Sodium-glucose co-transporter inhibitors

Clinical applications

**SUMMARY**

Inhibition of the sodium-glucose co-transporter 2 in the kidney lowers blood glucose by increasing glucose excretion in the urine. The associated osmotic diuresis and urinary loss of sodium reduces blood pressure.

Canagliflozin and dapagliflozin are sodium-glucose co-transporter 2 inhibitors that have been studied as monotherapy and in combination with other drugs for type 2 diabetes. They reduce concentrations of glycated haemoglobin by 6–9 mmol/mol (0.5–0.8%) more than placebo.

Patients may lose 2–3 kg during treatment. Hypoglycaemia is more likely to occur if a sodium-glucose co-transporter 2 inhibitor is used in combination with other drugs that lower blood glucose. Low density lipoprotein cholesterol increases during treatment.

Glycosuria increases the risk of genitourinary infections. Increased calcium excretion could potentially reduce bone density.

Long-term studies are investigating the cardiovascular safety of these drugs. These studies could also yield data about a possible increased risk of malignancy.

**Introduction**

The currently available oral therapies for type 2 diabetes all have limitations which mean that patients’ therapeutic goals may not be easily and safely achieved, even when combinations of drugs are prescribed. New blood glucose-lowering therapies that are effective and well tolerated are needed.

The role of the kidney in the maintenance of blood glucose has been relatively overlooked. It is now the target of the sodium-glucose co-transporter (SGLT) inhibitors.

**Renal glucose homeostasis**

The kidney has an important role in glucose homeostasis through gluconeogenesis and reabsorption of filtered glucose. In healthy adults, approximately 180 g/day of glucose is filtered at the glomerulus and virtually all is reabsorbed by SGLTs.

Drugs which inhibit the co-transporters increase glucose excretion and treat diabetes in a different way from other therapies. The associated natriuresis may also reduce blood pressure.

Many co-transporter inhibitors are in various stages of clinical development. Of greatest contemporary relevance to Australian prescribers are dapagliflozin and canagliflozin. Others in at least phase II development are empagliflozin, ertugliflozin and ipragliflozin.

**Clinical effects**

An aim of treatment for type 2 diabetes is to optimise glycaemic control (and thus reduce the risk of chronic complications) without inducing hypoglycaemia, weight gain or other adverse effects. SGLT2 inhibitors reduce the plasma glucose concentration without stimulating insulin release. Hypoglycaemia should thus be a risk only when these drugs are given with an insulin secretagogue (a sulfonylurea) or insulin. The loss of calories through glycosuria means that SGLT2 inhibitors promote weight loss.

**Glycaemic control**

The glycaemic efficacy of dapagliflozin has been studied in several thousand patients in a range of trials as monotherapy and in combination with other oral drugs or insulin. At its recommended dose of 10 mg daily, dapagliflozin produces placebo-adjusted mean reductions of 6–9 mmol/mol (0.5–0.8%) in glycated haemoglobin (HbA1c) from initial concentrations of 7.5% or over, when given for at least three months.

These effects are similar whether the drug is given as monotherapy, in initial combination with metformin, or as add-on therapy to metformin, a sulfonylurea, a thiazolidinedione or insulin. As with other oral therapies for type 2 diabetes, the greatest mean reductions (>1%) are in patients with the highest pre-treatment HbA1c (>75 mmol/mol (>9%)). There is also a fall in mean fasting plasma glucose of at least 1 mmol/L. These results are broadly similar to those in comparable studies of other oral drugs for lowering blood glucose. There is evidence from add-on studies with two-year follow-up that the glycaemic effect of dapagliflozin is sustained.
Dapagliflozin appears ineffective in patients with an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m$^2$. It has not been adequately assessed in patients aged 75 years or over and so is not currently recommended for use in this age group. Canagliflozin 300 mg daily appeared to have similar efficacy to dapagliflozin in a similar range of phase III studies ranging from monotherapy to add-on therapy with other oral drugs and insulin. It is possible, however, that the lower specificity for SGLT2 relative to SGLT1 might mean that canagliflozin has greater (SGLT1-associated) renal and gastrointestinal glucose losses than dapagliflozin. Such a hypothesis needs to be addressed in head-to-head studies which also consider relative tolerability and safety.

In contrast to studies of dapagliflozin in renal impairment which have not shown a statistically significant glycaemic effect, canagliflozin led to a significant mean reduction of 0.4% in HbA1c over placebo in patients with an eGFR of 30–50 mL/min/1.73 m$^2$.

**Weight**

Dapagliflozin causes weight loss (typically 2–3 kg and mostly visceral fat) in the first 2–3 months which then plateaus. Canagliflozin has a similar effect.

**Blood pressure**

In phase III studies both dapagliflozin and canagliflozin are associated with a significant mean reduction in systolic blood pressure of 1–6 mmHg more than placebo. This change in systolic pressure is more than expected from weight loss and mild dehydration (haematocrit typically increases 1–3%). It reflects the osmotic diuresis and natriuresis associated with the mechanism of action of these drugs. The concomitant drug-related reductions in diastolic blood pressure are smaller than the systolic changes, but are still statistically significant. There is no attenuation of blood pressure effects in the case of canagliflozin given to patients with an eGFR of 30–50 mL/min/1.73 m$^2$.

**Adverse effects**

In clinical trials of dapagliflozin, 3.2% of patients discontinued because of adverse events. These included genitourinary infections and raised serum creatinine.

**Cardiovascular safety**

The incidence of clinical events related to intravascular volume depletion (such as symptomatic postural hypotension and dehydration) was approximately double for dapagliflozin compared with placebo or comparator drugs in phase III studies. There was a similar result for canagliflozin. With both drugs, there was no significant excess of severe events associated with their use, and discontinuations due to polyuria, nocturia or dehydration were rare. In the case of canagliflozin, a reduction in intravascular volume was most evident when the drug was taken by patients with an eGFR less than 60 mL/min/1.73 m$^2$, who were aged 75 years or over, or taking loop diuretics. In these patient groups it is recommended that therapy begins with 100 mg rather than 300 mg daily.

Dapagliflozin and especially canagliflozin increase serum low density lipoprotein cholesterol (placebo-adjusted changes 4.6% and 8.2% respectively). A meta-analysis of 14 clinical studies of dapagliflozin did not show an increase in macrovascular disease, but longer-term studies are needed to detect whether the risk of atherosclerosis is increased. However, in a similar meta-analysis there was a transient excess of cardiovascular events (mainly stroke) in the first month of treatment with canagliflozin. This did not appear to be related to clinically evident reductions in intravascular volume that might facilitate thrombosis. This analysis included events from the long-term cardiovascular safety trial Canagliflozin Cardiovascular Assessment Study (CANVAS) which is ongoing. A postmarketing cardiovascular safety trial of dapagliflozin (DECLARE-TIMI58) that is designed to last up to six years is also in progress.

**Renal function and genitourinary infections**

In studies of dapagliflozin and canagliflozin, there have been small reversible falls in the eGFR. These were greatest (around 10%) in patients with moderate renal impairment. Monitoring of renal function is recommended before starting an SGLT2 inhibitor and at least yearly thereafter. Renal function should be checked before and periodically after starting other drugs that may influence renal function. More frequent monitoring (3–6 monthly) should be considered in patients with an eGFR approaching the level at which SGLT2 inhibition should be discontinued (60 mL/min/1.73 m$^2$ for dapagliflozin and 30 mL/min/1.73 m$^2$ for canagliflozin).

In patients with micro- or macroalbuminuria, canagliflozin is associated with an approximate 50% reduction in urinary albumin excretion. This is sustained for up to a year. Dapagliflozin does not appear to influence albuminuria. There is a mildly increased risk of non-recurrent uncomplicated urinary tract infection with SGLT2 inhibitors, especially in females and patients with a previous history of urinary tract infection. However, both dapagliflozin and canagliflozin increase the risk of genital fungal infections five-fold in both males and females. The most frequent are vulvovaginal infections (most commonly candidal) that respond...
Likely place in therapy

The current Australian indications for dapagliflozin in patients with type 2 diabetes managed with an appropriate diet and exercise regimen are:

- monotherapy when metformin is contraindicated or not tolerated
- initial combination therapy with metformin when metformin monotherapy is unlikely to achieve adequate glycaemic control (such as when the initial HbA1c is very high)
- add-on combination with metformin or a sulfonylurea when these drugs alone do not provide adequate glycaemic control
- add-on combination with insulin (alone or with one or both of metformin or a sulfonylurea) when these regimens do not provide adequate glycaemic control.

Canagliflozin has a similar range of indications, but with less restrictions than dapagliflozin based on renal function and age.

Blood glucose-lowering therapies that are associated with weight loss are understandably attractive to the majority of patients with type 2 diabetes who are either overweight or obese. The only other therapies with this property are metformin and especially the glucagon-like peptide 1 (GLP1) analogue class that includes exenatide and liraglutide. These analogues are injectable therapies and they can cause significant gastrointestinal symptoms, primarily nausea. However, they appear to have a more durable effect on body weight and are more potent blood glucose-lowering therapies than the SGLT2 inhibitors.

Given the cost of new diabetes therapies, and the long-term experience with metformin and sulfonylurea drugs, SGLT2 inhibitors could be an alternative to incretin-based therapies (dipeptidyl peptidase inhibitors or GLP1 analogues) in combination with either metformin or a sulfonylurea when one or other of these drugs is contraindicated or not tolerated. However, their mode of action suggests they may be a useful adjunct to more established therapies, including potential use in type 1 diabetes.

Conclusion

The inhibitors of the sodium-glucose co-transporter improve glycaemic control with a low incidence of hypoglycaemia and have beneficial effects on body weight and blood pressure. They have the convenience of once-daily dosing and their mechanism of action means that they can be combined safely with other oral glucose-lowering drugs and insulin.
Their main adverse effects are increases in genitourinary infections, dehydration-related symptoms including postural hypotension, and raised serum low density lipoprotein cholesterol. Ongoing surveillance including large-scale cardiovascular safety trials should provide objective data on the possible increased risk of stroke, fracture and malignancy.

**REFERENCES**


**FURTHER READING**

