



WHITEPAPER

PRACTICALITIES OF USING SGLT2 INHIBITORS IN COMORBID DIABETES AND HEART DISEASE

This Whitepaper is based on a Scientific Exchange meeting held on Saturday 14 December 2019

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EXECUTIVE SUMMARY

This whitepaper has developed out of a round table discussion that was convened in December 2019 to explore the public health and clinical benefits and risks of sodium-glucose co-transporter-2 inhibitors (SGLT2i). The aim of this paper is to identify the major clinical issues surrounding the safe prescription of these agents. It is intended that this process will form the basis of more formal advice and guidance to be issued by relevant professional bodies, including the ADS, CSANZ and RACGP. The meeting focus was on cardiologists and general practitioners; however, the group stated that other groups including nephrologists, general physicians and endocrinologists would also benefit from further education on SGLT2i, particularly for patients with heart failure.

Benefits of SGLT2i

- SGLT2i improve glycaemic control in type 2 diabetes mellitus (T2DM) by reducing renal glucose reabsorption leading to increased glucuresis and natriuresis.[1]
- Three large, randomised controlled trials (RCTs) (EMPA-REG,[4] CANVAS,[5] DECLARE[6]), as well as a recent meta-analysis by Zelniker et al 2019,[7] demonstrated SGLT2i have cardiovascular and reno-protective benefits in T2DM.
- Additionally, a recent study of stable, well-treated heart failure patients with reduced ejection fraction (DAPA-HF) has demonstrated cardiovascular protection irrespective of the presence or absence of diabetes.[8]
- In the systematic review and meta-analysis, Zelniker et al 2019[7] reported that SGLT2i use versus placebo resulted in a:
 - **14% reduction in major adverse cardiovascular events (MACE) in patients with previous atherosclerotic CV disease** (HR: 0.86 [95% CI: 0.80-0.93]; p=0.0002).
 - **23% reduction in heart failure (HF) hospitalisation/cardiovascular (CV) death** (0.77 [0.71-0.84]; p<0.0001), with a similar benefit in patients with and without pre-existing atherosclerotic CV disease, and with and without a history of heart failure.
 - **45% reduction in the progression of renal disease** (composite of renal worsening, end-stage renal disease or renal death) (HR: 0.55 [0.48-0.64]; p<0.0001) with a similar benefit in patients with atherosclerotic CVD and those with multiple CV risk factors.

- In the double-blind, placebo-controlled DAPA-HF trial in **stable heart failure patients** with reduced ejection fraction (**EF≤40%**),[8] dapagliflozin led to a:
 - **26% reduction in worsening heart failure or CV death** (primary endpoint) (HR: 0.74; 95% CI: 0.65-0.85; p<0.001) (NNT: 21). This primary outcome benefit was present **irrespective of the presence or absence of diabetes**.
 - **30% relative risk reduction in worsening heart failure event** (HR: 0.70 [0.59, 0.83]; p=0.00003).
 - **Significant improvement in quality of life:** The change in KCCQ total symptom score was 6.1 with dapagliflozin vs 3.3 for placebo; difference: 2.8 points [95% CI: 1.6, 4.0]; p<0.001]. Compared with placebo-treated patients, significantly more participants on dapagliflozin had an improvement in KCCQ score and significantly fewer participants on dapagliflozin had a deterioration in KCCQ score.
- The exact mechanism(s) for the cardiovascular and renal protective effects of SGLT2i, however, remain unclear.
- HbA1c is not a surrogate marker for SGLT2i reno-cardiovascular benefits.

Public health imperative

- The group agreed that there is a **public health imperative** to ensure SGLT2i are prescribed in appropriate patients, similar to initiation of other cardioprotective agents, such as ACE inhibitors, angiotensin receptor blockers (ARB), beta blockers and statins. To support this, it would be useful to not only quantify the absolute benefits of SGLT2i in terms of mortality, but also the impact of SGLT2i use on future dialysis and heart failure hospitalisation costs.

- The absolute mortality benefits of SGLT2i use can be modelled on data taken from the National Diabetes Services Scheme (NDSS), which was published in *The Dark Heart of Type 2 Diabetes Baker Institute Report 2017*. [9] According to this data, a 30% reduction in mortality with SGLT2i use, as achieved in EMPA-REG study, would equate to **2,095 deaths prevented each year (assuming there was a 100% uptake rate)**. **Even if the mortality benefit of SGLT2i use was only 10%, with a 50% uptake, there would still be 349 fewer deaths in one year.**

Risks of SGLT2i

- Any potential benefits of SGLT2 inhibition should outweigh any potential risks.
- Side-effects associated with SGLT2i include polyuria, genital infections, volume depletion in patients at risk of dehydration, and diabetic ketoacidosis (DKA).[4, 6]
- The two side effects of SGLT2i that cardiologists are most worried about are genital infections & DKA.
- GPs are generally familiar with treating genital infections, and are accustomed to managing patients on SGLT2i, however, they may be concerned about DKA, particularly with broader SGLT2i use in the community.
- Polyuria and genital infections are not usually dangerous, although they can be a nuisance for some patients. These AEs are usually mild to moderate and can be managed proactively by educating patients. Genital infections usually resolve with standard treatment, although recurrent genital infection may necessitate treatment discontinuation in a few patients.
- Cardiologists may be more concerned about genital infections, as compared with GPs, as they are not used to treating these conditions.
- For some patients, with a lower CV risk, the long-term benefits might not outweigh the inconvenience of frequent polyuria, nocturia or genital infections associated with SGLT2i. GLP-1 agonists may be a suitable alternative in some of these patients.

- Because of their natriuretic effect, SGLT2i can cause volume depletion in patients taking loop diuretics or in other individuals who are at risk of dehydration (e.g. acute gastrointestinal illness). Fluid status in these patients should be checked before initiating a SGLT2i. Non-heart failure clinicians require more guidance with respect to dose adjustment of diuretics in heart failure patients.
- DKA is a serious and potentially life-threatening condition caused by a “relative deficiency of insulin”. The American Diabetes Association defines DKA as the combination of blood pH<7.3, HCO₃⁻ ≤18 mmol/L and elevated ketones.
- A recent retrospective controlled cohort study across all public hospitals in Melbourne and Geelong confirmed that there is a small but significant increased absolute risk of DKA with SGLT2i [OR: 1.48; 95% CI: 1.02-2.15; p=0.037].[10]
 - Much of the excess risk of DKA occurred in people already admitted to hospital for other reasons, and **most cases of DKA that developed during hospital admission occurred in the context of surgery and fasting.**
 - In most cases of DKA, insulin was ceased in hospital when patients were fasting, and those involved in patient management may have been falsely reassured by blood glucose levels that were not particularly elevated, which could have contributed to the development of DKA in these patients.
 - **This study highlights the need to educate medical staff about the risks of DKA in patients with T2DM on SGLT2i.** However, it was also noteworthy that the absolute number of DKA cases was 3x higher in non-SGLT2i users, than in SGLT2i users. The most common probable precipitating factor for DKA in non-SGLT2i users was infection/acute illness.
- **SGLT2i should be withheld at least 2 days prior to surgery and not re-started until the patient is eating and drinking.**
- The working group determined further education about DKA was required and made a number of suggestions (please refer to Section 5, page 26 of this report).
- It is important to **put DKA into context**, given the overall absolute risk of DKA with SGLT2i was small, and given there is also a background risk of DKA in people with diabetes not taking a SGLT2i.

Barriers to SGLT2i use

The major barriers preventing clinicians prescribing a SGLT2i in appropriate patients are:

- **side effects** (e.g. polyuria, genital infections, DKA)
- **existing guidelines/indication/reimbursement** are based on glucose-lowering
- **cost**

SGLT2i Guidelines/ Consensus Statement

- It was determined that there was a need to develop SGLT2i Guidelines or a Consensus Statement in collaboration with ADS and CSANZ, with contribution from General Practice via the RACGP. A nephrologist should also have input into the document and, possibly a geriatrician.
- The Guidelines/Consensus Statement should clarify when to start SGLT2i. For example, should the SGLT2i be commenced during hospitalisation for HF or a CV event, at the first cardiology follow-up visit, by the endocrinologist or by the GP?
- Please refer to sections 7 and 8 for a list of suggestions and proposed follow-up actions with respect to developing and implementing SGLT2i guidelines.

Objective

1

The purpose of this whitepaper is to explore the benefits and risks of SGLT2i with the aim of ensuring the safe prescription of these agents in clinical practice. In particular, this whitepaper will explore:

1. safety issues of SGLT2i
2. clinical and public health benefits of intervention with SGLT2i.

This whitepaper will focus on cardiologists and general practitioners; however, it was stated that endocrinologists would also benefit from further education on SGLT2i particularly for patients with heart failure.

This whitepaper is hoped to act as a springboard for future collaboration with the Australian Diabetes Society (ADS) and the Cardiac Society of Australia and New Zealand (CSANZ) to develop a consensus/advisory statement for the safe use of SGLT2i.



Mechanism of Action of SGLT2 Inhibitors

2

Sodium-glucose co-transporters (SGLTs) are the specific mediators of renal glucose reabsorption, with 90% of this reabsorption being facilitated by the isoform termed SGLT2, and the remainder by SGLT1.[1] Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are known to improve

glycaemic control in type 2 diabetes mellitus (T2DM) by reducing renal glucose reabsorption leading to urinary glucose excretion (glucosuria). Blocking the SGLT2 receptor also increases sodium excretion (i.e. promotes natriuresis).[1]



In addition to glucose lowering effects, three large, randomised controlled trials (RCTs), as well as a recent meta-analysis, demonstrate SGLT2i have cardiovascular and reno-protective benefits in patients with T2DM.[4-7] Additionally, a recent study of patients with heart failure with reduced ejection fraction (HFrEF) has demonstrated cardiovascular protection irrespective of the presence or absence of diabetes.[11]

Glucose lowering effects

The glucose lowering effects of SGLT2i have been established in multiple randomised, controlled trials in T2DM. The average reduction in HbA1c is approximately 1 percentage point, although glucose reduction varies according to the underlying baseline HbA1c and other factors.[12] The glucose-lowering effect of SGLT2i may be reduced in patients with an estimated GFR<60 mL/min/1.73 m².

It is important to note that the renal and cardiovascular benefits of SGLT2i are independent of the effect on HbA1c. Therefore, even if there is only minimal glucose lowering, large RCTs have established there are cardiovascular and renal benefits with a SGLT2i [13, 14]. **Therefore, HbA1c is not a surrogate marker for SGLT2i reno-cardiovascular benefits, although it is an important marker of glucose-lowering.**

This may pose clinical challenges, as prescribers are generally accustomed to using an objective marker to track response to other medications. For example, the effect of an antihypertensive agent can be directly measured by blood pressure, and the effect of a cholesterol lowering agent can be measured by LDL-C or other lipid parameters. Therefore, without a biomarker to measure the renocardiovascular benefits of

SGLT2i, there may be reluctance to prescribe the agents for non-glucose lowering effects. Moreover, adherence to medication may be poor if there is no measurable effect.

Reduction in major adverse cardiovascular events (MACE)

Three large, phase 3, randomised, placebo-controlled multinational trials have investigated the effect of SGLT2i on cardiovascular outcomes in people with T2DM:

- **EMPA-REG** (empagliflozin)[4]
- **CANVAS** (canagliflozin)[5]
- **DECLARE-TIMI 58** (dapagliflozin)[6]

These studies have shown that SGLT2i led to a significant reduction in major cardiovascular events (i.e. **myocardial infarction, stroke and CV death**), and other CV outcomes such as **heart failure/CV death** in people with T2DM compared to placebo.[4-7]

The populations in these outcome studies had different levels of baseline CV risk. Most participants in these studies had established atherosclerotic CVD; however some of the participants in CANVAS and DECLARE studies had multiple risk factors for CVD. All of the participants in EMPA-REG, 65.6% of participants in CANVAS and 40.6% of participants in DECLARE had pre-existing atherosclerotic CVD.

Zelniker *et al* 2019 performed a systematic review and meta-analysis of the three SGLT2i CV outcomes trials (n=34,322) [7]. Compared to placebo-treated participants, the investigators reported that participants treated with a SGLT2i had a:

- **14% reduction in MACE in participants with previous atherosclerotic CV disease** (HR: 0.86 [95% CI: 0.80-0.93]; p=0.0002) (Figure 1). The hazard ratio for the reduction in MACE in participants without established atherosclerotic disease in this meta-analysis was 1.00 [95% CI: 0.87-1.16]; p=0.98).[7] The p value for subgroup differences was 0.0501.*

- **23% reduction in heart failure/CV death (0.77 [0.71-0.84]; p<0.0001)**, with a similar benefit in participants with and without pre-existing atherosclerotic CV disease, and with and without a history of heart failure (Figure 2). The p value for subgroup differences was 0.41'.[7]

Figure 1. Effect of SGLT2i on the composite of MACE (MI, stroke and CV death) in cardiovascular outcome trials in T2DM (stratified by the presence or absence of atherosclerotic CVD)

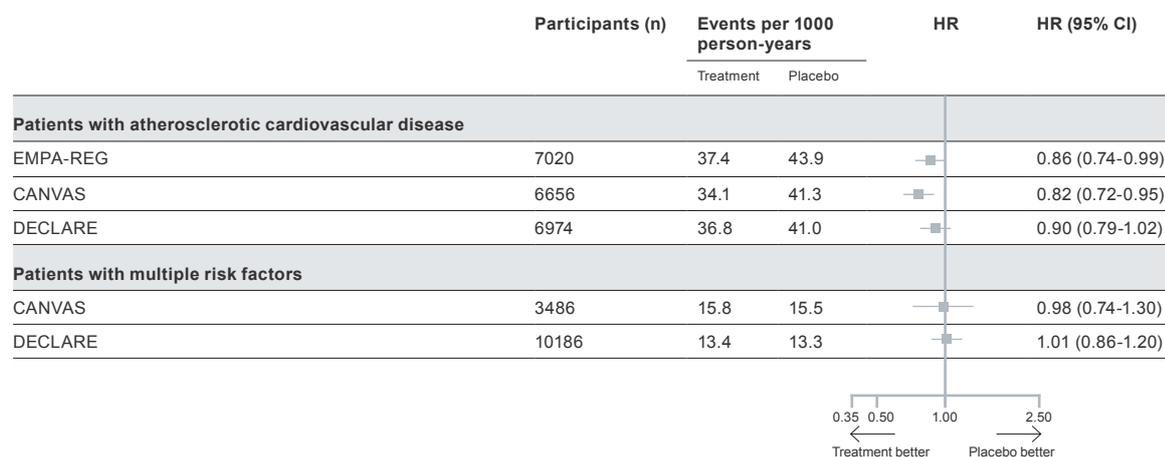


Figure based on Zelniker TA, et al. *Lancet* 2019.[7]

*NOTE: It is difficult statistically to draw firm conclusions regarding any potential differences between the subgroup of participants with previous atherosclerotic CVD and those with multiple risk factors for MACE, as the confidence intervals (CI) overlap. In situations where the treatment effect is relatively small, for example with an endpoint like MACE, which has a 14% relative risk reduction for SGLT2i vs placebo, a large number of events is needed to demonstrate a statistically significant benefit. For MACE, 1800 events are needed for 90% power to detect a statistical difference. In this analysis the event rate in the placebo arm in participants with multiple risk factors is very low, and the timeframe for follow-up may not be long enough to show benefit in this lower risk group. There are additional analyses underway, including data from CREDENCE, that will include more participants with CV risk factors; however, participants from CREDENCE have impaired renal function.

Figure 2. Effect of SGLT2i on the composite of heart failure and CV death in cardiovascular outcome trials in T2DM (stratified by the presence or absence of atherosclerotic CVD)

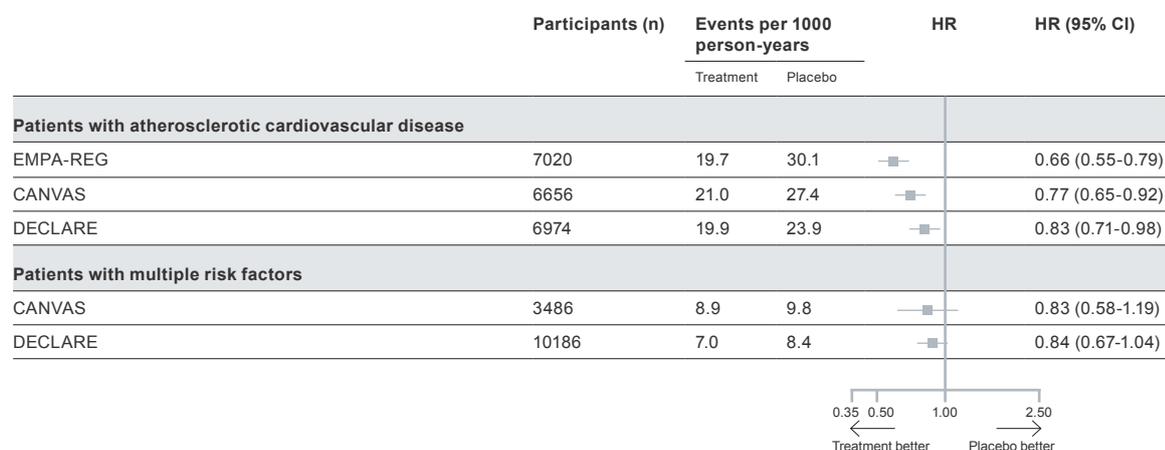


Figure based on Zelniker TA, et al. *Lancet* 2019.[7]

Renoprotection

In the three diabetes CV outcome studies, there was a significant reduction in renal deterioration with SGLT2i vs placebo[4-6] which was confirmed in the Zelniker *et al* 2019 meta-analysis[7]:

- **45% reduction in the progression of renal disease** (composite of worsening of estimated glomerular filtration rate (eGFR), end-stage renal disease or renal death) (HR: 0.55 [0.48-0.64]; $p < 0.0001$) with a similar benefit in participants with atherosclerotic CVD and those with multiple CV risk factors (Figure 6). The p value for risk reduction trend across eGFR subgroups shown below was 0.0258.[7]

Zelniker *et al* 2019 concluded:

These data suggest that SGLT2i should be considered in patients with type 2 diabetes regardless of presence of atherosclerotic cardiovascular disease or history of heart failure, given that they safely reduce HbA1c and reduce the risk of hospitalisation for heart failure and progression of renal disease broadly across the spectrum of these patients.[7]

Figure 3. Effect of SGLT2i on composite of worsening of eGFR, end-stage renal disease, or renal death in cardiovascular outcome trials in T2DM (stratified by baseline renal function)

	Participants (n)	Events per 1000 person-years		HR	HR (95% CI)
		Treatment	Placebo		
eGFR <60 mL/min per m²					
EMPA-REG	1801	NA	NA	0.66	(0.41-1.07)
CANVAS	2039	11.4	15.1	0.74	(0.48-1.15)
DECLARE	1265	8.9	15.2	0.60	(0.35-1.02)
eGFR 60 to <90 mL/min per m²					
EMPA-REG	3638	NA	NA	0.61	(0.37-1.03)
CANVAS	5625	4.6	7.4	0.58	(0.41-0.84)
DECLARE	7732	4.2	7.8	0.54	(0.40-0.73)
eGFR ≥90 mL/min per m²					
EMPA-REG	1529	NA	NA	0.21	(0.09-0.53)
CANVAS	2476	3.8	8.1	0.44	(0.25-0.78)
DECLARE	8162	2.5	4.9	0.50	(0.34-0.73)

Figure based on Zelniker TA, *et al. Lancet* 2019.[7]

Benefits in heart failure participants with reduced ejection fraction

Recently, a phase 3, placebo-controlled trial (DAPA-HF) demonstrated cardiovascular benefits in participants with heart failure and reduced ejection fraction (HFrEF) ($\leq 40\%$) (n=4,744), with dapagliflozin on top of standard care over a median of 18.2 months.[11] The primary endpoint in this study was the time to first occurrence of any of the composite of CV death, or worsening heart failure, defined by hospitalisation for heart failure or an urgent heart failure visit resulting in intravenous therapy for heart failure.

- **There was a 26% reduction in worsening heart failure or CV death** (primary endpoint) (HR: 0.74; 95% CI: 0.65-0.85; $p < 0.001$) in dapagliflozin- vs placebo-treated participants. This equates to a number needed-to-treat (NNT) of 21.[11]

In DAPA-HF, there were also statistically significant reductions with dapagliflozin vs placebo in the individual components of the composite primary outcome:

- **30% reduction in worsening heart failure event** (hospitalisation or urgent visit for heart failure) (HR: 0.70 [0.59, 0.83]; $p = 0.00003$)[11]; and
- **18% reduction in cardiovascular death** (HR: 0.82 [0.69, 0.98]; $p = 0.029$).[11]

Importantly, these benefits were present irrespective of the presence or absence of diabetes (Figure 4).

The “no diabetes” subgroup included many participants with pre-diabetes, although this was not thought to substantially influence the results.

[8] A further analysis of outcomes according to HbA1c tertiles [(i) $HbA1c \leq 5.6\%$; (ii) $HbA1c$ of 5.7-5.9% and (iii) $HbA1c \geq 6.0\%$] in participants without T2DM at baseline, showed dapagliflozin was more effective than placebo for the primary efficacy endpoint in all three HbA1c groups.[8]

Additionally, in the DAPA-HF study there was a:

- **Significant improvement in quality of life** as measured by an increase in Kansas City Cardiomyopathy Questionnaire (KCCQ) with dapagliflozin vs placebo. The change in KCCQ total symptom score (6.1 with dapagliflozin vs 3.3 for placebo; difference: 2.8 points [95% CI: 1.6, 4.0]; $p < 0.001$)[11]. This change in KCCQ total symptom score is similar to the quality of life improvement seen with ACE inhibitors and other heart failure treatments.

Note: The higher the KCCQ score the better, as this means the participant experiences fewer symptoms. A ≥ 5 -point change from baseline is considered “clinically relevant”.

- More participants in the dapagliflozin-treated group, compared to the placebo group, experienced a **clinically meaningful improvement** in KCCQ total symptom score from baseline (i.e. ≥ 5 points) (58% vs 51% respectively; OR: 1.15; $p < 0.001$).[11]
- Fewer participants in the dapagliflozin-treated group, compared to the placebo group, experienced a **clinically meaningful deterioration** in KCCQ total symptom score vs placebo-treated participants (25% vs 33% respectively; OR: 0.84; $p < 0.001$).[11]

Figure 4. Effect of dapagliflozin on heart failure events according to diabetes status in the DAPA-HF study

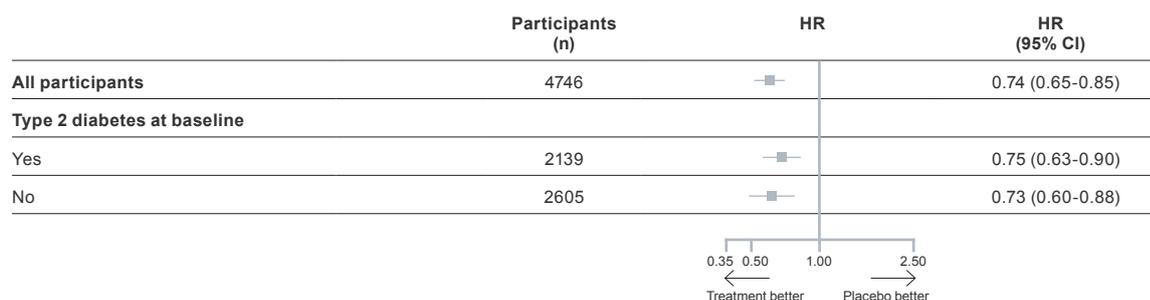


Figure based on McMurray J, *et al.* Dapagliflozin in Patients with Heart Failure & Reduced Ejection Fraction Presentation at ESC Congress: Aug 31-Sept 3, 2019, Paris.[8]

Absolute Mortality Benefit of SGLT2i

4

There is a need to consider the public health responsibility for ensuring SGLT2i are prescribed in appropriate patients (e.g. in heart failure patients following hospital discharge), similar to initiation of other cardioprotective agents, such as ACE inhibitors, angiotensin receptor blockers (ARB), beta blockers and statins.

The absolute benefits of SGLT2i can be modelled based on data taken from the National Diabetes Services Scheme (NDSS), which were published in *The Dark Heart of Type 2 Diabetes Report 2017*.^[9] This analysis estimated that there were 6,983 deaths in people with T2DM and prior cardiovascular disease in 2015 across Australia. The estimated number of deaths prevented in 1 year with a SGLT2i based on this data is summarised in Table 1 below.

Other information to help quantify the public health benefit could include:

- Determining the impact of SGLT2i use on future dialysis
- Estimating heart failure hospitalisation costs

Based on these data, a 30% reduction in mortality with SGLT2i use, as achieved in EMPA-REG,^[4] would equate to 2,095 deaths prevented in a single year (assuming there was a 100% uptake rate). Even if the mortality benefit of SGLT2i use was only 10% with a 50% uptake, this would still save 349 lives in one year.

The group agreed there is a “public health imperative” to ensure SGLT2i are prescribed in appropriate people and further information about the absolute benefits of SGLT2i use is warranted.

Table 1. The estimated number of deaths prevented in 1 year with a SGLT2i, according to effectiveness and uptake

Uptake (%)	Reduction in mortality (%)		
	10	20	30
100	698	1397	2095
90	628	1257	1885
80	559	1117	1676
70	489	978	1466
60	419	838	1257
50	349	698	1047

Based on data from Shaw J, *et al.* The Dark Heart of Type 2 Diabetes. Baker 2017.^[9]

Risks Associated with SGLT2 Inhibition

5

Rational prescribing of SGLT2i should consider not only the benefits, but the risk of adverse events (AEs) and other long-term safety aspects. Any potential benefits of SGLT2 inhibition should outweigh any potential risks.

AEs associated with SGLT2i include polyuria, genital infections, volume depletion in patients at risk of dehydration and diabetic ketoacidosis (DKA).

The two AEs of SGLT2i that cardiologists are most worried about are genital infections & DKA. GPs are generally familiar with treating genital infections, and are used to managing diabetic patients on SGLT2i, however, they may be concerned about DKA, particularly with broader use.

Polyuria/nocturia

Polyuria can generally be managed by proactively educating patients about potential side effects of SGLT2i. However, a minority of patients may not tolerate polyuria, particularly nocturia. In these cases, the clinician should undertake a risk/benefit discussion with the patient. In someone with a high CV risk, the inconvenience of polyuria, however, may be acceptable given the proven cardiovascular mortality and renal benefits of SGLT2 inhibition. For some patients, particularly those with a lower CV risk, the long-term benefits might not outweigh the inconvenience of frequent polyuria or nocturia associated with SGLT2i. GLP-1 agonists may be a suitable alternative in some patients.

Genital infections

All the trials have reported an increased risk of genital infections with SGLT2i, which, although not usually dangerous, can be a nuisance. Genital infections are usually managed with standard therapies, but on some occasions persistent or repeated infections may necessitate treatment discontinuation.

More information is required to help clinicians discuss good genital hygiene and to be able to treat genital infections if they occur.

Volume depletion

Because of their natriuretic effect, SGLT2i can cause volume depletion, particularly in patients taking loop diuretics or in individuals who are at risk of dehydration (e.g. acute gastrointestinal illness).

The fluid status in these patients should be checked before initiating a SGLT2i.

Non-heart failure clinicians require more guidance with respect to dose adjustment of diuretics in heart failure patients.

Amputations and fractures

A statistically significant increase in the frequency of amputations and also fractures was reported with canagliflozin in the CANVAS study [5], but not in the CREDENCE study, which also used canagliflozin.[16]

However, in the other trials, amputations and fractures with SGLT2i were not statistically different from placebo-treated patients. For example, in DECLARE the frequency of amputations was 1.4% with dapagliflozin and 1.3% in the placebo arm ($p=0.53$). The incidence of fractures for dapagliflozin and placebo were 5.3% vs 5.1% respectively ($p=0.59$).[6]

Diabetic ketoacidosis (DKA)

DKA is due to a “relative deficiency of insulin”. The American Diabetes Association defines DKA as a blood pH <7.3, HCO₃≤18 mmol/L and elevated ketones.[10] DKA is a serious, potentially life-threatening condition requiring hospitalisation. Rare cases of fatal DKA have been reported with SGLT2i use.

DKA is a rare class-effect of all SGLT2i. In the DECLARE study, the frequency of DKA with dapagliflozin was approximately double that observed in participants on placebo (0.3% vs 0.1%; HR: 2.18; [95% CI: 1.10-4.30]; p=0.02).[6]

There is an increased risk of DKA in people with diabetes on SGLT2i, particularly hospitalised patients who are fasting prior to surgery or who have a major infection. DKA can be present with SGLT2i use even in euglycaemic patients (i.e. those with a normal glucose level).[10]

Hamblin PS, *et al* 2019 recently published a retrospective controlled cohort study assessing the incidence of DKA in T2DM patients across all public hospitals in Melbourne and Geelong. [10] The incidence of DKA in patients with T2DM taking SGLT2i was compared with the incidence of DKA in non-SGLT2i (control group). Out of a total of 4321 medical records coded as DKA **over the 26-month study period there were 162 cases of verified DKA (37 SGLT2i users and 125 non-SGLT2i users)** with a physician adjudicated diagnosis of type 2 diabetes.[10]

- Among those with DKA, it developed during the course of an inpatient admission in 14 (38%) SGLT2i users vs 2 (2%) non-SGLT2i users (OR: 37.4; 95% CI: 8.0 to 175.9; p<0.0001).
- **The incidence of DKA over a 26-month period was 1.02 per 1000 (95% CI: 0.74 to 1.41 per 1000) in SGLT2i users vs 0.69 per 1000 (95% CI: 0.58 to 0.82 per 1000) in non-SGLT2i users** (OR: 1.48; 95% CI, 1.02 to 2.15; p=0.037).[10]
- Among those with DKA, deaths occurred in 2 of 37 (5%) SGLT2i users and in 11 of 125 (9%) non-SGLT2i users (p=0.73). Only one death (in a non-SGLT2i user) was thought to be directly due to DKA, with the remainder related to comorbidities.[10]

The **patients on SGLT2i who developed DKA had a significantly lower HbA1c** compared to the non-SGLT2i control group (9.3% vs 11.9% respectively; p<0.001), suggesting that the increased DKA risk was not caused by poorer glycaemic control.

There were no differences in age, sex, ethnicity, body mass index, duration of diabetes, or co-prescribed diabetes medications between SGLT2i users and non-SGLT2i users, with the exception of **metformin, which was prescribed in 32 (87%) SGLT2i users and 81 (65%) non-SGLT2i users** (p<0.001). The estimates of DKA incidence in the whole population did not take into account the duration of exposure because of the lack of data on the timing of SGLT2i initiation. Since SGLT2i use was rapidly increasing during the study time period, SGLT2i exposure was likely for a shorter time than the comparison agents. This may have resulted in the odds ratio comparing SGLT2i users with non-SGLT2i being an underestimate.

It is concluded that:

- **SGLT2i use was associated with a small but significant increased absolute risk of DKA** [OR: 1.48; 95% CI: 1.02-2.15]; p=0.037). [10]
- SGLT2i users were more likely to develop DKA as an inpatient compared with non-SGLT2i users. **Most cases of DKA that developed during hospital admission occurred in the context of surgery and fasting.**[10]
- In most cases of DKA in SGLT2i use, insulin was ceased in hospital when patients were fasting, and those involved in patient management may have been falsely reassured by blood glucose levels that were not particularly elevated, which could have contributed to the development of DKA in these patients.
- **This study highlights the need to educate medical staff about the risks of DKA in T2DM patients on SGLT2i, but also T2DM patients not on SGLT2i, as the absolute number of DKA cases in this group was three-fold that of SGLT2 users** (the most common probable precipitating factor for DKA in non-SGLT2i users was infection/acute illness).
- **SGLT2i should be withheld at least 2 days prior to surgery and not re-started until the patient is eating and drinking.**

DKA is particularly frightening for clinicians who are not familiar with SGLT2i and requires further education and guidance.

Suggestions with respect to the risk of DKA with SGLT2i use:

- Educate doctors regarding SGLT2i use and the risk of DKA and its management. Information and education should be from multiple sources.
- Pre-procedural advice is likely to be the most effective.
- Consider developing a “pre-op (theatre) check list” for patients undergoing surgery on a SGLT2i.
- Consider using a “patient leaflet on DKA” for people with diabetes who are prescribed a SGLT2i – including “sick day management”.
- Develop information for when the patient receives their SGLT2i script (pharmacy information)
- Doctors need to be educated to verbally discuss DKA with patients repeatedly, as leaflets are often misplaced or forgotten.
- Consider developing a “DKA checklist for doctors”. For example:
 - When to stop SGLT2i (and metformin) prior to major surgery
 - Avoid ketogenic/low carbohydrate diets
 - Check for ketones (using finger-prick ketone strip – not urine strip) if unwell, irrespective of blood glucose
 - When to re-start SGLT2i (i.e. when the patient is eating and drinking).
- Collaborate with the RACGP with respect to educating GPs and the risk of DKA with SGLT2i use. It is advisable to link DKA information with metformin as GPs are familiar with instructions for metformin use and surgery.
- The risk of DKA may be even greater in patients on insulin and/or metformin. Further information is required in terms of what to do with fixed dose combination products with metformin. It is easier to stop SGLT2i and metformin on the same day prior to surgery.

It is important to put DKA into context, given the overall absolute risk of DKA with SGLT2i was small, and given there is also a background risk of DKA in people with diabetes not taking a SGLT2i.

Following a small number of deaths reported in patients who developed DKA while taking a SGLT2i, some institutions have instigated mandatory measurement of ketones in all hospitalised people with diabetes on a SGLT2i. However, it is important that DKA is put into perspective. Clinicians need to understand most pre-surgery patients with diabetes will have ketosis, but this is not DKA. Many factors such as diet can increase ketone levels, but *acidosis* must also be present for the patient to have DKA.

Although the round table discussion was focused on the role of cardiologists and general practitioners (GPs), ongoing education of SGLT2i use with endocrinologists is also important as there may be an “emerging conservatism” within endocrinology because of fear of some of the side effects of SGLT2i, such as diabetic ketoacidosis (DKA).

AEs in elderly patients

A post-hoc analysis of DAPA-HF analysed the efficacy and safety of dapagliflozin according to age.[17] Although AEs and study drug discontinuation increased with age, neither was significantly more common with dapagliflozin in any age group. The authors concluded that there was no imbalance in tolerability or safety events between dapagliflozin and placebo, even in elderly individuals.[17]

AEs in patients without diabetes

Further information about any difference in the side effects in those patients with and without diabetes would be valuable.

An analysis of AEs in the diabetes and non-diabetes populations from DAPA-HF (presented by John McMurray at ESC) showed no statistically significant difference in the incidence of AEs compared to placebo in either the diabetes or non-diabetes groups. However, as expected there was a lower proportion of serious AEs in the people without diabetes compared to people with diabetes (which may be related to diabetes-related AEs) (Table 4).[8]

Table 2. Adverse events (AEs) reported with dapagliflozin and placebo from DAPA-HF study

	Diabetes			No diabetes		
	Placebo	Dapa	<i>P-value</i>	Placebo	Dapa	<i>P-value</i>
AE of interest (%)						
Volume depletion	7.8	7.8	1.00	6.1	7.3	0.24
Renal AE	8.7	8.5	0.94	6.0	4.8	0.19
Fracture	2.4	2.1	0.66	1.9	2.1	0.78
Amputation	0.8	1.1	0.66	0.2	0.1	N/A
Major hypoglycaemia*	0.4	0.4	N/A	0	0	N/A
Diabetic ketoacidosis	0	0.3	N/A	0	0	N/A
AE leading to treatment discontinuation (%)	5.4	4.0	0.15	4.5	5.3	0.41
Any serious AE (incl. death) (%)	48.3	41.7	0.002	36.9	34.6	0.24

* The safety population included patients receiving ≥ 1 dose of trial medication: dapagliflozin n=2368 and placebo n=2368.

* Major hypoglycemia defined as hypoglycemia requiring the assistance of another person to actively administer carbohydrates, glucagon, or take other corrective action.

Figure taken from McMurray J, et al. Dapagliflozin in Patients with Heart Failure & Reduced Ejection Fraction Presentation at ESC Congress: Aug 31-Sept 3, 2019, Paris.[8]

Barriers to SGLT2i Use

6

The major barriers preventing clinicians prescribing a SGLT2i in appropriate patients are:

- **cost**
- **side effects** (e.g. polyuria, genital infections, DKA)
- **difficulty with applying existing guidelines/indication/reimbursement based on glucose-lowering**

There is currently no guidance with respect to when to initiate SGLT2i, who should initiate the treatment and how long to continue SGLT2i use for their non-glucose lowering effects (see Section 7).

Current guidelines, drug approved indications and PBS reimbursement for SGLT2i use are based on HbA1c/glucose lowering. However, cardiovascular/renoprotective benefits of SGLT2i are irrespective of the blood glucose levels. Prescription of other cardiovascular protective agents (e.g. statins, ACEi, ARBs etc) are based on the patient's *underlying level of cardiovascular risk*.



Guidelines or Consensus Statement: When and Who Should Initiate SGLT2i?



When to start SGLT2i?

There is a need for further guidance with respect to *in whom* and *when* SGLT2i should be initiated for reno-cardiovascular benefits. For example:

1. Should SGLT2i be only started in those with hospitalisation for HF, and those with an acute CV event?
2. If the patient has not had an acute event, at what **level of cardiovascular risk** should a SGLT2i be initiated?
3. Should SGLT2i be introduced **before metformin** in a heart failure patient with newly diagnosed diabetes?
4. Should a SGLT2i be initiated by the **cardiologist pre-discharge**, following an **acute cardiovascular event**
5. Should the SGLT2i be initiated at the **first cardiology follow-up appointment** following an acute event?
6. Should the SGLT2i be started by the **endocrinologist**?
7. Should the specialist advise the **GP to initiate the SGLT2i** in the discharge letter following an acute event?

Starting a SGLT2i following an acute event

- The rationale for initiating a SGLT2i following an acute event (before a patient is discharged from hospital) is that other cardioprotective drugs (e.g. ACEi, ARBs, statins, etc) are initiated at this time. It may be the most efficient time to start the treatment and the patient may be more motivated to take CV treatment.
- However, initiating a SGLT2i immediately after an acute CV event (or before metformin) is not in line with the patient population used in the clinical studies. In the DAPA-HF trial, acute heart failure was an exclusion criterion and patients were already stable on other standard of care HF/EF/diabetes treatments (e.g. ACE

or ARB/ beta blocker/ MRA/ diuretic as well as diabetes medication such as metformin etc).[11]

- Given the current indication for SGLT2i use is only for patients with T2DM, the proposed recommendation for initiating therapy following an acute event would only be for patients with type 2 diabetes.
- Should there be a recommendation for initiating SGLT2i only following hospitalisation for acute *heart failure*, or after an acute *atherosclerotic* event such as an MI as well? Given the reduction in the primary study endpoint in heart failure with SGLT2i use was 26% vs 11% reduction in MACE, there is a stronger argument for initiating SGLT2i therapy post-acute heart failure compared to after an atherosclerotic event.[7, 11] However, post a CV event may be the 'easiest' group for cardiologists to initiate SGLT2i treatment. Furthermore, the benefit for heart failure outcomes was strong in those with a history of atherosclerotic disease whether or not they also had a history of heart failure.
- Should it be part of a forced titration strategy that is initiated by the specialist in the hospital, which is then followed up by the GP? This strategy might, for example, require the addition of an SGLT2i at 2 weeks post-discharge.
- There was a suggestion to look at data that has been collected in Queensland about the best time to start medication from an adherence point of view.

Complicating factors during the acute setting

- Apart from a lack of direct clinical trial evidence for initiating SGLT2i after an acute HF/CV event, there may be other complicating factors to consider, for example, the:
 - Large number of other medications to initiate in a patient post hospital admission
 - Patient's level of hydration in the case of heart failure
 - Patient's underlying renal function.

- There is confusion around the different “indications” for SGLT2i (i) glucose lowering (ii) CVD, renal and heart failure benefits. Guidelines should address this confusion by using a 2-step process. For example:

1. **Does the patient have T2DM and pre-existing CVD** (or multiple CVD risk factors)? If yes, then consider SGLT2i or GLP-1 agonist, irrespective of HbA1c.
2. **If not, does the patient have an elevated HbA1c?** If yes, then consider a range of glucose lowering drugs.

Mandatory advice or options

- It is hard to mandate initiation of SGLT2i immediately post an acute event, due to a lack of specific evidence at this time point, and due to the fact that individual factors need to be weighed up.
- However, the proposed guidelines could state that it was a “reasonable” option to consider starting a SGLT2i before hospital discharge.
- Other “options” are to start the patient on a SGLT2i at a follow-up specialist clinic, or the specialist could request the SGLT2i is started by the patient’s GP.
- However, if a SGLT2i is NOT started after an acute event, then the cardiologist should include the need to consider starting a SGLT2i in the patient’s hospital discharge letter.

Other considerations

1. Consider identifying a sub-group of those with established CVD, who are at low risk for SGLT2i complications, and in whom all cardiologists might be expected to be confident to initiate an SGLT2i. Criteria for such a GREEN LIGHT group might be:
 - HbA1c is >7.0%
 - Age is <80 years
 - EGFR is >45 mL/min/1.73 m²
 - The patient is not on insulin
 - Patient is not on a ketogenic diet
 - Patient does not have a history of recurrent genital infections
2. **“Contraindications or precautions”** for SGLT2i (i.e. RED or AMBER light system). For example if:

Do not use SGLT2i if eGFR<15 mL/min/1.73 m². Caution if eGFR 15-45 mL/min/1.73 m²

 - Patients on higher doses of insulin (because of increased risk of DKA).

3. Adjustment of other glucose lowering therapy

Although SGLT2i do not directly cause hypoglycaemia, they may precipitate it in people already on sulphonylureas or insulin. These drugs may therefore need adjusting or stopping, especially if HbA1c is already close to or at target. Given the large number of glucose lowering classes and drugs, many clinicians may lack confidence that they can readily adjust sulphonylureas and insulin, and that they can assess risk of hypoglycaemia.

4. **Provide appropriate advice on what to do if the patient becomes unwell**
5. **When to refer the patient to an endocrinologist**

Target a population who are most likely to benefit from SGLT2i

- An alternate approach to the “traffic light” approach described above, is to target just one group of patients who are most likely to benefit from a SGLT2i e.g. any T2DM patient who has documented CVD or chronic heart failure with a reduced LVEF.
- It may be easier to target one group where there is a “*compelling need*” to increase prescriber confidence with SGLT2i and then expand the guidelines to other groups.
- This could be a “proof of concept” approach where it may be possible to demonstrate good uptake and adherence in a target group.
- This approach should also include when to refer the patient to the endocrinologist/other specialist care.

Keep SGLT2i guidelines simple

- It is important to consider that there are many medications that are initiated and actions that must be taken in a patient post an acute event such as hospitalisation for heart failure; therefore, the instructions should be simple and accommodate other prescribing decisions at this time.
- Some patients may be “overwhelmed” with the number of new medications to be initiated and, therefore, for some patients it may be more appropriate for the GP to start the SGLT2i after discharge from hospital when they can have a discussion with their GP.
- General cardiologists may be unlikely to prescribe SGLT2i if the guidelines are too complex.

Monitoring SGLT2i prescription/guideline adoption

- At the present time very few patients are commenced on a SGLT2i post an acute event, although for many patients they may be more motivated to start heart medication at this time period.
- There should be a process to monitor SGLT2i prescription in appropriate patients on a national level. For example, hospital discharge codes could be used to take a baseline measurement of current SGLT2i prescription in diabetes patients who have had a HF/CV event. The measurement could be repeated after guideline intervention. It may be possible to link/use existing QLD heart failure data (which contains a register of patients who are referred to QLD heart failure services).

Should GLP-1 agonists be included in the guidelines?

- A consensus cannot be reached about the inclusion of GLP-1 agonists in any new SGLT2i guidelines.
- Some advisors said GLP-1 agonists may unnecessarily overcomplicate the guidelines and cardiologists are unfamiliar with these agents and don't generally prescribe them.
- However, another school of thought was that GLP-1 agonists should be included as there is a body of evidence supporting cardiovascular benefits with these agents, which could be an alternative treatment in people who cannot tolerate or who have a contraindication to a SGLT2i.
- The group was unsure if there are any proven benefits of GLP-1 agonists on heart failure outcomes.
- There may be some issues with the use of GLP-1 agonists in heart failure due to their effects on heart rate.

Who should initiate SGLT2i treatment?

There is the potential for a clinician not to prescribe SGLT2i in suitable patients as they may think it is another physician's responsibility (e.g. a cardiologist may assume the endocrinologist or GP will initiate the drug or vice versa). Therefore, **it is important there is clear guidance for who is responsible for initiating SGLT2i.**

- Is it the cardiologist's responsibility at hospital discharge, the GP or the endocrinologist's role?

- There is a potential for under-prescribing SGLT2i if there is insufficient communication between medical disciplines. For example, if a SGLT2i is not initiated after an acute HF/CV event, and no explanation is provided in the patient's discharge letter/medical notes, then the GP/cardiologist may think SGLT2i prescription has been considered, although it may have been inadvertently overlooked.
- The group discussed developing criteria for when an endocrinologist should be involved if a cardiologist/other physician initiates SGLT2i use.
- If cardiologists perceive SGLT2i as a "diabetes drug" they may be less likely to prescribe these agents. The group thought that this situation may be akin to ophthalmologists' reluctance to prescribe fenofibrate to reduce diabetic retinopathy because they thought it wasn't an ophthalmology drug. **Therefore, it is important when educating physicians that SGLT2i are not positioned as "diabetes only drugs".**
- Education is also required for other physicians (e.g. general physician, geriatricians, rehabilitation) as many heart failure patients are managed by these clinicians.

How long should SGLT2i treatment be continued?

Further guidance should be provided in terms of the duration of SGLT2i treatment. Long-term SGLT2i studies are warranted particularly in younger, lower risk patients.

Who should be involved with developing and endorsing consensus statement/guidelines?

- ADS
- CSANZ
- RACGP
- Nephrologist
- Geriatrician (*The group thought this group could be involved with the dissemination rather than development/endorsement*)

However, the more people who are involved generally the longer the process will take.

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