulcer duration (months) 9.6 ± 11, mean ulcer area (cm^2) 3.0 ± 2.0.

Comparator group(s) – N = 16, mean age 56 ± 14, gender: 9/16 (56%) male, 7/16 (44%) female, race: 13/16 (81%) Caucasian, 1/16 (6%) African-American, 2/16 (13%) Hispanic, type 1 diabetes 4/16 (25%), mean BMI 30.1 ± 4.5, HbA_{1c} (%) 8.6 ± 1.9, ulcer duration (months) 8.9 ± 7.7, mean ulcer area (cm^2) 1.9 ± 1.1.

Length of follow-up [11] 12 weeks study duration plus 6 month follow-up	Outcome(s) measured [12] No. completely healed, no. achieving > 75% closure

INTERNAL VALIDITY

Allocation [13] Randomisation was central. Patients were stratified according to ulcer duration (< 6 months versus > 6 months) and ulcer size (< 2 cm^2 versus > 2 cm^2).	Comparison of study groups [14] Similar baseline characteristics with the exception of gender (13-37% difference), Caucasian (12-24%), BMI (10-20%), ulcer size (13-37%).	Blinding [15] No personnel were informed of the blinding code before completion of the study	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, no loss to follow-up.

Overall quality assessment (descriptive) [18] The large number of patients lost during this study may have adversely affected the outcome, 8 of the 18 patients that withdrew were improving, of these only 1 was in the placebo group. It is also uncertain if the study was adequately powered. The study was of average quality.

RESULTS

Outcome [19]	Intervention group [20]		Control group [21]	Measure of effect/effect size [22] (95% CI) [25]		Benefits (NNT) [23] (95% CI) [25]
No. completely healed:	2.5% gel	8.5% gel		RR (2.5% vs P)	RR (8.5% vs P)	
End of treatment	3/15 (20%)	3/15 (20%)	3/16 (19%)	1.07 (0.27, 4.22)	1.07 (0.27, 4.22)	
30 days after treatment	5/15 (33%)	5/15 (33%)	3/16 (19%)	1.78 (0.55, 6.09)	1.78 (0.55, 6.09)	
90 days after treatment	4/15 (27%)	5/15 (33%)	3/16 (19%)	1.42 (0.40, 5.17)	1.78 (0.55, 6.09)	

No. achieving > 75% closure:	2.5% gel	8.5% gel		RR (2.5% vs P)	RR (8.5% vs P)	Harms (NNH) [24]
UD < 6 mo UA < 2 cm^2	1/3 (33%)	3/4 (75%)	1/3 (33%)	RR = 1	2.25 (0.62, 9.66)	(95% CI) [25]
UD < 6 mo UA > 2 cm^2	0/3 (0%)	2/2 (100%)	1/2 (50%)	0.00 (0.00, 2.17)	2.00 (0.71, 2.00)	
UD > 6 mo UA < 2 cm^2	1/1 (100%)	0/1 (0%)	1/4 (25%)	4.00 (0.53, 4.00)	0.00 (0.00, 8.80)	
UD > 6 mo UA > 2 cm^2	5/8 (63%)	3/8 (38%)	1/7 (14%)	4.38 (0.96, 26.1)	2.63 (0.47, 17.4)	
Overall	7/15 (47%)	8/15 (53%)	4/16 (25%)	1.87 (0.72, 5.09)	2.13 (0.86, 5.58)	
UD = ulcer duration UA = ulcer area	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.			Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.		

Any other adverse effects [28] There were 82 adverse events reported, with 26, 31 and 25 occurring in the placebo, 2.5% and 8.5% talactoferrin groups, respectively. The most frequent events were cellulitis, arthralgia, and localised infections, however, as the frequency was similar for all three groups, they were not considered to be related to the treatment received. Only one adverse event was considered to be related to the treatment, an episode of grade 1 burning sensation in a patient in the placebo group. 14 of these adverse events were serious and occurred in 13 patients but all were unrelated to the talactoferrin treatment. One placebo patient died due to renal failure, eight patients needed hospital treatment for ulcer-related wound infections and five required hospitalisation for other medical conditions.

EXTERNAL VALIDITY

Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.

Applicability [30] As the treatment does not provide a statistically significant benefit, any potential harms will probably outweigh any treatment benefits.

Comments [31] The authors have stated that treatment with 2.5% and 8.5% talactoferrin gel doubles the number of diabetic foot ulcers that improve > 75%, although it was not statistically significant. A larger trail needs to be undertaken to determine if treatment with talactoferrin gel does provide a clinical benefit.

STUDY DETAILS				
Reference [1] (Mahmoud et al 2008) "Split-skin graft in the management of diabetic foot ulcers." Journal of Wound Care 17(7): 303-306.				
Affiliation/source of funds [2] Soba University Hospital, Khartoum; Dept. of Surgery, Faculty of Medicine, University of Khartoum, Khartoum; Sudan				
Study design [3] cohort study	Level of evidence [4] III-2	Location/setting [5] Sudan Initially inpatient, and then outpatient		
Intervention [6] Split-skin grafting All patients offered skin grafting, those that refused given standard wound care. Debridement and skin grating undertaken by same plastic surgeon. Dressings as for control group, and first changed on the 5ht post-operative day and then twice weekly. Sample size [7] 50	Comparator(s) Standard wound care All patients underwent surgical debridement. Multilayered dressings comprised of paraffin gauze, diluted povidone-iodine soaked gauze, sterile gauze, and a roll bandage. Dressings were changed twice weekly. Patients also received off-loading as required Sample size [9] 50			
Selection criteria Inclusion criteria – 100 consecutive diabetic patients with diabetic foot ulcers attending the Jabir Abu Eliz Diabetic Centre or the Soba University Hospital between November 2004 and July 2006. Ulcer > 2 cm diameter on the plantar, heel, interdigital or dorsum of foot, or an unhealed foot stump, ankle brachial index of > 0.4. Exclusion criteria – ulcers with exposed bone, osteomyelitis, underlying infection with β-haemolytic streptococci, presence of c0-morbidities such as heart failure, uraemia, recent myocardial infarction and liver disease.				
Patient characteristics [10] Intervention group – N = 50; age (yrs) 51 ± 10; male 29/50 (58%); type 2 diabetes 43/50 (86%); ulcer size 2-5 cm^2 5/50 (10%); 5-10 cm^2 30/50 (60%); >10 cm^2 15/50 (30%); ulcer duration < 1 month 6/50 (12%); 1-2 months 14/50 (28%); 2-3 months 18/50 (36%); > 3 months 12/50 (24%); location: dorsum 12/50 (24%); plantar 11/50 (22%); heel 8/50 (16%); interdigital 4/50 (8%); stump 9/50 (18%); other site 6/50 (12%). Comparator group(s) – N = 50; age (yrs) 51 ± 7; male 30/50 (60%); type 2 diabetes 39/50 (78%); ulcer size 2-5 cm^2 7/50 (14%); 5-10 cm^2 26/50 (52%); >10 cm^2 17/50 (34%); ulcer duration < 1 month 5/50 (10%); 1-2 months 15/50 (30%); 2-3 months 20/50 (40%); > 3 months 10/50 (20%); location: dorsum 14/50 (28%); plantar 15/50 (30%); heel 6/50 (12%); interdigital 3/50 (6%); stump 7/50 (14%); other site 5/50 (10%). No significant difference in ankle brachial index between the two groups				
Length of follow-up [11] until complete healing then for up to 1 year	Outcome(s) measured [12] time to healing, length of hospital stay			
INTERNAL VALIDITY				
Allocation [13] Non-random Patient's choice	Comparison of study groups [14] Similar baseline characteristics	Blinding [15] None.	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, no loss to follow-up.
Overall quality assessment (descriptive) [18] Patients and Investigators were not blinded, therefore there is the potential for information bias. This study is of average quality.				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
Time to healing (days)	28 ± 5	122 ± 7	p < 0.05	
Length of hospital stay (days)	6 ± 2	18 ± 9	p < 0.05	Harms (NNH) [24] (95% CI) [25]
No. with ulcer recurrence	4/50 (8%)	Not measured		
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] None reported				
EXTERNAL VALIDITY				

Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] As the treatment provide a statistically significant benefit, treatment benefits may outweigh any harms.
Comments [31]. The authors have shown that the use of split-skin grafting improves the clinical outcomes for patients with diabetic foot ulcers compared to standard wound care alone by shortening the time to healing for these ulcers.

STUDY DETAILS

Reference [1] (Marston et al 2003) "The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial." Diabetes Care 26(6): 1701-1705.

Affiliation/source of funds [2] University of North Carolina School of medicine, Chapel Hill, North Carolina; Foot and ankle Institute of South Florida, South Miami, Florida; Valley Endocrine, Fresno, California; University of Texas Health Science Centre, San Antonio Texas; Dermagraft Joint Venture, La Jolla, California; USA. Funded by research grants from Advanced tissue Sciences Inc, La Jolla, CA, and Smith and Nephew Inc, Largo, FL.

Study design [3]	Level of evidence [4]	Location/setting [5]
single-blind RCT	II	USA Multicentre (35 sites),

Intervention [6]	Comparator(s) [8]
Dermagraft skin replacement therapy, first application on day 0, then received up to 7 additional applications at weekly intervals. Patients received the same standard wound care as control group except that Dermagraft was first layer over ulcer. Before randomisation all patients received sharp debridement and saline-moistened gauze dressings. Sample size [7] 130	Standard wound care, which included sharp debridement when necessary, wound dressings consisted of a non-adherent interface, saline-moistened gauze to fill ulcer, dry gauze, and adhesive fixation sheets. Patients were allowed to be ambulatory with extra-depth diabetic footwear with custom inserts or healing sandals. Sample size [9] 115

Selection criteria

Inclusion criteria – Diabetic patients, over 18 years, attending one of 35 clinics between December 1998 and March 2000, with a plantar ulcer (on forefoot or heel) of at least 2 weeks duration (later revised to > 6 weeks) and at least 1 cm^2 at day 0. The ulcer is of full-thickness without exposure of muscle, bone, tendon or joint capsule. Ulcer is free of necrotic tissue and made up of healthy vascularised tissue with adequate perfusion in limb.

Exclusion criteria – Gangrene on any part of affected foot, ulcer is over a Charcot deformity, ulcer area is > 20 cm^2, ulcer has increased or decreased in size by 50% or more during screening period, severe malnutrition (albumin < 2.0), random blood sugar reading > 450 mg/dl, urine ketones noted to be small, medium or large, a non-study ulcer is located within 7 cm of study ulcer, taking oral or parenteral corticosteroids, immunosuppressive or cytotoxic agents, Coumadin or heparin, history of bleeding disorder, patient has AIDS or is HIV positive, presence of cellulitis, osteomyelitis, or other evidence of infection.

Patient characteristics [10]

Intervention group – N = 130; age (yrs) 55.8 (27-83); Gender: male 90/130 (69%); female 40/130 (31%); Race: Caucasian 90/130 (69%); non-Caucasian 40/130 (31%); type 1 diabetes 32/130 (25%); ulcer duration (weeks) 41; ulcer located on forefoot/toe 112/130 (86%); heel 18/130 (14%); ulcer area (cm^2) 2.31 (0.75-16.7).

Comparator group(s) – N = 115; age (yrs) 55.5 (31-79); Gender: male 91/115 (79%); female 24/115 (21%); Race: Caucasian 87/115 (76%); non-Caucasian 28/115 (24%); type 1 diabetes 27/115 (23%); ulcer duration (weeks) 67; ulcer located on forefoot/toe 102/115 (89%); heel 13/115 (11%); ulcer area (cm^2) 2.53 (0.5-18.0).

Length of follow-up [11]	Outcome(s) measured [12]
12 week study period	complete healing by week 12 (100% epithelialisation with no drainage), % wound closure by week 12.

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Stratified by ulcer size than randomised (method not disclosed)	Similar baseline characteristics with the exception of ulcer duration (39% difference).	Patients were blinded	There was no difference in treatment and measurement between the groups	Yes, those that discontinued were included in the final analysis.

Overall quality assessment (descriptive) [18] This study was adequately powered but still potentially subject to bias as investigators could not be blinded. This is a good quality study.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
Complete healing:				
Interim analysis	19/71 (27%)	9/70 (13%)	RR = 2.08 [1.04, 4.29]	7 [4, 136]
Final analysis	39/130 (30%)	21/115 (18%)	*RR = 1.64 [1.04, 2.63]*	9 [5, 104]
Forefoot ulcers	33/112 (29.5%)	20/102 (19.6%)	RR = 1.50 [0.93, 2.45]	Harms (NNH) [24] (95% CI) [25]
Heel ulcers	6/18 (33%)	1/13 (8%)	RR = 4.33 [0.83, 26.82]	
% wound closure	91%	78%	$p = 0.044$	
No. infections Harms):	31/163 (19%)	48/151 (32%)	RR = 0.60 [0.40, 0.88] *included in Meta-analysis by Blozik and Scherer (2008)	8 [5, 32]

	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] 8% of Dermagraft group and 15% of control group required a surgical procedure, mostly related to osteomyelitis.		
EXTERNAL VALIDITY		
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.		
Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits will probably outweigh any harms.		
Comments [31] The authors have demonstrated that Dermagraft skin replacement therapy improves the clinical outcomes for people with diabetic foot ulcers.		

STUDY DETAILS

Reference [1] (Martínez-de Jesús et al 1997) "Randomized single-blind trial of topical ketanserin for healing acceleration of diabetic foot ulcers." Archives of medical research 28(1): 95-99.

Affiliation/source of funds [2] Division de Cirugia, Centro Medico Nacional Adolfo Ruiz Cortines, Instituto Mexicano del Seguro Social, Veracruz; Universidad Nacional Autonoma de Mexico, Mexico.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Mexico Hospital inpatient, followed by outpatient settings

Intervention [6] 2% Ketanserin ointment (in a hydrophilic polyethyleneglycol base). Ketanserin is a serotonergic-receptor anagonist, inhibits platelet aggregation, blocks vasoconstriction and improves tissue perfusion. Same standard care but gel was applied to ulcer and covered with standard dressings Sample size [7] 69	Comparator(s) [8] Normal saline. Ulcer dressings were removed every day, ulcers were cleaned with normal saline, covered with dry gauze dressings. Patients also received antibiotic treatment and pentoxyphilline at a dose of 1200 mg/day. Sample size [9] 71

Selection criteria

Inclusion criteria – Diabetic patients with neurotrophic non-healing foot ulcers of Wagner grade 2 or 3 that were referred to the National Medical Centre of Veracruz, from august 1993 to September 1994. All patients required hospital care for surgical debridement, aggressive parenteral antibiotics, foot rest, or correction of fasting hyperglycaemia caused by sepsis.

Exclusion criteria – patients with metabolic instability after discharge (> 160 mg/dl fasting plasma glucose)

Patient characteristics [10]

Intervention group – N = 69, mean age (yrs) 59.7 ± 10.7, gender: 31/69 (44.9%) male, 38/69 (55.1%) female, duration of diabetes (yrs) 23 ± 26.5, smoker 39/69 (56.5%), obesity 20/69 (28.9%), no. of previous amputations 0.5 ± 0.6, Wagner grade 2 44/69 (63.7%), grade 3 25/69 (36.3%), ulcer area (cm^2) 44.75 ± 20.8.

Comparator group(s) – N = 71, mean age (yrs) 60.7 ± 12.1, gender: 28/71 (39.4%) male, 43/71 (60.6%) female, duration of diabetes (yrs) 21.7 ± 9.5, smoker 27/71 (38%), obesity 23/71 (32.3%), no. of previous amputations 0.6 ± 0.7, Wagner grade 2 50/71 (70.4%), grade 3 21/71 (29.6%), ulcer area (cm^2) 39.70 ± 17.9.

Length of follow-up [11] 12 week study duration	Outcome(s) measured [12] % reduction in ulcer area

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Randomised by alternate assignment	Similar baseline characteristics with the exception of smoking status (19% difference).	Patients were blinded to differences in treatment	There was no difference in treatment and measurement between the groups	13% after 2 weeks (n=21)

Overall quality assessment (descriptive) [18] Potential for information bias as there was no blinding of investigators. Study was adequately powered so the results are probably due to intervention. This study was of average quality.

RESULTS

Outcome [19] mean % reduction in ulcer area:	Intervention group [20] area (cm^2)	Intervention group [20] mean %	Control group [21] area (cm^2)	Control group [21] mean %	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
Week 0 (baseline)	44.75 ± 20.8		39.70 ± 17.9			Harms (NNH) [24] (95% CI) [25]
Week 4	29.71 ± 16.8	34.4	31.10 ± 32.9	12.0	$p > 0.05$	
Week 8	16.20 ± 11.1	65.3	23.22 ± 12.3	42.7	$p < 0.001$	
Week 12	6.84 ± 6.5	87.0	15.45 ± 10.4	62.8	$p < 0.001$	
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.				Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] No adverse events detected.

EXTERNAL VALIDITY

Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.

Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits will probably outweigh any harms.

Comments [31] The authors have demonstrated that treatment with 2% Ketanserin ointment improves the rate of healing of diabetic foot ulcers.

STUDY DETAILS		
Reference [1] (Moustafa et al 2007) "Randomized, controlled, single-blind study on use of autologous keratinocytes on a transfer dressing to treat nonhealing diabetic ulcers." Regenerative medicine 2(6): 887-902.		
Affiliation/source of funds [2] Division of Clinical Sciences, School of Medicine, and Diabetes Clinic, Northern General Hospital, Sheffield; Foot Ulcer Trials Unit, Dept. of Diabetes and Endocrinology, City Hospital, Nottingham; Dept. of Diabetes, Leeds General Infirmary, Leeds; Diabetes Clinic, Royal Hallamshire Hospital, Sheffield; The Innovation Centre, CellTran Limited, Sheffield; Dept. of Engineering Materials and School of Biomedical Science and Medicine, The Kroto Research Institute, University of Sheffield, Sheffield; UK. Funded in part by CellTran Limited, Sheffield, UK.		
Study design [3] single-blind RCT	Level of evidence [4] II	Location/setting [5] Multicentre (4 sites), outpatient
Intervention [6] Myskin dressings (medical grade PVC with a plasma polymerised acrylic acid layer was used as a carrier dressing, which was seeded with autologous keratinocytes) plus standard wound care All patients underwent a 4 week lead-in period with standard wound care and optimal off-loading prior to recruitment. A split-thickness skin biopsy (2 x 2 cm; 0.4-0.6 mm thick) was taken (usually from thigh) at -2 weeks. Keratinocytes from skin biopsy were cultured and seeded onto carrier dressing Sample size [7] 9 patients; 11 ulcers	Comparator(s) Placebo Myskin dressing (without seeded keratinocytes) plus standard wound care After debridement and cleaning of ulcer, the Myskin dressings (active or placebo) were applied once per week for 6 weeks, then all patients received active treatment for an additional 6 weeks. Myskin dressing was covered with Lyofoam or Allevyn dressing, semi-compressed felt, and a second layer of Lyofoam or Allevyn, and taped into position. After 4 days the dressings were removed and wound redressed with Lyofoam or Allevyn and semi-compressed felt. Control patients were offered an additional 6 weeks active treatment if ulcers were not healed after the initial 12 week period. Sample size [9] 7 patients; 13 ulcers	
Selection criteria Inclusion criteria – Diabetic patients that attended diabetic outpatient clinics in the Northern General Hospital, Royal Hallamshire Hospital, Leeds General Infirmary, and Nottingham City Hospital. Exclusion criteria –		
Patient characteristics [10] Intervention group – N = 9; withdrew prior to treatment 2/9 (22%); % HbA_{1c}, 10.55 $\pm$ 1.43. Comparator group(s) – N = 7; withdrew prior to treatment 1/7 (14%); withdrew due to infection in week 8 1/7 (14%); % HbA_{1c}, 9.55 $\pm$ 1.24. Provided data on age, diabetes type, % HbA_{1c}, diabetes duration, ulcer site, ulcer duration for each individual patient but no average statistics for each group. N = 16; age 52.4 (24-78); ulcer duration (months) 14 (2-28); type 1 diabetes 10/16 (62.5%); duration (years) 12-34; type 2 diabetes 6/16 (37.5%); duration (years) 0.75-16; % HbA_{1c}, 7-14%; all index ulcers were Wagner grade 1.		
Length of follow-up [11] 12 weeks plus an additional 6 weeks for control patients receiving additional treatment	Outcome(s) measured [12] complete healing, no. improved by >50%, No. ulcers that recurred	

INTERNAL VALIDITY				
Allocation [13] Randomisation method not disclosed	Comparison of study groups [14] Uncertain	Blinding [15] Patients were blinded For first 6 weeks	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] No. patient that withdrew after 8 weeks was excluded.
Overall quality assessment (descriptive) [18] Investigators were not blinded, therefore there is the potential for information bias. Study was not adequately powered and probably did not reach statistical significance due to the small sample size. This study was of average quality.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. ulcer healed	4/7 (57%)	1/5 (20%)	RR = 2.86 [0.64, 17.44]	Harms (NNH) [24] (95% CI) [25]
No. improved by >50%	7/7 (100%)	5/5 (100%)	RR = 1	
No. ulcers that recurred	3/4 (75%)	0/1 (0%)	RR = not calculable	

	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] one patient withdrew from control group after 8 weeks due to infection.		
EXTERNAL VALIDITY		
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.		
Applicability [30] As the treatment provides some benefit, treatment benefits may outweigh any harms.		
Comments [31]. The use of Myskin with autologous cultured keratinocytes shows promising trends for improved clinical outcomes for patients with diabetic foot ulcers by increasing the likelihood of healing for these ulcers, but this did not reach statistical significance due to the small sample size. However, there was a worrying trend showing an increased likelihood of recurrence after Myskin treatment (also not statistically significant).		

STUDY DETAILS		
Reference [1] (Muthukumarasamy et al 1991) "Topical phenytoin in diabetic foot ulcers." Diabetes Care 14(10): 909-911.		
Affiliation/source of funds [2] Dept. of surgery, Madras Medical College, Madras, India. No funding source stated.		
Study design [3] nonrandomised controlled trial	Level of evidence [4] III-2	Location/setting [5] India Inpatient setting
Intervention [6] Topical application of phenytoin powder. Initially all wounds underwent meticulous debridement and were cleaned with saline. Phenytoin powder was then applied in a thin uniform layer and a sterile dry dressing was applied. This was repeated daily. Sample size [7] 50	Comparator(s) [8] Standard treatment. Ulcer was covered with a sterile occlusive dressing, changed daily. Ulcers were assessed at day 0, 7, 14, 21, 28 and 35. Sample size [9] 50	
Selection criteria Inclusion criteria – Non-insulin-dependent diabetic patients with a foot ulcer of Meggit's clinical classification type 1 or 2. Exclusion criteria – Patients with gross cellulitis, deep slough, ischemic gangrene due to major vessel involvement, and trophic ulcers. Severe diabetic patients with ketoacidosis and nephropathy.		
Patient characteristics [10] Groups were matched for age, sex, ulcer area, depth, and chronicity. Intervention group – N = 50, age: 40-50 yrs 12/50 (24%), 51-60 yrs 19/50 (38%), 61-70 yrs 15/50 (30%), 71-80 yrs 4/50 (8%), gender: 27/50 (54%) male, 23/50 (46%) female, Ulcer duration: 3 weeks 2/50 (4%), 4 weeks 7/50 (14%), 5 weeks 4/50 (8%), 6 weeks 10/50 (20%), 7 weeks 8/50 (16%), 8 weeks 9/50 (18%), 9 weeks 5/50 (10%), 10 weeks 5/50 (10%). Size of ulcer: 30 cm^2 18/50 (36%), 31-60 cm^2 13/50 (26%), 61-90 cm^2 11/50 (22%), >90 cm^2 8/50 (16%). Comparator group(s) – N = 50, age: 40-50 yrs 12/50 (24%), 51-60 yrs 19/50 (38%), 61-70 yrs 15/50 (30%), 71-80 yrs 4/50 (8%), gender: 27/50 (54%) male, 23/50 (46%) female, Ulcer duration: 3 weeks 2/50 (4%), 4 weeks 7/50 (14%), 5 weeks 4/50 (8%), 6 weeks 10/50 (20%), 7 weeks 8/50 (16%), 8 weeks 9/50 (18%), 9 weeks 5/50 (10%), 10 weeks 5/50 (10%). Size of ulcer: 30 cm^2 17/50 (34%), 31-60 cm^2 14/50 (28%), 61-90 cm^2 10/50 (20%), >90 cm^2 9/50 (18%).		
Length of follow-up [11] 35 days	Outcome(s) measured [12] No. ulcers healed, No. ulcers improved (with healthy granulation), No. improved or healed at 35 days..	

INTERNAL VALIDITY				
Allocation [13] Nonrandom assignment to match groups	Comparison of study groups [14] Closely matched for baseline characteristics	Blinding [15] None	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, all patients included in analysis.
Overall quality assessment (descriptive) [18] This study could be subject to information bias as there was no blinding. Study was relatively large, suggesting it was probably adequately powered. The results show a clear tendency towards improved healing rates in the intervention group. This study was of average quality.				

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. ulcers healed:				
Day 7	12% (6/50)	4% (2/50)	RR = 3.00 (0.73, 12.80)	
Day 14	14% (7/50)	0% (0/50)	RR = 14.00 (1.47, 141.60)	7.69 (6.76, 35.09)
Day 21	26% (13/50)	20% (10/50)	RR = 1.30 (0.64, 2.68)	
Day 28	32% (16/50)	20% (10/50)	RR = 1.60 (0.82, 3.19)	
Day 35	40% (20/50)	24% (12/50)	RR = 1.67 (0.93, 3.04)	
No. ulcers improved (with healthy granulation):				
Day 7	30% (15/50)	14% (7/50)	RR = 2.14 (0.99, 4.81)	
Day 14	46% (23/50)	20% (10/50)	RR = 2.30 (1.26, 4.33)	3.85 (2.43, 13.05)
Day 21	50% (25/50)	20% (10/50)	RR = 2.50 (1.39, 4.65)	3.33 (2.21, 8.70)
Day 28	48% (24/50)	20% (10/50)	RR = 2.40 (1.33, 4.49)	3.57 (2.31, 10.45)
Day 35	44% (22/50)	26% (13/50)	RR = 1.69 (0.98, 2.98)	
No. improved or healed at 35 days	84% (42/50)	50% (25/50)	RR = 1.68 (1.27, 2.11)	2.94 (2.09, 6.26)

				Harms (NNH) [24] (95% CI) [25]
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] None stated.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As the treatment provides statistically and clinically significant benefit, treatment benefits may outweigh any harms.				
Comments [31] The authors have demonstrated that topical application of phenytoin promotes faster wound healing than standard care alone, even though there was no statistically significant difference in the total number of ulcers completely healed at day 35..				

<table>
<tr><td colspan="5">STUDY DETAILS</td></tr>
<tr><td colspan="5">Reference [1] (Niezgoda et al 2005) "Randomized clinical trial comparing OASIS wound matrix to Regranex gel for diabetic ulcers." Advances in Skin & Wound Care 18(5): 258-266.</td></tr>
<tr><td colspan="5">Affiliation/source of funds [2] Centre for Comprehensive Wound Care and Hyperbaric Oxygen Therapy, St. Luke's Medical Centre, Milwaukee; Dixie Regional Medical Centre Wound Clinic and Foot and Ankle Institute, St. George, UT; Dept. of Surgery and Podiatry Section, Carl T. Hayden VA Medical Centre, Phoenix, AZ. Funded by Cook Biotech Inc., West Lafayette, IN.</td></tr>
<tr><td colspan="2">Study design [3] RCT</td><td colspan="2">Level of evidence [4] II</td><td>Location/setting [5] USA and Canada
Multicentre (9 sites), outpatient setting</td></tr>
<tr><td colspan="2">Intervention [6] OASIS Wound Matrix (acellular collagen-based extracellular matrix derived from pig small intestine submucosa).
At each visit, if still needed, the OASIS was cut slightly larger than the ulcer, placed on the wound bed and moistened with sterile normal saline. A secondary dressing was then applied.
Pressure-relief shoes were provided, although best method of off-loading was at the discretion of the clinician.
Sample size [7] 37</td><td colspan="3">Comparator(s) [8] Regranex Gel (becalpermin or rhPDGF-BB)
Patients were assessed weekly. At each visit, wounds were cleaned and underwent debridement as needed.
The regranex gel was applied daily by patient according to insert, covered with saline-moistened gauze dressing for 12 hours before removing gel with saline and redressing the wound.
Sample size [9] 36
Patients that were not healing after 12 weeks were offered the opportunity to cross-over into other treatment arm. If wound area reduced by 50% in 4 weeks, could continue treatment until healed for up to 8 weeks.</td></tr>
<tr><td colspan="5">Selection criteria
Inclusion criteria – Diabetic patients, at least 18 years of age, with chronic (> 1 month duration), non-healing, full-thickness (University of Texas classification grade 1 A) ulcers, and a viable wound bed with granulation tissue. (limited to 40 patients per site).
Exclusion criteria – exposed bone, tendon or fascia, severs arterial disease, history of radiation therapy to ulcer site, non-diabetic ulcers, corticosteroid or immunosuppressive therapy, malnutrition (albumin < 2,5 g/dl), known allergy to porcine products, known sensitivity to any component of Regranex Gel, religious or cultural objection to using porcine products, uncontrolled diabetes (HbA1c > 12%), previous organ transplant, clinically infected ulcer, cellulitis, osteomyelitis, necrotic or avascular bed, undergoing haemodyalisis, insufficient blood supply to ulcer ($TcPO_2$ < 30 mmHg), active Charcot or sickle cell disease, received treatment with any other investigational drug or device in last 30 days, unable to complywith protocol.</td></tr>
<tr><td colspan="5">Patient characteristics [10]
Intervention group – N = 37; age (yrs) 58 ± 2.3; gender: 23/37 (62%) male; 14/37 (38%) female; type 1 diabetes 18/37 (49%); BMI (kg/m^2) 31.7 ± 7.6; % HbA_{1c} 7.9 ± 1.8; $TcPO_2$ (mmHg) 63.2 ± 3.4; albumin (g/dl) 3.9 ± 0.9; toe-brachial index 1.06 ± 0.07; ulcer size (cm^2) 5.0 ± 1.4 (range 1.0-40.0); plantar location 27/37 (72%); duration: 1-3 months 17/37 (46%); 4-6 months 8/37 (22%); 7-12 months 5/37 (13%); > 12 months 7/37 (19%).
Comparator group(s) – N = 36; age (yrs) 57 ± 1.9; gender: 21/36 (58%) male; 15/36 (42%) female; type 1 diabetes 8/36 (22%); BMI (kg/m^2) 33.4 ± 7.4; % HbA_{1c} 8.8 ± 2.4; $TcPO_2$ (mmHg) 62.7 ± 13.7; albumin (g/dl) 3.8 ± 0.5; toe-brachial index 0.94 ± 0.07; ulcer size (cm^2) 3.2 ± 0.5 (range 1.0-20.0); plantar location 21/36 (58%); duration: 1-3 months 19/36 (53%); 4-6 months 4/36 (11%); 7-12 months 6/36 (17%); > 12 months 7/36 (19%).</td></tr>
<tr><td colspan="2">Length of follow-up [11] 12 week study period, 6-month recurrence follow-up</td><td colspan="3">Outcome(s) measured [12] Complete healing at 12 weeks</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Randomisation via a centralised computer system with a block (size 4) randomisation scheme.</td><td>Comparison of study groups [14]
Similar baseline characteristics with the exception of diabetes type (27% difference), ulcer size (36%), plantar ulcers (14%).</td><td>Blinding [15]
Investigators blinded to block size</td><td>Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups</td><td>Follow-up (ITT) [17]
No, patients that did not complete treatment were excluded from analysis – per protocol.</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18] Potential for information bias as there was no blinding after randomisation. However, it is likely that the results shown in this study are due to the interventions. This study was of aqverage quality.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
</table>

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
Complete healing at 12 weeks:				
All patients	18/37 (49%)	10/36 (28%)	RR = 1.75 (0.96, 3.27)	
Plantar ulcers	14/27 (52%)	3/21 (14%)	RR = 3.63 (1.37, 10.98)	3 (2, 9)
Type 1 diabetes	6/18 (33%)	2/8 (25%)	RR = 1.33 (0.41, 5.36)	
Type 2 diabetes	12/19 (63%)	8/28 (29%)	RR = 2.21 (1.14, 4.07)	3 (2, 17)
Time to healing (days)	67	73	*p* = 0.245	
6-month follow-up:	N = 19	N = 18		
Healed at 12 weeks	8/19 (42%)	6/18 (33%)	RR = 1.26 (0.56, 2.94)	
Remaining healed	6/19 (32%)	4/18 (22%)	RR = 1.42 (0.50, 4.21)	Harms (NNH) [24] (95% CI) [25]
% recurrence	2/8 (25%)	2/6 (33%)	RR = 0.75 (0.16, 3.70) *p* = 0.275	
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] 17 intervention and 10 control patients had an adverse event. These events were typical for a patient population with hard-to-heal diabetic foot ulcers such as: pain/discomfort, limb/skin injury, wound infection, gastrointestinal disorder, respiratory infection, death				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As the treatment provides some benefit, treatment benefits may outweigh any harms.				
Comments [31] The authors have demonstrated that OASIS wound Matrix promotes faster wound healing than Regranex gel, which contains rhPDGF-BB, in patients with either type 2 diabetes or plantar ulcers. There was no significant difference between the 2 treatments overall.				

STUDY DETAILS				
Reference [1] (O'Hare et al 1988) "Aldose reductase inhibition in diabetic neuropathy: clinical and neurophysiological studies of one year's treatment with sorbinil." Diabet Med 5(6): 537-542.				
Affiliation/source of funds [2] Dept. of Medicine, Bristol Royal Infirmary, UK. Funded by Pfizer Ltd.				
Study design [3] double-blind RCT	Level of evidence [4] II	Location/setting [5] UK Outpatient setting		
Intervention [6] Sorbinil tablets, 250 mg daily Initial 2 month run-in period where all patients received placebo tablets. Assessments made at 4, 6 and 8 weeks. Then randomised to take sorbinil tablets or placebo tablet for 12 months. Sample size [7] 21	Comparator(s) [8] Placebo tablets As for intervention group. Sample size [9] 10			
Selection criteria Inclusion criteria – Diabetic patients with the presence of clinically evident diffuse symmetrical peripheral somatic neuropathy of at least 6 months duration. Exclusion criteria – Women of reproductive age not on effective contraception, patients with severs debilitating intercurrent illness,, severs cardiovascular disease, or proteinuria of greater than 1 g/24 h, abnormal liver function, using tricyclics antidepressants, carbamazepine or strong analgesics. Patients with peripheral vascular disease with intermittent claudication or absent foot pulses.				
Patient characteristics [10] N = 31, mean age (yrs) 56 (35-64), gender: 23/31 (74.2%) male, 8/31 (25.8%) female, retinopathy 22/31 (71%), (6/22 – 27% – had proteinuria). Intervention group – N = 21, mean age (yrs) 55.6 ± 8.1, duration of diabetes (yrs) 16.5± 8.7, mean HbA_{1c} (%) 11.4 ± 1.9, median sensory NCV (m/s) 43.6 ± 7.2, peroneal motor NCV (m/s) 36.9 ± 4.3, heart rate variation on single breath (beats/min) 2.7 ± 1.9, tarsal vibration threshold (μm) 23.0 ± 34. No. on: insulin 15/21 (72%), oral hypoglycaemic agents 6/21 (28%). No. with retinopathy 16/21 (76%), proteinuria 4/21 (19%). Comparator group(s) – N = 10, mean age (yrs) 55.6 ± 11.1, duration of diabetes (yrs) 13.3± 8.9, mean HbA_{1c} (%) 11.1 ± 2.0, median sensory NCV (m/s) 45.0 ± 6.8, peroneal motor NCV (m/s) 38.5 ± 6.6, heart rate variation on single breath (beats/min) 1.8 ± 1.3, tarsal vibration threshold (μm) 10.0 ± 18.9. No. on: insulin 6/10 (60%), oral hypoglycaemic agents 4/10 (40%). No. with retinopathy 7/10 (70%), proteinuria 1/10 (10%).				
Length of follow-up [11] 12 months	Outcome(s) measured [12] No. developed ulcers			

INTERNAL VALIDITY				
Allocation [13] In random order, 2/3 receiving sorbinil and 1/3 receiving placebo	Comparison of study groups [14] Similar baseline characteristics with the exception of heart rate variation on single breath (33% difference), tarsal vibration threshold (57%), and insulin use (12%).	Blinding [15] Patients and investigators were blinded	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, those lost to follow-up were included in analysis.
Overall quality assessment (descriptive) [18] The double-blind study design is to minimise bias. However, this is a small study and it may not have been adequately powered. The data presented here do not even show any trends to suggest sorbinil has a positive effect. This study was of average quality.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. developed ulcers	4/21 (19%)	1/10 (10%)	RR = 1.91 (0.33, 12.40) ($p > 0.05$)	Harms (NNH) [24] (95% CI) [25]
	Clinical importance (1-4) [26] The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] 2 patients developed a hypersensitivity reaction (febrile illness with myalgia) within 2 days of treatment with sorbinil, which resolved on cessation of treatment.				

EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with peripheral neuropathy.
Applicability [30] As the treatment does not provide a statistically significant benefit, potential harms will probably outweigh any treatment benefits.
Comments [31] The authors have not demonstrated that the aldose reductase inhibitor, sorbinil, has any therapeutic benefit on neuropathy measures (data not presented here) or on likelihood of developing neuropathic ulcers.

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] (Paul et al 2009) "Maggot debridement therapy with Lucilia cuprina: a comparison with conventional debridement in diabetic foot ulcers." International Wound Journal 6(1): 39-46.</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2] Dept. of Orthopaedic Surgery, Sarawak General Hospital, Sarawak; Dept. of Entomology, Institute for Medical Research, Kuala Lumpur; Institute of Orthopaedics and Traumatology, Hospital Kuala Lumpur, Kuala Lumpur; Rehabilitation Unit, Dept. of Orthopaedics and Traumatology, Hospital University Kebangsaan Malaysia, Kuala Lumpur, Malaysia.</td></tr>
<tr><td colspan="2">Study design [3] non-randomised control trial</td><td colspan="2">Level of evidence [4] III-2</td><td colspan="2">Location/setting [5] Malaysia
Hospital inpatient setting</td></tr>
<tr><td colspan="3">Intervention [6] Maggot (Lucilia cuprina) debridement therapy (MDT).
Maggots were applied directly on the wound with a spatula (10/cm^2 ulcer area), covered with light gauze and then sealed with OpSite. Small fenestrations made to allow drainage of fluid. A gamgee was placed over this to absorb fluid and the entire foot was loosely bandaged with a crepe bandage, which were changed as necessary. A washout of the wound occurred after 48 h using normal saline. Maggots were reapplied if needed. If no change noticed after 3 applications then MDT was abandoned.
Sample size [7] 29 (25 completed therapy)</td><td colspan="3">Comparator(s) [8] Conventional surgical debridement (SD).
All patients were treated with subcutaneous insulin during the treatment period.
Control group wound dressing was performed daily with normal saline only and surgical debridement as indicated.
Ulcers were graded according to University of Texas Medical Branch (UTMB) classification system.
Sample size [9] 30 (29 completed therapy)</td></tr>
<tr><td colspan="6">Selection criteria
Inclusion criteria – Diabetic patients, aged 35-70 years, admitted to the orthopaedics wards in the Kuala Lumpur General Hospital for infected foot ulcers from December 2005 to May 2007 requiring debridement. All patients offered MDT and asked to sign consent form if agreeable.
Exclusion criteria – Gangrenous wounds, necrotising fasciitis, abscesses, ulcers with exposed bone or tendons, profusely bleeding ulcers, ischemic ulcers (ankle-brachial systolic index < 0.75), entomophobia.</td></tr>
<tr><td colspan="6">Patient characteristics [10]
Intervention group – N = 29, mean age (yrs) 56.6 (30.0-75.0), gender: 18/29 (62%) male, 11/29 (38%) female.
N = 25, mean age (yrs) 55.3 (30.0-69.2), peripheral neuropathy 11/25 (44%), antibiotic usage 24/25 (96%), mean serum albumin (g/dl) 35.4 (24.0-44.0), mean white cell count (x 10^9) 10.6 (7.6-17.6), mean HbA_{1c} (%) 10.0 (7.7-13.7), mean blood sugar (mmol/l) 11.1 (6.5-17.3), ankle-brachial systolic index 1.0 (0.81-1.86). UTMB: class 1B 4/25 (10%), class 2B 16/25 (30%), class 3B 5/25 (60%).
Comparator group(s) – N = 30, mean age (yrs) 55.6 (32.0-82.5), gender: 20/30 (66.7%) male, 10/30 (33.3%) female.
N = 29, mean age (yrs) 55.3 (32.0-82.5), peripheral neuropathy 10/29 (34.5%), antibiotic usage 28/29 (96.5%), mean serum albumin (g/dl) 37.4 (24.0-46.0), mean white cell count (x 10^9) 10.8 (7.5-18.0), mean HbA_{1c} (%) 10.8 (8.6-13.7), mean blood sugar (mmol/l) 9.8 (6.5-15.8), ankle-brachial systolic index 1.1 (0.90-1.50). UTMB: class 1B 8/29 (27.6%), class 2B 8/29 (27.6%), class 3B 13/29 (44.8%).</td></tr>
<tr><td colspan="3">Length of follow-up [11] up to 18 months</td><td colspan="3">Outcome(s) measured [12] length of hospital stay, No. amputations, No. healed</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Non-random</td><td>Comparison of study groups [14]
Similar baseline characteristics with the exception of ulcer classes 1B and 3B (11-18% difference).</td><td>Blinding [15]
None</td><td colspan="2">Treatment/ measurement bias [16]
Different wound outcome scoring systems for intervention and control groups.
MDT: 1A – 4, all categories included
Control (SD): 1A, 3A-B, 4 categories only.
Healed 1A: suitable for split-skin graft (SSG), flap coverage or self-healing
Healed 1B: Debridement + SSG/Flap coverage at same setting
Healed 1C: Assisted debridement to remove necrotic tendons or exposed bone.
Unhealed 2: SD (MDT abandoned)
Unhealed 3A: Minor amputation (below ankle)
Unhealed 3B: Major amputation (above ankle)
Other 4: patient withdrawal, discontinuation, death, etc</td><td>Follow-up (ITT) [17]
No. patients that did not complete treatment were excluded from analysis</td></tr>
</table>

Overall quality assessment (descriptive) [18] This study may be subject to selection and/or information bias as the method of assignment to a group was not random and there was no blinding. The authors also noted some differences in wound dressings by different staff members. In some cases no live maggots were recovered on wound washout. Suggesting that the wound dressing did not allow adequate seepage of fluid out from the wound. It is also unclear if the study was adequately powered. This study was of average quality.

RESULTS

Outcome [19]	Intervention group [20]		Control group [21]		Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. healed:		ITT		ITT		
Total	56% (14/25)	14/29	62% (18/29)	18/30	RR = 0.90 [0.58, 1.39]	
UTMB class 1B	100% (4/4)		75% (6/8)		RR = 1.33 [0.77, 1.33]	Harms (NNH) [24] (95% CI) [25]
UTMB class 2B	50% (8/16)		50% (4/8)		RR = 1.00 [0.50, 2.54]	
UTMB class 3B	40% (2/5)		61.5% (8/13)		RR = 0.65 [0.18, 1.52]	
No. amputations:						
Total	20% (5/25)	5/29	37.9% (11/29)	11/30	RR = 0.53 [0.21, 1.24]	
Major (above ankle)	4% (1/25)		20.7% (6/29)		RR = 0.19 [0.03, 1.11]	
Minor (below ankle)	16% (4/25)		17.2% (5/29)		RR = 0.93 [0.29, 2.94]	
Length of hospital stay (days) (range)	12.5 (2.0-32.0)		19.8 (3.0-47.0)		*p* = 0.01	
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.				Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] 2 of 29 intervention patients experienced pain. Most patients without neuropathy could feel the maggots crawling during treatment. A few patients experienced the 'yuk' factor.

EXTERNAL VALIDITY

Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.

Applicability [30] As the treatment does not provide any significant benefit over conventional surgical debridement, any harms may outweigh treatment benefits.

Comments [31] The data in this paper shows that debridement using maggots is as effective as surgical debridement; there is no statistical difference between the two groups. It is unknown how the 2 maggot species that have been used for debridement of diabetic foot ulcers (*Lucilia cuprina* and *Lucilia sericata*) compare in effectiveness.

STUDY DETAILS				
Reference [1] (Pollak et al 1997) "A human dermal replacement for the treatment of diabetic foot ulcers." Wounds: A Compendium of Clinical Research & Practice 9(6): 175-183.				
Affiliation/source of funds [2] San Antonio Podiatry associates, San Antonio, TX; University of Pittsburgh, Division of Plastic Surgery, PA; Diabetic Foot and Wound Centre, Denver, CO; Advanced tissue sciences Inc, La Jolla, CA; USA.				
Study design [3] single-blind RCT	Level of evidence [4] II	Location/setting [5] USA Multicentre (20 sites), outpatient setting		
Intervention [6] Dermagraft skin replacement therapy. Patients received same standard wound care as control patients with the addition of an application of Dermagraft at day 0 and then weekly for up to 8 applications. Discovered some patients did not receive Dermagraft that was metabolically active (within therapeutic range). Sample size [7] DG: N = 109 DG-½TR received active product first 2 apps and at least half apps in total, N = 61. DG-ATR received active product for all apps, N = 37.		Comparator(s) [8] Standard wound care with debridement, infection control, ulcer covered with a non-adherent interface, then with saline-soaked gauze to fill ulcer, and secured with an adhesive covering, and off-loading with special shoes and inserts. All patients initially underwent debridement and had standard wound care during screening period til wound was ready for skin graft. Sample size [9] 126		
Selection criteria Inclusion criteria – Diabetic patients with neuropathic full-thickness plantar surface foot ulcers of the forefoot or heel, > 1 cm^2 in size, with adequate perfusion for healing, and diabetes was controlled. Exclusion criteria – ulcers that were showing rapid healing in response to standard wound care or decreased below 1 cm^2 in size during 2-week screening period.				
Patient characteristics [10] Intervention group DG – N = 109; age (yrs) 55.3; Gender: male 80/109 (73%); female 29/109 (27%); insulin dependent 80/109 (73%); % HbA_{1c} 10.8; ankle-arm index 1.1; ulcer area (cm^2) 2.9; ulcer duration (weeks) 44.4. Intervention group DG-½TR – N = 61; age (yrs) 57.1; Gender: male 44/61 (72%); female 17/61 (28%); insulin dependent 43/61 (70%); % HbA_{1c} 10.9; ankle-arm index 1.1; ulcer area (cm^2) 2.9; ulcer duration (weeks) 56.6. Intervention group DG-ATR – N = 37; age (yrs) 57.5; Gender: male 26/37 (70%); female 11/37 (30%); insulin dependent 24/37 (65%); % HbA_{1c} 10.8; ankle-arm index 1.1; ulcer area (cm^2) 3.0; ulcer duration (weeks) 60.7. Comparator group – N = 126; age (yrs) 55.5; Gender: male 91/126 (72%); female 35/126 (28%); insulin dependent 87/109 (69%); % HbA_{1c} 11.6; ankle-arm index 1.1; ulcer area (cm^2) 2.8; ulcer duration (weeks) 46.5.				
Length of follow-up [11] 12 week study period then follow-up to week 32.		Outcome(s) measured [12] complete healing at 12 and 32 weeks, Median time to healing (weeks), Median time to ulcer recurrence (weeks), No. developed an infection (harm)		
INTERNAL VALIDITY				
Allocation [13] Sealed randomisation envelopes	Comparison of study groups [14] Similar baseline characteristics with the exception of ulcer duration (up to 27% difference).	Blinding [15] Patients	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] No. Per protocol – those that completed 12 week study were included?
Overall quality assessment (descriptive) [18] This study is potentially subject to information bias as only patients were blinded. Study was probably adequately powered, the lack of statistical significance for the number of ulcers healed after using Dermagraft skin replacement therapy compared to standard wound care can be explained by loss of biological activity in the graft prior to application. This raises issues about manufacturing quality controls and the appropriate storage of this product prior to use. This was an average quality study.				
RESULTS				
Outcome [19] Complete healing week 12: DG DG-½TR DG-ATR DG-½TR v DG DG-ATR v DG	Intervention group [20] 42/109 (39%) 31/61 (51%) 20/37 (54%)	Control group [21] 40/126 (32%)	Measure of effect/effect size [22] (95% CI) [25] *RR = 1.21 [0.86, 1.72]* RR = 1.60 [1.11, 2.24] RR = 1.70 [1.12, 2.41] p = 0.15 p = 0.12 *Included in meta-analysis by Blozik and Schere (2008)	Benefits (NNT) [23] (95% CI) [25] 5 [3, 24] 4 [3, 23]

Complete healing week 32: DG DG-½TR DG-ATR	 50/87 (58%) 30/52 (58%) 19/32 (59%)	 39/92 (42%)	 RR = 1.36 [1.01, 1.82] RR = 1.36 [0.97, 1.86] RR = 1.40 [0.94, 1.94]	7 [3, 235]
Median time to healing (weeks): Median time to ulcer recurrence (weeks): No. developed an infection (harm)	13 12 29/139 (21%)	28 7 34/142 (24%)	p < 0.05 RR = 0.87 [0.56, 1.35]	Harms (NNH) [24] (95% CI) [25]
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] None reported.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As the treatment provides some benefit, treatment benefits may outweigh any harms.				
Comments [31] The authors have demonstrated that Dermagraft skin replacement therapy promotes faster wound healing than standard wound care, in patients with diabetic foot ulcers.				

STUDY DETAILS

Reference [1] (Purandare & Supe 2007) "Immunomodulatory role of Tinospora cordifolia as an adjuvant in surgical treatment of diabetic foot ulcers: a prospective randomized controlled study." Indian journal of medical sciences 61(6): 347-355.

Affiliation/source of funds [2] Dept. of Surgery, Seth GS Medicqal College and KEM Hospital, Mumbai, India.

Study design [3] double-blind RCT	**Level of evidence** [4] II	**Location/setting** [5] India

Intervention [6]	**Comparator(s)** [8]
The purified and bio-standardised aqueous extract of the creeper *Tinospora cordifolia*. The extract was administered for 1 month. Method of administration (i.e. oral, IV, subcutaneous) is not disclosed. Description of wound treatment suggests that application was not topical. All patients were assessed weekly, until complete healing. **Sample size** [7] 23	Placebo All patients received conventional therapy for diabetes and standard wound care for ulcer, which included: sharp debridement as needed, gentle cleansing with half-strength 1.5% hydrogen peroxide solution and ample amounts of saline, topical antibiotics for superficial infections, oral antibiotics if required, gauze dressings, ambulation minimised, protective foot wear advised. **Sample size** [9] 22

Selection criteria

Inclusion criteria – Diabetic patients, aged over 18, admitted to surgical wards of KEM Hospital, with diabetic foot ulcer, Wagner grade 1 or 2, not less than 4 cm in diameter or or non-healing ulcers on foot with digital, ray or forefoot amputation.

Exclusion criteria – ulcers of any other aetiology, local or systemic disease or therapy that may interfere with wound healing, Wagner grade 3 or 4 ulcers, osteomyelitis.

Patient characteristics [10]

Intervention group – N = 23, mean age (yrs) 56.26 (32.4-80.6), gender: 17/23 (73.9%) males, 6/23 (26.1%) females, duration of diabetes (yrs) 5.95 (0-18), mean duration of ulcer (days) 21.08 (12-35).

Comparator group(s) – N = 22, mean age (yrs) 56.32 (32.4-80.6), gender: 19/22 (86.4%) males, 3/22 (13.6%) females, duration of diabetes (yrs) 8.27 (0-22), mean duration of ulcer (days) 30.36 (21-44).

Length of follow-up [11] 1 month	**Outcome(s) measured** [12] No. ulcers improved, Rate of change of: ulcer area, ulcer perimeter, ulcer depth, change in Pecoraro wound severity score.

INTERNAL VALIDITY

Allocation [13]	**Comparison of study groups** [14]	**Blinding** [15]	**Treatment/ measurement bias** [16]	**Follow-up** (ITT) [17]
Predesigned randomisation schedule.	Similar baseline characteristics (data not provided) with the exception of gender (13% difference), duration of diabetes (28%), and duration of ulcer (31%).	Patients and investigators were blinded	There was no difference in treatment and measurement between the groups	No, 2 patients from the intervention group and 3 patients from the control group that did not complete the study were excluded.

Overall quality assessment (descriptive) [18] The double-blind study design is aimed at minimising bias. However, this is a small study and it may not have been adequately powered. The data presented here show trends that suggest this herbal extract may have a positive effect on ulcer healing. This study was of average quality.

RESULTS

Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/effect size** [22] (95% CI) [25]	**Benefits** (NNT) [23] (95% CI) [25]
No. ulcers improved	73.9% 17/23	59.1% 13/22	RR = 1.25 (0.83, 1.82); p = 0.292	
Rate of change of:				
ulcer area (cm^2/day)	0.149 ± 0.996	-0.069 ± 0.894	p = 0.145	
ulcer perimeter (mm/day)	0.093 ±0.036	-0.073 ± 0.055	p = 0.089	**Harms** (NNH) [24] (95% CI) [25]
Mean difference in ulcer depth (cm)	2.17 ± 1.33	1.36 ±1.31	p = 0.096	
Change in wound severity score.	14.39 ± 8.39	10.59 ± 8.88	p = 0.149	

Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	**Relevance** (1-5) [27] 3. Evidence of an effect on proven surrogate outcomes but for a different intervention.

Any other adverse effects [28] None reported

EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] As the treatment does not provide a statistically significant benefit, any harms may outweigh treatment benefits.
Comments [31] The data in this paper shows a trend towards a faster healing rate in patients given the herbal extract. However, the result was not statistically significant, perhaps a larger study of longer duration may provide a more definitive result.

*Pecoraro wound grading score 0-3 based on: pain, itching, odour, discharge oedema slough, erythema, induration, fibrosis (scored 0-nil, 1-minimal, 2-moderate, 3-severe); granulation tissue (0-uniformly pink, 1-pale, 2-unhealthy, 3-absent

STUDY DETAILS

Reference [1] (Puttirutvong 2004) "Meshed skin graft versus split thickness skin graft in diabetic ulcer coverage." Journal of the Medical Association of Thailand = Chotmaihet thangphaet 87(1): 66-72.

Affiliation/source of funds [2] Surgery Section, Taksin Hospital, Bangkok, Thailand

Study design [3]	Level of evidence [4]	Location/setting [5]
RCT	II	Thailand

Intervention [6]	Comparator(s)
Meshed skin graft Wounds underwent debridement and standard wound care with wet-to-dry saline gauze until they were covered with granulation tissue. Sample size [7] 38	split thickness skin graft Thighs were used as donor site. Post-operative care same for both groups. After skin graft coverage was established, the dressings consisted of non-adhesive gauze, saline-soaked swab, and mild pressure outer layer. Dressings were changed every day Sample size [9] 42

Selection criteria

Inclusion criteria – Diabetic patients with infected ulcers of the lower extremities or feet that attended Taksin Hospital between January 2002 and June 2003. Wounds included deep abscesses, gangrene of the toes or feet, and necrotising fasciitis of the lower legs

Exclusion criteria – none listed.

Patient characteristics [10]

Intervention group – N = 38; age (yrs) 56.84 ± 8.96; size of ulcer (cm^2) 104.24 ± 152.

Comparator group(s) – N = 42; age (yrs) 55.02 ± 10.12; size of ulcer (cm^2) 82.00 ± 73.21.

N = 80; all had controlled FBS 150-200 mg%; hematocrit > 30%; rare bacterial colonisation $<10^5$/g tissue.

Length of follow-up [11]	Outcome(s) measured [12]
6 months	complete healing, time to healing, efficacy of treatment

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Randomisation method not disclosed	No difference in age, 21% difference in ulcer size, other characteristics unknown.	None.	There was no difference in treatment and measurement between the groups	Yes, no loss to follow-up.

Overall quality assessment (descriptive) [18] Patients and Investigators were not blinded, therefore there is the potential for information bias This study was probably adequately powered, and the lack of difference between the groups probably reflects the equivalence of the treatments. This study is of average quality.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. completely healed	38/38 (100%)	42/42 (100%)	RR = 1	Harms (NNH) [24] (95% CI) [25]
Efficacy of treatment score				
Excellent	19/38 (50%)	17/42 (40.5%)	RR = 1.24 [0.76, 1.99]	
Good	12/38 (31.6%)	18/42 (42.9%)	RR = 0.74 [0.41, 1.30]	
Fair	7/38 (18.4%)	5/42 (11.9%)	RR = 1.55 [0.56, 4.37]	
Poor	0/38 (0%)	2/42 (4.8%)	RR = not calculable	
Time to healing (days)	19.84 ± 7.37	20.36 ± 7.21	p = 0.282	
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] A few hypertrophic scars in both groups which subsided within 6 months. Poor drainage and minor infection in split thickness group caused some graft loss and longer time to healing. Also 1 case of recurrent ulcer and 1 of toe contracture in split thickness group.

EXTERNAL VALIDITY

Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] As the treatments both provide some benefit, treatment benefits may outweigh any harms.
Comments [31]. There is no difference in clinical outcomes for patients with diabetic foot ulcers treated with meshed skin grafts or with split thickness skin grafts.

Efficacy of treatment score: Excellent: skin grafts epithelialised or healed 95% within 14 days with a smooth scar; Good: skin grafts epithelialised or healed 95% within 21 days, hypertrophic scar subsided within 6 months; Fair: skin grafts epithelialised or healed 95% within 21 days, prone to abrasion from minor trauma, minor infected wound, obvious hypertrophic scar after 6 months; Poor: skin grafts epithelialised or healed 95% within 28 days, keloid, contracture of toes or joint, recurrent ulcer.

STUDY DETAILS				
Reference [1] (Ramani et al 1993) "Hemorheologic approach in the treatment of diabetic foot ulcers." Angiology 44(8): 623-626.				
Affiliation/source of funds [2] Depts. of Medicine and Surgery, Kasturba Medical College, Manipal, India.				
Study design [3] pseudo-RCT?	**Level of evidence** [4] III-1	**Location/setting** [5] India Hospital inpatients		
Intervention [6] 400 mg pentoxifylline (hemorheologic agent – decreases blood viscosity) orally thrice daily Also received vasodilators and standard care. Patients were instructed not to alter their smoking or exercise habits for the duration of the study. **Sample size** [7] 20	**Comparator(s)** [8] standard care (plus vasodialtors?) **Sample size** [9] 20			
Selection criteria **Inclusion criteria** – Diabetic patients with ischemic diabetic foot ulcers of Wagner grade 2 or more admitted to Kasturba Medical College Hospital, Manipal. **Exclusion criteria** – Neurotrophic ulcers.				
Patient characteristics [10] **Intervention group** – N = 20, mean age (yrs) 59.1, mean duration of diabetes (yrs) 11.5, mean duration of ulcer (days) 59.2, smoking 14/20 (70%), peripheral neuropathy 20/20 (100%), ischemic heart disease 10/20 (50%). Wagner grade 2 2/20 (10%), grade 3 6/20 (30%), grade 4 12/20 (60%), grade 5 0/20 (0%). **Comparator group(s)** – N = 20, mean age (yrs) 61.95, mean duration of diabetes (yrs) 12.5, mean duration of ulcer (days) 39.2, smoking 15/20 (75%), peripheral neuropathy 20/20 (100%), ischemic heart disease 10/20 (50%). Wagner grade 2 2/20 (10%), grade 3 6/20 (30%), grade 4 10/20 (50%), grade 5 2/20 (10%).				
Length of follow-up [11] from 8 to 20 weeks	**Outcome(s) measured** [12] response after 8 weeks, duration of hospital stay, No. amputations: toes, below-knee, above-knee, no. of deaths.			
INTERNAL VALIDITY				
Allocation [13] Unclear if randomised	**Comparison of study groups** [14] Baseline characteristics are similar with the exception of duration of ulcer (34% difference).	**Blinding** [15] None	**Treatment/ measurement bias** [16] There was no difference in treatment and measurement between the groups except if the control group also used vasodilators is unclear	**Follow-up** (ITT) [17] Yes, no loss to follow-up.
Overall quality assessment (descriptive) [18] This study may be subject to selection and/or information bias as the method of assignment to a group was unclear and there was no blinding. Also the small sample size suggests that this study may not have been adequately powered. This study was of average quality.				
RESULTS				

Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/effect size** [22] (95% CI) [25]	**Benefits** (NNT) [23] (95% CI) [25]
Response after 8 weeks	16/20 (80%)	10/20 (50%)	RR = 1.60 (1.01, 2.32) (p = 0.047)	3.33 (1.93, 228.3)
Duration of hospital stay (days)	67 ±30.7	95 ± 66.2	p = 0.09	**Harms** (NNH) [24] (95% CI) [25]
No. amputations:				
Toes	10/20 (50%)	8/20 (40%)	RR = 1.25 (0.63, 2.48)	
Below-knee	0/20 (0%)	3/20 (15%)	RR = 0.00 (0.00, 1.19)	
Above-knee	0/20 (0%)	1/20 (5%)	RR = 0.00 (0.00, 3.78)	
Total	10/20 (50%)	12/20 (60%)	RR = 0.83 (0.48, 1.45)	
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.		**Relevance** (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] One patient had nausea and vomiting while on the pentoxifylline regimen, but continued treatment.

EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with Ischemic Foot Ulcers.
Applicability [30] As the treatment provides some benefit, treatment benefits may outweigh any harms.
Comments [31] The data in this paper shows a trend towards a reduction in major amputation rates when taking pentoxifylline. Thus, this study should be repeated on a larger scale to obtain a more definitive result. The authors also show that there is a significant difference in response after 8 weeks between the 2 groups, but this 'response' has not been clearly defined so it is difficult to assess the validity of this claim.

<table>
<tr><td colspan="5">STUDY DETAILS</td></tr>
<tr><td colspan="5">Reference [1] (Razzak et al 1997) "Local insulin therapy in diabetic foot." JK Practitioner 4(1): 6-8.</td></tr>
<tr><td colspan="5">Affiliation/source of funds [2] Riyadh Central Hospital, Saudi Arabia. Funding source not stated.</td></tr>
<tr><td colspan="2">Study design [3] RCT</td><td colspan="2">Level of evidence [4] II</td><td>Location/setting [5] Saudi Arabia
Hospital inpatients</td></tr>
<tr><td colspan="2">Intervention [6]
Same treatment as control group, except daily dressing with saline soak impregnated with 5-10 units of insulin (depending on size of wound).
Sample size [7] 12</td><td colspan="3">Comparator(s) [8] Standard care
Treatment included antibiotic therapy, control of hyperglycaemia, local surgical treatment (drainage of abscess, wound debridement or local amputation of gangrenous toe). Foot was dressed daily with diluted povidon solution.
Sample size [9] 12</td></tr>
<tr><td colspan="5">Selection criteria
Inclusion criteria – Diabetic patients with foot complications that were admitted to the General Surgery Dept. of Riyadh Central Hospital over a 4 year period (April 1988-1992).
Exclusion criteria – Patients with osteomyelitis or extensive involvement of the foot or distal leg, which required an initial below or above knee amputation.</td></tr>
<tr><td colspan="5">Patient characteristics [10]
Intervention group – N = 12, mean age (yrs) 58.3, mean duration of diabetes (yrs) 16.4, insulin dependent 5/12 (41.7%), mean blood sugar on admission (mmol/l) 17.1, neuropathy 6/12 (50%), distal pulses present 6/12 (50%). Ankle-brachial index < 1 5/12 (41.7%). Type of lesion: ulcer 8/12 (66.7%), abscess 2/12 (16.7%), gangrene 2/12 (16.7%).
Comparator group(s) – N = 12, mean age (yrs) 61.1, mean duration of diabetes (yrs) 8, insulin dependent 2/12 (16.7%), mean blood sugar on admission (mmol/l) 13.8, neuropathy 4/12 (33.3%), distal pulses present 8/12 (66.7%). Ankle-brachial index < 1 5/12 (41.7%). Type of lesion: ulcer 4/12 (33.3%), abscess 7/12 (58.3%), gangrene 3/12 (25%).</td></tr>
<tr><td colspan="2">Length of follow-up [11] from 6 months to 4 years.</td><td colspan="3">Outcome(s) measured [12] Ave. duration of hospital stay.
Mode of healing: granulation, skin graft</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Randomisation method not disclosed</td><td>Comparison of study groups [14]
Similar baseline characteristics with the exception of duration of diabetes (51% difference), insulin use (25%), neuropathy (17%), presence of distal pulses (17%), presence of ulcer (34%).</td><td>Blinding [15]
None</td><td>Treatment/ measurement bias [16]
There was no difference in treatment and measurement between the groups</td><td>Follow-up (ITT) [17]
Yes, no loss to follow-up</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18] This study may be subject to information bias as there was no blinding and may also have been underpowered due to its small size. This study was of average quality.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td rowspan="3">Outcome [19]

Ave. duration of hospital stay (days) (range)
Mode of healing:
granulation
skin graft</td><td>Intervention group [20]

19.6 (15-35)

75% (9/12)
25% (3/12)</td><td>Control group [21]

53.5 (33-71)

66.7% (8/12)
33.3% (4/12)</td><td>Measure of effect/effect size [22] (95% CI) [25]

p < 0.001

RR = 1.13 (0.70, 1.73)
RR = 0.75 (0.22, 2.53)</td><td>Benefits (NNT) [23] (95% CI) [25]

Harms (NNH) [24] (95% CI) [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.</td><td colspan="2">Relevance (1-5) [27] 3. Evidence of an effect on proven surrogate outcomes but for a different intervention.</td></tr>
<tr><td colspan="5">Any other adverse effects [28] None stated</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Applicable to other diabetics with foot complications, not specific for diabetic foot ulcers.</td></tr>
<tr><td colspan="5">Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits may outweigh any harms.</td></tr>
</table>

Comments [31] The authors have demonstrated that topical application of Insulin on diabetic wounds increases the rate of healing and shortens their hospital stay.

<table>
<tr><td colspan="5">STUDY DETAILS</td></tr>
<tr><td colspan="5">Reference [1] (Rerkasem et al 2007) "The development and application of diabetic foot protocol in Chiang Mai University Hospital with an aim to reduce lower extremity amputation in Thai population: a preliminary communication." International Journal of Lower Extremity Wounds 6(1): 18-21.
(Rerkasem et al 2009) "A multidisciplinary diabetic foot protocol at Chiang Mai University Hospital: cost and quality of life." International Journal of Lower Extremity Wounds 8(3): 153-156.</td></tr>
<tr><td colspan="5">Affiliation/source of funds [2] Dept. of surgery, Dept. of Internal Medicine, Dept. of Rehabilitation Medicine, Dept. of Family Medicine, Faculty of Medicine, Faculty of Nursing, Chiang Mai University, Thailand.
Faculty of Medicine and Faculty of Economics, Chiang Mai University, Thailand. Funded by the consortium of Thai medical Schools and the Thai Health Foundation.</td></tr>
<tr><td colspan="2">Study design [3] historical control study</td><td colspan="2">Level of evidence [4] III-3</td><td>Location/setting [5] Thailand
Inpatient hospital records, outpatient survey</td></tr>
<tr><td colspan="3">Rerkasem et al (2007)
Intervention [6] Patients with diabetic foot ulcers attending Chiang Mai University Hospital between August 2005 and July 2006.
In August 2005, a dedicated diabetic foot team (consisting of endocrinologists, a rehabilitation physician, a family doctor, nurses, and plastic and vascular surgeons) was set up and a diabetic foot protocol was developed. Ulcers were assessed for risk category and standardised ulcer assessment and management protocols for each risk group were implemented. Preventative services were provided routinely, including self-care education, palliative foot care, and provision of protective footwear.
Sample size [7] 61
Rerkasem et al (2009)
All patients invited to participate in an interview and fill out a questionnaire
Sample size [7] 56</td><td colspan="2">Comparator(s) [8] Patients with diabetic foot ulcers attending Chiang Mai University Hospital between August 2003 and July 2005.
Prior to August 2005, patients received standard care, such as debridement. There were no detailed guidelines for specific services. Consultations and preventative measures were undertaken at the discretion of the attending physician.
Sample size [9] 110
Rerkasem et al (2009)
All patients invited to participate in an interview and fill out a questionnaire
Sample size [9] 40</td></tr>
<tr><td colspan="5">Selection criteria
Inclusion criteria – Diabetic patients that attended Chiang Mai University Hospital between August 2003 and July 2006 with a foot ulcer needing treatment.
Exclusion criteria – none stated.</td></tr>
<tr><td colspan="5">Patient characteristics [10]
Rerkasem et al (2007)
Intervention group – N = 61; age (yrs) 57.8; males 20/61 (32.8%); hypertension 42/61 (68.9%); history of smoking 26/61 (42.6%); hyperlipidaemia 27/61 (44.3%).
Comparator group(s) – N = 110; age (yrs) 60.6; males 37/110 (33.6%); hypertension 49/110 (44.6%); history of smoking 55/110 (50%); hyperlipidaemia 73/110 (66.4%).
Rerkasem et al (2009)
Intervention group – N = 56; age (yrs) 61.3 ± 1.6; males 24/56 (42.9%); number of outpatient visits 8.0 ± 5.7; mean stay in hospital (days) 7.1 ± 13.5.
Comparator group(s) – N = 40; age (yrs) 62.5 ± 2.1; males 20/40 (50%); number of outpatient visits 3.7 ± 4.0; mean stay in hospital (days) 8.7 ± 12.8.</td></tr>
<tr><td colspan="3">Length of follow-up [11] all patients were contacted by letter or telephone to collect accurate data.</td><td colspan="2">Outcome(s) measured [12] amputation rates, SF-36 quality of life.</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Non-random</td><td>Comparison of study groups [14]
Similar baseline characteristics for age, gender and history of smoking. 24% difference for number of patients with hypertension and 22% difference for those with hyperlipidaemia.</td><td>Blinding [15]
None</td><td>Treatment/ measurement bias [16] Different treatment for different time periods.</td><td>Follow-up (ITT) [17]
Yes, no loss to follow-up</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18] this study is of average quality.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
</table>

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. of minor amputations:				
Toe	2/61 (3.3%)	10/110 (9.1%)	RR = 0.36 [0.09, 1.40]	
Transmetatarsal	0/61 (0%)	4/110 (3.6%)	RR = not calculable	
Syme	0/61 (0%)	1/110 (0.9%)	RR = not calculable	
Total	2/61 (3.3%)	15/110 (13.6%)	RR = 0.24 [0.06, 0.89]	10 [7, 87]
No. of major amputation:				
Below knee	2/61 (3.3%)	12/110 (10.9%)	RR = 0.30 [0.08, 1.14]	
Above knee	0/61 (0%)	3/110 (2.7%)	RR = not calculable	
Total	2/61 (3.3%)	15/110 (13.6%)	RR = 0.24 [0.06, 0.89]	10 [7, 87]
Total no. of all amputations	4/61 (6.6%)	30/110 (27.3%)	RR = 0.24 [0.09, 0.60]	5 [4, 11]
				Harms (NNH) [24] (95% CI) [25]
SF-36 scores:				
1. Physical functioning	37.6 ± 33.9	18.9 ± 23.4	p < 0.01	
2. Physical role limitation	45.1 ± 42.5	27.5 ± 40.4	p = 0.04	
3. Emotional role limitation	57.2 ± 45.7	32.5 ± 43.7	p < 0.01	
Physical health dimension	45.7 ± 23.5	37.0 ± 18.4	p = 0.05	
Total SF-36 score	54.7 ± 21.6	46.0 ± 16.5	p = 0.03	
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] None reported				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As the diabetic foot protocol provides a statistically significant benefit in the reduction of amputation rates compared to standard care, treatment benefits may outweigh any harms.				
Comments [31] The authors have demonstrated that treatment of diabetic foot ulcers with a diabetic foot protocol provides a statistically significant benefit compared to standard care.				

STUDY DETAILS		
Reference [1] Rerkasem, K., N. Kosachunhanun, et al. (2009). "A multidisciplinary diabetic foot protocol at Chiang Mai University Hospital: cost and quality of life." International Journal of Lower Extremity Wounds 8(3): 153-156.		
Affiliation/source of funds [2] Faculty of Medicine and Faculty of Economics, Chiang Mai University, Thailand.		
Study design [3] retrospective cohort	Level of evidence [4] III-3	Location/setting [5] Thailand Inpatient hospital records
Intervention [6] Patients with diabetic foot ulcers attending Chiang Mai University Hospital between August 2005 and July 2006. In August 2005, a dedicated diabetic foot team (consisting of endocrinologists, a rehabilitation physician, a family doctor, nurses, and plastic and vascular surgeons) was set up and a diabetic foot protocol was developed. Ulcers were assessed for risk category and standardised ulcer assessment and management protocols for each risk group were implemented. Preventative services were provided routinely, including self-care education, palliative foot care, and provision of protective footwear. Sample size [7] 61	Comparator(s) [8] Patients with diabetic foot ulcers attending Chiang Mai University Hospital between August 2003 and July 2005. Prior to August 2005, patients received standard care, such as debridement. There were no detailed guidelines for specific services. Consultations and preventative measures were taken at the discretion of the attending physician. Sample size [9] 110	
Selection criteria Inclusion criteria – Diabetic patients that attended Chiang Mai University Hospital between August 2003 and July 2006 with a foot ulcer needing treatment. Exclusion criteria – none stated.		
Patient characteristics [10] Intervention group – N = 61; age (yrs) 57.8; males 20/61 (32.8%); hypertension 42/61 (68.9%); history of smoking 26/61 (42.6%); hyperlipidaemia 27/61 (44.3%). Comparator group(s) – N = 110; age (yrs) 60.6; males 37/110 (33.6%); hypertension 49/110 (44.6%); history of smoking 55/110 (50%); hyperlipidaemia 73/110 (66.4%).		
Length of follow-up [11] all patients were contacted by letter or telephone to collect accurate data.	Outcome(s) measured [12] amputation rates	

INTERNAL VALIDITY				
Allocation [13] Non-random	Comparison of study groups [14] Similar baseline characteristics for age, gender and history of smoking. 24% difference for number of patients with hypertension and 22% difference for those with hyperlipidaemia.	Blinding [15] None	Treatment/ measurement bias [16] Different treatment for different time periods.	Follow-up (ITT) [17] Yes, no loss to follow-up
Overall quality assessment (descriptive) [18]				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. of minor amputations:				
Toe	2/61 (3.3%)	10/110 (9.1%)	RR = 0.36 [0.09, 1.40]	
Transmetatarsal	0/61 (0%)	4/110 (3.6%)	RR = not calculable	
Syme	0/61 (0%)	1/110 (0.9%)	RR = not calculable	
Total	2/61 (3.3%)	15/110 (13.6%)	RR = 0.24 [0.06, 0.89]	10 [7, 87]
No. of major amputation:				
Below knee	2/61 (3.3%)	12/110 (10.9%)	RR = 0.30 [0.08, 1.14]	
Above knee	0/61 (0%)	3/110 (2.7%)	RR = not calculable	
Total	2/61 (3.3%)	15/110 (13.6%)	RR = 0.24 [0.06, 0.89]	10 [7, 87]
Total no. of all amputations	4/61 (6.6%)	30/110 (27.3%)	RR = 0.24 [0.09, 0.60]	5 [4, 11]
				Harms (NNH) [24] (95% CI) [25]

	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] None reported		
EXTERNAL VALIDITY		
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.		
Applicability [30] As the diabetic foot protocol provides a statistically significant benefit in the reduction of amputation rates compared to standard care, treatment benefits may outweigh any harms.		
Comments [31] The authors have demonstrated that treatment of diabetic foot ulcers with a diabetic foot protocol provides a statistically significant benefit compared to standard care.		

STUDY DETAILS				
Reference [1] (Reyzelman et al 2009) "Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study." International Wound Journal 6(3): 196-208.				
Affiliation/source of funds [2] advanced clinical Research, LLC, Castro Valley, CA; Scholl's Centre for Lower Extremity ambulatory Research, Rosalind Franklin University of Medicine and Science, North Chicago, IL; Park ridge Hospital Wound Care Centre, Asheville, NC; Fresno area Podiatry Associates, Fresno, CA; Richmond Foot and ankle centre, Richmond, IN; Foot and ankle Medical centre, Phoenix, AZ; Global Wound Care, Royston, GA; The Whittier Institute for diabetes Research, La Jolla, CA; American Health Network of Indiana, LLC, Carmel, IN; Dept. of surgery, and southern Arizona Linb Salvage Alliance, University of Arizona college of Medicine, Tuscon, AZ; USA. Supported by Wright Medical Technology Inc, Arlington, TN, USA.				
Study design [3] RCT	**Level of evidence** [4] II		**Location/setting** [5] USA. Multicentre (11 sites), outpatient	
Intervention [6] GraftJacket, a human acellular dermal regenerative tissue matrix. Ulcers underwent surgical debridement, the graft was sutured or stapled in place and covered with a silver-based non-adherent dressing. Secondary dressings (hydrogel or moist gauze) were applied routinely until complete epithelialisation or end of study. **Sample size** [7] 46			**Comparator(s)** [8] Moist wound therapy. Consisted of application of alginates, foams, hydrocolloids or hydrogels to ulcer, and dressings were changed daily. Off-loading for all patients with removable cast walker. Antibiotics were prescribed as needed. **Sample size** [9] 39	
Selection criteria **Inclusion criteria** – Diabetic patients, aged over 18 years, with a University of Texas grade 1 or 2 diabetic foot ulcer of 1-25 cm^2, and with no signs of infection, with adequate perfusion to affected limb. **Exclusion criteria** – Poor metabolic control (HbA_{1c} > 12%), serum creatinine > 3.0 mg/dl, sensitivity to gentamycin, cefoxilin, linocmycin, polymyxin B or vancomycin, ulcer probing to bone, wounds treated with growth factors within last 30 days.				
Patient characteristics [10] **Intervention group** – N = 46; age (yrs) 55.4 ± 9.6; BMI (kg/m^2) 33.1 ± 6.7; diabetes type 1 5/46 (10.9%); % HbA_{1c} 8.2 ± 2.0; ulcer duration (weeks) 23.3 ± 22.4; ulcer size (cm^2) 3.6 ± 4.3; ulcer located on toe 15/46 (32.6%); foot 15/46 (32.6%); heel 4/46 (8.7%); other 5/46 (10.9%). **Comparator group(s)** – N = 39; age (yrs) 58.9 ± 11.6; BMI (kg/m^2) 34.6 ± 8.5; diabetes type 1 2/39 (5.1%); % HbA_{1c} 7.6 ± 1.6; ulcer duration (weeks) 22.9 ± 29.8; ulcer size (cm^2) 5.1 ± 4.8; ulcer located on toe 5/39 (12.8%); foot 17/39 (43.6%); heel 8/39 (20.5%); other 3/39 (7.7%).				
Length of follow-up [11] 12 week study period			**Outcome(s) measured** [12] no. of ulcers that healed completely, time to healing. For ulcers that did not heal: no. reduced in size, no increased in size, % healed.	
INTERNAL VALIDITY				
Allocation [13] method not disclosed	**Comparison of study groups** [14] Similar baseline characteristics with the exception of gender (unknown) and ulcer size (29% difference).	**Blinding** [15] None	**Treatment/ measurement bias** [16] There was no difference in treatment and measurement between the groups	**Follow-up** (ITT) [17] Yes, analysis done on number enrolled in trial
Overall quality assessment (descriptive) [18] This study could potentially be subject to information bias as there was no blinding. This study was of average quality.				
RESULTS				
Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/effect size** [22] (95% CI) [25]	**Benefits** (NNT) [23] (95% CI) [25]
No. ulcers completely healed	32/46 (69.6%)	18/39 (46.2%)	OR = 2.67 [1.10, 6.44] RR = 1.51 [1.04, 2.18]	4 [2, 42]
Time to healing (weeks)	5.7 ± 3.5	6.8 ± 3.3	*p* = 0.28	
For ulcers that did not heal:				**Harms** (NNH) [24] 95% CI) [25]
No. reduced in size	12/14 (85.7%)	15/21 (71.4%)	RR = 1.20 [0.83, 1.48]	
No increased in size	0/14 (0%)	5/21 (23.8%)	RR = not calculable	
% reduction in ulcer size	49.1 ± 35.9	47.2 ± 52.0	*p* = 0.91	

	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] 6 adverse events not related to study therapy were reported.		
EXTERNAL VALIDITY		
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.		
Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits may outweigh any harms.		
Comments [31] The authors have demonstrated that treatment of diabetic foot ulcers with GraftJacket regenerative tissue matrix is of marginal statistical ly significant benefit compared to treatment with moist wound therapy..		

STUDY DETAILS		
Reference [1] (Richard et al 1995) "Effect of topical basic fibroblast growth factor on the healing of chronic diabetic neuropathic ulcer of the foot. A pilot, randomized, double-blind, placebo-controlled study." Diabetes Care 18(1): 64-69.		
Affiliation/source of funds [2] Dept. of Dietetics and Diabetology, Centre Medical, Le Grau du Roi; Dept. of endocrinology and Dept. of Medical Information, Lapeyronie University Hospital, Montpellier; Dept. of Internal Medicine and Diabetology, Caremeau University Hospital, Nimes, France. Pharmacia Laboratory, Saint-Quentin, France and Milano, Italy. Funded by Farmitalia Carlo Erba Laboratory, Milano, Italy.		
Study design [3] double-blind RCT	**Level of evidence** [4] II	**Location/setting** [5] France Two-centre inpatient setting (6 weeks) then outpatient
Intervention [6] 50 µg basic fibroblast growth factor (bFGF) reconstituted at 5 µg/ml in saline and sprayed on the ulcer. A volume of 50 µl (containing 500 ng bFGF) was sprayed over 4.15 cm^2 area. One or two sprays per ulcer, depending on size were applied daily for the first 6 weeks or until healed and then twice weekly for another 12 weeks as needed. **Sample size** [7] 9		**Comparator(s)** [8] placebo lyophilate reconstituted in normal saline sprayed on ulcer. Patients received initial intensive insulin treatment to tightly control diabetes before randomisation. After spraying, ulcer were covered with sterile petroleum-impregnated gauze or dry compresses and evaluated weekly. **Sample size** [9] 8
Selection criteria **Inclusion criteria** – Diabetic patients with chronic, non-healing, neuropathic, Wagner grade 1-3 ulcer, of at least 0.5 cm length, on the plantar surface of the foot. **Exclusion criteria** – Significant infection, osteomyelitis, uncontrolled diabetes.		
Patient characteristics [10] **Intervention group** – N = 9, mean age (yrs) 61.9 ± 10.0, gender: 9/9 (100%) male, 0/9 (0%) female, BMI (kg/m^2) 26.4 ± 4.6, duration of diabetes (yrs) 20.9 ± 12.3, fructosamine (mmol/l) 295.1 ± 75.0, HbA_{1c} (%) 7.9 ± 1.7, vibration perception threshold (V) 46.3 ± 6.4. Ulcer: duration (months) 22.4 ± 27.9, largest diameter (mm) 18.0 ± 12.0, Wagner grade 1 2/9 (22.2%), grade 2 4/9 (44.4%), grade 3 3/9 (33.3%). **Comparator group(s)** – N = 8, mean age (yrs) 63.6 ± 7.9, gender: 7/8 (87.5%) male, 1/8 (12.5%) female, BMI (kg/m^2) 29.3 ± 2.6, duration of diabetes (yrs) 18.8 ± 9.5, fructosamine (mmol/l) 284.4 ± 42.2, HbA_{1c} (%) 7.1 ± 1.7, vibration perception threshold (V) 37.3 ± 14.9. Ulcer: duration (months) 27.9 ± 42.2, largest diameter (mm) 18.1 ± 6.2, Wagner grade 1 1/8 (12.5%), grade 2 4/8 (50%), grade 3 3/8 (37.5%).		
Length of follow-up [11] 18 week study duration		**Outcome(s) measured** [12] No. ulcers healed, No. ulcers improved, % reduction of ulcer perimeter, % reduction of ulcer area, time to healing, time to 50% healing.

INTERNAL VALIDITY				
Allocation [13] Randomisation method not disclosed	**Comparison of study groups** [14] Similar baseline characteristics with the exception of gender (13% difference).	**Blinding** [15] Patients and investigators were blinded	**Treatment/ measurement bias** [16] There was no difference in treatment and measurement between the groups	**Follow-up** (ITT) [17] Yes, analysis done on number enrolled in trial
Overall quality assessment (descriptive) [18] The double-blind study design is intended to minimise bias. However, this study was very small and was unlikely to be adequately powered. This study should be repeated to ensure that the results reflect the effectiveness of the intervention. This study was of average quality.				

RESULTS				
Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/effect size** [22] (95% CI) [25]	**Benefits** (NNT) [23] (95% CI) [25]
No. ulcers healed	3/9 (33.3%)	5/8 (62.5%)	RR = 0.53 (0.20, 1.47)	
No. ulcers improved	5/9 (55.5%)	6/8 (75.0%)	RR = 0.74 (0.44, 1.47)	**Harms** (NNH) [24] (95% CI) [25]
% reduction of ulcer perimeter	35.8 ± 49.6	47.2 ± 36.4	$p = 0.6$	
% reduction of ulcer area	59.3 ±44.5	75.0 ± 39.1	$p = 0.45$	
Time to healing (weeks)	87.7 ± 38.0	64.8 ± 29.5	$p = 0.19$	
Time to 50% healing (weeks)	9.3 ± 2.1	5.8 ± 0.4	$p = 0.0003$	

	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] Observed no clinical drug-related adverse events or abnormalities in haematological and biochemical data.		
EXTERNAL VALIDITY		
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.		
Applicability [30] As the treatment does not provide a statistically significant benefit, any harms may outweigh treatment benefits.		
Comments [31] The authors have not demonstrated any clinical benefit to using bFGF on diabetic foot ulcers.		

STUDY DETAILS				
Reference [1] (Robson et al 2002) "Effects of transforming growth factor β2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial." Journal of Applied Research 2(2): 133-145.				
Affiliation/source of funds [2] Genzyme Tissue Repair, Genzyme Corporation, Framingham MA				
Study design [3] double-blind RCT	Level of evidence [4] II	Location/setting [5] USA Multi-centre (15 centres)		
Intervention [6] Topical collagen sponges containing rhTGF-β2 at (3) 0.05, (4) 0.5 or (5) 5 µg/cm2, respectively. Patient also received standardised care. Dressings and sponges were changed twice per week. Wounds were monitored during weekly clinic visits. Sample size [7] (3) n=43, (4) n=44, (5) n=44	Comparator(s) [8] (1) standardised care (non-blinded), Sharp debridement, coverage with non-adherent dressing, and weight off-loading. (2) topical placebo collagen sponge (double-blinded). Sample size [9] (1) n=24, (2) n=22)			
Selection criteria Inclusion criteria – diabetic patients over 18 years with a neuropathic full thickness ulcer, without exposed bones or tendons) present for at least 8 weeks on the plantar surface of the foot and an area of 1-20 cm^2 after debridement, adequate peripheral arterial circulation. Exclusion criteria – radiographically documented osteomyelitis, clinical infection of ulcer, use of systemic steroids in previous 30 days, HbA_{1c} > 13%, serum creatininie > 2.5 mg/dl or serum albumin < 2mg/dl.				
Patient characteristics [10] Intervention group (3) 0.05 µg/cm^2 rhTGF– N = 43, mean age (yrs) 56 ± 11, gender: 33/43 (77%) male, 10/43 (23%) female, height (cm) 177 ± 10, weight (kg) 99 ± 26, Caucasian 29/43 (67%), Hispanic 9/43 (21%), African American 5/43 (12%), current smoker 10/43 (23%), duration of ulcer (weeks) 51.0 ± 64, ulcer area (cm^2) 2.1 ± 3.1. Intervention group (4) 0.5 µg/cm^2 rhTGF– N = 44, mean age (yrs) 56 ± 12, gender: 34/44 (77%) male, 10/44 (23%) female, height (cm) 176 ± 10, weight (kg) 100 ± 26, Caucasian 34/44 (77%), Hispanic 6/44 (14%), African American 4/44 (9%), current smoker 3/44 (7%), duration of ulcer (weeks) 59.0 ± 74, ulcer area (cm^2) 2.7 ± 3.6. Intervention group (5) 5 µg/cm^2 rhTGF – N = 44, mean age (yrs) 56 ± 8, gender: 34/44 (77%) male, 10/44 (23%) female, height (cm) 178 ± 12, weight (kg) 102 ± 32, Caucasian 32/44 (73%), Hispanic 10/44 (23%), African American 2/44 (5%), current smoker 10/44 (23%), duration of ulcer (weeks) 54.0 ± 72, ulcer area (cm^2) 2.7 ± 3.5. Comparator group (2) Placebo – N = 22, mean age (yrs) 60 ± 10, gender: 18/22 (82%) male, 4/22 (18%) female, height (cm) 180 ± 10, weight (kg) 96 ± 15, Caucasian 18/22 (82%), Hispanic 4/22 (18%), African American 0/22 (0%), current smoker 2/22 (9%), duration of ulcer (weeks) 41.0 ± 47, ulcer area (cm^2) 2.7 ± 3.0. Comparator group (1) Standard care only – N = 24, mean age (yrs) 55 ± 9, gender: 22/24 (92%) male, 2/24 (8%) female, height (cm) 182 ± 6, weight (kg) 104 ± 21, Caucasian 21/24 (88%), Hispanic 2/24 (8%), African American 1/24 (4%), current smoker 4/24 (17%), duration of ulcer (weeks) 59.0 ± 103, ulcer area (cm^2) 2.1 ± 1.9.				
Length of follow-up [11]20 week treatment period, monthly visits for up to 3 months	Outcome(s) measured [12] closure of wound by week 21, % wound area reduction by week 21. Time to wound closure.			
INTERNAL VALIDITY				
Allocation [13] Computer generated randomisation lists	Comparison of study groups [14] Similar baseline characteristics with the exception of gender (10-15% differences), Caucasian (10-21%),smoking status (10-14%), duration of ulcer (20-30%), ulcer size (22%).	Blinding [15] Double-blind for 4 groups. Comparator group could not be blinded as did not receive sponge.	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, analysis done on number enrolled in trial
Overall quality assessment (descriptive) [18] This is quite a large study so should be adequately powered. I find the results to be sufficiently reliable to find that there is some benefit in using rhTGF-β2 gel to reduce the healing time of diabetic foot ulcers. Study was of good quality.				

<table>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td>Outcome [19]</td><td colspan="3">Intervention group [20]
0.05 | 0.5 | 5µg/cm²</td><td colspan="2">Control grp [21]
placebo | st. care</td><td>Measure of effect/effect size [22] (95% CI) [25]</td><td>Benefits (NNT) 95% CI [23,25]</td></tr>
<tr><td>Complete wound closure by week 21</td><td colspan="3">25/43 (58%) p = 0.046 | 25/44 (57%) 0.056 | 27/44 (61%) 0.025</td><td colspan="2">7/22 (32%) | 17/24 (71%) p = 0.009</td><td>rhTGF-β2 vs placebo
RR (0.05) = 1.83 (1.01, 3.64)
RR(0.5) = 1.79 (0.99, 3.57)
RR(5) = 1.93 (1.08, 3.8)

RR (SCvsP)= 2.23(1.22,4.01)</td><td>3.8 (2.1, 156.5)
4.0 (2.2, ∞)
3.4 (2.0, 25.2)

2.6 (1.6, 9.8)</td></tr>
<tr><td></td><td colspan="3"></td><td colspan="2"></td><td>rhTGF-β2 vs standard care
RR (0.05) = 0.82 (0.61, 1.21)
RR(0.5) = 0.80 (0.59, 1.19)
RR(5) = 0.87 (0.65, 1.26)</td><td>Harms (NNH) [24]
95% CI [25]</td></tr>
<tr><td>% mean wound area reduction by week 21</td><td colspan="3">83±32 p = 0.065 | 80±36 0.116 | 85±28 0.041</td><td colspan="2">74±36 | 79±38 p = 0.047</td><td></td><td></td></tr>
<tr><td>Median time to wound closure (wk)</td><td colspan="3">16 p = 0.133 | 12 0.085 | 13 0.030</td><td colspan="2">N/A | 9 p = 0.009</td><td></td><td></td></tr>
<tr><td></td><td colspan="4">Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.</td><td colspan="2">Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.</td></tr>
<tr><td colspan="6">Any other adverse effects [28] most common causes: infection, skin ulcer, pain, cellulitis, peripheral oedema, vesiculobullous rash and pharyngitis.</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.</td></tr>
<tr><td colspan="6">Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits may outweigh any harms.</td></tr>
<tr><td colspan="6">Comments [31] The authors have demonstrated that the application of rhTGF-β2 improves the healing rates of diabetic foot ulcers compared to the placebo. However, there is no significant difference between the interventions groups and standard care group. The</td></tr>
</table>

STUDY DETAILS

Reference [1] (Roeckl-Wiedmann et al 2005) "Systematic review of hyperbaric oxygen in the management of chronic wounds." Br J Surg 92(1): 24-32.

Affiliation/source of funds [2] First published as a Cochrane Review.

Study design [3]	Level of evidence [4]	Location/setting [5]
Systematic Review	I	Germany

Intervention [6] hyperbaric oxygen therapy (HBOT)	Sample size [7]	Comparator(s) [8]	Sample size [9]
(1) Doctor et al, 1992. *J Postgrad Med* 38(3): 112-4, 111.		Doctor et al, 1992	
Multi-disciplinary wound care plus HBOT 4 times, 45 min, 3 ATA	15/30	Multi-disciplinary wound care	15/30
(2) Faglia et al, 1996. *Diabetes Care* 19(12): 1338-1343		Faglia et al, 1996	
Multi-disciplinary wound care plus HBOT 30 times, 90 min, 2.5 ATA	36/70	Multi-disciplinary wound care	34/70
(3) Kessler et al, 2003. *Diabetes Care* 26(8): 2378-82.		Kessler et al, 2003	
Multi-disciplinary wound care plus HBOT 20 times, 90 min, 2.5 ATA	14/28	Multi-disciplinary wound care	13/28
(4) Abidia et al, 2003. *Eur J Vasc Surg* 25(6): 513-518.		Abidia et al, 2003	
Multi-disciplinary wound clinic plus HBOT 30 times, 90 min, 2.4 ATA	9/18	Multi-disciplinary wound clinic plus sham (air)	9/18
	Total 74		Total 71

Selection criteria

Inclusion criteria – RCTs that compared the effect of HBOT with no HBOT or sham therapy on air for chronic wound healing, where allocation to treatment was random, chronic wounds associated with diabetes mellitus, venous or arterial disease, or external pressure.

Exclusion criteria –

Patient characteristics [10]

Intervention/Comparator groups –

Doctor et al, 1992	any diabetic with foot lesion
Faglia et al, 1996	> 3 months, Wagner grade 2-4, signs of neuropathy similar in both groups
Kessler et al, 2003	> 3 months, Wagner grade 1-3, signs of neuropathy in all patients
Abidia et al, 2003	> 6 weeks, ischemic, 1-10 mm diameter

Length of follow-up [11]	Outcome(s) measured [12]
	Proportion healed within 2 weeks of treatment, major amputations at discharge, after 7 weeks and after 1 year, minor amputations after discharge and after 1 year.

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]		Jadad score	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
		Abidia et al, 2003	blinded all participants	5		
		Doctor et al, 1992	unblinded	2		
		Faglia et al, 1996	unblinded	2		
		Kessler et al, 2003	unblinded	2		

Overall quality assessment (descriptive) [18] The meta-analysis in this review is quite small as only 4 studies with outcomes of interest to this review could be compared, with no more than three studies examining any one outcome. The combined results of the 3 studies for decrease in major amputation rate after HBOT were statistically significant. Good.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
Proportion healed within 2 weeks of treatment *n* = 46 (studies 3, 4)	7/24 (29%)	1/22 (5%)	RR = 4.78 (0.94, 24.24)	(major amputations)
Major amputations at discharge, after 7 weeks and after 1 year *n* = 118 (studies 1, 2, 4)	6/60 (10%)	19/58 (33%)	RR = 0.31 (0.13, 0.71)	NNT = 4 (3, 11)
Minor amputations after discharge and after 1 year *n* = 48 (studies 1, 4)	5/24 (21%)	2/24 (8%)	RR = 2.20 (0.56, 8.72)	Harms (NNH) [24] (95% CI) [25]

Clinical importance (1-4) [26] Major amputations: 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention. Proportion healed: 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects. Minor amputations: 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] Abidia et al, 2003 and Doctor et al, 1992 reported that there were no adverse events Faglia et al, 1996 and Kessler et al, 2003 reported 2 instances of aural barotraumas, 1 causing withdrawal from treatment	
EXTERNAL VALIDITY	
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.	
Applicability [30] As the treatment shows a trend towards improving the healing time of diabetic foot ulcers and shows a statistically significant reduction in the major amputation rate, treatment benefits should outweigh any harms.	
Comments [31] This systematic review indicates that there are definite benefits for limb salvage from HBOT and also shows a trend suggesting that ulcers subjected to HBOT heal completely at a quicker rate than with standard wound care alone.	

STUDY DETAILS		
Reference [1] (Rullan et al 2008) "Treatment of chronic diabetic foot ulcers with bemiparin: a randomized, triple-blind, placebo-controlled, clinical trial." Diabetic Medicine 25(9): 1090-1095.		
Affiliation/source of funds [2] Pollenca Primary Care Centre, Ib-Salut, Health Science Research University Institute, Illes Balears University, Primary Care Research Unit and Endocronology Unit, Hospital Son Llatzer Foundation, Son Ferriol, Mallorca, Spain. This study was funded by the Primary Health Care Management of Mallorca (Ib-Salut), Carlos III Health Institute, Ministry of Health, Public Health Research Fund and Laboratorios Farmaceuticos Rovi, SA, Spain.		
Study design [3] triple-blind RCT	Level of evidence [4] II	Location/setting [5] Mallorca, Spain Multicentre (39 primary care centres) outpatient setting
Intervention [6] Syringe of bemiparin (low molecular weight heparin) 3500 or 2500 IU in 0.2 ml water. Bemiparin was administered by subcutaneous injection at a dose of 3500 IU/day for the first 10 days, followed by 2500 IU/day for 3 months. Sample size [7] 37		Comparator(s) [8] Identical placebo-filled syringe. All patients received standard outpatient care including debridement, wet and dry dressings with saline or hydrogel, and oral antibiotics at signs of infedtion. Patients were visited 9 times in the 3 month study duration Sample size [9] 33
Selection criteria Inclusion criteria – Diabetic patients, aged > 18 years, with diabetes for at least 3 years and with a foot ulcer persisting for > 3 months between June 2001 and April 2003. Gave informed consent. Exclusion criteria – clinical signs of infection unresponsive to oral antibiotics, anti-coagulant therapy at time of inclusion, renal of hepatic impairment, bleeding disorders, proliferative retinopathy, terminal illness with life expectancy of < 3 months.		
Patient characteristics [10] Intervention group – N = 37, mean age (yrs) 61.5 ± 9.3, gender: 25/37 (67.6%) male, 12/37 (32.4%) female, BMI (kg/m^2) 31.7 ± 5.7, duration of diabetes (yrs) 16 (2-38), type I diabetes 9/37 (24.3%), insulin therapy 18/37 (48.6%),glucose (mmol/l) 11.5 ± 4.8, HbA_{1c} (%) 7.9 ± 1.6, ankle-brachial index 0.88 ± 0.27, smoker 12/37 (32.4%), hypertension 23/37 (62.2%), dislipidaemia 11/37 (29.7%), chronic venous insufficiency 14/37 (37.8%), ischemic heart disease 4/37 (10.8%), cerebrovascular disease 3/37 (8.1%), heart failure 3/37 (8.1%), previous peripheral revascularisation 7/37 (18.9%), intermittent claudication 12/37 (32.4%), previous amputation 12/37 (32.4%), sign of infection 1/37 (2.7%), Wagner grade 1 23/37 (62.2%), grade 2 14/37 (37.8%), ulcer area (mm^2) 163 (8-1954). Comparator group(s) – N = 33, mean age (yrs) 67.8 ± 13.4, gender: 22/33 (66.7%) male, 11/33 (33.3%) female, BMI (kg/m^2) 29.7 ± 4.1, duration of diabetes (yrs) 10 (3-42), type I diabetes 11/33 (33.3%), insulin therapy 17/33 (51.5%),glucose (mmol/l) 8.6 ± 3.6, HbA_{1c} (%) 7.3 ± 2.7, ankle-brachial index 0.88 ± 0.25, smoker 4/33 (12.1%), hypertension 18/337 (54.5%), dislipidaemia 9/33 (27.3%), chronic venous insufficiency 5/33 (15.2%), ischemic heart disease 4/33 (12.1%), cerebrovascular disease 5/33 (15.2%), heart failure 6/33 (18.2%), previous peripheral revascularisation 3/33 (9.1%), intermittent claudication 8/33 (24.2%), previous amputation 13/33 (39.4%), sign of infection 3/33 (9.1%), Wagner grade 1 28/33 (84.8%), grade 2 5/33 (15.2%), ulcer area (mm^2) 157 (7-4837).		
Length of follow-up [11] 3 month study duration plus 9-month follow-up visit	Outcome(s) measured [12] Ulcer improvement (*defined as > 50% reduction in area or decrease in Wagner ulcer grade at 3 months), complete healing.	

INTERNAL VALIDITY				
Allocation [13] Central computer-generated randomisation scheme balanced by blocks of 4 numbers	Comparison of study groups [14] Similar baseline characteristics with the exception of duration of diabetes (37% difference), glucose level (25%), smoking status (20%), chronic venous insufficiency (22%), ulcer grade (23%).	Blinding [15] Blinded for patients, investigators and statisticians.	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, those that discontinued treatment were included in the final analysis
Overall quality assessment (descriptive) [18] This study seems adequately powered, and was designed to minimise bias. Therefore, the data presented in this paper are probably reflective of the differences between the intervention and control treatments. This study was of a good quality.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. completely healed	13/37 (35.1%)	11/33 (33.3%)	RR = 1.05 (0.56, 2.03),	
-Wagner grade 1	6/23 (26.1%)	11/28 (39.3%)	RR = 0.66 (0.29, 1.46)	
-Wagner grade 2	7/14 (50%)	0/5 (0%)	RR = 5.00 (0.78, 49.90)	

No. ulcer improved*	26/37 (70.3%)	15/33 (45.5%)	RR = 1.55 (1.03, 2.31), *p* = 0.035	4.03 (2.21, 59.01)
-Wagner grade 1	14/23 (60.9%)	13/28 (46.4%)	RR = 1.31 (0.78, 2.12)	
-Wagner grade 2	12/14 (85.7%)	2/5 (40%)	RR = 2.14 (1.01, 5.75), *p* = 0.046	2.19 (1.29, 167.46)
No. ulcer area decreased > 50%	21/37 (56.8%)	14/33 (42.4%)	RR = 1.34 (0.84, 2.17)	
No. ulcer decreased Grade	17/37 (46.0%)	13/33 (39.4%)	RR = 1.17 (0.68, 2.03)	Harms (NNH) [24] (95% CI) [25]
No. completely healed at 9 month follow-up 50/70 (71.4% of patients)	19/37 (51.4%)	12/33 (36.4%)	RR = 1.41 (0.83, 2.45)	
Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.			Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] There was one bleeding event in each group. One minor conjunctival haemorrhage in the bemiparin group and one major post-procedure bleeding episode in the placebo group. There were no other adverse events related to study medication. There were no cases of thrombocytopenia or osteoporosis, and it did not alter the activated partial thromboplastin time.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] There were no reported harms. As the treatment provides some benefit, treatment benefits may outweigh any harms.				
Comments [31]] The authors have demonstrated that administering bemiparin improves the healing rate of diabetic foot ulcers a little, especially Wagner grade 2 ulcers, but not sufficiently to affect the total number of ulcers that healed completely during the 3 month study.				

STUDY DETAILS				
Reference [1] (Sabolinski & Veves 2000) "Graftskin (APLIGRAF) in neuropathic diabetic foot ulcers." Wounds: A Compendium of Clinical Research & Practice 12(5): 33A-36.				
Affiliation/source of funds [2] Organogenesis Inc., Canton, and Joslin Beth Israel Deaconess Foot Centre and Harvard Medical School, Boston, Massachusetts.				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] USA Foot Centre in Boston, Massachusetts		
Intervention [6] Diabetic patients with ulcers were subjected to aggressive debridement followed by standard wound care (according to the American Diabetes Association): including woven gauze dressings kept moist by saline and changed twice per day for one week. If not responding adequately to treatment, patients are randomised into intervention group to receive Graftskin treatment once a week for up to 5 applications. Sample size [7] 16	Comparator(s) [8] Diabetic patients with ulcers were subjected to aggressive debridement followed by standard wound care (according to the American Diabetes Association): including woven gauze dressings kept moist by saline and changed twice per day for one week. If not responding adequately to treatment, patients are randomised into control group to continue to receive standard wound care. Sample size [9] 17			
Selection criteria Inclusion criteria – Diabetic patients with ulcers that were subjected to aggressive debridement followed by standard wound care (according to the American Diabetes Association for one week and did not respond adequately to treatment. Exclusion criteria – Diabetic patients that did respond adequately to the standard wound care treatment.				
Patient characteristics [10] Unknown. Authors did not provide the data. All participants were diabetic patients that attended the Foot Centre and had an ulcer for at least 2 weeks prior to the start of the study that did not respond adequately to the standard wound care treatment during the one-week screening phase. Intervention group – Comparator group(s) –				
Length of follow-up [11] up to 12 weeks	Outcome(s) measured [12] time to healing, complete healing			
INTERNAL VALIDITY				
Allocation [13] Method of randomisation not disclosed	Comparison of study groups [14] All had non-responding ulcers	Blinding [15] none	Treatment/ measurement bias [16] Unlikely to be a bias due to differences in diagnosis of endpoint (complete healing)	Follow-up (ITT) [17] Yes: no withdrawals from trial.
Overall quality assessment (descriptive) [18] This paper provides little detail on basic characteristics of the patients or their ulcers. Assuming that there are no significant differences between the intervention and control groups due to effective randomisation, I find the results to be reliable. Even though it is a small study, a statistically significant result was achieved. Poor.				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] (95% CI) [25]
Median time to healing (days)	38.5	91	p = 0.01	2.96 (1.69, 1195.88)
Healed within 12 weeks	12/16 (75%)	7/17 (41%)	RR = 1.82 (1.00, 3.04)	Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] None				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] There were no reported harms. As the treatment provides a statistically significant benefit, treatment benefits will outweigh any harms.				

Comments [31] The basic characteristics of the patients that participated in this study were very poorly described. It is unclear if the study was adequately powered, the RR healing results may have been more clearly statistically significant with a larger sample size.

<table>
<tr><td colspan="5">STUDY DETAILS</td></tr>
<tr><td colspan="5">Reference [1] (Saldalamacchia et al 2004) "A controlled study of the use of autologous platelet gel for the treatment of diabetic foot ulcers." Nutrition, metabolism, and cardiovascular diseases : NMCD 14(6): 395-6.</td></tr>
<tr><td colspan="5">Affiliation/source of funds [2] Dept. of clinical and Experimental medicine, and Immunochematologu and Transfusional Centre Dept., “Frederico II” Universoty of Naples; XI Dept. of General Medicine, Diabetes Unit, ‘Cardarelli” Hospital, Naples, Italy. No funding source stated.</td></tr>
<tr><td colspan="2">Study design [3] RCT</td><td colspan="2">Level of evidence [4] II</td><td>Location/setting [5] Italy
Cardarelli Hospital, Naples</td></tr>
<tr><td colspan="3">Intervention [6] Standard care plus weekly topical applications of autologous platelet gel for 5 weeks
Sample size [7] 7</td><td colspan="2">Comparator(s) [8] Standard care

Sample size [9] 7</td></tr>
<tr><td colspan="5">Selection criteria
Inclusion criteria – Diabetic patients with Wagner grade II or III ulcers, of at least 8 week duration and with no sign of infection.
Exclusion criteria – Infected ulcer.</td></tr>
<tr><td colspan="5">Patient characteristics [10]
Intervention group – N = 7, mean age 61.1 ± 9.4, male 57.1%, duration of diabetes (yrs) 16.3 ± 7.9, HbA_{1c} (%) 9.5 ± 1.7, ankle brachial index 0.95 ± 0.18, wound surface area (mm^2) 273 ± 156.
Comparator group(s) – N = 7, mean age 58.1 ± 7.8, male 28.6%, duration of diabetes (yrs) 19.7 ± 9.9, HbA_{1c} (%) 8.8 ± 1.7, ankle brachial index 1.02 ± 0.10, wound surface area (mm^2) 170 ± 89.</td></tr>
<tr><td colspan="3">Length of follow-up [11] 5 weeks</td><td colspan="2">Outcome(s) measured [12] % reduction in wound area, 50-100% healing</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Random, stratified by ankle-brachial pressure index.</td><td>Comparison of study groups [14]
Similar baseline characteristics</td><td>Blinding [15]
Assessors of wound area were blinded.</td><td>Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups.</td><td>Follow-up (ITT) [17]
Yes. All patients included in final analysis.</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18] This is a very small study and is most likely underpowered. The results are indicative of a beneficial effect with using intervention but needs larger study to confirm results. Average.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td>Outcome [19]

% reduction in wound area
50-100% healing</td><td>Intervention group [20]

71.9 ± 22.5

5/7 (71.4%)</td><td>Control group [21]

9.2 ± 67.8

2/7 (28.6%)</td><td>Measure of effect/effect size [22] (95% CI) [25]

p = 0.039

p = 0.286
RR = 2.5 (0.83, 7.53)</td><td>Benefits (NNT) [23]

95% CI [25]

Harms (NNH) [24]

95% CI [25]</td></tr>
<tr><td></td><td colspan="2">Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.</td><td colspan="2">Relevance (1-5) [27] 2. Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention.</td></tr>
<tr><td colspan="5">Any other adverse effects [28] None reported</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.</td></tr>
<tr><td colspan="5">Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits may probably outweigh any harms but safety was not assessed to confirm this.</td></tr>
<tr><td colspan="5">Comments [31] The authors have demonstrated that the application of autologous platelet gel increases rate of healing for diabetic foot ulcers. However, not all measures of healing differences were statistically significant, probably because this study was very small and probably is underpowered.</td></tr>
</table>

STUDY DETAILS

Reference [1] (Sert et al 2008) "Effects of iloprost (a prostacyclin analogue) on the endothelial dysfunction and foot ulcers in diabetic patients with peripheral arterial disease." International Journal of and Metabolism 16(1): 7-11.

Affiliation/source of funds [2] Faculty of Medicine Dept. Of Internal Medicine, Division of Endocrinology, and Dept. of Radiology, Cukurova University, Adana, Turkey. No funding source stated.

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Turkey Hospitalised at University clinic

Intervention [6] Were administered iloprost at a dose of 0.5-2 ng/kg/min over 6 h infusion for 10 days, in addition to routine treatment strategies. Sample size [7] 30	Comparator(s) [8] Were subjected to routine treatment strategies only. Sample size [9] 30

Selection criteria

Inclusion criteria – Patients with type 2 diabetes mellitus and a severe peripheral ischemic foot ulcer unsuitable for revascularisation, hospitalised at the Cukurova University Endocrinology and Metabolism Clinic in Adana, between June 2004 and October 2006.

Exclusion criteria – Patients that had septic shock, renal and liver failure, decompensated heart failure, acute or subacute coronary syndromes, active peptic ulcer, acute cerebral haemorrhage, using anticoagulant drugs, known contraindication to iloprost.

Patient characteristics [10]

Intervention group – N = 30, mean age (yrs) 60.5 ± 9.1, gender: 18/30 (60%) male, 12/30 (40%) female, duration of diabetes (yrs) 14.53 ± 8.12, oral 11/30, insulin 10/30, fasting blood glucose (mg/dl) 236.7 ± 105.5, HbA_{1c} (%) 10.4 ± 2.1, retinopathy 29/30, nephropathy 28/30, neuropathy 30/30, coronary artery disease, 7/30, smoking history (pack years) 22.53 ± 28.52, duration of ulcer (days) 69.83 ± 69.16, osteomyelitis 16/30, Wagner grade: 3.4 ± 0.89.

Comparator group(s) – N = 30, mean age (yrs) 63.1 ± 9.2, gender: 18/30 (60%) male, 12/30 (40%) female, duration of diabetes (yrs) 14.10 ± 7.26, oral 16/30, insulin 13/30, fasting blood glucose (mg/dl) 232.8 ± 103.4, HbA_{1c} (%) 10.8 ± 2.3, retinopathy 30/30, nephropathy 30/30, neuropathy 30/30, coronary artery disease, 13/30, smoking history (pack years) 19.83 ± 19.23, duration of ulcer (days) 68.67 ± 35.46, osteomyelitis 16/30, Wagner grade: 3.4 ± 0.89.

Length of follow-up [11] 30 days	Outcome(s) measured [12] Amputation rates, no. healed without amputation

INTERNAL VALIDITY

Allocation [13] Randomly divided Method not disclosed.	Comparison of study groups [14] Similar baseline characteristics	Blinding [15] None	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups.	Follow-up (ITT) [17] Yes. No loss to follow-up, all failures included

Overall quality assessment (descriptive) [18] Assuming that there is no bias between the intervention and control groups due to open-label study design, and that the study was not underpowered, I find the results to be reliable. The lack of a statistically significant result may be due to a lack of effect of the intervention in this study. Average.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Minor amputations	12/30 (40%)	12/30 (40%)	RR =1.00 (0.54, 1.85)	
Major amputations	13/30 (43.3%)	17/30 (56.7%)	RR = 0.77 (0.46, 1.27)	Harms (NNH) [24] 95% CI [25]
Healed without amputation	5/30 (16.7%)	1/30 (3.3%)	RR = 5.0 (0.84, 32.0)	
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] 3 patients had adverse reaction to iloprost: macula-papular skin lesions, itching, dyspnea, tachycardia, headache, hypertension. Treatment was discontinued in 2 of these patients.

EXTERNAL VALIDITY

Generalisabilty [29] Applicable to other diabetics with Ischemic Foot Ulcers.

Applicability [30] As there does not seem to be a treatment effect, any potentials harms will outweigh the benefits

Comments [31] It is unclear if the study was adequately powered, however, iloprost does not seem to influence amputation rates.

STUDY DETAILS		
Reference [1] (Sherman 2003) "Maggot therapy for treating diabetic foot ulcers unresponsive to conventional therapy." Diabetes Care 26(2): 446-451.		
Affiliation/source of funds [2] Veterans Affairs Medical Centre, Long Beach, California, and Dept. of Medicine, University of California, Irvine, California. Funded by the Spinal Cord Research Foundation of the Paralysed Veterans of America; California Paralysed Veterans of America; Andus Foundation of the American Association of Retires Persons		
Study design [3] non-randomised control study	Level of evidence [4] III-2	Location/setting [5] USA Veterans Affairs Medical Centre - Inpatient
Intervention [6] (1) Maggot (*Lucilia sericata*) therapy (2) Standard therapy first, followed by maggot therapy. Maggot therapy involved applying 5-8 disinfected fly larvae per cm^2 to the wound within a cage-like dressing which was left in place for 48 h. Maggots were then removed by wiping up the larvae with a wet gauze pad. 1-2 cycles were applied each week and saline- or 0.125% sodium hypochlorite-moistened gauze dressings were applied between treatments. Sample size [7] (1) 6 ulcers, (2) 8 ulcers	Comparator(s) [8] Standard therapy. Patients received the conventional surgical or non-surgical therapy selected by their primary care staff. Sample size [9] 6 ulcers	
Selection criteria Inclusion criteria – Diabetic patients with non-healing foot and leg ulcers referred to the maggot therapy service between 1990 and 1995, and found to be appropriate candidates after evaluation. Ulcers with contours that could be measured by planimetry. Exclusion criteria – osteomyelitis, rapidly advancing soft-tissue infection.		
Patient characteristics [10] Intervention group – N = 14 (6 group 1 + 8 group 2 wounds), mean age (yrs) 63 (53-74), mean % ideal body weight 129, smoker 2/14 (14%), mean Hb (g/dl) 13.2, mean albumin (g/dl) 3.7, peripheral venous or arterial disease 13/14 (93%), receiving systemic antibiotics 3/14 (21%). Ulcer characteristics: neuropathic 9/14 (64%), ischemic 1/14 (7%), mixed or undefined 4/14 (29%), duration of ulcer (weeks) 44 (4-318), size of ulcer (cm^2) 13.3 (0.9-42), circumference (cm) 13.5 (3.3-27.7), depth to peristeum or bone 21%, necrotic tissue (% total surface) 38 (0-90), granulation tissue (% total surface) 19 (0-100). Prior treatment: dry gauze, saline, petroleum, aloe, other gel 3/14 (21.4%), topical antimicrobial 1/14 (7.1%), chemical debridement agent 0/14 (0%), sharp debridement, incision and drainage, other surgical procedure 8/14 (57.1%), three or more different nonsurgical methods 2/14 (14.3%). Comparator group(s) – N = 14 (6 control + 8 group 2 wounds), mean age (yrs) 68 (53-82), mean % ideal body weight 114, smoker 3/14 (21%), mean Hb (g/dl) 12.4, mean albumin (g/dl) 3.7, peripheral venous or arterial disease 9/14 (64%), receiving systemic antibiotics 2/14 (14%). Ulcer characteristics: neuropathic 12/14 (86%), ischemic 1/14 (7%), mixed or undefined 1/14 (7%), duration of ulcer (weeks) 40 (4-312), size of ulcer (cm^2) 6.3 (0.5-15.5), circumference (cm) 9.4 (2.5-16.6), depth to peristeum or bone 14%, necrotic tissue (% total surface) 44 (0-100), granulation tissue (% total surface) 18 (0-90). Prior treatment: dry gauze, saline, petroleum, aloe, other gel 3/14 (21.4%), topical antimicrobial 1/14 (7.1%), chemical debridement agent 1/14 (7.1%), sharp debridement, incision and drainage, other surgical procedure 5/14 (35.7%), three or more different nonsurgical methods 4/14 (28.5%).		
Length of follow-up [11] at least 8 weeks or until hospital discharge.	Outcome(s) measured [12] No. ulcers completely closed, healing rate (change in surface area divided by the mean circumference over time), change in surface area of ulcer, time to healing.	

INTERNAL VALIDITY				
Allocation [13] Non-random, control group did not consent to maggot therapy.	Comparison of study groups [14] Similar baseline characteristics with the exception of peripheral venous or arterial disease (29% difference), neuropathic ulcers (22%), size of ulcer (53%), ulcer circumference (25%), surgical procedure (21%), 3 or more nonsurgical methods (14%).	Blinding [15] None	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups.	Follow-up (ITT) [17] Yes, all patients were included in the final analysis.
Overall quality assessment (descriptive) [18] Assuming that there is no bias between the intervention and control groups due to non-randomisation and non-blinding, I find the results to be reliable. The lack of a statistically significant result for all effects may be because the study was underpowered for those outcomes. Average.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
% wound completely closed	36% (7-65)	21% (0-44)	$p > 0.05$	

Weekly % change in surface area (range) Mean healing rate (cm^2/day): At 4 weeks (range) At 8 weeks Ave. Time (weeks) to healing (range)	-2% (-22 to 18) (decrease) 0.08 (0.2-0.14) 0.07 (0.04-0.11) 15 (3-26)	+27% (4.1 to 50) (increase) -0.08 (-0.15 to -0.0002) -0.02 (-0.08 to 0.04) 18 (8-28)	$p < 0.05$ $p < 0.05$ $p < 0.05$ p = NS	Harms (NNH) [24] (95% CI) [25]
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] Two patients complained of pain during maggot treatment, but not severe enough to stop treatment. They also complained of pain during conventional dressing changes.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As the treatment provide some benefit, treatment benefits may outweigh any harms.				
Comments [31] The authors have demonstrated that it may be beneficial to use maggots for wound debridement. However, not all measures of healing differences were statistically significant. It is unknown how the 2 maggot species that have been used for debridement of diabetic foot ulcers (*Lucilia cuprina* and *Lucilia sericata*) compare in effectiveness.				

STUDY DETAILS		
Reference [1] (Smiell et al 1999) "Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies." Wound Repair & Regeneration 7(5): 335-346.		
Affiliation/source of funds [2] Dept. of surgery, University of Louisville School of medicine, Louisville, Kentucky and RW Johnson Pharmaceutical Research Institute, Raritan, New Jersey.		
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] USA outpatient setting (results for 1 centre of multicentre trial)
Intervention [6] Becaplermin (rhPDGF-BB) gel – consisted of 100 µg of becaplermin per g of vehicle gel. Initially sharply debridement of the target ulcer was undertaken, moist saline dressings were changed twice daily and patients instructed to apply a continuous thin layer of gel to entire ulcer area once daily, preferably in the evening when dressing was changed. The amount of gel was based on ulcer area and was determined at each visit. Sample size [7] 128	Comparator(s) [8] Placebo – consisted of vehicle gel (sodium carboxymethylcellulose aqueous based gel containing parabens, m-cresol and L-lysine). All patients visited the clinic weekly for the first 6 weeks and then fortnightly, for up to 20 weeks, debridement was carried out if needed at each visit. Good wound care consisted of the dressing changes, debridement, off-loading, and adequate control of infection if present. Sample size [9] 124	
Selection criteria Inclusion criteria – Diabetic patients aged over 18 years, with at least 1 full-thickness (International Association of Enterostomal Therapy (IAET) stage III or IV chronic ulcer of the lower extremities. If more than 1 ulcer, then the one that was considered to need the longest time to heal with good wound care practice was designated the target ulcer. Ulcers had to be of at least 8 weeks duration with adequate arterial circulation ($TcPO_2$ > 30 mmHg). Eligibility for randomisation was determined by a full medical history, complete physical exam, and lower extremity radiographs. Written informed consent. Exclusion criteria – ulcers resulting from any cause other than diabetes, osteomyelitis in area of target ulcer, if after initial sharp debridement ulcer area was < 1cm^2 or > 40 cm^2, or the sum of all ulcers present exceeded 100 cm^2. Concommitant diseases such as connective tissue disease, patients undergoing treatments with radiotherapy, corticosteroids, chemotherapy, or immunosuppressive agents. Pregnant women, nursing mothers and women of childbearing potential that refuse to use contraceptives.		
Patient characteristics [10] Intervention group – N = 128, mean age 59 ± 10.8, gender: 91/128 (71.1%) male, 37/128 (28.9%) female, race: 104/128 (81.3%) White, 24/128 (18.7%) non-white, mean weight (lbs) 221 ± 57.5, foot dorsum $TcPO_2$ (mmHg) 59.7 ± 24.49, ulcer duration (weeks) 59 ± 72.4, mean ulcer area (cm^2) 3.2 ± 4.73. Comparator group(s) –N = 124, mean age 60 ± 11.9, gender: 87/124 (71.3%) male, 35/124 (28.7%) female, race: 97/124 (79.5%) White, 25/124 (20.5%) non-white, mean weight (lbs) 213 ±44.3, foot dorsum $TcPO_2$ (mmHg) 55.9 ± 18.13, ulcer duration (weeks) 82 ± 156.6, mean ulcer area (cm^2) 2.5 ± 3.82.		
Length of follow-up [11] 20 weeks	Outcome(s) measured [12] No. ulcers completely healed	

INTERNAL VALIDITY				
Allocation [13] Randomised to one of two groups	Comparison of study groups [14] Similar baseline characteristics with the exception of ulcer duration (28% difference) and ulcer size (22%)	Blinding [15] The evaluator is blinded	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes, all patients except 2 patients which did not participate any further than signing the consent forms
Overall quality assessment (descriptive) [18] Study seems adequately powered, and randomisation of participants ans blinding the evaluator minimises selection and information bias. Thus, the differences between groups should reflect the effectiveness of the treatment. The study was of good quality.				

RESULTS				
Outcome [19] No. ulcers completely healed	Intervention group [20] 46/128 (36%)	Control group [21] 40/124 (32%)	Measure of effect/effect size [22] (95% CI) [25] RR = 1.11 (0.79, 1.57)	Benefits (NNT) [23] (95% CI) [25] Harms (NNH) [24] (95% CI) [25]
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] Most adverse events were related to the ulcers, underlying conditions or the age of the patient. The incidence of treatment-related adverse events, particularly infections such as osteomyelitis and cellulitis, were similar in both groups.
EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] As the treatment with Becaplermin (100 µg) gel does not appear to provide a benefit in this study, treatment harms may outweigh any benefits.
Comments [31] This study shows no clinical advantage for using Becaplermin (100 µg) gel

STUDY DETAILS				
Reference [1] (Steed et al 1992) "Randomized Prospective Double-Blind Trial in Healing Chronic diabetic foot ulcers - Ct-102 Activated Platelet Supernatant, Topical Versus Placebo." Diabetes Care 15(11): 1598-1604.				
Affiliation/source of funds [2] Dept. of surgery and Dept. of Dermatology, University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania, and the Maricopa Medical Centre, Phoenix, Arizona. Research partly funded by Curative Technologies Inc, Setauket, New York.				
Study design [3] double-blind RCT	**Level of evidence** [4] II	**Location/setting** [5] USA Clinical outpatient setting		
Intervention [6] 0.01 dilution of CT-102 activated platelet supernatant. Ulcers for both groups were dressed every 12 hours, either CT-102 or plain saline was applied to a cotton gauze sponge and placed on the wound in the evening. This was covered with petroleum-impregnated gauze to keep area moist. The following morning the dressing was removed and a normal saline cotton gauze was applied to the wound for the next 12 h. **Sample size** [7] 7	**Comparator(s)** [8] Placebo – plain saline Aggressive debridement was carried out before entry into trial. Patients were evaluated each week for the first 3 weeks and then fortnightly until the wound healed or the patient completed 20 weeks of therapy **Sample size** [9] 6			
Selection criteria **Inclusion criteria** – Diabetic patients referred to the Wound Healing/Limb Preservation Clinic, University of Pittsburgh or Wound clinic at the Maricopa Medical Centre, in 1989, because their wounds had not healed under the care of their personal physicians. Ulcers were of at least 8 weeks duration and with adequate perfusion (periwound $TcPO_2$ > 30 mmHg), ulcers were > 700 mm^3 in volume but < 50,000 mm^3. Wounds were less than 100 cm^2 in area. **Exclusion criteria** – Patients with ulcers with clinical signs of infection and/or requiring antibiotic treatment.				
Patient characteristics [10] **Intervention group** — N = 7, mean age (yrs) 58.7 ± 12.4, gender: 5/7 (71.4%) male, 2/7 (28.6%) female, duration of diabetes (yrs) 26 ± 6.6, mean HbA_{1c} (%) 7.1 ± 1.4, $TcPO_2$ (mmHg) 51 ± 8.4, transferrin (mg/dl) 254.3 ± 32.8. Ulcer characteristics: duration of ulcer (months) 17.08 ± 15.87, wound volume (mm^3) 7385.1 ± 7184.1, surface area (mm^2) 864.3 ± 457.6. **Comparator group(s)** – N = 6, mean age (yrs) 54.2 ± 12.9, gender: 4/6 (66.7%) male, 2/6 (33.3%) female, duration of diabetes (yrs) 10.3 ± 5.9, mean HbA_{1c} (%) 7.5 ± 1.4, $TcPO_2$ (mmHg) 45 ± 7.4, transferrin (mg/dl) 274.3 ± 67.2. Ulcer characteristics: duration of ulcer (months) 13.00 ± 14.37, wound volume (mm^3) 4391.2 ± 3553.8, surface area (mm^2) 412.2 ± 259.5.				
Length of follow-up [11] 20 weeks	**Outcome(s) measured** [12] No. ulcers healed, Ave % of wound healed by 20 wks, Ave daily reduction in ulcer volume Ave daily reduction in ulcer area.			

INTERNAL VALIDITY				
Allocation [13] Randomised to one of two groups, method not disclosed	**Comparison of study groups** [14] Similar baseline characteristics with the exception of duration of diabetes (60% difference), $TcPO_2$ (12%), ulcer duration (24%), wound volume (40%) and ulcer surface area (52%).	**Blinding** [15] Double-blind study Both patients and clinicians were blinded	**Treatment/ measurement bias** [16] There was no difference in treatment and measurement between the groups	**Follow-up** (ITT) [17] Yes, all patients except 2 patients which did not participate any further than signing the consent forms
Overall quality assessment (descriptive) [18] Study was very small and was probably underpowered leading to a potential type 2 error. However, this was only a pilot study and the results justify undertaking a larger study. This study was of good quality.				

RESULTS				
Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/effect size** [22] (95% CI) [25]	**Benefits** (NNT) [23] (95% CI) [25]
No. ulcers healed	5/7 (71.4%)	1/6 (16.7%)	RR = 4.29 (1.01, 24.31)	1.83 (1.26, 246.7)
Ave % of wound healed by 20 wks	94%	73%	$p < 0.02$	**Harms** (NNH) [24] (95% CI) [25]
Ave daily reduction in ulcer volume (mm^3)	73.8 ± 112.2	21.8 ± 19.9	$p < 0.05$	
Ave daily reduction in ulcer area (mm^2)	6.2 ± 4.8	1.8 ± 1.1	$p < 0.03$	
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		**Relevance** (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] None reported
EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] There were no reported harms. As the treatment provides a statistically significant benefit, treatment benefits will outweigh any harms.
Comments [31] The authors have demonstrated that the application of Ct-102 improves the rate of healing and the clinical outcomes of diabetic foot ulcers. However, this is only a small pilot study, and a larger study must be undertaken to confirm these results.

STUDY DETAILS				
Reference [1] (Steed et al 1995) "Promotion and Acceleration of Diabetic Ulcer Healing by Arginine-Glycine-Aspartic-Acid (RGD) Peptide Matrix." Diabetes Care 18(1): 39-46.				
Affiliation/source of funds [2] Dept. of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania; State University of New York, Buffalo, New York; Pacific Medical Research services, Atherton, California; University of Tennessee, Memphis, Tennessee; Washington University, St. Louis, Missouri; Diabetes and Glandular Disease Clinic, San Antonio, Texas; USA. Funded by a grant from Telios Pharmaceuticals, San Diego, California, USA.				
Study design [3] double-blind RCT	Level of evidence [4] II	Location/setting [5] USA Multicentre (6 sites), outpatients		
Intervention [6] Argidene Gel, a RGD peptide matrix containing a synthetic 18-amino acid peptide (including arginine-glycine-aspartic acid cell attachment sequence needed for cell recognition, and sodium hyaluronate to form a sterile clear viscous gel formulated in phosphate-buffered saline. Treatment applications and dressing changes were performed twice weekly at the clinic. Additionally, ulcers were treated with standard wound care, cleaned with saline, underwent debridement as needed, at each visit. Sample size [7] 40		Comparator(s) [8] Standard wound care with saline-moistened gauze dressings. Dressings were covered with petroleum-impregnated gauze, followed by a non-adherent dressing, and finally a gauze wrap. Patients were given shoes for off-loading on first visit. Sample size [9] 25		
Selection criteria Inclusion criteria – Diabetic patients aged over 18, with neuropathic foot ulcers of at least 1 month duration and penetrating into dermis without exposure of bone or tendon and 1-15 cm^2 in size. Ulcers were free of infection and diabetes was controlled (HbA_{1c} < 10%), adequate perfusion to limb Exclusion criteria – osteomyelitis, receiving medication that might adversely affect healing, any medical conditions that might affect healing				
Patient characteristics [10] Intervention group – N = 40; age (yrs) 61.8 ± 1.9; male 29/40 (72.5%); ulcer duration (months) 16.5 ± 2.7; ulcer area (cm^2) 3.5 ± 0.5; ulcer location on plantar surface 25/40 (62%); toes 7/40 (18%); lateral, medial or dorsal aspects 8/40 (20%). Comparator group(s) – N = 25; age (yrs) 61.0 ± 2.2; male 20/25 (80%); ulcer duration (months) 19.0 ± 3.5; ulcer area (cm^2) 3.5 ± 0.6; ulcer location on plantar surface 17/25 (68%); toes 4/25 (16%); lateral, medial or dorsal aspects 4/25 (16%). No differences detected for type, duration and complications of diabetes, physical examination results, ulcer characteristics (location, granulation eschar and necrotic tissue). There were no significant differences in patient data and baseline ulcer characteristics among the 6 investigational centres.				
Length of follow-up [11]10 weeks		Outcome(s) measured [12] no. of ulcers healed, no. ulcers > 50% healed by week 10, % reduction in ulcer size.		
INTERNAL VALIDITY				
Allocation [13] Randomised 2:1 according to prearranged randomisation order designated for each centre	Comparison of study groups [14] Most baseline data not provided, reported that there are no significant differences. There is a 13% difference in ulcer duration.	Blinding [15] Investigators were blinded (a member of study support staff applied treatment). Patients blinded by placebo syringe	Treatment/ measurement bias [16] There was no difference in measurement between the groups	Follow-up (ITT) [17] Yes, all patients included in final analysis.
Overall quality assessment (descriptive) [18] This study was blinded for both patients and investigators, minimising the potential for bias. It was also adequately powered. This study is of good quality				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. healed	14/40 (35%)	2/25 (8%)	RR = 4.38 [1,29, 16.80]	3.70 [2.76, 16.60]
No. achieved > 50% healing by week 10	30/40 (75%)	12/25 (48%)	RR = 1.56 [1.05, 2.39]	3.70 [2.07, 33.13]
% reduction in ulcer size	72.3 ± 6.8	29.9 ± 26.8	p < 0.0001	

				Harms (NNH) [24] (95% CI) [25]
	Clinical importance (1-4) [26] 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] 26 adverse events in intervention group, 29 adverse events in placebo group. Only 3 events (cellulitis) in the intervention group and 4 events (malodorous exudate, inflammation, increased erythema, and cellulitis) were classified as possibly related to the study treatment and all 7 resolved without surgery or long-term antibiotics.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits may outweigh any harms.				
Comments [31]. The authors have shown that Argidene Gel improves the clinical outcomes for patients with diabetic foot ulcers by increasing the likelihood of healing and shortening the time to healing for these ulcers.				

STUDY DETAILS

Reference [1] (Steed 1995) "Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. Diabetic Ulcer Study Group." J Vasc Surg 21(1): 71-78; discussion 79-81.

(Steed et al 1996) "Effect of extensive debridement and treatment on the healing of diabetic foot ulcers." Journal of the American College of Surgeons 183(1): 61-64.

(Steed 2006) "Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers." Plastic and Reconstructive Surgery 117(7 Suppl): 143s-9s.

Affiliation/source of funds [2] University of Pittsburgh, Presbyterian University Hospital, Pittsburgh. Funded by RW Johnson Pharmaceutical Research Institute, Raritan, NJ.

Study design [3] double-blind RCT	**Level of evidence** [4] II	**Location/setting** [5] USA Multicentre (10 sites), outpatient setting

Intervention [6] 30 µg rhPDGF-BB/g gel Gel was applied to target ulcer at a dose of 2.2 µg rhPDGF-BB/cm^2, spread evenly over ulcer area, daily for 20 weeks or completely healed. A non-adherent saline-soaked gauze dressing was placed over the ulcer and the foot wrapped in gauze. After 12 h the gel was removed by irrigation with saline, then dressed as above without gel. At the next dressing change, 12 h later, the gel was reapplied. **Sample size** [7] 61	**Comparator(s)** [8] matching placebo gel only. Same treatment as intervention group. Before randomisation, patients underwent aggressive surgical debridement of ulcer and further debridement occurred during the trial as required. Patients were assessed weekly for 1 month and then fortnightly, until completion. **Sample size** [9] 57

Selection criteria

Inclusion criteria – Diabetic patients, aged > 18 years, with chronic (of at least 8 weeks duration), non-healing, full-thickness, lower-extremity ulcers resulting from diabetes mellitus that gave informed consent. Ulcer surface area (length x width) of between 1 and 100 cm^2, free of infection, and with adequate blood supply ($TcPO_2$ > 30 mmHg).

Exclusion criteria – women of childbearing potential and nursing mothers, hypersensitivity to any component of study gel, more than 3 ulcers, non-diabetic ulcers, osteomyelitis, malignancy or terminal disease, known alcohol or drug abuse, use of investigational drug within the last 30 days, evidence of thermal, electrical or radiation burn wounds at site of ulcer, use of immunosuppressive agents, radiation or chemotherapy.

Patient characteristics [10]

Intervention group – N = 61, mean age (yrs) 63.2, gender: 43/61 (70.5%) male, 18/61 (29.5%) female, $TcPO_2$ (mmHg) at wound edge 45.7, at foot dorsum 58.6. Ulcer characteristics: duration of ulcer (weeks) 81.8 (6.6-536.0), surface area (cm^2): median 3.1, mean (range) 5.5 (0.2-57.4), mean depth (cm) 0.64. Size ranges: < 2.4 cm^2.23/61 (37.7%), 2.4-5.7 cm^2 20/61 (32.8%), > 5.7 cm^2 18/61 (29.5%).

Comparator group(s) – N = 57, mean age (yrs) 58.3, gender: 46/57 (80.7%) male, 11/57 (19.3%) female, $TcPO_2$ (mmHg) at wound edge 58.9, at foot dorsum 59.7. Ulcer characteristics: duration of ulcer (weeks) 74.5 (6.7-349.6), surface area (cm^2): median 4.9, mean (range) 9.0 (0.6-111.2), mean depth (cm) 0.65. Size ranges: < 2.4 cm^2.15/57 (26.3%), 2.4-5.7 cm^2 18/57 (31.6%), > 5.7 cm^2 24/57 (42.1%).

Length of follow-up [11] 20 weeks study period	**Outcome(s) measured** [12] complete healing, % reduction in ulcer area, time to healing

INTERNAL VALIDITY

Allocation [13] Computer-generated randomisation schedule for each centre.	**Comparison of study groups** [14] Similar baseline characteristics with the exception of $TcPO_2$ at wound edge (22% difference), ulcer surface area (37-39%), % ulcers > 5.7 cm^2 (12%).	**Blinding** [15] Both patients and investigators were blinded.	**Treatment/ measurement bias** [16] There was no difference in treatment and measurement between the groups.	**Follow-up** (ITT) [17] Yes. All patients included in final analysis.

Overall quality assessment (descriptive) [18] This is quite a large study so should be adequately powered. Assuming that no significant selection or information bias was introduced, I find the results to be sufficiently reliable to find that there is a benefit in using rhPDGF-BB gel to reduce the healing time of diabetic foot ulcers. Good.

RESULTS

Outcome [19]	**Intervention group** [20]	**Control group** [21]	**Measure of effect/ effect size** [22] 95% CI [25]	**Benefits** (NNT) [23,25] 95% CI)
No. completely healed	29/61 (48%)	14/57 (25%)	RR = 1.94 (1.17, 3.28) *p* = 0.01	4.35 (2.62, 17.66)

Mean % of office visits requiring further debridement	46.8%	48%	No relationship between frequency of debridement and healing rate	Harms (NNH) [24] 95% CI [25]
% reduction in ulcer area	98.8%	82.1%	*p* = 0.09	
Recurrence rate	26% in mean of 8.6 weeks	46% in mean 8.5 weeks		
Time to healing (dys)	Decreased by 30-40 days	compared to control	*p* = 0.01	
Adverse events	10/61 (16%)	10/57 (18%)	RR = 0.93 (0.43, 2.06)	
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] 10/61 (16%) of the intervention group and 10/57 (18%) of the control group reported having an adverse event, considered to have a known or unknown relationship to the study medication. Most were mild to moderate and transient.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits will probably outweigh any harms.				
Comments [31] The authors have demonstrated that the application of rhPDGF-BB gel increases the likelihood that a diabetic foot ulcer will heal faster. However, not all measures of healing differences were statistically significant. No data on time to healing was provided other than there was a difference of 30-40 days with (*p* = 0.01).				

STUDY DETAILS		
Reference [1] (Tankova et al 2002) "Zinc hyaluronate in the treatment of diabetic foot ulcers: A controlled randomized open-label study." Diabetologia Croatica 30(3): 93-96.		
Affiliation/source of funds [2] Dept. of Diabetology, Clinical Centre of Endocrinology, Medical University, Sofia, Bulgaria. No funding source stated.		
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Bulgaria Hospital clinic, inpatient and outpatient
Intervention [6] Treated the same as the control group plus zinc hyaluronate applied daily at a dose of 2-4 drops onto the ulcer. Sample size [7] 35 patients with 43 ulcers N=43 27 neuropathic ulcers, 16 neuroischemic ulcers	Comparator(s) [8] Treated with standard care methods: debridement, local antiseptics, immobilisation of foot, and antibiotics if necessary. Sample size [9] 24 patients with 28 ulcers N=28 17 neuropathic ulcers, 11 neuroischemic ulcers	
Selection criteria Inclusion criteria –diabetic patients with foot ulcers Exclusion criteria –		
Patient characteristics [10] Baseline characteristics before randomisation: N = 59, gender: 37/59 (62.7%) male, 22/59 (37.3%) female, type 1 27/59, insulin 51/59, mean age (yrs) 55.7 ± 12.4, mean duration of diabetes (yrs) 8.4 ± 5.6, mean duration of ulcer (months) 6.7 ± 4.2, total no. ulcers = 71, neuropathic 44/71, neuroischemic 27/71. Intervention group – N = 35, no. ulcers = 43, neuropathic 27/43 (63%), neuroischemic 16/43 (37%), infection present 29/43 (67%), Wagner grade: W1 21/43 (49%), W2 16/43 (37%), W3 5/43 (12%), W4 1/43 (2%), ulcer area (cm^2) 10.32 ± 4.61, ulcer depth (mm) 9.3 ± 3.1. Comparator group(s) – N = 24, no. ulcers = 28, neuropathic 17/28 (61%), neuroischemic 11/28 (39%), infection present 20/28 (71%), Wagner grade: W1 14/28 (50%), W2 10/28 (36%), W3 3/28 (11%), W4 1/28 (4%), ulcer area (cm^2) 11.46 ± 5.39, ulcer depth (mm) 8.5 ± 5.3.		
Length of follow-up [11] until healed?	Outcome(s) measured [12] no. ulcers healed, time to healing.	

INTERNAL VALIDITY				
Allocation [13] Method of randomisation not disclosed	Comparison of study groups [14] Similar baseline characteristics.	Blinding [15] None	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes. No loss to follow-up, all failures included
Overall quality assessment (descriptive) [18] Paper provides basic characteristics of all patients prior to randomisation. As method of randomisation was not disclosed, cannot tell if equal distribution between groups. Also there was no blinding of participants or investigators and the follow-up period of this study was not clearly stated. Assuming that no significant selection or information bias was introduced, I find the results to be sufficiently reliable to find that the reduction in healing time after zinc hyaluronate treatment is statistically significant. However, it made no difference to the number of ulcers that would eventually heal. Average.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] 95% CI [25]
No. ulcers healed:				
Neuropathic	27/27 (100%)	16/17 (94%)	RR = 1.06 (0.98, 1.06)	Harms (NNH) [24]
Neuroischemic	13/16 (81%)	7/11 (64%)	RR = 1.28 (0.83, 1.94)	
Wagner grade 1	20/20 (100%)	13/13 (100%)		95% CI [25]
Wagner grade 2	16/16 (100%)	9/10 (90%)	RR = 1.11 (0.97, 1.11)	
Wagner grade 3	4/5 (80%)	1/3 (33.3%)	RR = 2.4 (0.75, 9.86)	
Wagner grade 4	0/2 (0%)	0/2 (0%)		
Time to healing (days)	74 ± 31	92 ± 25	*P* = 0.008	
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] no local or systemic side-effects reported
EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] As the treatment provides a statistically significant benefit, treatment benefits will probably outweigh any harms.
Comments [31] The authors have demonstrated that the application zinc hyaluronate improves the time to healing of diabetic foot ulcers

STUDY DETAILS		
Reference [1] (Tsang et al 2003) "Human epidermal growth factor enhances healing of diabetic foot ulcers." Diabetes Care 26(6): 1856-1861.		
Affiliation/source of funds [2] BioClick Technologies Ltd, Hong Kong		
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Hong Kong Diabetes clinic (outpatient)
Intervention [6] Both intervention groups were treated the same as the control group except that the Actovegin 5% cream also contained either 0.02% or 0.04% human epidermal growth factor (hEGF). Sample size [7] both groups contained 21 patients	Comparator(s) [8] All patients received standard wound care including debridement and assessment of ulcer and a complete foot assessment 2 weeks prior to study group allocation. Patients in the control group were treated with daily saline cleansing of the ulcer, local application of Actovegin 5% cream and covered with sterile gauze. Wound parameters such as size, exudates, signs of infection, granulation of tissue, presence of necrotic tissue and healing (epithelialisation), were assessed regularly. Sample size [9] 19	
Selection criteria Inclusion criteria – Diabetic patients with Wagner grade I or II ulcer located below the ankle, with adequate perfusion (ABI > 0.7) Exclusion criteria – poor sugar control (HbA_{1c} > 12%), Wagner grade III or IV ulcers, patients whose ulcer healed > 25% during 2 weeks between assessment and study beginning.		
Patient characteristics [10] Intervention group 0.04% hEGF – N = 21, mean age (yrs) 62.24 ± 13.68, gender: male 6/21 (28.6%), female 15/21 (71.4%), BMI (kg/m^2) 23.83 ± 3.17, duration of diabetes (yrs) 9.05 ± 6.19, insulin use 9/21 (43%), HbA_{1c} (%) 8.5 ± 1.34, serum creatinine > 2 mg 3/21 (14%), ankle brachial index 1.05 ± 0.19, vibration threshold > 25 13/21 ((62%), abnormal 10 g monofilament test 10/21 (48%), nephropathy 12/21 (57%), retinopathy 16/21 76%), other comorbidities 19/21 (90%), ulcer duration (weeks) 11.48 ± 14.68, ulcer area (cm^2) 3.4 ± 1.1. Ulcer location: toes 10/21 (48%), sole 6/21 (29%), ankle 4/21 (19%), other 1/21 (5%). Intervention group 0.02% hEGF – N = 21, mean age (yrs) 68.76 ± 10.45, gender: male 13/21 (61.9%), female 8/21 (38.1%), BMI (kg/m^2) 23.33 ± 3.11, duration of diabetes (yrs) 9.85 ± 7.79, insulin use 7/21 (33%(, HbA_{1c} (%) 8.7 ± 1.99, serum creatinine > 2 mg 2/21 (10%), ankle brachial index 1.03 ± 0.22, vibration threshold > 25 14/21 (67%), abnormal 10 g monofilament test 10/21 (48%), nephropathy 16/21 (76%), retinopathy 12/21 (57%), other comorbidities 16/21 (76%), ulcer duration (weeks) 8.24 ± 5.55, ulcer area (cm^2) 2.78 ± 0.82. Ulcer location: toes 11/21 (52%), sole 3/21 (14%), ankle 5/21 (24%), other 2/21 (10%). Comparator group(s) – N = 19, mean age (yrs) 64.37 ± 11.67, gender: male 10/19 (53%), female 9/19 (47%), BMI (kg/m^2) 25.69 ± 5.21, duration of diabetes (yrs) 10.11 ± 8.29, insulin use 9/19 (47%), HbA_{1c} (%) 7.97 ± 1.81, serum creatinine > 2 mg 3/19 (16%), ankle brachial index 0.99 ± 0.16, vibration threshold > 25 13/19 (68%), abnormal 10 g monofilament test 6/19 (32%), nephropathy 12/19 (63%), retinopathy 9/19 ((47%), other comorbidities 17/19 (89%), ulcer duration (weeks) 12.00 ± 15.47, ulcer area (cm^2) 3.48 ± 0.82. Ulcer location: toes 11/19 (58%), sole 2/19 (11%), ankle 2/19 (11%), other 4/19 (21%).		
Length of follow-up [11] length of treatment – up to 12 weeks Follow-up – up to 24 weeks (only blinded for first 12 weeks)	Outcome(s) measured [12] healing within 12 weeks of study	

INTERNAL VALIDITY				
Allocation [13] Randomisation by drawing envelopes	Comparison of study groups [14] Similar baseline characteristics with the exception of gender (24-33% difference), abnormal 10 g monofilament test (16%), nephropathy (13-19%), retinopathy (19-29%), other comorbidities (13-14%), ulcer duration (26-31%), ulcer area (20%), ulcers location: sole (15-18%), other (11-16%).	Blinding [15] Both patients and investigators were blinded	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] No patients lost to follow up so analysis was based on ITT.
Overall quality assessment (descriptive) [18] Authors have attempted to minimise bias in their study design. I find the benefits for using o.04% hEGF compared to standard treatment to be significant. Good.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No patients healed within 12 weeks for:				1.88 (1.63, 3.77)
0.04% hEGF	20/21 (95%)	8/19 (42%)	RR = 2.26 (1.47, 2.62)	Harms (NNH) [24] 95% CI [25]
0.02% hEGF	12/21 (57%)	8/19 (42%)	RR = 1.36 (0.73, 2.57)	

Clinical importance (1-4) [26] 0.04% - 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention. 0.02% - 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] None reported	
EXTERNAL VALIDITY	
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.	
Applicability [30] There were no reported harms. As the treatment provides a statistically significant benefit, treatment benefits will outweigh any harms.	
Comments [31] The authors have demonstrated that the application of a cream containing 0.04% hEGF improves the clinical outcomes of diabetic foot ulcers	

STUDY DETAILS				
Reference [1] (Van De Weg et al 2008) "Wound healing: total contact cast vs. custom-made temporary footwear for patients with diabetic foot ulceration." Prosthetics and orthotics international 32(1): 3-11.				
Affiliation/source of funds [2] Rehabilitation Centre Amsterdam; EMGO Institute and Dept. of General Practice, VU University Medical Centre, Amsterdam; Dept. of Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands. Funded by Convated Netherlands, and Ontwikkelingfonds Orthopedisch Maatschoeisel.				
Study design [3] RCT	Level of evidence [4] II	Location/setting [5]Netherlands Rehabilitation centres of 2 hospitals		
Intervention [6] Total Contact Cast (TCC) After debridement, the wound was dressed with aquacell wound dressing. Adhesive foam was used over bony prominences. Prior to casting a single layer of cast padding is applied. A well moulded cast that maintains contact with entire plantar aspect of foot was applied. A cast shoe with a polyplastic rocker was supplied, cast was changed on a weekly basis for duration of trial (up to 16 weeks) Sample size [7] 23		Comparator(s) [8] Custom-made Temporary Footwear (CTF) Same wound care as intervention. A custom made shoe of felt was supplied with a rigid leather socket stiffened with Rhenoflex. The custom-made insoles were made from cork and a plastazote covering. Extra depth was provided in the inlay for the ulcer. Patients were instructed to wear the shoe at all times when out of bed. Sample size [9] 20		
Selection criteria Inclusion criteria – confirmed diabetes, sensory neuropathy, plantar ulcer of Wagner grade I or II. Exclusion criteria – patients unable to walk indoors, with dementia or life-threatening co-morbidity, ankle-brachial index <0.4 and/or ostoemyelitis.				
Patient characteristics [10] Intervention group – N = 23, mean age 64.8 ± 10.8, female 32%, duration of diabetes (yrs) 12 (IQR 6.20), HbA_{1c} (%) 7.8 ± 0.3, ankle arm index 0.69 ± 0.25, prescription of antibiotics 41%, duration of ulcer (weeks) 4 (IQR 3, 8), mean wound surface area 4.2 ± 3.1, ulcer grade 1 2/23 (8.7%), forefoot location 20/23 (90%). Comparator group(s) – N = 20, mean age 58.1 ± 11.1, female 10%, duration of diabetes (yrs) 12 (IQR 7.17), HbA_{1c} (%) 8.7 ± 2.2, ankle arm index 0.65 ± 0.21, prescription of antibiotics 45%, duration of ulcer (weeks) 5 (IQR 4, 8), mean wound surface area 3.0 ± 3.1, ulcer grade 1 2/20 (10%), forefoot location 18/20 (90%).				
Length of follow-up [11] 16 week study period		Outcome(s) measured [12] time to healing, complete healing, mean size reduction of ulcer		
INTERNAL VALIDITY				
Allocation [13] Random using opaque, sealed envelopes	Comparison of study groups [14] Baseline characteristics differed for gender (22% difference), ulcer area (29%).	Blinding [15] none	Treatment/ measurement bias [16] There was no difference in measurement between the groups	Follow-up (ITT) [17] Yes. Analysis of effectiveness was done according to ITT
Overall quality assessment (descriptive) [18]] Assuming that there is no bias between the intervention and control groups due to non-blinding and/or confounders such as age, and that the study was not underpowered, I find the results to be reliable. The lack of a statistically significant result may be due to a lack of effect of the intervention. Average.				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] 95% CI [25] Harms (NNH) [24] 95% CI [25]
No. patients healed	6/23 (26.1%)	6/20 (30%)	RR = 0.97 (0.34, 2.25)	
Time to healing (days)	59 ± 39	90 ± 12	*p* = 0.11 (*t*-test)	
Mean size of unhealed ulcers (cm^2) at:				
baseline	4.2 ± 3.1	3.0 ± 3.1		
16 wks	1.5 ± 1.6	1.1 ± 1.2		
Ave. % reduction in ulcer size at 16 weeks	35.7%	36.7%	diff in means = 1%	
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] 2 comparator patients developed minor abrasion not requiring treatment stop, 5 intervention patients developed complications related to the device requiring treatment stop in 2 cases (leading to amputation In 1).				

EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] As the intervention treatment does not provide a benefit compared with the comparator, treatment harms may outweigh any benefits.
Comments [31] The total contact cast does not seem to offer any benefits over the custom-made footwear.

STUDY DETAILS				
Reference [1] (Veves et al 2001) "Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers - A prospective randomized multicenter clinical trial." Diabetes Care 24(2): 290-295.				
Affiliation/source of funds [2]Joslin-Beth Israel Deaconess foot centre and Harvard medical School, Boston, Massachusetts; Dept. of Dermatology and Skin Surgery, Roger Williams Medical Centre, Providence, Rhode Island; Boston University School of Medicine, Boston, Massachusetts; Dept. of surgery, Southern Arizona Veterans affairs medical centre, Tucson, Arizona; Organogenesis, Canton, Massachusetts; USA. Funded by a research grant from Organogenesis, Canton, Massachusetts, USA.				
Study design [3] RCT	**Level of evidence** [4] II		**Location/setting** [5]USA Multicentre (24 sites), outpatient	
Intervention [6] Graftskin skin replacement therapy. Day 0, ulcer underwent debridement and irrigated with sterile saline prior to application of Graftskin directly over the ulcer, trimmed to fit, then covered with saline-moistened Tegapore, which was secured with hypoallergenic tape. The ulcer was then covered with a layer of dry gauze, and a layer of petroleum gauze and Kling. Graftskin could be reapplied weekly for a maximum of 5 applications. Inner dressings were change by investigator at twice weekly visits for 5 weeks, patients changed outer layers (from dry gauze) daily. All patients were required to use crutches or a wheelchair for first 6 weeks. They were also provided with customised tridensity sandals to be worn throughout study period. **Sample size** [7] 112			**Comparator(s)** [8] Standard wound care The ulcer was covered by a layer of saline-moistened Tegapore and secured with hypoallergenic tape, this was then covered with saline-moistened gauze, followed by a layer of dry gauze and a layer of petroleum gauze, and wrapped in Kling. The patients changed only the secondary dressings twice daily for the first 5 weeks. The investigators performed complete dressing changes twice weekly. **Sample size** [9] 96 After week 5, ulcers that did not heal in both groups were covered with a layer of saline-moistened gauze and a layer of petroleum gauze, and wrapped in Kling. Dressings were changed twice daily til study week 12.	
Selection criteria **Inclusion criteria** – Diabetic patients, aged over 18 years, with full-thickness neurpopathic ulcers (excluding dorsum of foot and calcaneus) of > 2 weeks duration, and 1-16 cm^2 after debridement, HbA_{1c} between 6 and 12%, dorsal pedis and posterior tibial pulses audible by Doppler. **Exclusion criteria** – Clinical infection at ulcer site, clinically significant lower-extremity ischemia (ABI < 0.65), active charcot's disease, non-diabetic ulcer, significant medical conditions that would impair wound healing, patients with ulcer that responded (> 30% decrease in ulcer size) to standard wound care (sharp debridement and saline-moistened gauze dressings) during the 7-day screening period				
Patient characteristics [10] **Intervention group** – N = 112; age (yrs) 58 ± 10; Gender: male 88/112 (79%); female 24/112 (21%); Race: Caucasian 77/112 (69%); African-American 20/112 (18%); Hispanic 14/112 (13%); BMI (kg/m^2) 30.9 ± 6.54; % HbA_{1c} 8.6 ± 1.5; ankle brachial index 0.65-0.8 10/112 (8.9%); 0.8-1.00 50/112 (36%); > 1.00 59/112 (53%); ulcer duration (months) 11.5 ± 13.3; ulcer area (cm^2) 2.97 ± 3.10. **Comparator group(s)** – N = 96; age (yrs) 56 ± 10; Gender: male 74/96 (77%); female 22/96 (23%); Race: Caucasian 67/96 (70%); African-American 14/96 (15%); Hispanic 13/96 (14%); BMI (kg/m^2) 33.1 ± 7.72; % HbA_{1c} 8.6 ± 1.4; ankle brachial index 0.65-0.8 10/96 (10.4%); 0.8-1.00 29/96 (30.2%); > 1.00 54/96 (56.3%); ulcer duration (months) 11.1 ± 12.5; ulcer area (cm^2) 2.83 ± 2.45.				
Length of follow-up [11] 12 week study period, up to 6 months follow-up with monthly visits			**Outcome(s) measured** [12] complete healing,	
INTERNAL VALIDITY				
Allocation [13] Computer-generated randomisation schedule provided by the sponsor	**Comparison of study groups** [14] Similar baseline characteristics	**Blinding** [15] None	**Treatment/ measurement bias** [16] There was no difference in treatment and measurement between the groups	**Follow-up** (ITT) [17] Yes, all patients that received treatment were included in final analysis
Overall quality assessment (descriptive) [18] This study has the potential for information bias as there was no blinding. This is quite a large, multicentre study so the results should be reflective of the treatment. This was a good quality study.				
RESULTS				
Outcome [19] No. ulcers completely healed	**Intervention group** [20] 63/112 (56%)	**Control group** [21] 36/96 (38%)	**Measure of effect/effect size** [22] (95% CI) [25] OR = 2.14 [1.23, 3.74] *RR = 1.50 [1.12, 2.03]* *included in Meta-analysis by Blozik and Scherer (2008)	**Benefits** (NNT) [23] (95% CI) [25] 5 [3, 19]

Median time to complete closure (days) No. of amputations No. of infections (harms) No. of ulcers that recurred	65 7/112 (6.3%) 25/112 (22.3%) 3/51 (5.9%)	90 15/96 (15.6%) 31/96 (32.3%) 4.31 (12.9%)	*p* = 0.0026 RR = 0.40 [0.17, 0.91] RR = 0.69 [0.44, 1.08] RR = 0.45 [0.12, 1.74]	Harms (NNH) [24] (95% CI) [25] 11 [6, 103]
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] as listed above.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As the treatment provides a clinically significant benefit, treatment benefits will outweigh any harms.				
Comments [31] Graftskin skin replacement therapy has been shown to improve the clinical outcomes of diabetic foot ulcers in this study. More ulcers healed in a reduced period of time after Graftskin therapy than in the group that received standard care.				

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] (Wang et al 2009) "Extracorporeal Shockwave Treatment for Chronic diabetic foot ulcers." Journal of Surgical Research 152(1): 96-103.</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2] Dept. of Orthopaedic Surgery, Dept. of Plastic and Reconstructive Surgery, Dept. of Internal Medicine, and Dept. of Medical Research, Chang Gung Memorial Hospital-Kaohsiung Medical Centre, Chang Gung University College of Medicine, Taiwan. Funded by the National Science Council, Tissue Regeneration Technologies, and National Health Research Institute.</td></tr>
<tr><td colspan="2">Study design [3] RCT</td><td colspan="2">Level of evidence [4] II</td><td colspan="2">Location/setting [5] Taiwan Hospital</td></tr>
<tr><td colspan="3">Intervention [6] Extracorporeal shockwave treatment (ESWT)
Treatment as outpatient with no anaesthesia. Ulcer covered with cellulose barrier, ultrasound gel applied to area of skin in contact with shockwave tube. Treatment shockwave application was 300 + 100 cm^2 impulses at 0.11 mJ/cm^2 energy flux density, applied once every 2 weeks for a total of 3 treatments in 6 weeks. A repeat course of treatment was performed with incomplete healing. Combined with standard wound care protocols.
Sample size [7] 36 patients, 38 ulcers</td><td colspan="3">Comparator(s) [8] Hyperbaric oxygen treatment (HBO)
Treatment was performed in a sealed multi-place chamber at 2.5 ATAs. 100% medical grade oxygen was inhaled through a facemask for 25 min with a 5 min break for a total of 90 mins.. Tretment was performed once per day, 5 days a week for a total of 20 treatments. Combined with same standard wound care as intervention group.

Sample size [9] 38 patients, 38 ulcers</td></tr>
<tr><td colspan="6">Selection criteria
Inclusion criteria – Diabetic patients with recurrent chronic foot ulcers of more than 3 months duration. Patients with deep wound sepsis or gangrenous changes required surgical debridement and wound care until ulcers were stable prior to treatment. Patients with quiescent osteomyelitis without recurrent symptoms for > 1 year were not excluded.
Exclusion criteria – Patients with cardiac arrhythmia or a pacemaker, pregnancy, skeletal immaturity, malignancy, inability to comply.</td></tr>
<tr><td colspan="6">Patient characteristics [10]
Intervention group – N = 34, no. of ulcers = 36, mean age 58.6 ± 12.6, HbA_{1c} (%) 9.08 ± 1.21, ankle brachial index 1.22 ± 0.19, ulcer duration (months) 22.7 ± 20.9, mean ulcer area (mm^2) 11.2 ± 20.0, ulcer location: dorsal 23/36 (64%), plantar 13/36 (36%).
Comparator group(s) – N = 36, no. of ulcers = 36, mean age 63.4 ± 10.3, HbA_{1c} (%) 8.84 ± 2.11, ankle brachial index 1.26 ± 0.27, ulcer duration (months) 19.0 ± 19.5, mean ulcer area (mm^2) 10.5 ± 20.0, ulcer location: dorsal 17/36 (47%), plantar 19/36 (53%).</td></tr>
<tr><td colspan="3">Length of follow-up [11] average follow-up of 12 months</td><td colspan="3">Outcome(s) measured [12] completely healed, >50% improved</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Random depending on even or odd day of week.</td><td>Comparison of study groups [14] Similar baseline characteristics with the exception of ulcer location (16% difference)</td><td>Blinding [15]
None</td><td>Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups</td><td colspan="2">Follow-up (ITT) [17]
No. those lost to follow up were excluded from analysis.</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18] Assuming that there is no bias between the intervention and control groups due to non-blinding, I find the results to be reliable. The lack of a statistically significant result between the intervention and comparator, and the statistically significant difference in improvement between before and after treatment suggest that both treatments are equally effective. Average.</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td>Outcome [19]

No. ulcers healed
No. >50% improved
No. unchanged

Comparison of before and after treatment for > 50% improvement (non-ITT)</td><td>Intervention group [20]

11/38 (28.9%)
21/38 (55.3%)
3/38 (7.9%)

0% before compared to 89% after treatment</td><td>Control group [21]

8/38 (21.1%)
18/38 (47.3%)
10/38 (26.3%)

0% before compared to 72% after treatment</td><td>Measure of effect/effect size [22] 95% CI [25]

RR = 1.38 (0.63, 3.04)
RR = 1.17 (0.76, 1.80)

Paired t-test $p < 0.001$ for both intervention and comparator</td><td>Benefits (NNT) [23]

95% CI [25]

Harms (NNH) [24]
95% CI [25]</td></tr>
<tr><td colspan="3">Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.</td><td colspan="3">Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.</td></tr>
</table>

Any other adverse effects [28] None reported.
EXTERNAL VALIDITY
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.
Applicability [30] There were no reported harms. As the treatment provides a benefit, treatment benefits will outweigh any harms.
Comments [31] Hyperbaric oxygen therapy has been demonstrated to improve the clinical outcomes of diabetic foot ulcers in other studies. This study shows that ESWT treatment is as effective as HBO.

STUDY DETAILS

Reference [1] (Wieman et al 1998) "Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers - A phase III randomized placebo-controlled double-blind study." Diabetes Care 21(5): 822-827.

Affiliation/source of funds [2] Dept. of surgery, University of Louisville School of medicine, Louisville, Kentucky and RW Johnson Pharmaceutical Research Institute, Raritan, New Jersey.

Study design [3]	Level of evidence [4]	Location/setting [5]
double-blind RCT	II	USA Multicentre (23 sites), outpatient setting

Intervention [6]	Comparator(s) [8]
Becaplermin (rhPDGF-BB) gel – consisted of 100 μg or 30 μg of becaplermin per g of vehicle gel. Initially sharply debridement of the target ulcer was undertaken, moist saline dressings were changed twice daily and patients instructed to apply a continuous thin layer of gel to entire ulcer area once daily, preferably in the evening when dressing was changed. The amount of gel was based on ulcer area and was determined at each visit. Sample size [7] B 100 μg: N= 123, B 30 μg: N = 132	Placebo – consisted of vehicle gel (sodium carboxymethylcellulose aqueous based gel containing parabens, m-cresol and L-lysine). All patients visited the clinic weekly for the first 6 weeks and then fortnightly, for up to 20 weeks, debridement was carried out if needed at each visit. Good wound care consisted of the dressing changes, debridement, off-loading, and adequate control of infection if present. Sample size [9] 127

Selection criteria

Inclusion criteria – Diabetic patients aged over 18 years, with at least 1 full-thickness (International Association of Enterostomal Therapy (IAET) stage III or IV chronic ulcer of the lower extremities. If more than 1 ulcer, then the one that was considered to need the longest time to heal with good wound care practice was designated the target ulcer. Ulcers had to be of at least 8 weeks duration with adequate arterial circulation ($TcPO_2$ > 30 mmHg). Eligibility for randomisation was determined by a full medical history, complete physical exam, and lower extremity radiographs. Written informed consent.

Exclusion criteria – ulcers resulting from any cause other than diabetes, osteomyelitis in area of target ulcer, if after initial sharp debridement ulcer area was < 1cm^2 or > 40 cm^2, or the sum of all ulcers present exceeded 100 cm^2. Concomitant diseases such as connective tissue disease, patients undergoing treatments with radiotherapy, corticosteroids, chemotherapy, or immunosuppressive agents. Pregnant women, nursing mothers and women of childbearing potential that refuse to use contraceptives.

Patient characteristics [10]

Intervention group 1 B 100 μg – N = 123, mean age 57 ± 11.5, gender: male 82/123 (67%), female 41/123 (33%), race: White 101/123 (81%), Black 14/123 (11%), Asian 0/123 (0%), Hispanic 8/123 (6.5%), other 0/123 (0%), foot dorsum $TcPO_2$ (mmHg) 55.0 ± 22.60, ulcer duration (weeks) 46 ± 54.7, mean ulcer area (cm^2) 2.6 ± 3.41, ulcer depth (cm) 0.4 ± 0.46.

Intervention group 2 B 30 μg –N = 132, mean age 58 ± 11.3, gender: male 82/132 (62%), female 50/132 (38%), race: White 108/132 (82%), Black 15/132 (11%), Asian 0/132 (0%), Hispanic 9/132 (6.8%), other 0/132 (0%), foot dorsum $TcPO_2$ (mmHg) 54.1 ± 20.94, ulcer duration (weeks) 56 ± 80.3, mean ulcer area (cm^2) 2.6 ± 2.69, ulcer depth (cm) 0.5 ± 0.48.

Comparator group(s) –N = 127, mean age 58 ± 11.8, gender: male 91/127 (72%), female 36/127 (28%), race: White 100/127 (79%), Black 18/127 (14%), Asian 1/127 (0.8%), Hispanic 7/127 (5.5%), other 1/127 (0.8%), foot dorsum $TcPO_2$ (mmHg) 55.5 ± 19.61, ulcer duration (weeks) 46 ± 52.1, mean ulcer area (cm^2) 2.8 ± 4.14, ulcer depth (cm) 0.5 ± 0.54.

Length of follow-up [11]	Outcome(s) measured [12]
20 weeks	No. ulcers completely healed, time to complete healing.

INTERNAL VALIDITY

Allocation [13]	Comparison of study groups [14]	Blinding [15]	Treatment/ measurement bias [16]	Follow-up (ITT) [17]
Randomised to one of three groups	Similar baseline characteristics with the exception of ulcer duration (18% difference).	Double-blind study, patients and investigators were blinded	There was no difference in treatment and measurement between the groups	Yes, all patients except 1 from B 100 μg groups which was lost with no post-baseline data.

Overall quality assessment (descriptive) [18] Study seems adequately powered, and a double-blind placebo-controlled study design is used to minimise bias. Assuming that the blinding procedures were effective, the differences between groups should reflect the effectiveness of the treatment. The study was of good quality.

RESULTS

Outcome [19]	Intervention group [20] B 100 μg	 B 30 μg	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
No. ulcers completely healed	61/123 (50%)	48/132 (36%)	44/127 (35%) 44/127 (35%)	RR = 1.43 (1.07, 1.93) p = 0.007 RR = 1.05 (0.76, 1.46)	6.7 (3.75, 36.9)
Median time to complete healing (days)	86		127	= 32% reduction (p = 0.013)	Harms (NNH) [24] (95% CI) [25]

Clinical importance (1-4) [26] B 100 µg - 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects. B 30 µg - 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] Most adverse events were related to the ulcers, underlying conditions or the age of the patient. The incidence of treatment-related adverse events, particularly infections such as osteomyelitis and cellulitis, were similar in all three groups.	
EXTERNAL VALIDITY	
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.	
Applicability [30] As the treatment with Becaplermin (100 µg) gel appears to provide a benefit, treatment benefits may outweigh any harms.	
Comments [31] This study suggests that Becaplermin (100 µg) gel improves the clinical outcomes of diabetic foot ulcers by increasing the healing rate.	

<table>
<tr><td colspan="5">STUDY DETAILS</td></tr>
<tr><td colspan="5">Reference [1] (Yamaguchi et al 2004) "Rapid healing of intractable diabetic foot ulcers with exposed bones following a novel therapy of exposing bone marrow cells and then grafting epidermal sheets." The British journal of dermatology 151(5): 1019-1028.</td></tr>
<tr><td colspan="5">Affiliation/source of funds [2] Dept. of Dermatology, Graduate School of Medicine, Osaka University, Osaka, Japan; Laboratory of Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. Funded by a Grant-in-aid for Scientific Research from the Ministry of Education, Science, Sports and Cullture of Japan; a grant from the Uehara Memorial Foundation; a grant from the Tissue Engineering Research Project managed by the New Energy and Industrial Technology Development Organisation.</td></tr>
<tr><td colspan="2">Study design [3] non-randomised controlled study</td><td>Level of evidence [4] III-2</td><td colspan="2">Location/setting [5] Japan
Osaka University Hospital, inpatient and outpatient</td></tr>
<tr><td colspan="3">Patients without exposed bone:
Intervention [6], wound was covered with an occlusive dressing (Tegaderm plus, a thin polyurethane membrane iodine; 3M Health Care, USA) for up to 2 weeks, until granulation tissue formed, suitable for an epidermal graft. Epidermal sheets were obtained from suction blisters harvested under local anaesthetic from donor skin (abdomen of inner thigh).
Sample size [7] 10
Patients with exposed bone:
Intervention [6] Bone was shaved with a bone scraper until bleeding from the bone marrow was observed, and then immediately covered wound with Tegaderm plus for 3-8 days. Finally, epidermal grafts were applied to the wound bed prepared by the marrow and occlusive dressing.
Sample size [7] 11</td><td colspan="2">Patients without exposed bone:
Comparator(s) [8] standard wound care, including sharp debridement, bed rest, special casts and antibiotics as needed.
Sample size [9] 8
Patients with exposed bone:
Comparator(s) [8] Conventional treatment, which includes covering bone with adjacent muscle and/or skin grafts, or leave as is.
Sample size [9] 9</td></tr>
<tr><td colspan="5">Selection criteria
Inclusion criteria – Asian patients with intractable diabetic foot ulcers attending Osaka University Hospital from 17 December 1998 to 17 March 2002. Intractable ulcers were defined as those that did not respond to conservative treatments for more than 2 months.
Exclusion criteria – non stated</td></tr>
<tr><td colspan="5">Patient characteristics [10]
Two treatment arms, patients were stratified depending on the presence of exposed bone after sharp en bloc debridement.
Patients without exposed bone: N = 18
Intervention group – N = 10; age (yrs) 60.3 ± 4.4; gender: male 5/10 (50%); female 5/10 (50%); ulcer size (cm^2) 4.7 ± 1.1; ulcer duration (months) 2.8 ± 0.3; infected 8/10 (80%); bone exposure 0/10 (0%).
Comparator group(s) – N = 8; age (yrs) 58.9 ± 5.0; gender: male 5/8 (63%); female 3/8 (37%); ulcer size (cm^2) 6.5 ± 2.7; ulcer duration (months) 4.6 ± 1.4; infected 7/8 (88%); bone exposure 0/8 (0%).
Patients with exposed bone: N = 20
Intervention group – N = 11; age (yrs) 58.1 ± 4.9; gender: male 8/11 (73%); female 3/11 (27%); ulcer size (cm^2) 5.6 ± 2.1; ulcer duration (months) 12.3 ± 7.6; infected 8/11 (72%); bone exposure 11/11 (100%).
Comparator group(s) – N = 9; age (yrs) 64.8 ± 3.8; gender: male 7/9 (78%); female 2/9 (22%); ulcer size (cm^2) 3.4 ± 0.9; ulcer duration (months) 6.6 ± 1.2; infected 7/9 (78%); bone exposure 9/9 (100%).</td></tr>
<tr><td colspan="2">Length of follow-up [11] up to 24 weeks</td><td colspan="3">Outcome(s) measured [12] time to healing, no. of amputations</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Not random – patients chose their treatment</td><td>Comparison of study groups [14]
Patients without exposed bone: similar baseline characteristics except for gender (13% difference), ulcer size (28%), and ulcer duration (39%).
Patients with exposed bone: similar baseline characteristics except for ulcer size (39%), and ulcer duration (46%).</td><td>Blinding [15]
None</td><td>Treatment/ measurement bias [16] There were some differences in treatment, but not measurement between the groups.</td><td>Follow-up (ITT) [17]
Yes, all patients included in final analysis</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18] This study has the potential for information bias as there was no blinding. Study was probably underpowered leading to a potential type 2 error for some outcomes. The differences in size of ulcer may bias the outcomes. This study is of average quality.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
</table>

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
Time to healing (weeks):				
No exposed bone	4.3 ± 0.6	11.6 ± 3.4	p = 0.04	
Exposed bone	5.1 ± 0.7	6.2 ± 2.5	p = 0.86	Harms (NNH) [24] (95% CI) [25]
Number amputations				
No exposed bone	0/10 (0%)	1/8 (13%)	p = 0.26	
Exposed bone	0/11 (0%)	8/9 (89%)	p < 0.0001	
	Clinical importance (1-4) [26] No exposed bone - 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects. Exposed bone - 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] None reported.				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				
Applicability [30] As the treatment using epidermal grafts for ulcers with and without exposed bone appears to provide a statistically significant benefit, treatment benefits may outweigh any harms.				
Comments [31] This study suggests that epidermal grafts compared to standard wound care improve reduces the time to healing for diabetic foot ulcers without exposed bone, and the risk of amputation for ulcers with exposed bone.				

STUDY DETAILS

Reference [1] (Yonem et al 2001) "Effects of granulocyte-colony stimulating factor in the treatment of diabetic foot infection." Diabetes Obes Metab 3(5): 332-337.

Affiliation/source of funds [2] Dept. of Endocrinology, Gulhane School of Medicine, and Dept. of Endicrinology and Metabolism, Ankara Education and Research Hospital, Ankara, Turkey..

Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Turkey Hospital inpatient

Intervention [6] Subcutaneous injection of G-CSF (Filgrastin) was administered daily for 7 days. Initial dose at 5 μg/kg, after 3 doses: lowered to 2.5 μg/kg given on alternate days if absolute neutrophil count higher than 30 x 10^9/L, if count above 45 x 10^9/L, G-CSF treatment was stopped. Also given same standard wound care plus antibiotic therapy as control group. Sample size [7] 15	Comparator(s) [8] Standard wound care plus appropriate antibiotic therapy (according to cultured isolates' susceptabilities). Local wound care was carried out by a plastic surgeon or orthopaedist when necessary. Sample size [9] 15

Selection criteria

Inclusion criteria – Diabetic patients with infected foot ulcers (Wagner grade 2 or less) or pedal cellulitis, absolute neutrophil count > 1.5 x 10^9/L and < 20 x 10^9/L.

Exclusion criteria – haematological diseases, history of malignancy, renal or hepatic failure, pregnancy or lactation, severe leg ischaemia, deep or severe infections, immunosuppressive therapy.

Patient characteristics [10]

Intervention group – N = 15, mean age (yrs) 60.3 ± 1.3, gender: male 7/15 (46.7%), female 8/15 (53.3%), duration of diabetes(yrs) 13.5 ± 1.2, mean fasting plasma glucose (mmol/l) 12.7 ± 1.0, total cholesterol (mmol/l) 6.1 ± 0.2, LDL (mmol/l) 3.8 ± 0.2, HDL (mmol/l) 1.0 ± 0.0, triglycerides (mmol/l) 2.8 ± 0.3, total white blood cell count (n/mm^2) 10300 ± 700, neutrophil count (n/mm^2) 5200 ± 500, lymphocyte count (n/mm^2) 4300 ± 500, basal phagocytosis test (%) 70.4 ± 2.0, basal respiratory burst (mV) 1.6 ± 0.3.

Comparator group(s) – N = 15, mean age (yrs) 61.0 ± 1.4, gender: male 6/15 (40%), female 9/15 (60%), duration of diabetes(yrs) 12.7 ± 0.9, mean fasting plasma glucose (mmol/l) 12.8 ± 0.9, total cholesterol (mmol/l) 5.9 ± 0.3, LDL (mmol/l) 3.7 ± 0.3, HDL (mmol/l) 1.0 ± 0.0, triglycerides (mmol/l) 2.8 ± 0.4, total white blood cell count (n/mm^2) 9800 ± 700, neutrophil count (n/mm^2) 5700 ± 600, lymphocyte count (n/mm^2) 3800 ± 400, basal phagocytosis test (%) 68.1 ± 2.2, basal respiratory burst (mV) 2.0 ± 0.4.

Length of follow-up [11]	Outcome(s) measured [12] length of hospital stay, No. of amputations, time to resolution of cellulitis.

INTERNAL VALIDITY

Allocation [13] Randomisation method not disclosed	Comparison of study groups [14] Similar baseline characteristics	Blinding [15] None	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes. All patients were included in the analysis.

Overall quality assessment (descriptive) [18] Assuming that there is no information bias between the intervention and control groups due to non-blinding, I find the results to be reliable. The lack of an effect difference is probably due to the intervention having no effect. However, the small sample size of the study suggests that it may have been underpowered and the lack of a statistically significant result may be due to this. This study was of average quality.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
Length of hospital stay (days)	26.9 ± 2.0	28.3 ± 2.2	$p > 0.05$	Harms (NNH) [24] (95% CI) [25]
Time to resolution of cellulitis (days)	23.6 ± 1.8	22.3 ± 1.7	$p > 0.05$	
No. of amputations	2/15 (13.3%)	3/15 (20%)	RR = 0.67 (0.14, 3.04)	
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] None stated

EXTERNAL VALIDITY

Generalisabilty [29] Applicable to other diabetics with infected diabetic foot ulcers.
Applicability [30] There were no reported harms. As the treatment does not appear to provide a benefit in this study, any potential harms will outweigh treatment benefits.
Comments [31] This small study suggests that administering G-CSF (Filgrastin) does not improve the clinical outcomes of diabetic foot ulcer infectionss. However, the study was small and may have been underpowered.

STUDY DETAILS		
Reference [1] Zimny, S., H. Schatz, et al. (2003). "The effects of applied felted foam on wound healing and healing times in the therapy of neuropathic diabetic foot ulcers." Diabetic medicine : a journal of the British Diabetic Association 20(8): 622-625.		
Affiliation/source of funds [2] EVK Bethesda, Medizinische Klinik I, Duisburg and Klinik der BG, Kliniken Bergmannsheil Bochum, Universitatesklinik, Ruhr-Univeritat, Bochum, Germany. No funding source stated.		
Study design [3] RCT	Level of evidence [4] II	Location/setting [5] Germany Outpatient clinic
Intervention [6] Standard wound care as for comparator but pressure relief provided by felted foam dressing. Rubber foam, 0.635 cm thick, with a layer of felt glued with rubber glue was measured to fit plantar aspect of foot with hole cut out for ulcer. This was wrapped in gauze to hold in place and the wound was covered with saline-soaked sponge, which was changed every day Sample size [7] 24	Comparator(s) [8] Standard wound care including debridement, and daily careful monitoring of the ulcer. Signs of soft tissue infection were treated with appropriate antibiotics. Pressure-relief was provided by the half-shoe. Wound healing was assessed by planimetric measurement every fortnight. Sample size [9] 30	
Selection criteria Inclusion criteria – Diabetic patients with neuropathic plantar forefoot foot ulcers (Wagner grade 1 or 2) attending the clinic. Exclusion criteria – Patients with ulcer under heel or midfoot, multiple ulcers, or those suggestive of osteomyelitis. Patients with vascular occlusive disease, and with a vibration perception threshold of < 3/8.		
Patient characteristics [10] Intervention group – N = 24, mean age 62.1 ± 13.0, gender: 13/24 (54.2%) male, 11/24 (45.8%) female, BMI 27.4 ± 4.9, duration of diabetes (yrs) 18.2 ± 7.6, type 1 diabetes 7/24 (29%), HbA_{1c} (%) 7.9 ± 0.6, $TcPO_2$ (kPa) 8.9 ± 1.3, ankle brachial index 1.0 ± 0.1, ulcer localisation metatarsal head: I-III 19/24 (79%), IV-V 5/24 (21%), ulcer area (mm^2) 102.3 ± 45.3 Wagner grade 1 6/24 (25%), grade 2 18/24 (75%). Comparator group(s) – N = 30, mean age 62.1 ± 10.8, gender: 17/30 (56.7%) male, 13/30 (43.3%) female, BMI 28.5 ± 4.3, duration of diabetes (yrs) 22.1 ± 11.8, type 1 diabetes 13/30 (43%), HbA_{1c} (%) 7.5 ± 1.2, $TcPO_2$ (kPa) 8.7 ± 1.0, ankle brachial index 1.0 ± 0.2, ulcer localisation metatarsal head: I-III 24/30 (80%), IV-V 6/30 (20%), ulcer area (mm^2) 112.5 ± 50.8 Wagner grade 1 7/30 (23%), grade 2 23/30 (77%).		
Length of follow-up [11] at least 10 weeks	Outcome(s) measured [12] mean wound radius reduction, time to healing	

INTERNAL VALIDITY				
Allocation [13] Randomisation method not disclosed	Comparison of study groups [14] Similar baseline characteristics with the exception of type 1 diabetes (14% difference)	Blinding [15] None	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] Yes. No loss to follow-up, all failures included
Overall quality assessment (descriptive) [18] Assuming that there is little information bias between the intervention and control groups due to investigators not being blinded, I find the results to be reliable, showing that the intervention has a statistically significant benefit over standard care. Average.				

RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] (95% CI) [25]
Mean wound radius reduction	0.48 (95% CI 0.42, 0.56)	0.39 (0.35, 0.42)	-0.09 p = 0.005	
Time to healing (days)	75.2 (95% CI 67, 84)	85.2 (79, 92)	10 p= 0.03	Harms (NNH) [24] (95% CI) [25]
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 2. Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention.	
Any other adverse effects [28] No adverse effects due to rubber glue				
EXTERNAL VALIDITY				
Generalisabilty [29] Applicable to other diabetics with diabetic foot ulcers.				

Applicability [30] There were no harms reported. As the treatment appears to provide a benefit, treatment benefits may outweigh any harms.
Comments [31] This study suggests that felted foam dressing improves the clinical outcomes of diabetic foot ulcers.

STUDY DETAILS		
Reference [1] Reiber, G. E., Smith, D. G. et al (2002). 'Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial', JAMA: Journal of the American Medical Association, 287 (19), 2552		
Affiliation/source of funds [2] Health Services and Rehabilitation Research and Development; VA Puget Sound Health Care System; Department of Veterans Affairs; Departments of Health Services, Epidemiology, Orthopaedic Surgery, Biostatistics, and Family Medicine, University of Washington; Joslin Diabetes Center at Swedish Medical Center, Seattle, WA, USA. Supported by Rehabilitation Research and Development, Health Services Research and Development, the Epidemiology Research and Information Center, Department of Veterans Affairs; the National Institute of Diabetes and Digestive and Kidney Diseases; Centers for Disease Control and Prevention.		
Study design [3] RCT	Level of evidence [4] Level II intervention	Location/setting [5] 2 health care centres in Washington State, USA
Intervention [6] Therapeutic footwear with insert of either one of prefabricated or custom-made material. Sample size [7] 240 diabetic patients	Comparator(s) [8] Wear of usual footwear. Sample size [9] 160 diabetic patients	
Selection criteria Inclusion criteria – Diagnosis of diabetes, age 45 to 84 years, history of full-thickness foot lesion or foot infection requiring antibiotics, shoe size of 8 to 12½ for men or 7 to 10½ for women, ability to walk one block and climb one flight of stairs per day, consent to randomisation and study footwear provisions. Exclusion criteria – Foot deformities requiring custom shoe, previous lower extremity amputation of >1 digit, unhealed/healed lesion in prior month, non-ambulatory status, terminal illness with 2-year survival unlikely, Charcot feet.		
Patient characteristics [10] Intervention group – Comparator group(s) –		

	Therapeutic shoes, cork inserts	Therapeutic Shoes, prefabricated inserts	Controls (usual footwear)
Age (yrs), mean (SD)	61 (10.1)	62 (10.1)	63 (10)
Female (%)	22	23	23
Ethnicity (%)			
White	79	82	74
Black	12	10	14
Other	8	8	12
Education (yrs), mean (SD)	15 (2.8)	14 (2.4)	14 (3.5)
Married/de facto (%)	66	62	57
Employment status (%)			
Employed	37	33	28
Unemployed	1	1	2
Disabled	21	23	31
Retired	41	43	39
Site of medical care (%)			
VA Puget Sound Health Care System	46	46	48
Group Health Cooperative	54	54	52
Body Mass Index (kg/m^2), mean (SD)	33 (6.8)	32 (6.9)	33 (7.2)
Type 1 diabetes (%)	7	5	8
Years with diagnosed diabetes (%)			
<6	35	35	30.2
6-24	11	8	14.4
≥25	54	57	55.4

Foot findings (%)			
Moderate/severe oedema	11	8	11
No palpable pulses	1	1	2
Insensate to monofilament	59	66	52
Moderate foot deformity	6	22	35

Length of follow-up [11] 2 years	Outcome(s) measured [12] Foot reulceration in diabetics with previous foot ulcer (cutaneous erosion extending into/through dermis or other cuts with failed healing after 30 days).

INTERNAL VALIDITY

Allocation [13] Computer-generated randomization	Comparison of study groups [14] Similarity between groups for known characteristics, except subjects allocated to prefabricated inserts group who had a notably lower percentage of moderate foot deformity.	Blinding [15] Physicians reviewing foot outcomes blinded. Patient blinding was not possible for this intervention.	Treatment/ measurement bias [16] All subjects underwent similar review at the same intervals during the 2 year follow-up.	Follow-up (ITT) [17] 200/240 = 80% subjects in intervention groups and 134/160 = 83.7% in the control group. During follow-up, physicians prescribed custom shoes for 2.5% of controls and custom inserts for an additional 4.4%; 13% of controls purchased therapeutic shoes and an additional 17% purchased over-the-counter inserts. The study design assumed 33% of controls would cross over to some type of custom shoes/insoles and powered accordingly.

Overall quality assessment (descriptive) [18] A notably lower percentage of foot deformity was observed among the group assigned therapeutic shoes with pre-fabricated inserts. Despite this potential confounder, no effect was observed in favour of the alternative hypothesis among this group. The nature of the intervention made patient blinding unfeasible and reporting bias could not be excluded. Issues with cross-over appear adequately addressed.

RESULTS

Outcome [19]	Intervention group [20]		Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
	Cork inserts	Pre-fabricated inserts	Usual footwear	RR (cork inserts) = 0.88 [0.51, 1.52]	Harms (NNH) [24] 95% CI [25]
Diabetics with ≥ 1 foot ulcer	15% (18/121)	14% (17/119)	17% (27/160)	RR (pre-fabricated) = 0.85 [0.48, 1.48]	N/A
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.			Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] None reported.

EXTERNAL VALIDITY

Generalisabilty [29] Generalisable to other diabetics with history of foot ulcer.

Applicability [30] Benefit of therapeutic shoes with either type of insert over conventional footwear inconclusive. Harm unlikely.
Comments [31] This study does not provide evidence for provision of therapeutic shoes and inserts as a clinically effective measure to reduce foot reulceration among diabetics.

STUDY DETAILS

Reference [1] Piaggesi, A., Macchiarini, S. et al (2007). 'An off-the-shelf instant contact casting device for the management of diabetic foot ulcers: a randomized prospective trial versus traditional fiberglass cast', Diabetes Care, 30 (3), 586-590

Affiliation/source of funds [2]Section of Diabetes and Metabolic Diseases, Department of Endocrinology and Metabolism, University of Pisa and Azienda Ospedaliera Pisana, Pisa, Italy. Supported by Salvatelli SRL, Civitanova Marche, Italy, manufacturers of the Optima Diab Molliter walkers trialled in this study.

Study design [3] RCT	Level of evidence [4] Level II intervention	Location/setting [5] Diabetic foot clinic of the University of Pisa.

Intervention [6] Optima Diab Molliter walker, a novel instant contact casting device for off-loading pressure to the ulcerated diabetic foot. The walker is secured to be non-removable by the patient with specialised plastic lace and can be repositioned at check-ups during the treatment period by means of new lace. Sample size [7] 20 diabetic patients	Comparator(s) [8] Conventional fibreglass total contact casting device for treatment of diabetic foot ulcer. Multiple devices are often required during treatment since repositioning is not possible and removal is only at check-up by means of oscillating saw. Sample size [9] 20 diabetic patients

Selection criteria

Inclusion criteria – Type 1 or 2 diabetes for minimum period of 5 years, peripheral neuropathy characterised by insensitivity to 10g monofilament, vibration perception threshold (at the malleolus) minimum of 25 volts, presence of forefoot plantar ulcer for minimum 3 weeks with area > 1cm^2 graded 1A or 2A according to Texas University classification.

Exclusion criteria – Peripheral vascular disease with ankle-brachial pressure index < 0.9, presence of infection (clinically apparent from oedema, erithema, increased local skin temperature, secretion, fever or leukocytosis confirmed by culture exams), previous ulcer in same site in previous 6 months, probing to bone and/or radiographic signs of osteomyelitis; Charcot's neuroarthropathy (foot), bilateral ulceration, serum creatinine > 2mg/dl, any systemic pathology or therapy that might interfere with healing, severe visual or motor disability that may expose patient to accident risk during study participation, life expectancy < 1 year.

Patient characteristics [10]

	Intervention group	Comparator group(
Age, yrs	61.1 ± 6.4	59.8 ± 8.2
Duration of diabetes, yrs	13.4 ± 7.5	14.7 ± 11.1
AIC (%)	7.6 ± 0.9	7.9 ± 1.1
Vibration perception threshold, volts	39.1 ± 8.6	36.8 ± 7.4
Area of foot lesions (cm^2)	3.9 ± 1.8	3.7 ± 1.6

All data are means ± SD, all differences non-significant.

Length of follow-up [11] 12 weeks or until complete re-epithelialisation of ulcer.	Outcome(s) measured [12] Ulcer healing rate (percentage of patients) at the 12 week end-point, overall healing time, number of adverse events.

INTERNAL VALIDITY

Allocation [13] Computer-generated, concealed list randomization	Comparison of study groups [14] Study groups not significantly different for any known characteristics.	Blinding [15] Patient blinding not possible for this intervention. Not stated whether investigators or outcome assessors were blinded.	Treatment/ measurement bias [16] Besides the differences unique to the two casting devices applied, all patients were treated and reviewed similarly.	Follow-up (ITT) [17] No loss to follow-up or cross-over occurred.

Overall quality assessment (descriptive) [18] A largely unbiased study with no apparent confounding factors. However, small sample size presents likelihood that the study is underpowered and this may preclude its generalisability.

RESULTS

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Healing rate at 12 weeks	85% (17/20)	95% (19/20)	RR = 0.89 [0.82, 1.09]	N/A
Healing time	6.7 ± 3.4 weeks	6.5 ± 4.4 weeks	Mean difference = 0.2 [-2.72, 2.32] (p=0.87)	Harms (NNH) [24] 95% CI [25]
No. of adverse events*				N/A
Skin maceration	2	4		
Infection	1	1		
Transient paresthesia	1	0		
Superficial emathoma	1	0		
Device damage	0	1		
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

*Data insufficient to determine the number of patients associated with each adverse event

Any other adverse effects [28] No additional effects stated.

EXTERNAL VALIDITY

Generalisabilty [29] Generalisability is highest for diabetics with foot ulcer under the proviso that specialist care exceeding conventional standards is available. However, in consideration also of small sample size, generalisability is unlikely to be more than fair.

Applicability [30] Benefits in terms of healing conferred by the interventional and control devices are shown to be similar in this small (low power) study. Harms are also similar. Cost of treatment with the interventional device shown to be significantly less than treatment with the control device.

Comments [31] The results indicate similar performance and potential for harm between the devices compared. However, the Optima Diab Molliter walker was shown to be the significantly more affordable treatment.

STUDY DETAILS				
Reference [1] Armstrong, D. G. & Nguyen, H. C. (2000). 'Improvement in healing with aggressive edema reduction after debridement of foot infection in persons with diabetes', Arch Surg, 135 (12), 1405-1409.				
Affiliation/source of funds [2] Department of Orthopaedics, University of Texas Health Science Center, San Antonio, TX. Department of Surgery, Southern Arizona Veterans Affairs Medical Center, Tuscon, AZ. Research grant from Kinetics Concepts Inc, San Antonio, TX.				
Study design [3] Double-blind RCT	**Level of evidence** [4] Level II intervention		**Location/setting** [5] University teaching hospital	
Intervention [6] Functional foot compression (pneumatic) device proposed to reduce oedema and confer improved healing of foot wounds **Sample size** [7] 59 diabetic patients with foot infections requiring incision and debridement		**Comparator(s)** [8] Placebo foot compression device rendered non-functional by fenestration, but in all other respects identical to the functional device. **Sample size** [9] 56 diabetic patients with foot infections requiring incision and debridement		
Selection criteria **Inclusion criteria** – Diabetes mellitus diagnosed according to WHO criteria, foot infection requiring incision and debridement **Exclusion criteria** – Diagnosed congestive heart failure, end-stage renal disease, serum creatinine > 177μmol/L (> 2mg/dL) on day of hospital admission, lower extremity bypass graft within the period of the study.				
Patient characteristics [10]				
	Intervention group		**Comparator group**	
Age, yrs	49.3 ± 10.3		51.8 ± 10.2	
No. male (%)	38 (73)		34 (76)	
Ethnicity (%)*				
Mexican American	45 (87)		35 (78)	
Non-Hispanic white	6 (12)		8 (18)	
African American	1 (2)		2 (4)	
Duration of diabetes, yrs	12.5 ± 8.7		12.7 ± 11.3	
Glycosylated haemoglobin level, %	9.7 ± 1.9		9.2 ± 2.5	
Vibration perception threshold	39.1 ± 11.3		41.9 ± 9.8	
Transcutaneous oxygen tension, mmHg	42 ± 13.9		50.8 ± 23.2	
Wound size, cm^2	6.7 ± 9.6		7.5 ± 15.7	
Data are means ± SD unless otherwise specified *Percentages may not total 100 due to rounding				
Length of follow-up [11] 12 weeks		**Outcome(s) measured** [12] Proportion of wound healing in each group after 12 weeks		
INTERNAL VALIDITY				
Allocation [13] Computer-generated randomization.	**Comparison of study groups** [14] No clinical or statistically significant difference apparent.	**Blinding** [15] Double-blinding. Only the medical technician who applied the device knew its status and was not involved in discussion or analysis.	**Treatment/ measurement bias** [16] Patients in both groups treated and assessed similarly.	**Follow-up** (ITT) [17] 52/59 (88%) in the intervention group, 45/56 (80%) in the controls group. Both groups assessed according to ITT.
Overall quality assessment (descriptive) [18] A well designed and conducted study. The intervention device is shown to have a significant and clinically important advantage over the non-functioning placebo device. Good external validity.				
RESULTS				

<table>
<tr><td rowspan="2">Outcome [19]

Wound healing</td><td>Intervention group [20]
75% (39/52)</td><td>Control group [21]

51% (23/45)</td><td>Measure of effect/effect size [22]
OR = 2.9

95% CI [25]
[1.2, 6.8] (p<0.02)</td><td>Benefits (NNT) [23] 5

95% CI [25] [2, 21]

Harms (NNH) [24]

95% CI [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the ‘null’) rules out a clinically unimportant effect of the intervention</td><td colspan="2">Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.</td></tr>
<tr><td colspan="5">Any other adverse effects [28] 2 patients (1 in the intervention and 1 in the control group) reported irritation to the dorsal surface of the foot.</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Generalisable to diabetics with foot infection requiring incision and debridement.</td></tr>
<tr><td colspan="5">Applicability [30] Minimal harms associated with the intervention. Potential for benefit high.</td></tr>
<tr><td colspan="5">Comments [31] Good evidence for improved healing of foot infection among diabetics using the pneumatic foot compression device to reduce oedema.</td></tr>
</table>

STUDY DETAILS		
Reference [1] Katz, I. R., A. Harlan, et al. (2005). "A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers." Diabetes Care 28(3): 555-559		
Affiliation/source of funds [2] Source of funding not stated. Authors are affiliated with University of Miami School of Medicine, Tucson Veterans Administration Medical Affairs Center and the Rosalind Franklin University of Medicine and Science (Scholl's Center for Lower Extremity Ambulatory Research). It is not obvious that any of these affiliations are related to either the experimental or control intervention.		
Study design [3] RCT	Level of evidence [4] Level II intervention	Location/setting [5] Referral clinic dedicated to the treatment of diabetic foot ulcers
Intervention [6] Removable Cast Walker rendered irremovable by fibreglass casting material (iTCC) Sample size [7] 21 diabetic patients with chronic plantar foot ulcer	Comparator(s) [8] Standard total contact cast (TCC) Sample size [9] 20 diabetic patients with chronic plantar foot ulcer	
Selection criteria Inclusion criteria – Diagnosis of diabetes Chronic (≥ 7 days with surrounding callus), non-ischaemic, non-infected ulcers staged IA or IIA according to University of Texas criteria. Moderate to severe neuropathy (neuropathy disability score ≥ 6) and biothesiometer vibration perception threshold score ≥ 25 volts at the apex of the hallux on the affected side. Exclusion criteria – Clinical evidence of active infection at the ulcer site Charcot neuroarthropathy Significant peripheral arterial disease (absent dorsalis pedis or posterior tibial pulse) Inability to walk		
Patient characteristics [10]		

	Intervention group	Comparator group
Lost to follow-up	4 (19)	3 (15)
Age, yrs	50.7 (29–65)	51 (23–65)
Male	15 (71)	14 (65)
Race White Black Hispanic	 3 (14) 6 (29) 13 (62)	 2 (10) 8 (40) 12 (60)
Type 2 diabetes	20 (95.2)	18 (90)
Duration of diabetes, yrs	14 (5–33)	14.3 (2–27)
Current smoker	3 (14)	2 (10)
Ever smoked	11 (52)	7 (35)
Insulin requiring	8 (38)	11 (55)
Neuropathy Disability Score	9.2 (7–10)	9.2 (6–10)
Vibration perception threshold, volts	47 (44–51)	45 (41–48)
Ulcer surface area, cm^2	3.1 (1.6, 0.9–3.5)	2.9 (1.9, 0.9–3.9)
Ulcer duration, days	228 (55, 14–260)	202 (76, 19–263)
Ulcer distribution Forefoot Midfoot Heel	 14 (65) 6 (30) 1 (5)	 15 (76) 5 (24) 0 (0)
Data are n (%), means (range/median, 1st and 3rd quartile)		

Length of follow-up [11] 12 weeks			Outcome(s) measured [12] Proportion of healed ulcers at ≤ 12 weeks, healing rates, adverse events	
INTERNAL VALIDITY				
Allocation [13] Pre-prepared random number table.	Comparison of study groups [14] Intervention and control groups similar for known characteristics.	Blinding [15] Patient blinding unfeasible. Unclear whether investigators or outcome assessors were blinded.	Treatment/ measurement bias [16] Patients in both groups received similar treatment and assessment.	Follow-up (ITT) [17] 17/21 (81%) in the intervention group, 17/20 (85%) in the control group. Both groups assessed as per ITT.
Overall quality assessment (descriptive) [18] The number of subjects healed within the 12 week study period was not reported. However, a non-significant p-value was provided, indicating both patient groups received treatments with similar efficacy. Small sample size could preclude generalisability.				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Proportion healed ≤ 12 weeks	80 ± 41%	74 ± 45%*	p = 0.65	Harms (NNH) [24] 95% CI [25]
Median (1st–3rd quartile) healing time	4 (3–7weeks)	5 (3–7) weeks		
Adverse events			RRR = 41%, ARR = 27% [-4.3, 58]	
Unspecified complications	8 (38)	13 (65)		
Maceration	6 (29)	7 (35)		
Broken cast	1 (5)	3 (15)		
Second ulcer	1 (5)	2 (10)		
Abrasions	0	2 (10)		
Toe amputation	1 (5)	1 (5)		
Oedema	0	1 (5)		
Kissing ulcer	0	1 (5)		
Fall	1 (5)	0		
	Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
*Only percentages reported. Number of patients healed not given.				
Any other adverse effects [28] No additional effects reported.				
EXTERNAL VALIDITY				
Generalisabilty [29] Possibly generalisable to diabetics with chronic, non-infected, non-ischaemic plantar foot ulcer.				
Applicability [30] Harms to both groups are likely to be similar as shown by no clinically or significantly different health outcomes between study groups. The benefits of the intervention and control device are similar and likely to outweigh harms.				
Comments [31] It is not clear how the random number table is used to allocate the patient to the study or control intervention and therefore it is not certain that the randomization is entirely masked. Inclusion and exclusion criteria are well defined; however, it is not clear how presence of infection (which excluded patients from the study) was assessed. This is unlikely to have affected the outcomes showing comparable performance of TCC and iTCC for the healing of foot ulcer.				

STUDY DETAILS		
Reference [1] Caravaggi, C., Faglia, E. et al (2000). 'Effectiveness and safety of a nonremovable fiberglass off-bearing cast versus a therapeutic shoe in the treatment of neuropathic foot ulcers: a randomized study', Diabetes Care, 23 (12), 1746-1751		
Affiliation/source of funds [2] Center for the Study and Treatment of Diabetic Foot Pathology, Ospedale di Abbiategrasso; Internal Medicine Unit, Policlinico Multimedica, Sesto S. Giovanni (Milan); Institute of Medical Statistics and Biometry, University of Milan, Italy. Source of funds not stated.		
Study design [3] RCT	Level of evidence [4] Level II intervention	Location/setting [5] Center for the Study and Treatment of Diabetic Foot Pathology
Intervention [6]Non-removable fibreglass off-bearing cast Sample size [7] 26 diabetics with neuropathic plantar ulcers	Comparator(s) [8] Specialised cloth shoe with rigid sole and unloading alkaform insole Sample size [9] 24 diabetics with neuropathic plantar ulcers	
Selection criteria Inclusion criteria – Insensitivity to Semmes-Weinstein 5.07 monofilament, vibration perception threshold of 25 volts measured at the malleolus with a biothesiometer. Exclusion criteria – Clinical presence of deep/superficial tissue infection, underlying osteomyelitis, transcutaneous PO_2 (30mmHg and /or ankle-brachial index (ABI) = 0.6, severe equilibrium problems, severe visual impairment, skin lesions of foot/leg (excluding ulcer under study), limb amputation, plantar bilateral ulcerations.		
Patient characteristics [10]		
	Intervention group	Comparator group
Age, yrs	60.5 ± 10.7	59.2 ± 9.9
Female/Male	8/18	8/16
Tablet treatment	13	12
Insulin treatment	13	12
Diabetes duration, yrs	17.3 ± 10.7	16.2 ± 9.1
Prior lesion	10	9
BMI, kg/m^2	27 ± 1.6	27.3 ± 2.5
Smoking	5	10
Hypertension	13	11
Retinopathy	14	13
Microalbuminuria	4	4
Proteinuria	5	3
Renal impairment	5	2
ABI	1.00 ± 0.7	1.03 ± 0.8
Transcutaneous oxygen tension on dorsum of foot	53.5 ± 12.6	52.6 ± 11.6
Data are n or means ± SD		
Length of follow-up [11] 30 days	Outcome(s) measured [12] Rapidity of foot ulcer size reduction and complete ulcer healing rate (trend measured as per cent of patients healed per quintile	
INTERNAL VALIDITY		

<table>
<tr><td>Allocation [13] Random number tables were consulted to assign patients by means of phone call to the trial centre.</td><td>Comparison of study groups [14] No apparent clinical or statistical differences between intervention group and controls.</td><td>Blinding [15] Patient blinding unfeasible. Not stated if investigators or assessing physicians were blinded.</td><td>Treatment/ measurement bias [16] Excluding the intervention treatment, patients in both groups treated and assessed similarly.</td><td>Follow-up (ITT) [17] No loss to follow-up mentioned. No evidence against ITT.</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18] Study of average internal validity with promising results for clinical application. Shows possible benefit associated with an off-loading cast device in comparison to shoes designed for the same purpose.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td>Outcome [19]

Trend in ulcer area reduction, quintiles
1.00
0.75
0.50
0.25
0.00
-0.25</td><td>Intervention group [20]

50.0% (13/26)
26.9% (7/26)
19.2% (5/26)
3.8% (1/26)
0
0</td><td>Control group [21]

20.8% (5/24)
12.5% (3/24)
25.0% (6/24)
8.3% (2/24)
25.0% (6/24)
8.3% (2/24)</td><td>Measure of effect/effect size [22]

95% CI [25]

RR = 2.40 [1.07, 5.76]
RR = 2.15 [0.68, 7.24]
RR = 0.77 [0.27, 2.14]
RR = 0.46 [0.06, 3.41]</td><td>Benefits (NNT) [23] 4
95% CI [25] [-2, 20]

3 [2, 39]

Harms (NNH) [24]
95% CI [25]</td></tr>
<tr><td></td><td colspan="2">Clinical importance (1-4) [26] 2. The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects.</td><td colspan="2">Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.</td></tr>
<tr><td colspan="5">Any other adverse effects [28] The authors reported that no adverse effects were experienced by any patients.</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Fair generalisability to diabetics with neuropathic plantar ulcer.</td></tr>
<tr><td colspan="5">Applicability [30] No harms reported with either the intervention or control group. Intervention cast shown to be statistically superior to the control shoe. Benefit of intervention should outweigh harm.</td></tr>
<tr><td colspan="5">Comments [31] Valid results supporting the hypothesis that off-loading cast devices provide superior (faster and more complete) ulcer healing than shoes with unloading alkaform insoles.</td></tr>
</table>

STUDY DETAILS		
Reference [1] Mueller, M. J., Diamond, J. E. et al (1989). 'Total contact casting in treatment of diabetic plantar ulcers. Controlled clinical trial', Diabetes Care, 12 (6), 384-388		
Affiliation/source of funds [2] Walter Johnston Rehabilitation Institute, Program in Physical Therapy, and Division of Orthopedic Surgery, Department of Surgery, Washington University School of Medicine, St. Louis, Missouri, USA. Supported by grant from the Foundation for Physical Therapy.		
Study design [3] RCT	Level of evidence [4] Level II intervention	Location/setting [5] Diabetic foot center and physical therapy department at Washington University School of Medicine.
Intervention [6] Total contact casting (TCC) for off-loading pressure to ulcerated foot. Sample size [7] 21	Comparator(s) [8] Traditional dressing treatment (TDT). Sample size [9] 19	
Selection criteria Inclusion criteria – Diagnosis of diabetes mellitus, current plantar ulcer. Exclusion criteria – No evidence of gross infection (no significant oedema or drainage), osteomyelitis (determined by radiograph or radionuclide scans), gangrene (visibly discoloured or necrotic tissue).		
Patient characteristics [10]		

	Intervention group	Comparator group
Age, yrs	54 ± 10	55 ± 12
n, M/F	13/8	14/5
Insulin/non-insulin dependent	5/16	6/13
Duration of diabetes, yrs	17 ± 6	17 ± 9
Ulcer duration, days	155 ± 195	175 ± 200
Ulcer size Area, cm^2 Depth, mm	 1.8 ± 2.5 3.6 ± 3.2	 2.8 ± 3.4 2.4 ± 0.9
Ulcer grade 1 2	 15 6	 13 6
Sensation (Semmes-Weinstein monofilament) 4.17 (Intact) 5.07 (Decreased) 6.10 (Severely decreased) > 6.10 (Absent)	 0 0 6 15	 0 1 6 12
Vascular disease Ankle/brachial ratios 0.5 – 0.99 Ankle/brachial ratios < 0.5	 2 1	 3 1
Data all n, except where indicated		
Length of follow-up [11] 6 weeks	Outcome(s) measured [12] Number of patients with ulcers healed (complete skin coverage and no drainage), healing time, complications (infection, amputation)	
INTERNAL VALIDITY		

<table>
<tr><td>Allocation [13] Method of randomization not explicit</td><td>Comparison of study groups [14]</td><td>Blinding [15] Patient blinding appears infeasible. Blinding of investigators/assessor not stated.</td><td>Treatment/ measurement bias [16] Treatment for intervention and control groups, except for casting, was stated to be identical. However, while those assigned TCC were instructed to ‘limit ambulation to 33% of their usual activity’, controls were instructed to ‘avoid bearing weight on the involved lower extremity’. Both groups were provided with walkers/crutches to assist their compliance.</td><td>Follow-up (ITT) [17] Subjects who refused to receive treatment in their assigned group before complete ulcer healing were considered unhealed. 19/22 controls received treatment for the duration of the study and no drop out occurred among the intervention group.</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18] Some potential for confounding bias associated with inability to readily quantify compliant behaviour among intervention and control groups, especially in relation to the avoidance of bearing weight on limbs affected by ulcers. Patient blinding not possible, however, potential for blinding of assessing physicians should be possible, but no information indicated whether this blinding was undertaken. Average internal validity with some clinically important outcomes.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td>Outcome [19]</td><td>Intervention group [20]</td><td>Control group [21]</td><td>Measure of effect/effect size [22]
95% CI [25]</td><td>Benefits (NNT) [23] 2
95% CI [25] [1, 3]
Harms (NNH) [24]
95% CI [25]</td></tr>
<tr><td>Patients healed</td><td>90% (19/21)</td><td>32% (6/19)</td><td>RR = 2.9 [1.5, 5.6]</td><td></td></tr>
<tr><td>Healing time</td><td>42 ± 29 days</td><td>65 ± 29 days</td><td>Mean difference = 23 [4.4, 41.6]</td><td></td></tr>
<tr><td>Complications
Infection
Amputation</td><td>
14.3% (3/21)
0</td><td>
26.3% (5/19)
10.5% (2/19)</td><td>
RR = 0.54 [0.15, 1.97]
ARR = 0.11 [-0.07, 0.31]</td><td></td></tr>
<tr><td></td><td colspan="2">Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.</td><td colspan="2">Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.</td></tr>
<tr><td colspan="5">Any other adverse effects [28] None reported</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Generalisable to patients with diabetic plantar ulcer.</td></tr>
<tr><td colspan="5">Applicability [30] This study has shown that there is a statistically lower risk of infection among diabetic patients receiving the intervention treatment. The benefits (statistically higher rates of healing) should outweigh the reported harms.</td></tr>
<tr><td colspan="5">Comments [31] Some valid results providing evidence for the alternative hypothesis of a difference in ulcer healing between the two study groups.</td></tr>
</table>

STUDY DETAILS				
Reference [1] Armstrong, D. G., Lavery, L. A. et al (2005). 'Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial', Diabetes Care, 28 (3), 551-554				
Affiliation/source of funds [2] Center for Lower Extremity Ambulatory Research, the Dr William M Scholl College of Podiatric Medicine at Rosalind Franklin University of Medicine, Chicago, Illinois; the Department of Surgery, Southern Arizona Veterans Affairs Medical Center, Tucson, Arizona; the Department of Medicine, Manchester Royal Infirmary, University of Manchester; Manchester, UK, Department of Surgery, Texax A&M University, Temple, Texas. Supported by US Department of Veterans Affairs, Health Services Research and Development Award IIR 20-059 and the Rehabilitation Research and Development Merit Award A2150RC.				
Study design [3] RCT	Level of evidence [4] Level II intervention	Location/setting [5] Not specified which of the affiliated organisations provided the study location.		
Intervention [6] Removable cast walker wrapped with a cohesive bandage, rendering it irremovable by the patient, i.e. an 'instant' total contact cast (iTCC) Sample size [7] 23 diabetics with plantar ulcer	Comparator(s) [8] Removable cast walker (RCW) Sample size [9] 27 diabetics with plantar ulcer			
Selection criteria Inclusion criteria – Diagnosis of diabetes confirmed with primary care physician or by medical record review, loss of protective sensation (> 25 volts) quantified by vibration perception threshold meter, at least one palpable foot pulse, neuropathic plantar ulcer corresponding to 1A (University of Texas Diabetic Foot Wound Classification System). Exclusion criteria – Active infection, non-ambulatory status, ulcers of the foot other than the plantar aspect, severe peripheral vascular disease (as indicated by absence of both foot pulses on the affected extremity).				
Patient characteristics [10]				

	Intervention group	Comparator group
Age, yrs	66.9 ± 10.1	64.6 ± 9.8
Male	87 (20)	88.9 (24)
BMI, kg/m^2	33.3 ± 6.8	33.5 ± 6.2
Wound area, cm^2	2.7 ± 1.3	2 ± 1.1
Vibration perception threshold, volts	37 ± 8.1	37.3 ± 7
HbA	8.5 ± 1.5	8 ± 1.4

Data are means ± SD or % (n)

Length of follow-up [11] 12 weeks	Outcome(s) measured [12] Number of patients with healed ulcer, ulcer healing time, complications (maceration, infection)

INTERNAL VALIDITY				
Allocation [13] Computer-generated randomization	Comparison of study groups [14] No clinically or statistically significant differences between study groups.	Blinding [15] Patient groups could not be blinded. Not stated if investigators/assessing physicians blinded.	Treatment/ measurement bias [16] Both study groups were treated and assessed similarly.	Follow-up (ITT) [17] 89% (24/27) of controls, 96% (22/23) from the intervention group. Patients lost to follow-up were considered as non-healed for ITT analysis purposes.
Overall quality assessment (descriptive) [18] A study of average internal validity. Results require caution in interpretation due to anomalies in the reporting of statistical data.				
RESULTS				

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 3 95% CI [25] [2, 23]
Patients healed	82.6% (19/23)	51.9% (14/27)	OR = 4.41* [1.18, 16.44] RR=1.59 [1.07, 2.12]	Harms (NNH) [24] 95% CI [25]
Ulcer healing time	41.6 ± 18.7 days	58.0 ± 15.2 days	Mean difference = 16.4 [6.76, 26.04]	
Complications				
Maceration	68.2% (15/23)	37.5% (9/27)	OR = 3.75† [1.16, 12.12]	
Infection	27.3% (6/23)	41.7% (10/27)	OR = 0.6 [0.18, 2.02]	
	Clinical importance (1-4) [26] Patients healed: 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention. Ulcer healing time: 1. A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention. Maceration: 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect. Infection: 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	
Any other adverse effects [28] None reported.				
EXTERNAL VALIDITY				
Generalisabilty [29] Fair generalisability to diabetics with plantar foot ulcer.				
Applicability [30] The benefit conferred by the iTCC (compared to RCW) appears to be higher than indicated from author-reported statistics. However, iTCC showed a statistically higher maceration rate than RCW. Confidence intervals in both instances were wide and contained values approaching values of no effect, making it difficult to establish whether benefits are likely to outweigh harms.				
Comments [31] Odds ratios reported by authors were notably different from those calculated from raw data for the purposes of this evidence table. Interpretation and extrapolation of the results requires caution.				

* This calculation is based on raw study data but differs substantially from the OR reported by the authors = 1.8 [1.1, 2.9].
†OR reported by the authors = 1.8 [1, 3.3].

STUDY DETAILS

Reference [1] Armstrong, D. G., Nguyen, H. C. et al (2001). 'Off-loading the diabetic foot wound: a randomized clinical trial', Diabetes Care, 24 (6), 1019-1022

Affiliation/source of funds [2] Audie L Murphy Veterans Affairs Medical Center, Tucson Arizona; the Department of Orthopaedics, University of Texas Health Science Center, San Antonio, Texas; the Department of Medicine, Manchester Royal Infirmary, University of Manchester; Manchester, UK; the Department of Surgery, Southern Arizona Veterans Affairs Medical Center, Tucson, Arizona. Funded by the US Department of Veterans Affairs Rehabilitation R&D Merit Award Grant A2150RC and the Aircast Research Foundation.

Study design [3] RCT	Level of evidence [4] Level II intervention	Location/setting [5] Not specified which of the affiliated organisations provided the study location.

Intervention [6] Total contact cast (TCC) for off-loading pressure to the ulcerated diabetic foot. Sample size [7] 19	Comparator(s) [8] Removable cast walker (RCW), half-shoe Sample size [9] RCW: 20, Half-shoe: 24

Selection criteria

Inclusion criteria – Diagnosis of diabetes confirmed by primary care providers or medical record review, loss of protective sensation (> 25 volts) quantified by vibration perception threshold (VPT) meter, at least one palpable foot pulse or a transcutaneous oximetry ($TcPO_2$) measurement > 40mmHg at the dorsal level of forefoot, neuropathic (inability to sense Semmes-Weinstein10g monofilament) plantar ulcer corresponding to 1A University of Texas Diabetic Foot Wound Classification System.

Exclusion criteria – Active infection, non-ambulatory status, ulcers of the foot other than the plantar aspect, severe peripheral vascular disease (as indicated by absence of both foot pulses on the affected extremity).

Patient characteristics [10]

Intervention group –

Comparator group(s) –

	TCC	RCW	Half-shoe
% Male	73.7	90.0	83.3
Duration of diabetes, yrs	17.8 ± 8.7	18.2 ± 10.1	15.3 ± 7.9
$TcPO_2$	60.7 ± 9.0	62.0 ± 16.3	58.6 ± 10.4
Ulcer area, cm^2	1.3 ± 0.8	1.4 ± 1.4	1.3 ± 1.2
Ulcer duration, months	4.3 ± 5.7	5.6 ± 6.2	5.5 ± 7.1
VPT, volts	41.5 ± 10.5	46.7 ± 4.8	45.4 ± 7.7

Data are means ± standard error of the means

Length of follow-up [11] 12 weeks	Outcome(s) measured [12] Proportion of patients with ulcer healing (complete re-epithelialisation) after 12 weeks, healing time

INTERNAL VALIDITY

Allocation [13] Computer-generated randomization	Comparison of study groups [14] Groups similar for known characteristics. Mean ages of groups not provided, so comparison on this characteristic not possible, although authors claimed no difference.	Blinding [15] Patient blinding not feasible. Investigator/assessor blinding not stated.	Treatment/ measurement bias [16] Patients across the three arms treated and assessed similarly.	Follow-up (ITT) [17] TCC: 68% (13/19) RCW: 75% (15/20) Half-shoe: 96% (23/24). ITT analysis not clear.

Overall quality assessment (descriptive) [18] A study of average internal validity, generalisable to patients being considered for the guideline. The statistical and clinical significance of the results may have been stronger if more subjects in the TCC arm had been followed up.

RESULTS

<table>
<tr><td rowspan="3">Outcome [19]</td><td>Intervention group [20]</td><td colspan="2">Control groups [21]</td><td>Measure of effect/effect size [22]
95% CI [25]</td><td>Benefits (NNT) [23]
95% CI [25]</td></tr>
<tr><td>TCC</td><td>RCW</td><td>Half-shoe</td><td rowspan="2">OR (TCC vs controls overall) = 5 [1.1, 26.1]

TCC vs half-shoe, p = 0.005
TCC vs RCW, p = 0.07</td><td>Harms (NNH) [24]

95% CI [25]</td></tr>
<tr><td>Proportion patients with ulcer healing

Healing time, days</td><td>89.5%

33.5 ± 5.9</td><td>65.0%

50.4 ± 7.2</td><td>58.3%

61.0 ± 6.5</td></tr>
<tr><td></td><td colspan="3">Clinical importance (1-4) [26] 1. A clinically important benefit for the full range of plausible estimates.The confidence limit closest to the measure of no effect (the ‘null’) rules out a clinically unimportant effect of the intervention.</td><td colspan="2">Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.</td></tr>
<tr><td colspan="6">Any other adverse effects [28] Authors state that no falls or device-related ulcerations occurred during the study.</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisabilty [29] Generalisable to diabetics with plantar ulcers.</td></tr>
<tr><td colspan="6">Applicability [30] The benefit conferred by the TCC is likely to outweigh any potential harms associated with its use.</td></tr>
<tr><td colspan="6">Comments [31] The confidence interval for the odds ratio comparing TCC with the combined results for RCW and half-shoe is wide. At the lower limit approaches a value that is only marginally significant, suggesting that improved ulcer healing associated with TCC is not strongly evidenced. Authors claim the study was designed to detect a 40 per cent difference between any two arms with a power exceeding 80 per cent for n = 60. However, loss-follow-up, especially in the TCC arm meant that only 51 patients were subject to final analysis. Stronger evidence (a lower confidence limit of greater statistical significance) may have been observed if more subjects in the TCC were followed up.</td></tr>
</table>

STUDY DETAILS				
Reference [1] Uccioli, L., Faglia, E. et al (1995). 'Manufactured shoes in the prevention of diabetic foot ulcers', Diabetes Care, 18 (10), 1376-137				
Affiliation/source of funds [2] Cattedra di Endicrinologia, Dipartimento di Medicina Interna, Università "Tor Vergata", Rome; Servizio di Diabetologia, Ospedale Niguarda, Milan, Italy. Supported in part by Buratto SpA, Italy (supply of therapeutic shoes and insoles).				
Study design [3] Multicentre RCT	Level of evidence [4] Level II intervention	Location/setting [5] Two teaching hospitals (Rome, Milan).		
Intervention [6] Therapeutic shoes Sample size [7] 33 diabetics with previous foot ulcer	Comparator(s) [8] Usual shoes Sample size [9] 36 diabetics with previous foot ulcer			
Selection criteria Inclusion criteria – No current ulceration, absence of minor/major amputations, no major foot deformities, e.g. Charcot joints. Exclusion criteria – None specified.				
Patient characteristics [10]				

	Intervention group	Comparator group
Age, yrs	59.6 ± 11	60.2 ± 8.2
Male/Female	20/13	23/13
Duration of diabetes, yrs	16.8 ± 12.7	17.5 ± 8
Type I/II diabetes	8/25	9/27
Ankle/brachial index	0.95 ± 0.2	1 ± 0.2
Vibration perception threshold, mV	33 ± 9	31 ± 12

Length of follow-up [11] One year	Outcome(s) measured [12] Proportion of patients with ulcer relapses during follow-up, association between relapse and therapeutic shoes (correlation coefficient)

INTERNAL VALIDITY				
Allocation [13] Not specified.	Comparison of study groups [14] Both groups similar at inception.	Blinding [15] Patient blinding not feasible. Investigator/assessor blinding not stated.	Treatment/ measurement bias [16] Groups treated and assessed similarly.	Follow-up (ITT) [17] No loss-to-follow up evident, i.e. 100% follow-up for both groups.
Overall quality assessment (descriptive) [18] The evidence provided by this study for the benefit of therapeutic shoes is not conclusive. The confidence interval for the odds ratio is compatible clinically with values that indicate normal footwear may be no different in the re-occurence of ulcers. However, the confidence interval associated with the correlation coefficient provides slightly stronger evidence of benefit from therapeutic shoes.				
RESULTS				
Outcome [19] Proportion of patients with ulcer relapse	Intervention group [20] 27.7% (absolute number not specified)	Control group [21] 58.3% (absolute number not specified)	Measure of effect/effect size [22] 95% CI [25] OR = 0.26 [0.2, 1.54] ρ = -0.32 [-0.54, -0.08] p < 0.01	Benefits (NNT) [23] 95% CI [25] Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect		Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.	

Any other adverse effects [28] None reported.
EXTERNAL VALIDITY
Generalisabilty [29] Generalisable to diabetics with history of foot ulcer.
Applicability [30] No harms directly reported. Point estimate shows a benefit associated with therapeutic shoes. However, the confidence interval is not conclusive as it contains values that indicate benefits may not outweigh harms.
Comments [31] Insufficient evidence of a truly random sample in this study may present some bias.

STUDY DETAILS

Reference [1] Agas, C. M., Bui, T. D. et al (2006). 'Effect of window casts on healing rates of diabetic foot ulcers', J Wound Care, 15 (2), 80-83

Affiliation/source of funds [2] University of California Irvine Medical Center Wound Clinic, Irvine, California; Veterans Affairs Long Beach Healthcare System, Department of Vascular Surgery, Long Beach, California; Dr William M Scholl College of Podiatric Medicine, Rosalind Franklin University of Medicine, Chicago. Source of funds not stated.

Study design [3] RCT	Level of evidence [4] Level II intervention	Location/setting [5] Veterans Affairs Medical Center

Intervention [6]

(1) Topical platelet derived growth factor (PDGF) plus shoes

(2) PDGF plus off-loading cast.

Note: study design does accommodate a strict definition of "intervention" and "comparator" and as such outcomes do not adequately address a defined question. Statistical comparison is only possible between patients within these two "intervention" arms.

Sample size [7]

(1) 21 diabetics with foot ulcer/unhealed surgical incision

(2) 17 diabetics with foot ulcer/unhealed surgical incision

Comparator(s) [8]

(1) Topical placebo hydrogel plus shoes

(2) Hydrogel plus off-loading cast

Note: Results were available for individuals outcomes for both "comparator" groups, but could not be directly compared with the results of the "intervention" groups.

Sample size [9]

(1) 5 diabetics with foot ulcer/unhealed surgical incision

(2) 3 diabetics with foot ulcer/unhealed surgical incision

Selection criteria

Inclusion criteria – Diagnosis of type II diabetes, full-thickness ulcer (Wagner grade II-III) 1 – 16cm^2 in area and minimum duration of one month before study entry. Ulcers could be on any part of the foot and postoperative incisions that failed to heal were also accepted.

Exclusion criteria – Presence of infection involving a joint, tendon or bone, Charcot's deformity, malignancy, concomitant use of anti-neoplastic drugs or corticosteroids, malnutrition, significant arterial ischaemia (ABPI < 0.7).

Patient characteristics [10]

	Intervention groups		Comparator groups	
	PDGF + shoes	PDGF + cast	Hydrogel + shoes	Hydrogel + cast
Age, years	56 ± 9	61 ± 10	56 ± 10	53 ± 6
Duration of wound, days	411 ± 1253	317 ± 283	190 ± 153	200 ± 76
Initial wound area, mm^2	438 ± 389	351 ± 442	536 ± 685	305 ± 281

Data are means ± SD

Length of follow-up [11]

PDGF + shoes group mean follow-up was 110 ± 75 days.

PDGF + cast group mean follow-up was 59 ± 41 days.

"Comparator" groups follow-up unclear.

Note: follow-up appears concordant with mean ± SD days of treatment, however this was assessed *retrospectively*.

Outcome(s) measured [12] Proportion of wounds healed, duration of therapy, amputations

INTERNAL VALIDITY

<table>
<tr><td>Allocation [13] PDGF/hydrogel allocation was at a 2:1 ratio among patients with preceding failure of five month treatment with PDGF. Allocation of shoes was based on clinical grounds and not random, as reported by authors.</td><td>Comparison of study groups [14] Notable differences in wound duration initial wound size. Other known characteristics similar.</td><td>Blinding [15] Authors state that investigators were blinded to the treatment options. It is assumed/implied patients were not aware of their PDGF/hydrogel receiving status, whereas blinding to shoe/cast status was infeasible.</td><td>Treatment/ measurement bias [16] Shoe/cast wearing was discretionary. Therefore treatment allocation may be biased. Groups differed also on PDGF/hydrogel status, raising the issue of a inappropriately determined (multiple) interventions.</td><td>Follow-up (ITT) [17] Inadequately addressed. “Retrospective” study.</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18] The patients evaluated in this study formed one centre’s participants from a larger, but unpublished multi-centre study. The study was sponsored by Johnson & Johnson. The design and lack of a clearly defined research question with opposing hypotheses result in poor internal validity and inability to judiciously generalise results to relevant populations. Treatment allocation bias is likely, however the nature of possible effects is uncertain.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td>Outcome [19]

Wounds healed (%)

Therapy duration, days

Amputations</td><td>Intervention group [20]<table><tr><td>PDGF + shoes</td><td>PDGF + cast</td></tr><tr><td>6 (25)</td><td>15 (83)</td></tr><tr><td>110 ± 75</td><td>59 ± 41</td></tr><tr><td>5</td><td>0</td></tr></table></td><td>Control group [21] No comparable results reported.</td><td>Measure of effect/effect size [22]
95% CI [25]

Wounds healed, p = 0.002, Note: since PDGF is common to both groups, this value indicates a difference in healing associated with shoes and cast, but cannot establish a difference between PDGF and hydrogel, which would require revision of the study design and development of a clearer research question.

Duration of therapy, p = 0.046</td><td>Benefits (NNT) [23] N/A

95% CI [25]

Harms (NNH) [24] N/A

95% CI [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.</td><td colspan="3">Relevance (1-5) [27] 3. Evidence of an effect on proven surrogate outcomes but for a different intervention</td></tr>
<tr><td colspan="5">Any other adverse effects [28] No additional adverse events reported.</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisabilty [29] Research question not specific, therefore results not readily applicable to patients even with the same characteristics.</td></tr>
<tr><td colspan="5">Applicability [30] Inadequately defined research question precludes applicability of observed benefits or harms.</td></tr>
<tr><td colspan="5">Comments [31] The authors concluded that a prospective RCT would be required to enable comparison between PDGF and hydrogel. The evaluator agrees with their assessment that the key question for such a study is whether PDGF plus casting is superior to hydrogel with identical off-loading.</td></tr>
</table>

STUDY DETAILS				
Reference [1] Nube, V. L., Molyneaux, L. et al (2006). 'The use of felt deflective padding in the management of plantar hallux and forefoot ulcers in patients with diabetes', Foot, 16 (1), 38-43				
Affiliation/source of funds [2] Diabetes Centre, Royal Prince Alfred Hospital, Camperdown, NSW; Discipline of Medicine, University of Sydney, Australia.				
Study design [3] RCT	Level of evidence [4] Level II intervention		Location/setting [5] Australian hospital diabetes centre	
Intervention [6] Felt deflective padding (FDP) applied directly to skin, with aperture at the ulcer site Sample size [7] 15 diabetics		Comparator(s) [8] FDP applied within shoe, with aperture at the ulcer site. Note: Data for patients in both groups were pooled after primary analysis to compare outcomes by ulcer location (forefoot or hallux). Sample size [9] 17 diabetics		
Selection criteria Inclusion criteria – Type I or II diabetes; plantar neuropathic foot ulcer of hallux or metatarsal area, grade IA or IB (Texas Wound Grading System), with neuropathy defined as vibration perception threshold > 30 volts when tested with biothesiometer. Exclusion criteria – Impalpable pedal pulses or ankle brachial inex < 0.6; highly exudative ulcer; deep focus of suppuration; patients deemed to require antibiotics were graded as infected (B), but not excluded; if infection was gross, prospective patients were delayed from entering the study for 2 weeks until clinical signs were diminished or resolved using an alternative method of off-loading.				
Patient characteristics [10]				

	Intervention group	Comparator group
Age, yrs	59 (50–70)	56 (55–66)
Males, n	14	12
Type II diabetes, n	14	16
Duration of diabetes, yrs	14 (10–19)	12 (6–19)
HbA1c, %	10.4 (6.8–11.4)	8.5 (7.3–9.9)
Vibration perception threshold, volts	50 (48–50)	50 (50–50)
Duration of ulcer, months	11.5 (3.0–123.0)	4.5 (2.0–12.5)
Area of ulcer, cm^2	0.5 (0.2–1.3)	0.5 (0.2–0.8)

Length of follow-up [11] 4 weeks	Outcome(s) measured [12] Percentage of ulcer size reduction comparing skin and shoe applications of FDP. Subsequently, data were pooled and percentage of ulcer size reduction was compared by ulcer location (hallux or forefoot).

INTERNAL VALIDITY				
Allocation [13] Randomisation by drawing of lots	Comparison of study groups [14] Duration of ulcer was notably higher among the intervention (skin) group. Other known characteristics similar.	Blinding [15] Investigators reported that blinding was difficult due to treatment modalities.	Treatment/ measurement bias [16] Investigators noted that attempts were made to control for variables such as dressings and shoe types but some variation, particularly in regard to footwear, is evident.	Follow-up (ITT) [17] 73% (11/15) for intervention group, 88% (15/17) for comparator group. No evidence against analysis conducted according to ITT.
Overall quality assessment (descriptive) [18] A small study, possibly lacking power to detect any statistically significant difference in the treatments. Loss-to-follow-up is of borderline concern within the intervention group, and some bias due to variation in footwear among the comparator group could affect the results. Average internal validity.				
RESULTS				

Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22]	Benefits (NNT) [23]
Percentage of ulcer reduction, by intervention	74% (range:87–55)	73% (84–63)	95% CI [25] p = 0.9	95% CI [25] Harms (NNH) [24]
Percentage of ulcer size reduction, by ulcer location	Hallux: 75% (range: 89–40)	Forefoot: 72% (range: 83–58)	p = 0.9	95% CI [25]
	Clinical importance (1-4) [26] 3. The confidence interval does not include any clinically important effects.		Relevance (1-5) [27] 5. Evidence confined to unproven surrogate outcomes.	
Any other adverse effects [28] Authors reported that no serious adverse effects were observed with either treatment. One patient from both treatment groups had minor skin tears, one patient in the intervention group had maceration and there were three cases of tinea pedis. All resolved rapidly.				
EXTERNAL VALIDITY				
Generalisabilty [29] Fair generalisability to diabetics with foot ulcer.				
Applicability [30] Harms likely to be minimal. Results for both study groups were not statistically different, suggesting each treatment is equally beneficial.				
Comments [31] The analysis of ulcer reduction by location (hallux or forefoot) did not control for treatment, precluding extraction of results relevant to the guideline for this outcome.				

Question 7

STUDY DETAILS				
Reference [1] (Chantelau et al 1996) Antibiotic treatment for uncomplicated neuropathic forefoot ulcers in diabetes: a controlled trial. Diabetic medicine : a journal of the British Diabetic Association 156-159.				
Affiliation/source of funds [2] Diabetic Foot Clinic, Heinrich-Heine-University of Dusseldorf, Germany. Funded by SmithKline-Beecham Company Munich, Germany.				
Study design [3] double-blind RCT	Level of evidence [4] II	Location/setting [5] Germany Diabetic Foot Clinic		
Intervention [6] 500 mg amoxicillin plus 125 mg clavulanic acid tablets, three times a day in addition to standard wound treatment of debriding, cleansing and sterile dressings, relieving pressure Sample size [7] 22	Comparator(s) [8] Same wound treatment but received placebo tablets to be taken orally three times a day. Sample size [9] 22			
Selection criteria Inclusion criteria – Diabetic patients over 18 years of age, with a skin and soft tissue forefoot lesion of Wagner grade 1A (superficial, with or without cellulitis) to 2A (deeper, reaching to joints or tendons), presence of polyneuropathy, and were willing to participate. Exclusion criteria – Known hypersensitivity to amoxicillin or augmentin, any antibiotic treatment during the preceding 7 days, bilateral foot lesions, osteomyelitis, pregnancy, peripheral vascular disease, serum creatinine level >130 μmol/ml, immune depression, amoxicillin or clavulanic acid resistant bacterial infection, or inability of patient to comply with the wound-monitoring protocol.				
Patient characteristics [10] Intervention group – N = 22, Age (yrs) 58 [54, 62], Gender: male 16/22 (72.7%), female 6/22 (27.3%), Duration of diabetes (yrs) 22 [17, 27], Insulin therapy 11/22 (50%), Current smokers 2/22 (9.1%), HbA_{1c} < 8% 9/22 (40.9%), Diabetic retinopathy 13/22 (59.1%), Proteinuria > 500 mg/L 4/22 (18.2%), Ulcer size (mm^2) 214 [154, 274]. Comparator group(s) – N = 22, Age (yrs) 59 [55, 63], Gender: male 12/22 (54.5%), female 10/22 (45.5%), Duration of diabetes (yrs) 19 [14, 24], Insulin therapy 12/22 (54.5%), Current smokers 5/22 (22.7%), HbA_{1c} < 8% 10/22 (45.5%), Diabetic retinopathy 12/22 (54.5%), Proteinuria > 500 mg/L 2/22 (9.1%), Ulcer size (mm^2) 220 [162, 422].				
Length of follow-up [11] 3-20 days	Outcome(s) measured [12] healing of ulcer, mean reduction in ulcer radius (mm/day)			
INTERNAL VALIDITY				
Allocation [13] Computer-generated randomisation code, placebo and antibiotic tablets appeared identical and were in neutral containers	Comparison of study groups [14] Baseline characteristics were similar between the groups with the exception of gender (18% difference) and smoking status (13% difference).	Blinding [15] Participants, staff administering the treatment and investigators were blinded	Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups	Follow-up (ITT) [17] No: 2 control and 3 intervention patients that withdrew from treatment were not included in the final analysis
Overall quality assessment (descriptive) [18] Although patients and investigators were blinded, the distribution of some key confounders was unequal and the analysis was not ITT. It is highly likely that the lack of a statistically significant result is due to the small sample size. This study was of average quality.				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22] (95% CI) [25]	Benefits (NNT) [23] 95% CI [25]
Healed within 20 days	6/22 (27%)	10/22 (45%)	RR = 0.6 (0.26, 1.37)	Harms (NNH) [24]
Mean reduction in ulcer radius(mm/day)	0.27 (95% CI 0.15, 0.39)	0.41 (95% CI 0.21, 0.61)	0.14	95% CI [25]

	Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.	Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
Any other adverse effects [28] Minor self-limiting diarrhoea in 1 patient receiving the antibiotics. Patient continued to participate in trial.		
EXTERNAL VALIDITY		
Generalisabilty [29] Applicable to other diabetics with infected diabetic foot ulcers.		
Applicability [30] As there does not seem to be a statistically significant treatment effect, it is unknown whether or not the potentials benefits will outweigh the harms.		
Comments [31] The details regarding the randomisation and blinding procedures followed were very poorly described. It is likely the study was not adequately powered due to the small sample size and wide confidence intervals around the point estimates.		

Wagner Classification Grade I = superficial ulcer, Grade II = deep ulcer to tendon, capsule or bone, Grade III = deep ulcer with abscess, osteomyelitis or joint sepsis, Grade IV = localized gangrene of forefoot or heel, Grade V = gangrene of entire foot

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] (Hirschl & Hirschl 1992) "Bacterial flora in mal perforant and antimicrobial treatment with ceftriaxone." Chemotherapy 38(4): 275-280.</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2] Vascular Outpatient Clinic, Hanusch Hospital and Dept. of Clinical Microbiology, Hygiene Institute, Vienna, Austtria.</td></tr>
<tr><td colspan="2">Study design [3] historically controlled study</td><td colspan="2">Level of evidence [4] III-3</td><td colspan="2">Location/setting [5]Austria/ Vascular Outpatient Clinic</td></tr>
<tr><td colspan="3">Intervention [6] 2 g ceftriaxone/day i.v. Plus treatment with alprostadil, prostaglandin, daily cleaning of ulcer with saline, application of sterile dressing, provision of orthopaedic shoe to reduce pressure
Sample size [7] 25</td><td colspan="3">Comparator(s) [8] same treatment without the antibiotic – ceftriaxone.

Sample size [9] 25</td></tr>
<tr><td colspan="6">Selection criteria
Inclusion criteria – Diabetic patients with neurotrophic ulcer that were enrolled in the study.
Control group - Historical group of 25 consecutive patients with neurotrophic ulcer who had been treated without antibiotics prior to the start of the study
Exclusion criteria – None stated</td></tr>
<tr><td colspan="6">Patient characteristics [10]
Intervention group – N = 25, Age (yrs) 70 ± 11, Gender: male 15/25 (60%), female 10/25 (40%), Duration of diabetes (yrs) 13 ± 8, Insulin therapy 12/25 (48%), % HbA_{1c} 8.0 ± 2.3, Mal perforant 14/25 (56%), Mal perforant + lymphangitis 7/25 (28%), Mal perforant + necrosis 4/25 (16%), Additional macroangiopathy 7/25 (28%).
Comparator group(s) – N = 25, Age (yrs) 67 ± 9, Gender: male 13/25 (52%), female 12/25 (48%), Duration of diabetes (yrs) 11 ± 6, Insulin therapy 14/25 (56%), % HbA_{1c} 7.7 ± 2.0, Mal perforant 16/25 (64%), Mal perforant + lymphangitis 6/25 (24%), Mal perforant + necrosis 3/25 (12%), Additional macroangiopathy 8/25 (32%).</td></tr>
<tr><td colspan="3">Length of follow-up [11] 17- 42 days</td><td colspan="3">Outcome(s) measured [12] cure or complete healing; improvement >50%; improvement <50%; no change.</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Non-randomised Consecutive patients</td><td>Comparison of study groups [14] Baseline characteristics were similar between the groups</td><td>Blinding [15]
No</td><td>Treatment/ measurement bias [16] There was no difference in treatment and measurement between the groups</td><td colspan="2">Follow-up (ITT) [17]
Yes. The 2 withdrawals from treatment have been included.</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18] Did not do any statistical analysis of data although they have provided raw data (number of patients with each outcome) for both groups. This may be because the number of participants was small. They also provide data to show that most patients with <50% improvement have pathogens that are resistant to ceftriaxone. Overall, it appears that differences in the healing of the two groups was due to the intervention. This study was of average quality.</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="4">Outcome [19]

Cure
Improvement >50%
Improvement <50%</td><td>Intervention group [20]

11/25
5/25
4/25</td><td>Control group [21]

6/25
5/25
10/25</td><td>Measure of effect/effect size [22] (95% CI) [25]

RR = 1.83 (0.80,4.19)
RR = 1.00 (0.34, 2.95)
RR = 0.40 (0.14, 1.03)</td><td colspan="2">Benefits (NNT) [23]
95% CI [25]

Harms (NNH) [24]
95% CI [25]</td></tr>
<tr><td colspan="3">Clinical importance (1-4) [26] 4. The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.</td><td colspan="3">Relevance (1-5) [27] 1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.</td></tr>
<tr><td colspan="6">Any other adverse effects [28] 2 patients withdrew from treatment after 3 and 5 days due to severe diarrhoea</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisabilty [29] Applicable to other diabetics with infected diabetic foot ulcers.</td></tr>
</table>

Applicability [30] As there does not seem to be a statistically significant treatment effect, it is unknown whether or not the potentials benefits will outweigh the harms.
Comments [31]. There is the potential for information bias to occur due to use of a historical control group. It is unclear if the study was adequately powered, so it is possible that a statistically significant result may be obtained with a larger study.

Appendix F Excluded references

Question 1

Incorrect comparator

Beckert, S., Witte, M. et al (2006). 'A new wound-based severity score for diabetic foot ulcers - A prospective analysis of 1,000 patients', *Diabetes Care,* 29 (5), 988-992.

Margolis, D. J., Allen-Taylor, L. et al (2002). 'Diabetic neuropathic foot ulcers - The association of wound size, wound duration, and wound grade on healing', *Diabetes Care,* 25 (10), 1835-1839.

Margolis, D. J., Allen-Taylor, L. et al (2003). 'Diabetic neuropathic foot ulcers: predicting which ones will not heal', *Am J Med,* 115 (8), 627-631.

Incorrect intervention

Ahroni, J. H. (1997) Walden University, pp. 206 p.

Apelqvist, J., Larsson, J. & Agardh, C. D. (1992). 'Medical risk factors in diabetic patients with foot ulcers and severe peripheral vascular disease and their influence on outcome', *J Diabetes Complications,* 6 (3), 167-174.

Calle-Pascual, A. L., Duran, A. et al (2001). 'Reduction in foot ulcer incidence: Relation to compliance with a prophylactic foot care program [1]', *Diabetes Care,* 24 (2), 405-407.

Castronuovo, J. J., Jr., Adera, H. M. et al (1997). 'Skin perfusion pressure measurement is valuable in the diagnosis of critical limb ischemia', *J Vasc Surg,* 26 (4), 629-637.

Chu, J. & Singh Joy, S. D. (2009). 'Journal watch. Foot care clinic decreased amputations in diabetes', *American Journal of Nursing,* 109 (6), 33-34.

Ince, P., Abbas, Z. G. et al (2008). 'Use of the SINBAD classification system and score in comparing outcome of foot ulcer management on three continents', *Diabetes Care,* 31 (5), 964-967.

Oyibo, S. O., Jude, E. B. et al (2001). 'The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers', *Diabet Med,* 18 (2), 133-138.

Oyibo, S. O., Jude, E. B. et al (2002). 'Clinical characteristics of patients with diabetic foot problems: changing patterns of foot ulcer presentation', *Practical Diabetes International,* 19 (1), 10-12.

Incorrect language

Gesslein, M. & Schrinner, S. (2006). 'The diabetic foot syndrome: Classification helps in optimal wound care', *MMW-Fortschritte der Medizin,* 148 (24), 16.

Incorrect outcomes

Abbott, C. A., Carrington, A. L. et al (2002). 'The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort', *Diabet Med,* 19 (5), 377-384.

Apelqvist, J., Castenfors, J. et al (1989). 'Prognostic value of systolic ankle and toe blood pressure levels in outcome of diabetic foot ulcer', *Diabetes Care,* 12 (6), 373-378.

Apelqvist, J., Larsson, J. & Agardh, C. D. (1990). 'The importance of peripheral pulses, peripheral oedema and local pain for the outcome of diabetic foot ulcers', *Diabet Med,* 7 (7), 590-594.

Armstrong, D. G. (2005). 'Detection of diabetic peripheral neuropathy: strategies for screening and diagnosis', *Johns Hopkins Advanced Studies in Medicine,* 5 (10D), S1033.

Armstrong, D. G. & Lavery, L. A. (1997). 'Monitoring healing of acute Charcot's arthropathy with infrared dermal thermometry', *Journal of Rehabilitation Research & Development,* 34 (3), 317-321.

Bharara, M., Viswanathan, V. & Cobb, J. E. (2008). 'Warm immersion recovery test in assessment of diabetic neuropathy -- a proof of concept study', *International Wound Journal,* 5 (4), 570-576.

Bird, L. & McGoldrick, S. (1998). 'Development of a diabetic foot screening programme in Walsall', *Diabetic Foot,* 1 (4), 151-154.

Bowling, F. L., King, L. et al (2009). 'An assessment of the accuracy and usability of a novel optical wound measurement system', *Diabetic Medicine,* 26 (1), 93-96.

Boyko, E. J., Ahroni, J. H. & Stensel, V. L. (2001). 'Skin temperature in the neuropathic diabetic foot', *J Diabetes Complications,* 15 (5), 260-264.

Brooks, B., Dean, R. et al (2001). 'TBI or not TBI: that is the question. Is it better to measure toe pressure than ankle pressure in diabetic patients?', *Diabet Med,* 18 (7), 528-532.

Burton, K. (2001). 'Peripheral neurological testing procedures in screening', *Diabetic Foot,* 4 (2), 87.

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Appendix G Scoring systems

DEPA score

(Younes & Albsoul 2004)

Table 165 DEPA scoring system

DEPA score	Score		
	1	2	3
Depth of the ulcer	Skin	Soft tissue	Bone
Extent of bacterial colonisation	Contamination	Infection	Necrotising infection[a]
Phase of ulcer	Granulating[b]	Inflammatory[c]	Nonhealing[d]
Associated etiology	Neuropathy	Bone deformity	Ischaemia[e]

[a] Infected ulcer with surrounding cellulitis or fasciitis; [b] evidence of granulation tissue formation; [c] hyperaemic ulcer with no granulation tissue < 2 weeks duration; [d] nongranulating ulcer > 2 weeks duration; [e] clinical signs and symptoms of chronic lower-limb ischaemia.

Table 166 Grading of ulcers based on DEPA score

Grade of ulcer	DEPA score
Low	< 6
Moderate	7–9
High	10–12 or ulcer in association with wet gangrene

Wagner grading system

(Oyibo et al 2001b)

Table 167 Grading of ulcers by Wagner classification

Grade	Clinical assessment
1	Superficial wound
2	Deep wound involving tendons and capsules but not bone
3	Bony involvement
4	Localised gangrene
5	Generalised gangrene

UT grading system

(Oyibo et al 2001b; Armstrong et al 1998)

Table 168 Grading and staging of ulcers by UT classification

Grade	Clinical assessment	Stage (four stages in each grade)	Clinical assessment
0	Complete epithelialisation (pre- or post- lesion)	A	No infection or ischaemia
1	Superficial wound	B	Infection
2	Deep wound involving tendons but not bone	C	Ischaemia
3	Bone involvement, localised and generalised gangrene	D	Infection and ischaemia

(S(AD)SAD) system

(Parisi et al 2008)

Table 169 Grading of ulcers by S(AD)SAD system

Grade	Area	Deep	Sepsis	Arteriopathy	Denervation
0	Skin intact	Skin intact	–	Pedal pulses present	Intact
1	Lesion < 1cm^2	Superficial (skin and subcutaneous tissue)	No infected lesions	Pedal pulses reduced or one missing	Reduced
2	Lesion 1–3cm^2	Lesion penetrating to tendon, periosteum and joint capsule	Cellulitis-associated lesions	Absence of both pedal pulses	Absent
3	Lesion > 3cm^2	Lesion in bones or joint space	Lesions with osteomyelitis	Gangrene	Charcot joint

Diabetic ulcer severity score (DUSS)

(Beckert et al 2006)

Table 170 Scoring of ulcer severity using DUSS

Clinical assessment	Score	
	1	0
Pedal pulses	Absent	Present
Bone involvement (probing to bone)	Yes	No
Site of ulceration	Foot	Toe
Multiple ulcers	Yes	No

M.A.I.D

(Beckert et al 2009)

Table 171 Scoring of ulcer severity using M.A.I.D

Clinical assessment	Score	
	1	0
Pedal pulses	Absent	At least one present
Wound history/duration (> 130 days)	Yes	No
Wound size (> 4cm^2)	Yes	No
Multiple ulcers	Yes	No

Scottish foot risk score

(Leese et al 2007)

Table 172 Scottish foot risk score

Low risk	Moderate risk	High risk
Able to detect at least one pulse per foot AND	Unable to detect both pulses in a foot OR	Previous ulceration or amputation OR
Able to feel 10g monofilament AND	Unable to feel 10g monofilament OR	Absent foot pulses AND unable to feel 10 monofilament OR
No foot deformity, physical or visual impairment. No previous ulcer.	Foot deformity OR	One of the above with callus or deformity
	Unable to see or reach foot (No history of previous foot ulcer)	

Curative Health Services classification

(Margolis et al 2002; Margolis et al 2003)

Table 173 Curative Health Center classification of foot ulcers

Grade	Criteria
1	Partial thickness involving only dermis and epidermis
2	Full thickness and subcutaneous tissues
3	Grade 2 plus exposed tendons, ligament, and/or joint
4	Grade 3 plus abscess and/or osteomyelitis
5	Grade 3 plus necrotic tissue in wound
6	Grade 3 plus gangrene in the wound and surrounding tissue

Clinical and physical examination and MRI

(Edelman et al 1997)

Table 174 Clinical and physical examination components

Clinical examination	Physical examination	Investigation
Age	General examination of leg	MRI
Race	Width of ulcer	
Sex	Depth of ulcer	
Smoking status	Oedema in affectedleg	
	Location of ulcer	
Medication	Palpable posterior tibial pulse in affected leg	
Duration of diabetes	Palpable pedal pulses	
Furation of ulcer	Ankle-brachial index	
Previous amputation	Visible bone in ulcer	
Fever	Cyanosis in affected leg	
Chills or sweats	Erythaema	
Painful ulcer	Purulence	
claudication	Necrosis	
	Induration	
	Crepitus	
	Likelihood of osteomyelitis	

MRI = Magnetic resonance imaging

International Working Group on the diabetic foot

Table 175 Criteria for wound classification according to the International Working Group on the diabetic foot

Perfusion	Depth of wound	Infection	Sensation
Grade 1 No symptoms or signs of iscahaemia, palpable pedal pulses, 0.9 < ABI < 1.1	Grade 1 Superficial ulcers not penetrating any structure below the dermis	Grade 1 No signs or symptoms of infection	Grade 1 No loss of sensation of the affected foot
Grade 2 Signs and symptoms of intermittent claudication, or ABI < 0.9 with ankle pressure > 50 mmHg	Grade 2 Deep ulcers penetrating down to subcutaneous structures, fascia, muscles, and tendons.	Grade 2 Infection involving skin and subcutaneous tissues without systemic signs: Local swelling and induration; erythaema > 0.5–2 cm around ulcer; local tenderness or pain; local warmth; purulent discharge	Grade 2 No pressure sensation with a 10g monofilament on two ro three sites on the plantar side of the foot. No vibration sense with a 128 Hz tuning fork on both sides of the hallux.
Grade 3 Critical limb ischaemia defined by systolic ankle pressure < 50mmHg	Grade 3 Deep ulcers penetrating down to the bone and/or joint.	Grade 3 Erythaema > 2cm Deep abscess; osteomyelitis; septic arthritis and fasciitis.	
		Grade 4 Any foot infection associated with systemic inflammatory response syndrome. Temperature > 38°C or < 36°C; heart rate > 90 beats/min; respiratory rate > 20 breaths/min; total white cell count > 12,000 or < 4000/cm	

ABI = ankle-brachial index

Van Acker / Peter classification

Table 176 Classification of foot ulcers using Van Acker/Peter classification

Reproduced from (Van Acker et al 2002)

Type of lesion	Superficial epidermis dermis	Minor soft tissue dermis	Major soft tissue	Periostitis	Complicated osteomyelitis*
Degree of risk	1	2	3	4	5
Foot pathology A. Insensitive foot					
B. Insensitive plus bone deformations					
C. Charcot's foot					
D. Ischaemic foot					
E. Mixed insensitive plus vascular					

The horizontal axis shows the extent of the wound infections. These classes are:

Class 1: Extremely superficial ulcer without important signs of infection.

Class 2: Small ulcer with cellulitis without involvement of tendons and bone.

Class 3: More severe infected ulcer with involvement of tendons and/or bone and with/without abscess

Class 4: Periostitis = involvement of the bone without signs of destructive osteomyelitis; typical = bone contact without visible defects on radiography

Class 5: Overt radiographic destructive osteomyelitis

On the vertical axis, we find the physiopathologic characteristics of the diabetic foot ulcers, which are coded as:

A: Insensitive foot

B: Insensitive foot and bone deformities (hammer toes, hallux valgus, overriding toe, and limited joint mobility)

C: Charcot's foot

D: Ischaemic foot

E: Mixed neuropathy and vasculopathy

The clinical interpretation of this classification is "the whiter, the more favourable, and the darker, the more amputation becomes probable."

* Osteomyelitis with major destruction and fracture of bone and major involvement of soft tissue or bone contact

Appendix H Risk models for poor foot outcomes

Abbott et al (1998)

Model adjusted for age; vibration perception threshold (VPT); Michigan diabetic polyneuropathy score

Boyko et al (1996)

Model 1 adjusted for incident foot ulcer; age; diabetes duration; type of diabetes; oral hypoglycaemic agent; insulin use; pack-years smoked; prior amputation; prior ulcer

Model 2 adjusted for (all self-reported) ankle-brachial index (ABI); sensory neuropathy; congestive heart failure; myocardial infarction; cerebrovascular disease; retinopathy; laser photocoagulation; renal disease; claudication symptoms; numbness in feet

Bruce et al (2005)

Mobility impairment:

Model adjusted for age; cardiovascular disease (CVD) or history; any exercise; current smoker; insulin treatment; Ln (urinary albumin:creatinine ratio); neuropathy; arthritis; married

Activities of daily living disability:

Model adjusted for age; CVD or history; any exercise; ex- smoker; claudication; mobility problems; depression; non-fluent in English; Indigenous Australian

Cowley et al (2008)

Model adjusted for neuropathy; age; body mass index (BMI); insulin medication; ulcer history; and amputation history

Davis et al (2006)

Model adjusted for history of CVD; HbA_{1c}; retinopathy; neuropathy; Ln (urinary:creatinine) ratio; ABI; foot ulcer

Everheart et al (1988)

Model adjusted for age; sex; 2 hour post-load plasma glucose; blood pressure; serum cholesterol; VPT; ankle reflexes; medial arterial calcification; proteinuria; BMI

Hamalainen et al (1999)

Model adjusted for VPT; ABI; history of retinopathy; visual handicap; male sex

HDS (1993)

Model adjusted for age at diabetes diagnosis; gender; ethnic group; cholesterol; triglycerides and smoking

Klein et al (2007)

Model adjusted for central retinal arteriolar equivalents; central retinal venular equivalents; age; gender; glycosylated haemoglobin; pulse pressure; history of sores/ulcers.

Ledoux et al (2005)

Model adjusted for male sex; age; BMI; duration of diabetes; neuropathy; foot type; hallux valgus; hammer/claw toes; hallux limitus

Lee et al (1993)

Model adjusted for retinopathy; use of insulin; systolic blood pressure; diastolic blood pressure; duration of diabetes; fasting blood glucose; plasma cholesterol; and stratified by gender

Lehto et al (1996)

Likely to only be adjusted for age and sex

LeMaster et al (2003)

Model adjusted for time in study; age; marital status; presence of a co-morbidity; education; ethnicity; duration of diabetes; frequency of self-monitoring of blood glucose; BMI; current smoker; and physical and mental health as measured by SF-36

Litzelman et al (1997)

Seattle wound classification ≥ 1.2

Model adjusted for intervention status; baseline wound; monofilament testing; thermal sensitivity

Seattle wound classification ≥ 1.3

Model adjusted for intervention status; baseline wound; monofilament testing; high density lipoprotein

Nelson et al (1988)

Model adjusted for age; sex and diabetes duration

Moss et al (1992) (amputation)

Younger onset:
Model adjusted for age; history of ulcers; diastolic blood pressure; glycosylated haemoglobin; and retinopathy

Older onset:
Model adjusted for history of ulcers; duration of diabetes; glycosylated haemoglobin; sex and proteinuria

Moss et al (1992) (ulceration)

Younger onset:
Model adjusted for age; glycosylated haemoglobin; and retinopathy

Older onset:
Model adjusted for; duration of diabetes; diastolic blood pressure and retinopathy; glycosylated haemoglobin; sex and proteinuria

Moss et al (1996) (amputation)

Younger onset:
Model adjusted for age; history of ulcers; diastolic blood pressure; glycosylated haemoglobin; sex; and retinopathy

Older onset:
Model adjusted for history of ulcers; diastolic blood pressure; glycosylated haemoglobin; sex and proteinuria

Moss et al (1999) (amputation)

Younger onset:
Model adjusted for age; history of ulcers; duration of diabetes; diastolic blood pressure; glycosylated haemoglobin; sex; retinopathy; and proteinuria

Older onset:
Model adjusted for history of ulcers; glycosylated haemoglobin; sex and proteinuria

Otiniano et al (1992)

Model adjusted for eye problems; kidney problems; amputations; age; sex; living arrangements; smoking; alcohol consumption; and self-reported history of stroke; heart attack; hypertension; cancer and hip fracture

Pham et al (2000)

Model adjusted for neuropathic disability score; VPT; semmes Weinstein monofilaments (SWF); foot pressure

Resnick et al (2004)

Model adjusted for age; sex; education; centre; duration of diabetes; HbA_{1c}; systolic blood pressure; BMI; microalbuminuria; macroalbuminuria; ABI

Roy et al (2008)

Model 1

Model adjusted for duration of diabetes; systolic blood pressure; foot/ankle ulcer; male gender

Model 2

Model adjusted for duration of diabetes; foot/ankle ulcer; male gender; retinopathy severity

Volpato et al (2005)

Model adjusted for knee osteoarthritis; stroke; insulin therapy; overweight; obesity; lower extremity pain and summary physical performance

Wallace et al 2002

Model adjusted for age; sex; diabetes duration; BMI; ever smoked; study footwear group; ≥ 1 co-morbid condition; insensate feet; foot deformity; and veteran affairs care source

Winkley et al (2007)

Mortality

Model adjusted for age; gender; smoking; macrovascular complications; HbA_{1c}; deep ulcer; VPT; ABI; depression

Amputation

Model adjusted for age; gender; smoking; deep ulcer; ulcer size; depression

Recurrence

Model adjusted for age; gender; type of diabetes; insulin use; smoking; microvascular complications; location of ulcer; depression

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