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ARTICLE

Sodium-glucose co-transporter 2 inhibitors beyond diabetes

SUMMARY

Sodium-glucose co-transporter 2 (SGLT2) inhibitors lower blood glucose by reducing the reabsorption of glucose in the kidney. They are a second-line therapy for type 2 diabetes.

During clinical trials it was noticed that SGLT2 inhibitors had favourable effects on cardiovascular and renal disease. This led to further trials that included patients without diabetes.

In studies of heart failure, SGLT2 inhibitors were beneficial in treating patients with a reduced left ventricular ejection fraction. A recent study has also reported benefits in patients with a preserved ejection fraction.

In chronic kidney disease, SGLT2 inhibitors may reduce disease progression. However, a decline in the glomerular filtration rate may be seen at the start of treatment.

As most experience with SGLT2 inhibitors is in diabetes, patients without diabetes need to be aware of why they are being prescribed these drugs. Some of the potential indications for SGLT2 inhibitors beyond diabetes are not yet approved by regulatory authorities.

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Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors lower blood glucose and are an established second-line therapy in patients with type 2 diabetes.[1] They increase glucose excretion by reducing its renal reabsorption. The drugs currently available in Australia are dapagliflozin, empagliflozin and ertugliflozin.

Benefits beyond lowering glycated haemoglobin (HbA1c) have been reported in patients with type 2 diabetes who have multiple cardiovascular risk factors or established cardiovascular disease. Consistent reductions in hospitalisations due to heart failure and renal benefits have led to studies in patients with heart failure and chronic kidney disease. These have reported clear benefits regardless of the patient's diabetes status. SGLT2 inhibitors therefore have an emerging role in the treatment of heart failure and chronic kidney disease. In some cases, these new indications have not yet been approved by the Therapeutic Goods Administration (TGA).

SGLT2 inhibitors in type 2 diabetes

Several SGLT2 inhibitors have been evaluated in cardiovascular outcome trials in patients with type 2 diabetes. They include empagliflozin, canagliflozin, dapagliflozin and ertugliflozin. A consistent finding in all these trials was a reduction in hospitalisation due to heart failure. A meta-analysis of placebo-controlled trials reported a 22% relative risk reduction in cardiovascular death or heart failure hospitalisation. In patients randomised to SGLT2 inhibitor therapy, there was also a 38% relative risk reduction in composite renal outcomes, comprising worsening estimated glomerular filtration rate (eGFR) or creatinine, end-stage kidney disease, kidney death or cardiovascular death.[2]

SGLT2 inhibitors in heart failure

Heart failure can be classified according to left ventricular function. SGLT2 inhibitors have been studied in patients with reduced and preserved left ventricular ejection fraction.

Reduced ejection fraction

Two large randomised, double-blind, placebo-controlled trials have reported that SGLT2 inhibitors are beneficial for patients who have heart failure with a reduced left ventricular ejection fraction (40% or below), regardless of their diabetes status.[3,4] The mechanism of this benefit is not fully understood. It may relate to the drug's natriuretic effect, enhanced erythropoiesis, beneficial changes in cellular energetics or reversal of adverse ventricular remodelling.[5]

The DAPA-HF trial reported a 26% relative risk reduction in cardiovascular death or worsening heart failure in patients randomised to receive dapagliflozin.[3] The magnitude of benefit was similar irrespective of the patient's background therapy for heart failure.

The EMPEROR-Reduced trial compared empagliflozin to placebo. It also found a significant relative reduction in cardiovascular death or heart failure

hospitalisation.[4] The combined risk was 25% lower in patients given empagliflozin, mainly due to a lower risk of hospitalisation for heart failure.[4]

Due to the results of these trials, both the American Heart Association/American College of Cardiology/Heart Failure Society of America and European Society of Cardiology heart failure guidelines have included SGLT2 inhibitors as first-line therapy for patients with heart failure and a reduced left ventricular ejection fraction.[6,7]

Both dapagliflozin and empagliflozin are listed on the Pharmaceutical Benefits Scheme (PBS) for patients with heart failure with left ventricular ejection fraction less than or equal to 40%, who are receiving optimal standard chronic heart failure treatment, which must include a beta blocker and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor, unless contraindicated or cannot be tolerated.

Preserved ejection fraction

Patients who had heart failure with a preserved left ventricular ejection fraction were studied in the EMPEROR-Preserved trial.[8] This reported a 21% relative risk reduction in the composite primary end point of cardiovascular death or heart failure hospitalisation in patients randomised to receive empagliflozin. This result was predominantly driven by a 29% relative risk reduction in heart failure hospitalisation. This is the first major outcome study of heart failure with a preserved left ventricular ejection fraction to show a benefit. The ongoing DELIVER study is evaluating the safety and efficacy of dapagliflozin in heart failure with a preserved left ventricular ejection fraction, with results expected in 2022.

The most recent American Heart Association/American College of Cardiology/Heart Failure Society of America heart failure guidelines recommend the use of SGLT2 inhibitors in patients with heart failure with a preserved ejection fraction to reduce heart failure hospitalisations and cardiovascular mortality.[6]

SGLT2 inhibitors in chronic kidney disease

The reported improvements in renal function with SGLT2 inhibitors probably relate at least partly to reduced intraglomerular pressure, but the mechanism of action remains an active area of investigation. The improved renal outcomes seen in patients with diabetes led to trials specifically investigating renal end points.

The DAPA-CKD trial studied patients with chronic kidney disease with or without type 2 diabetes (67.5% had diabetes). They had an eGFR of 25–75 mL/minute/1.73 m^2 and a urinary albumin:creatinine ratio (mg/g) of 200–5000.[9] Compared with placebo, dapagliflozin led to a 39% reduction in the relative risk for a sustained fall in eGFR, end-stage kidney disease or death from cardiovascular or renal causes. The benefits were similar in patients with and without diabetes. Recently, dapagliflozin has been approved by the TGA to reduce the progression of proteinuric chronic kidney disease, however this indication is not listed on the PBS. The ongoing EMPA-KIDNEY trial is studying the effect of empagliflozin on cardiovascular and renal outcomes in patients with chronic kidney disease.

SGLT2 inhibitor prescribing

The SGLT2 inhibitors are generally well tolerated and the process of prescribing these drugs is relatively uncomplicated compared to other treatments for heart failure, with no requirement for dose titration in the majority of patients. SGLT2 inhibitors should not be used in patients with type 1 diabetes due to a significant increased risk of ketoacidosis.[10] They should also not be used in patients who are pregnant or lactating or in patients requiring dialysis.[10,11]

While most of the safety data were derived from patients with type 2 diabetes, recent studies that included patients without diabetes have reported a favourable safety profile. Indeed, there were no reported cases of ketoacidosis in the patients without diabetes enrolled in the DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved and DAPA-CKD studies. Postmarketing follow-up continues to be necessary as adverse drug reactions are often detected and these should be reported to the TGA. A reduction in systolic blood pressure due to volume depletion may be observed, which may require a reduction in diuretic dosing provided there is no clinical evidence of congestion.

Considerations before prescribing

There are adverse effects and comorbidities to consider before starting SGLT2 inhibitors (Table).[11]

Renal function

A transient reduction in renal function is common when starting SGLT2 inhibitors due to their mechanism of action, but is not a reason to stop therapy, unless the decline progresses. Recheck renal function to confirm that this acute deterioration is not continuing.

Ketoacidosis

Ketoacidosis is uncommon, but life-threatening. SGLT2 inhibitors should not be used in patients with a history of ketoacidosis, unless under specialist supervision. It is more likely in patients with diabetes, or during periods of acute illness or fasting (peri-procedural fasting, bowel preparation,

Table **Adverse effects of sodium-glucose co-transporter 2 inhibitors**

Adverse effect	Practice point
Genitourinary infections	
Increased risk of mycotic infections. Candida vaginitis in women, balanitis in men (common >1%). Urinary tract infections (largely non-severe and resolve quickly, common >1%). Cases of necrotising fasciitis of the perineum (Fournier's gangrene) have been reported (rare <0.1%).	Patient education: perineal hygiene and advice on signs and symptoms of urinary or genital infection, including fever and pain, tenderness or swelling in the genital area. Prompt assessment and treatment to avoid more serious systemic infections, including Fournier's gangrene and necrotising fasciitis, urosepsis and pyelonephritis.
Ketoacidosis	
Postmarketing studies have reported an increased risk of ketoacidosis, especially during periods of acute illness or fasting (i.e. peri-procedural fasting, bowel preparation, low carbohydrate diet, excess alcohol consumption, vomiting or diarrhoeal illnesses) and reductions in insulin dose. Ketoacidosis is rare (<0.1%) but can be life-threatening. It may occur even in the absence of elevated blood glucose.	Patient education regarding symptom monitoring and the importance of temporary cessation during periods of acute illness or fasting. Provide written sick-day plan. Refer to local guidelines regarding peri-procedural management. For example, Periprocedural Diabetic Ketoacidosis (DKA) wth SGLT2 Inhibitor Use (Alert Update September 2020).
Volume depletion/renal function	
Volume depletion may occur due to a natriuretic and diuretic effect (infrequent 0.1–1%). Temporary decline in renal function is due to tubuloglomerular feedback (common >1%).	Assess volume status and renal function at baseline. May require adjustment of baseline diuretic therapy. May reduce systolic blood pressure. Consider monitoring of renal function in at-risk patients.
Hypoglycaemia	
Risk is increased if co-prescribed sulfonylureas or insulin, or there is a history of frequent hypoglycaemic episodes (common >1%).	May require dose reduction of insulin and sulfonylureas.
Fracture risk	
An increased incidence of fractures was observed in a trial of canagliflozin (not available in Australia) in patients with type 2 diabetes and a high cardiovascular risk. However, these findings have not been observed in other studies evaluating the safety of SGLT2 inhibitors.	Assess harm versus benefit before prescribing.
Lower limb amputation	
An increased incidence of lower limb amputations was observed in a trial of canagliflozin (not available in Australia) in patients with type 2 diabetes and a high cardiovascular risk. However, these findings have not been observed in other studies evaluating the safety of SGLT2 inhibitors.	Patient education regarding preventive foot care.

Source: adapted from reference 11

low carbohydrate diet, excess alcohol consumption, vomiting or diarrhoeal illnesses) and following reductions in insulin dose. Ensure a written plan about managing sick days is provided to all patients. While there are no specific sick-day plans for heart failure, the principles are similar to those used in diabetes. Consider ketoacidosis in patients taking SGLT2 inhibitors who present with signs and symptoms of metabolic acidosis, even if their blood glucose is not elevated.

Urogenital infections

While urinary tract infections are listed as adverse effects of SGLT2 inhibitors, recent randomised control trials have not reported a significant excess risk compared to placebo. Treat promptly if patients present with signs and symptoms of urinary tract infections to reduce the risk of progression to urosepsis or pyelonephritis.

Fungal genital infections are more likely in patients treated with SGLT2 inhibitors and occur more commonly in women. These infections are usually mild.

Cases of necrotising fasciitis of the perineum (Fournier's gangrene) have been reported. Patients who present with pain, tenderness, erythema or swelling in the genital or perineal area should be urgently examined. Necrotising fasciitis is a medical emergency.

Conclusion

In Australia, the uptake of SGLT2 inhibitors to treat patients with non-diabetic indications is evolving as it appears the benefits extend beyond glucose lowering. Their role in medical therapy for heart failure with either reduced or preserved left ventricular ejection fraction has been recognised in international guidelines, regardless of the patient's diabetes status. Given the results of the DAPA-CKD study, it is likely that future guidelines will also recommend SGLT2 inhibitors in patients with proteinuric chronic kidney disease.

The adverse effects of SGLT2 inhibitors are mainly known from studies in diabetes. Patients without diabetes will need advice on how the drugs are used in other conditions. <

Conflicts of interest: John Atherton has been a member of advisory boards and received honoraria and travel support to attend conferences and educational meetings from AstraZeneca, Boehringer Ingelheim and Eli Lilly.

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