

# Current evidence and practical guidance for the use of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes

**Aakansha Zala**, Louise J Maple-Brown, Jonathan E Shaw, Matthew JL Hare

## Background

The burden of type 2 diabetes (T2D) and its associated complications continues to grow in Australia. In recent years, sodium-glucose co-transporter-2 (SGLT2) inhibitors have become a key component of diabetes care with rapid uptake into routine clinical practice. There is growing evidence of their clinical efficacy, but also potential adverse effects.

## Objective

The aim of this article is to review the use of SGLT2 inhibitors in T2D by exploring data surrounding clinical efficacy and safety as well as providing practical advice for prescribing clinicians.

## Discussion

SGLT2 inhibitors have multiple metabolic benefits including reducing glycated haemoglobin, weight and blood pressure. Additionally, there are strong cardiovascular benefits and renoprotective effects in selected populations. Current evidence suggests that SGLT2 inhibitors should be considered for the secondary prevention of cardiovascular disease and to delay progression of early chronic kidney disease in people with T2D. Clinicians should also be aware of common side effects and potential rare severe complications.

**MORE THAN 1.2 MILLION** adult Australians have diabetes, the vast majority having type 2 diabetes (T2D).<sup>1</sup> Glycaemia is known to be associated with microvascular and macrovascular complication risk. Earlier trials demonstrated that improving glycaemic levels resulted in fewer microvascular complications but without a clear cardiovascular benefit.<sup>2-6</sup>

It became apparent that a stronger focus on cardiovascular safety of diabetes therapeutics was required when a meta-analysis suggested rosiglitazone may increase myocardial infarction risk.<sup>7</sup> In 2008, the United States Food and Drug Administration (US FDA) mandated that all new diabetes treatments be evaluated in large cardiovascular safety outcome trials. These regulatory changes have led to revolutionary data demonstrating cardiovascular and renal benefits of sodium-glucose co-transporter-2 (SGLT2) inhibitors and some glucagon-like peptide-1 receptor agonists (GLP-1RAs).<sup>8-15</sup> In addition, there is growing awareness of the importance of individualising diabetes therapies and glycaemic targets, taking into consideration patients' risk profiles, comorbidities, age and duration of disease.

Within the past decade, four SGLT2 inhibitors have been approved by the Australian Therapeutic Goods Administration (TGA): canagliflozin,

dapagliflozin, empagliflozin and ertugliflozin. The latter three are currently available on the Pharmaceutical Benefits Scheme (PBS). This review summarises the available evidence regarding the efficacy, effectiveness and safety of SGLT2 inhibitors and provides suggestions on how they should be adopted into clinical practice.

## Mechanism of action

SGLT2 transporters, located in the proximal renal tubule, are responsible for >90% of renal glucose reabsorption.<sup>16</sup> The remainder occurs via SGLT1. Typically, glycosuria occurs above a glycaemic threshold of approximately 10 mmol/L. People with T2D have higher thresholds and greater SGLT2 expression.<sup>16</sup>

## Cardiovascular disease benefit

While designed to demonstrate safety, SGLT2 inhibitor cardiovascular outcome trials have in fact demonstrated benefit (summarised in Table 1). Published trials have shown a reduction in heart failure hospitalisation with all agents. Reduction in major adverse cardiovascular events was demonstrated with empagliflozin and canagliflozin, but not dapagliflozin or ertugliflozin.<sup>9-12</sup> These trials have been conducted in high-risk cohorts with

different proportions of people with either established cardiovascular disease (CVD) or with multiple risk factors for atherosclerotic CVD. The results are therefore not directly comparable and not necessarily generalisable to people with T2D who are at lower CVD risk. Nevertheless, the positive findings have been largely replicated in a multinational study of real-world health records data in which there was a lower prevalence of established CVD.<sup>17</sup> Mechanisms behind the cardiovascular benefits of these agents are unclear but are independent of improvements in glycaemia. Trials of both empagliflozin and dapagliflozin in people with heart failure with reduced ejection fraction (HFrEF) have shown similar mortality and hospitalisation

benefits, irrespective of whether participants had diabetes.<sup>18,19</sup>

### Renal benefits

SGLT2 inhibitors reduce progression of renal disease despite an initial reversible elevation in serum creatinine.<sup>8–11</sup> In a dedicated renal outcome study among patients with T2D and pre-existing stage 2–3 chronic kidney disease (CKD), canagliflozin treatment led to a reduced incidence of the primary outcome of end-stage kidney disease (dialysis, transplantation, or a sustained estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m<sup>2</sup>), doubling of serum creatinine, or death from renal or cardiovascular causes (hazard ratio

[HR] 0.70; 95% confidence interval [CI]: 0.59, 0.82).<sup>8</sup> There were improvements in each component of this combined endpoint. Similar renal benefits have been observed with dapagliflozin in people with and without T2D.<sup>20</sup> The renal benefits observed to date with SGLT2 inhibitors are comparable to those seen in trials of renin–angiotensin system blockers.<sup>21</sup> These agents are likely to similarly become a cornerstone of CKD prevention in diabetes.

### Metabolic benefits

SGLT2 inhibitors have beneficial effects on glycated haemoglobin (HbA1c), weight and blood pressure (summarised in Table 2). On average, SGLT2 inhibitors

**Table 1. Summary of the primary and secondary outcomes of the major SGLT2 inhibitor cardiovascular outcome trials among people with type 2 diabetes<sup>9–12</sup>**

| SGLT2 inhibitor | Trial name, year published | Study population (n) | Pre-existing CVD | Median follow-up (years) | Primary outcomes (HR for treatment vs placebo)                             | Notable secondary outcomes (HR for treatment vs placebo)  |
|-----------------|----------------------------|----------------------|------------------|--------------------------|--|---|
| Canagliflozin   | CANVAS 2017                | 10,142               | 66%              | 2.42                     | HR 0.86 for MACE*  | HR 0.67 for heart failure hospitalisation*<br>HR 0.87 for all-cause mortality<br>HR 0.87 for CV death<br>HR 0.60 for combined renal endpoint*       |
| Dapagliflozin   | DECLARE TIMI 2019          | 17,160               | 41%              | 4.2                      | HR 0.93 for MACE<br>HR 0.83 for CV death or heart failure hospitalisation* | HR 0.73 for heart failure hospitalisation*<br>HR 0.93 for all-cause mortality<br>HR 0.98 for CV death<br>HR 0.76 for combined renal endpoint*       |
| Empagliflozin   | EMPA-REG 2015              | 7020                 | 99%              | 3.1                      | HR 0.86 for MACE*  | HR 0.65 for heart failure hospitalisation*<br>HR 0.68 for all-cause mortality*<br>HR 0.62 for CV mortality*<br>HR 0.54 for combined renal endpoint* |
| Ertugliflozin   | VERTIS-CV 2020             | 8246                 | 100%             | 3.5                      | HR 0.97 for MACE   | HR 0.70 for heart failure hospitalisation*<br>HR 0.92 for CV mortality<br>HR 0.81 for combined renal endpoint                                       |

\*Statistically significant

Note: The combined renal endpoints vary between the trials but include a sustained reduction in estimated glomerular filtration rate or increase in serum creatinine, commencement of dialysis or death from renal causes. In EMPA-REG the combined renal endpoint was not a pre-specified secondary outcome. CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; MACE, major adverse cardiovascular event; SGLT2, sodium–glucose co-transporter-2

reduce HbA1c by 7–9 mmol/mol (0.6–0.9%),<sup>22</sup> with the effect being greater at higher starting levels of HbA1c.

### Safety and tolerability

SGLT2 inhibitors are relatively new and have several side effects that warrant caution, including the unique risks of diabetic ketoacidosis (DKA), mycotic genital infections and possibly lower limb amputations.

### Diabetic ketoacidosis

While the absolute risk is small, SGLT2 inhibitor therapy increases risk of DKA.<sup>8,9</sup> As a result of the insulin-independent effect of SGLT2 inhibition on glycaemia, a significant proportion of DKA cases occur with only slightly elevated blood glucose levels, which may lead to delayed diagnosis and management.<sup>23</sup> In the major trials, the rates of DKA were 0.1–0.5% over four to eight years,<sup>8–10</sup> while a large Australian observational study demonstrated a DKA rate of 0.1% over 26 months.<sup>23</sup> The risk is increased in people who are acutely unwell, fasting, perioperative or have a history of excess alcohol consumption.<sup>24</sup> As such, SGLT2 inhibitors should be withheld when patients are unwell, fasting and three days pre-operatively. In the event of acute illness that warrants medical attention (especially in the setting

of nausea, vomiting or abdominal pain), measurement of capillary blood ketone or blood beta-hydroxybutyrate levels should be considered. Urine ketone testing may be unreliable because of altered urinary ketone excretion.<sup>25</sup> The absence of severe hyperglycaemia is not adequate to exclude SGLT2 inhibitor-associated DKA.

### Genital and urinary infections

As a result of the glycosuric effect of SGLT2 inhibitors, there is an increased risk of genital infections. Each of the major trials has shown an increased rate of mycotic infections (up to 11%), especially among women.<sup>10</sup> Of concern is the risk of Fournier's gangrene. Among individuals prescribed SGLT2 inhibitors, there were 55 cases of Fournier's gangrene reported to the US FDA from 2013 to 2019 in comparison to 19 cases with other oral glucose-lowering agents over 35 years.<sup>26</sup> As such, patients should be advised to monitor for symptoms suggestive of genital infection and maintain good genital hygiene. For candidiasis, a single course of a topical antifungal is usually effective. SGLT2 inhibitor cessation should be considered in the event of persistent or recurrent candidiasis or a more serious infection. There is also a small increase in risk of urinary tract infections (UTIs), particularly among women.<sup>10,12,27</sup>

### Amputations for diabetes-related foot disease

Concern about amputations was raised by the CANVAS trial which showed greater amputation risk (primarily at the level of the toe or metatarsal) with canagliflozin (HR 1.97; 95% CI: 1.41, 2.75).<sup>11</sup> This was not observed in the empagliflozin or dapagliflozin trials, nor in the subsequent CREDENCE trial of canagliflozin.<sup>8</sup> However, a registry-based study from Sweden and Denmark found increased amputation risk with SGLT2 inhibitor use when compared with GLP-1RA use.<sup>28</sup> In this population the vast majority were taking either dapagliflozin or empagliflozin. It remains unclear whether SGLT2 inhibitors affect the risk of needing a peripheral amputation. Patients with vascular disease may benefit from the cardioprotective effects of these agents. Nevertheless, it may be wise to avoid SGLT2 inhibitors in patients with active diabetes-related foot disease or peripheral vascular disease without reperfusion.

### Polyuria, volume depletion and hypotension

As a result of the diuretic effect of SGLT2 inhibitors, a number of patients experience polyuria. The degree of polyuria is typically higher in people with more marked hyperglycaemia. The diuretic effect can lead to volume loss and potentially hypotension,<sup>27</sup> with some trials showing an increase in risk of volume depletion,<sup>8,11,18</sup> and others showing no excess.<sup>9,10</sup> In 2016, the US FDA issued a warning about the risk of acute kidney injury (AKI) with SGLT2 inhibitors. However, growing evidence suggests that they are in fact protective against AKI, despite adverse events related to hypovolaemia.<sup>29</sup> As a result of changes in renal haemodynamics, an initial decline in eGFR is expected following SGLT2 inhibitor commencement. This has been shown to be reversible and is thought to be related to a beneficial reduction in renal hyperfiltration. We suggest that up to a 20% decline in eGFR should be tolerated in the first month, provided that there is no clinical evidence of hypovolaemia or an alternate pathology that could be contributing to AKI. A more severe or

**Table 2. Metabolic benefits of TGA-approved SGLT2 inhibitors compared with placebo<sup>12,22</sup>**

| SGLT2 inhibitor      | Absolute HbA1c reduction, % (mmol/mol) | Systolic blood pressure reduction (mmHg) | Weight loss (kg) |
|----------------------|--|--|------------------|
| Canagliflozin 100 mg | 0.8 (8.3)                              | 3.9                                      | 1.9              |
| 300 mg               | 0.9 (9.4)                              | 4.9                                      | 2.5              |
| Dapagliflozin 10 mg  | 0.7 (7.2)                              | 2.8                                      | 2.2              |
| Empagliflozin 10 mg  | 0.6 (6.6)                              | 3.3                                      | 2.1              |
| 25 mg                | 0.7 (7.2)                              | 3.7                                      | 2.2              |
| Ertugliflozin 5 mg   | 0.5 (5.5)                              | 2.6                                      | 2.4              |
| 15 mg                | 0.5 (5.5)                              | 3.2                                      | 2.8              |

Data are mean differences compared with placebo from a large meta-analysis of randomised control trials. All differences were statistically significant.

HbA1c, glycated haemoglobin; SGLT2, sodium–glucose co-transporter-2; TGA, Therapeutic Goods Administration

**Table 3. Important potential adverse effects of SGLT2 inhibitors and considerations for clinical practice**

| Adverse effect                     | Suggested clinical considerations  |
|------------------------------------|--|
| Polyuria, dehydration, hypotension | <ul style="list-style-type: none"> <li>Advise patients regarding potential effect</li> <li>Educate regarding maintaining adequate hydration (mindful of any fluid restrictions required for renal disease or heart failure)</li> <li>For patients on diuretics, consider a dose reduction in diuretic therapy if euvoelaemic at time of SGLT2 inhibitor commencement with close home monitoring of weight</li> <li>Note severity of polyuria is often glycaemia-dependent (improving uncontrolled glycaemia with other agents may lessen the polyuria)</li> <li>For elderly patients or those on other antihypertensives, blood pressure should be reassessed one to two weeks after SGLT2 inhibitor commencement</li> </ul> |
| Genital infections                 | <ul style="list-style-type: none"> <li>Advise both men and women of potential effect</li> <li>Encourage maintenance of basic genital hygiene</li> <li>Advise patients to seek medical attention if there are symptoms of urogenital infection</li> <li>Use topical antifungal and temporarily withhold SGLT2 inhibitors if there are symptoms of urogenital infection</li> <li>Consider ceasing therapy if persistent or recurrent candidiasis</li> </ul>  |
| Urinary tract infection (UTI)      | <ul style="list-style-type: none"> <li>Advise patients, especially women, of potential risk. SGLT2 inhibitors may not be appropriate in patients with a history of recurrent UTIs</li> <li>Withhold SGLT2 inhibitors in setting of significant UTI (eg pyelonephritis, prostatitis, urosepsis, prolonged clinical course)</li> <li>Consider cessation if patient develops recurrent UTIs</li> </ul>  |
| Euglycaemic diabetic ketoacidosis  | <ul style="list-style-type: none"> <li>Withhold SGLT2 inhibitors for two days prior and on day of elective surgery</li> <li>Advise patients to withhold when fasting or when unwell</li> <li>Advise patients to seek medical review if unwell, especially if experiencing nausea, vomiting or abdominal pain, for consideration of ketone measurement</li> <li>Clinics involved in care of people with diabetes should have access to ketone testing. Urine ketone testing is unreliable</li> <li>Provide patients with written information about sick-day and periprocedural management plans</li> </ul>  |
| Amputations                        | <ul style="list-style-type: none"> <li>Impact on amputation risk is unclear</li> <li>Regular podiatry review and foot care advised for all patients</li> <li>Consider avoiding SGLT2 inhibitors in patients with active high-risk foot disease or compromised peripheral vascular supply</li> </ul>  |
| Hypoglycaemia                      | <ul style="list-style-type: none"> <li>Advise regular home blood glucose monitoring when commencing SGLT2 inhibitors in patients on sulphonylureas or insulin and ensure patient is familiar with hypoglycaemia symptoms and management</li> <li>If patients are prone to hypoglycaemia or have tight glycaemic control, consider dose reduction of sulphonylurea or insulin when commencing SGLT2 inhibitors. Concurrent cessation of insulin therapy should be avoided as this has contributed to reported cases of diabetic ketoacidosis</li> </ul>   |

SGLT2, sodium–glucose co-transporter-2

prolonged decline in eGFR should prompt further investigation.

### Hypoglycaemia

As the glucose-lowering mechanism of SGLT2 inhibitors is glycaemia-dependent, hypoglycaemia risk is low. However, hypoglycaemia may occur when SGLT2 inhibitors are used in conjunction with sulphonylurea or insulin therapy.

### When and how to prescribe SGLT2 inhibitors

The Australian Diabetes Society has recently changed their guidelines to include SGLT2 inhibitors as an option for second-line therapy for T2D after lifestyle modification and metformin.<sup>30</sup> Improving glycaemia has previously been the key rationale for commencing glucose-lowering agents, but SGLT2 inhibitors, as well as some GLP-1RAs, have created a paradigm shift in this approach. These agents should be considered for secondary prevention of CVD and delaying progression of early CKD in people with T2D, irrespective of the current HbA1c. For the patients at highest risk, SGLT2 inhibitors should be seen as cardio- and reno-protective medications, not just glucose-lowering medications. For Australian prescribers, the PBS currently restricts subsidised SGLT2 inhibitor use to specific scenarios and the relevant TGA approvals state that SGLT2 inhibitors should only be prescribed with eGFR  $\geq 45$  mL/min/1.73m<sup>2</sup>.<sup>31</sup> Prescribers should take into account the clinical considerations suggested in Tables 3 and 4 and select appropriate patients for SGLT2 inhibitor use. Patients should be able to report side effects and follow a sick-day management plan. GLP-1RAs are not within the scope of this article but can also be considered as alternative second-line agents in individuals with atherosclerotic cardiovascular disease or obesity.<sup>30</sup>

### Conclusion

With their impressive cardiovascular, renal and metabolic benefits, SGLT2 inhibitors have modified the paradigm in which we approach diabetes management. SGLT2

**Table 4. Sick-day and perioperative considerations with SGLT2 inhibitors<sup>25</sup>**

| Clinical scenario   | Sick-day and perioperative considerations   |
|---|---|
| Day procedures, including gastroscopy   | Withhold SGLT2 inhibitors on the day of the procedure.  |
| Surgery and other procedures requiring hospitalisation or 'bowel preparation' | Withhold SGLT2 inhibitors at least three days pre-operatively (two days prior to surgery and the day of surgery). Blood glucose levels should be monitored, and other glucose-lowering agents may need to be increased.                           |
| Perioperative period  | If the patient becomes unwell or has prolonged limited oral intake, perform both blood glucose and blood ketone monitoring.   |
| Acute illness   | Withhold SGLT2 inhibitors, especially if there is reduced oral intake or vomiting. Patients should monitor blood glucose levels and clinicians should consider checking ketone levels, especially if there is nausea, vomiting or abdominal pain. |

SGLT2, sodium–glucose co-transporter-2

inhibitors (and, similarly, GLP-1RAs) have become important treatment options for T2D. Current evidence suggests they be considered for all people with T2D and either pre-existing CVD or early CKD, irrespective of current HbA1c, and taking into account individual patient characteristics and potential for adverse effects. SGLT2 inhibitors are also a useful therapeutic option for improving glucose levels, with favourable effects on weight and low risk of hypoglycaemia.

### Authors

Aakansha Zala MBBS, FRACP, Endocrinologist, Department of Endocrinology, Princess Alexandra Hospital, Woolloongabba, Qld; Endocrinology Research Fellow, The University of Queensland Diamantina Institute, Translational Research Institute, Qld

Louise J Maple-Brown MBBS, FRACP, PhD, Head, Department of Endocrinology, Royal Darwin Hospital, NT; Head, Diabetes across the Lifecourse: Northern Australia Partnership, Menzies School of Health Research, Charles Darwin University, NT

Jonathan E Shaw MD, FRACP, FRCP(UK), FAAHMS, Deputy Director (Clinical and Population Health), Baker Heart and Diabetes Institute, Vic; Professor, School of Public Health and Preventive Medicine, Monash University, Vic

Matthew JL Hare MBBS, BMedSc, FRACP, Endocrinologist, Department of Endocrinology, Royal Darwin Hospital, NT; Menzies School of Health Research, Charles Darwin University, NT

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**Correspondence to:** matthew.hare@menzies.edu.au

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