Themes

- Outcomes in diabetes
- Atherosclerosis and diabetes
- Coronary disease in the diabetic patient
- Diabetic heart
- Therapeutic aspects
Years of Life Lost (YLL) for the leading disease and injury categories – Indigenous persons 2003

CVD & Diabetes

- CVD + Diabetes: 31%
- Cancers: 11%
- Injuries -unintentional: 9%
- Injuries -intentional: 5%
- Chronic Resp Disease: 5%
- Mental Disorders: 5%
- Nervous system & sense disorders: 5%
- Infectious & parasitic diseases: 4%
- Neonatal causes: 4%
- Other: 3%

Page 2: Baker IDI
Hypertension

Abdominal obesity

Dyslipidaemia

Diabetes

- 80% of deaths in diabetes due to CVD
- 80% of heart attack sufferers have impaired glucose tolerance
- 85% of the population have one or more of these risk factors
The same factors drive ‘epidemics’ of diabetes, hypertension, dyslipidaemia and CVD

- Ageing of the population
- Dietary changes
- Reduction in physical activity
- The obesity phenomenon
- Treatment gaps
T2D complications- mainly vascular

Diabetic retinopathy
Leading cause of blindness in working-age adults¹

Diabetic nephropathy
Leading cause of end-stage renal disease²

Stroke
2- to 4-fold increase in cardiovascular mortality and stroke³

Cardiovascular disease
8/10 diabetic patients die from cardiovascular events⁴

Diabetic neuropathy
Leading cause of non-traumatic lower extremity amputations⁵ Disablity from autonomic neuropathy

Type 2 diabetes increases the risk of a broad range of cardiovascular diseases.

Adjusted for age, race, income, cholesterol, systolic blood pressure, smoking

Cardiovascular disease in people with diabetes

Diabetes vs. No Diabetes

Men

- Diabetes: 9.1% (28d–1y), 15.4% (Hospitalization–28d), 22.1% (Out of Hospital)
- No Diabetes: 4.2% (28d–1y), 9.6% (Hospitalization–28d), 22.7% (Out of Hospital)

Women

- Diabetes: 11.1% (28d–1y), 22.7% (Hospitalization–28d), 11.9% (Out of Hospital)
- No diabetes: 2.8% (28d–1y), 9.0% (Hospitalization–28d), 11.9% (Out of Hospital)

Diabetes & Cardiac Outcomes

Aksnes et al. 2007 New Onset Diabetes & Cardiac Outcome Hypertension 50:467-473
# Average annual costs of diabetes

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Cardiovascular disease in people with diabetes - Morbidity

Proportion of hospital bed days for the treatment of the complications of diabetes

Diabetes impacts on “Human Capital” as an economic issue

Council of Australian Governments – Elevating diabetes above a health issue
Cardiovascular disease risk factors in diabetes

Metabolic Syndrome increases the risk of coronary heart disease still further

- Metabolic syndrome
- No metabolic syndrome

Prevalence of coronary heart disease (%)

- NGT: $P = 0.04$
- IFG/IGT: $P = 0.06$
- Type 2 diabetes: $P < 0.001$

‘Double jeopardy’: type 2 diabetes and hypertension and cardiovascular risk

No diabetes
Diabetes

CVD death rate (per 10,000 person-year)

Systolic blood pressure (mmHg)

< 120
120–139
140–159
160–179
180–199
≥ 200

Hypertension management in diabetes

- Treatment gap - drugs indicated
- Treatment gap - OK with lifestyle
- Therapeutic inertia - more therapy needed
- Therapeutic inertia - OK with lifestyle
- Meeting target

9857 males and 8332 females in Australian general practice

Owen, Retegan, Rockell, Jennings and Reid CEPP Nov 2008
Atherosclerosis in the setting of diabetes
Features of atherosclerosis in diabetes

Human carotid artery specimens

Atherosclerosis of diabetes is associated with higher levels of inflammatory cells –

Composition varies but not extent of restenosis

Implication? – Increased plaque instability

Cipollone et al. Circ. 2003
Diabetes has a predilection for peripheral arteries
Coronary disease
Single vessel disease is less common in diabetes

Human coronary artery disease

“Normal” acute proximal lesion

Coronary artery atherosclerosis

Diffuse distal disease of diabetes

Causes: Matrix production/lipoprotein binding/cell proliferation etc.
A gene that predisposes to coronary disease in the presence of poor glycaemic control in T2D (9p21 locus)

Doria et al. 2008 Interaction between Poor Glycemic Control and 9p21 Locus on Risk Of Coronary Artery Disease in T2D
JAMA 300;20:2389-2397
CLINICAL TIP

Restenosis is 3x more common in diabetic than non diabetic subjects with bare metal stent. Less likely with drug eluting stent but still more than in non diabetics

Early outcomes with drug eluting stent match CABG (NY registry) but confounding likely-

FREEDOM
CABG better than drug eluting stent better than bare metal stent in diabetes-ARTS

ARTS I-BMS vs. CABG (96/112 diabetes)
ARTS II DES (sirolimus) (159 diabetes)

Daemen JACC 2008:52;1957
Revascularisation in diabetes

**CABG**
- Early and long-term morbidity and mortality higher than in non diabetics
- Less likely to have CK rise!
- Similar
  - graft patency @ 4y (BARI)
  - Cognitive decline
- More likely to have
  - Wound infection
  - Stroke
  - Reduced QOL

**Angioplasty and stent**
- Procedural complications more likely (risk related)
- Mortality higher long term (1.8 vs. 1.3% ACC-NCV data registry)
- LOS longer (2.7 vs. 2.4 days)
- Renal dysfunction more common
- Similar enzyme rise
- PCI for vein graft problematic (Insulin treated DM associated with calcific vein graft degeneration)
- No difference in stent thrombosis
- More new lesions in the treated vessel @ 9 months (PRESTO)

*Berry et al JACC 2007; 49: 643-656*
Flow diagram of cardiac event patient journeys in Central Australia
Rates of Cardiac Procedures During Index ACS

NTACS Cohort 2001-2002

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Is there a diabetic cardiomyopathy?

- Some due to complications of
  - Hypertension
  - Coronary heart disease etc
- Experimental models convincing
- Diabetes over represented in IDCM
- Mostly associated with micro vascular complications of diabetes (these parallel hyperglycaemia)
- Metabolic factors are associated with fibrosis/hypertrophy
  - Directly
  - Indirectly via RAS, autonomic neuropathy, Ca++
Diabetes effects on the myocardium

- A distinct diabetic cardiomyopathy
  - independent of diabetic macrovascular disorders
  - cardiomyocyte hypertrophy, cardiac fibrosis
  - Early LV diastolic impairment
    - prolonged LV filling & relaxation
    - ↓ diastolic distensibility

![Graph showing time to fatal or non-fatal heart failure](image)

- Diastolic function (↓ LV filling)

![Bar chart showing Ea/Aa ratio](image)
Diabetes and cardiomyopathy

100 diabetics with no evidence of structural heart disease: Echo findings

Left Ventricular Dysfunction (LVD) – high negative predictability with clinical variables but not BNP: SBP, Gender, BMI

Event free survival over 48.5 ± 9 months

BNP predicted events: OR 3.5

Kienke et al Eur J Heart failure 2010 June 25 E pub
Heart failure with preserved ejection fraction (HFPEF)

During Acute Pulmonary Edema
Blood pressure, 240/144 mm Hg

After Treatment
Blood pressure, 149/75 mm Hg

End Diastole
End Systole

EF=0.59

EF=0.50

Both presentations of heart failure have adverse prognosis.

![Graph showing survival over years with preserved and reduced ejection function, with a statistically significant difference (P=0.03).]
Systolic BP difference and risk

Stroke

Myocardial infarction

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### Avoid hypoglycaemia

#### Severe Hypoglycaemia and the Risk of an Adverse Clinical Outcome or Death - ADVANCE

<table>
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<tr>
<th>Events</th>
<th>Severe Hypoglycaemia (N=231)</th>
<th>No Severe Hypoglycaemia (N=10,909)</th>
<th>Hazard Ratio (95% CI)</th>
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<td>Unadjusted model</td>
<td>33 (15.9)</td>
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<td><strong>Major microvascular events</strong></td>
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Therapeutic targets for hyperglycaemia

- **Increased Hepatic Glucose Production**
  - Weight loss, exercise, biguanides, insulin, thiazolidinediones, possibly bile acid sequestrants

- **Increased Insulin Resistance**
  - Weight loss, exercise, biguanides, thiazolidinediones, D2 dopamine–receptor agonists

- **Increased Glucagon Secretion**
  - GLP-1–receptor agonists, DPP-IV inhibitors, amylin mimetics

- **Increased Appetite**
  - GLP-1–receptor agonists, amylin mimetics

- **Decreased Insulin Secretion**
  - Sulfonylureas, meglitinides, GLP-1–receptor agonists, DPP-IV inhibitors

- **Increased Rate of Gastric Emptying**
  - GLP-1–receptor agonists, amylin mimetics

- **Carbohydrate Absorption**
  - Alpha-glucosidase inhibitors

- **Decreased Amylin Secretion**
  - Amylin mimetics

- **Impaired Incretin Effect**
  - GLP-1–receptor agonists, DPP-IV inhibitors, possibly bile acid sequestrants

We treat diabetes to reduce complications
Hypoglycaemic drugs are a mixed blessing

*May increase CVD:*
Thiazolidinedione (rosiglitazone)

*May reduce CVD:*
Biguanides (metformin)
GLP1 receptor agonist (exanatide, liraglutide)
Thiazolidinedione (pioglitazone)
α glucosidase inhibitor (miglitol, voglibose, acarbose)
We treat diabetes to reduce complications. Hypoglycaemic drugs are a mixed blessing.

**Increase weight:**
- Thiazolidinediones (rosiglitazone, pioglitazone)
- Meglitinide
- Insulin

**Decrease weight:**
- Sulphonylureas
- GLP1 receptor agonist (exanatide, liraglutide)
- Amylin analogue (pramlinitide)
Aspirin in diabetes

Meta-analysis of trials examining the effects of aspirin on risk of CVD events in patients with diabetes. ETDRS, Early Treatment of Diabetic Retinopathy Study; HOT, Hypertension Optimal Treatment; JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; PHS, Physicians' Health Study; POPADAD, Prevention of Progression of Arterial Disease and Diabetes; PPP, Primary Prevention Project; TPT, Thrombosis Prevention Trial; and WHS, Women's Health Study.


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Diabetes risk and statins

But CVD risk reduced in diabetes with statin therapy

doi: 10.2337/dc09-0738
Conclusions

• The link between diabetes and CVD is strong but can be mitigated
  – Primary prevention
  – Achieve blood pressure targets
  – Achieve glycaemia targets (?)
  – Special role for RAS inhibition
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