SGLT-2 inhibitors

Practical prescription advice for the generalist

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Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are an increasingly popular oral therapy for patients with type 2 diabetes owing to their glycaemic, cardiovascular and other benefits. However, risks include dehydration, urogenital infections and ketoacidosis. A four-phase approach to selecting, counselling and following up patients can help GPs prescribe SGLT-2 inhibitors safely and effectively.

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On the strength of cardiovascular outcome trial results, the sodium-glucose cotransporter-2 (SGLT-2) inhibitor medication class has become an increasingly popular diabetes therapy in Australia.[1] Four SGLT-2 inhibitors were approved by the TGA for use in patients with type 2 diabetes mellitus: dapagliflozin, empagliflozin, ertugliflozin and canagliflozin. All except canagliflozin are currently available through the Pharmaceutical Benefits Scheme (PBS), both alone and in fixed-dose combinations with metformin or a dipeptidyl-peptidase-4 (DPP-4) inhibitor (linagliptin, saxagliptin or sitagliptin).

However, enthusiasm about the encouraging cardiovascular and renal benefits of SGLT-2 inhibitors must be tempered by an understanding of their potentially harmful side effects. In particular, the risk of ketoacidosis (including sometimes but not always euglycaemic ketoacidosis) has led to recent warnings.[2] An understanding of the risks and a pragmatic approach to their mitigation can allow confident, appropriate use of SGLT-2 inhibitors. This article aims to provide GPs with a point-of-care summary of the risks, benefits and practical considerations of prescribing SGLT-2 inhibitors safely and effectively.

Mechanism of action

SGLT-2 inhibitors function by inhibiting sodium-glucose cotransporter type 2 (SGLT-2), a high-capacity, low-affinity glucose transporter in the proximal renal tubule that is responsible for 90% of renal glucose reabsorption.[3] This inhibition induces a glycosuric diuresis, through a reduction in the renal threshold for glucose and natriuresis that leads to increased sodium intake by the juxtaglomerular apparatus, activation of tubuloglomerular feedback and reduction in intraglomerular pressure. SGLT-2 is highly specific to the kidneys with minimal expression elsewhere, reducing the scope for off-target effects.[4]

1. RECOMMENDATIONS ACROSS THE SGLT-2 INHIBITOR PRESCRIPTION LIFE CYCLE

Phase 1 – Considering prescribing an SGLT-2 inhibitor

SGLT2 inhibitor medications:

- are a preferred second-line oral type 2 diabetes medication in patients with established atherosclerotic cardiovascular disease or chronic kidney disease or when weight loss is desired
- are equally preferred second-line therapy in all other situations
- are contraindicated when eGFR is less than 45 mL/min/1.73 m^2 for empagliflozin, ertugliflozin and dapagliflozin
- are strongly relatively contraindicated in patients with previous ketoacidosis
- should be prescribed only with specialist oversight in patients with type 1 diabetes

Phase 2 – Initial counselling

At the time of initial SGLT-2 inhibitor prescription:

- reduce or cease other diuretic medications (e.g. furosemide, hydrochlorothiazide)
- counsel patient on maintaining genital hygiene
- counsel patient on maintaining adequate hydration (e.g. drinking to thirst)
- counsel patient on sick day management (see Box 2)
- counsel patient on perioperative cessation of the SGLT-2 inhibitor

Phase 3 – First follow up

At the first follow-up visit after SGLT2 inhibitor initiation, assess for:

- glycaemic efficacy, both hypoglycaemia and hyperglycaemia, especially if other therapy for type 2 diabetes was reduced or ceased
- hypotension and dehydration
- genital infection
- renal dysfunction

Phase 4 – Unmet target

If the HbA_{1c} target is not reached despite SGLT-2 inhibitor initiation, first assess for adherence and then consider additional or alternative therapy or seek specialist advice.

Abbreviations: HbA_{1c} = glycated haemoglobin; SGLT-2 = sodium-glucose cotransporter-2.

Prescribing SGLT-2 inhibitors

When prescribing SGLT-2 inhibitors, one must consider the four phases of the medication prescription life cycle: considering prescription, initial counselling, the first follow-up consultation and when glycaemic targets are unmet. Practical advice on these phases is summarised in Box 1. A decision tree for commencing an SGLT-2 inhibitor is shown in the Flowchart.

Phase 1. Considering prescribing

The Australian Diabetes Society recommends SGLT-2 inhibitor medications as a second-line therapy for type 2 diabetes.[5] At present, SGLT-2 inhibitors can be prescribed through the PBS with all classes of diabetes medications except glucagon-like peptide-1 (GLP-1) receptor agonists and thiazolidinediones.

Expected benefits of SGLT-2 inhibitors

Glycaemic efficacy

The glycaemic efficacy of SGLT-2 inhibitors is similar to that of other second-line oral agents for type 2 diabetes. A systematic analysis of 45 randomised controlled trials (RCTs) found that SGLT-2 inhibitors were associated with a mean change in glycated haemoglobin (HbA_{1c}) level of -0.66 percentage points versus placebo (95% confidence interval [CI] -0.73 to -0.58 percentage points).[6]

The HbA_{1c} decrease was greater with a higher baseline HbA_{1c} at treatment commencement.[7] For example, for a given glomerular filtration rate, an HbA_{1c} of 10.0% (86 mmol/mol) at commencement of an SGLT-2 inhibitor may reduce by 1.5 percentage points (17 mmol/mol), whereas an HbA_{1c} of 8.0% (64 mmol/mol) may reduce by only 0.5 percentage points (6 mmol/mol).[7]

Cardiovascular risk reduction

The cardiovascular benefits of SGLT-2 inhibitors are increasingly recognised and exceed the benefits expected from glycaemic improvement alone. The EMPA-REG OUTCOME cardiovascular outcome trial has been celebrated for its finding of a hazard ratio (HR) of 0.86 (95% CI 0.74 to 0.99) for empagliflozin versus placebo for a composite of cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke in patients with established cardiovascular disease.[8]

Similar results were found for canagliflozin in the CANVAS cardiovascular outcome trial.[9] Results for dapagliflozin in the DECLARE-TIMI 58 trial, which involved a greater proportion of participants without cardiovascular disease, followed the same trend, although not statistically significant.[10] Additionally, all three trials found a reduction in heart failure hospitalisations, a benefit primarily attributed to SGLT-2 inhibitor-related diuresis.

Results of the VERTIS-CV trial of ertugliflozin are yet to be reported. However, the evidence to date suggests cardiovascular protection is a class effect, although the magnitude may differ between agents and between primary and secondary prevention.

Renal protection and weight reduction

Empagliflozin, canagliflozin and dapagliflozin are all associated with improved long-term composite renal outcomes in patients at risk of and also with diabetic kidney disease.[8-12] Further, use of these medications resulted in a clinically significant 1.6 to 2.0 kg weight loss at three years compared with placebo, related to glycosuria-mediated urinary calorie loss, with most weight reduction occurring in the first six months of treatment, followed by a plateau.[8-11]

Recommendations

The results above have prompted the US and European peak diabetes bodies to recommend SGLT-2 inhibitors as the preferred oral medication class following metformin in patients with:

- established atherosclerotic cardiovascular disease
- chronic kidney disease
- heart failure or
- a need to minimise weight gain or promote weight loss.[13]

The SGLT-2 inhibitor class is an equally preferred agent in other contexts.[13]

Contraindications to SGLT-2 inhibitors

The major contraindications to SGLT-2 inhibitors are chronic kidney disease or a history of ketoacidosis. The glycosuric mechanism of action means SGLT-2 inhibitors lose effectiveness when renal function is reduced, and they are therefore not recommended when the estimated glomerular filtration rate (eGFR) falls below 45 mL/min/1.7 m^2.[14] However, within the recommended eGFR range, there is no attenuation of effect or increase in the adverse effects seen with lower eGFR.[15] Ketoacidosis, otherwise rare in patients with type 2 diabetes, can occur in patients taking SGLT-2 inhibitors.[2,16] Thus, SGLT-2 inhibitors are relatively contraindicated in patients with previous ketoacidosis.

Trials of SGLT-2 inhibitors have been completed in patients with type 1 diabetes mellitus.[17] However, use in type 1 diabetes remains an off-label prescription in Australia, with a high risk of ketoacidosis. If use of an SGLT-2 inhibitor is being considered for a patient with type 1 diabetes, we recommend specialist referral.

Phase 2. Initial counselling

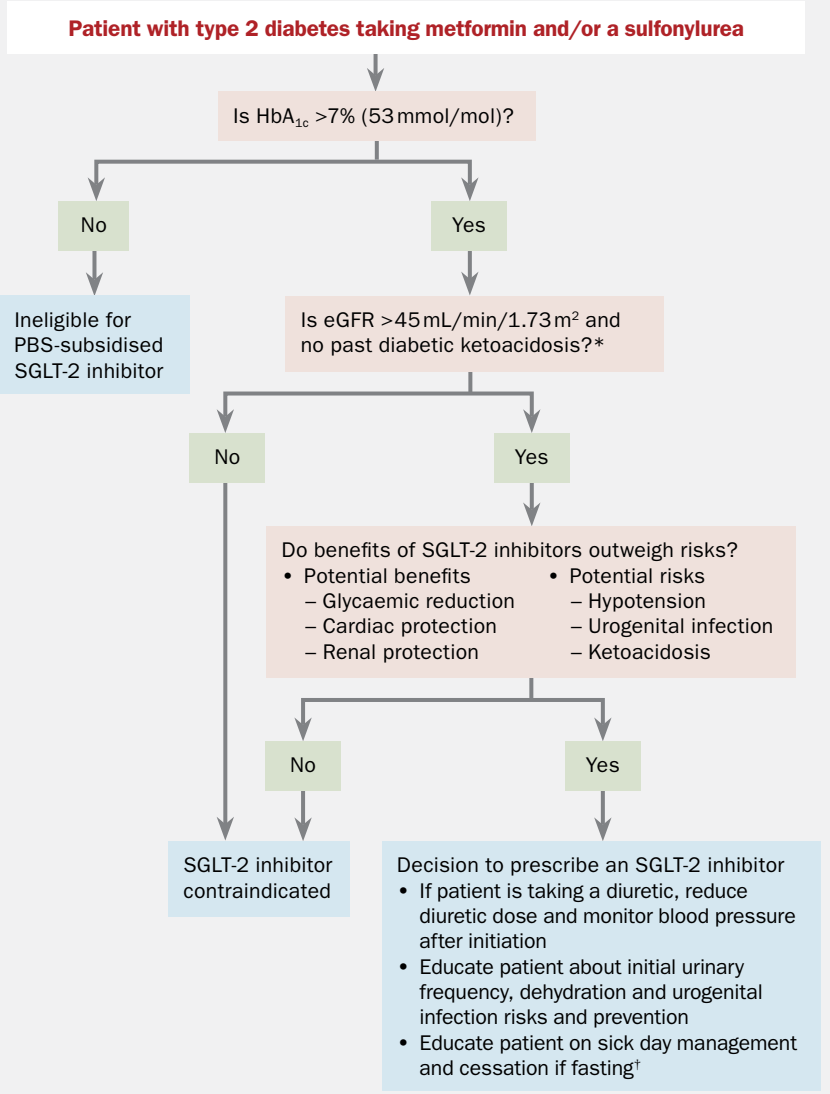
Following the decision to prescribe an SGLT-2 inhibitor, other medications may need to be rationalised during the consultation when the SGLT-2 inhibitor is prescribed. The patient should also be counselled on avoiding and mitigating side effects.

Diuretic modification and hydration

The first change to be considered is diuretic modification. As SGLT-2 inhibitors are diuretics themselves, they cause polyuria and may cause hypotension. Analysis of 12 RCTs of SGLT-2 inhibitors found an odds ratio (OR) for hypotension of 1.57 (95% CI 0.73 to 3.35) versus placebo and 2.68 (95% CI 1.14 to 6.29) versus other oral hypoglycaemic agents.[6] Thus, in patients taking concomitant diuretic medications such as furosemide, the diuretic dose should be reviewed and consideration given to its reduction or cessation when an SGLT-2 inhibitor is started. A 50% reduction in the diuretic dose has been recommended by some experts.[14]

Diuresis does not typically result in acute kidney injury, with no increase versus placebo with canagliflozin or empagliflozin.[8,9,12] It is advisable to avoid administration of an SGLT-2 inhibitor or combination after midday to prevent any contribution to nocturia. Patients should also be counselled on maintaining

DECISION TREE FOR COMMENCING AN SGLT-2 INHIBITOR



Abbreviations: eGFR = estimated glomerular filtration rate; HbA_{1c} = glycated haemoglobin; SGLT-2 = sodium-glucose cotransporter-2.

* When eGFR is less than 60 mL/min/1.73 m^2, glycaemic reduction associated with SGLT-2 inhibitor medications is often reduced.

† An example of sick-day instructions is shown in Box 2.

2. EXAMPLE OF SICK DAY MANAGEMENT INSTRUCTIONS FOR PATIENTS TAKING SGLT-2 INHIBITOR MEDICATIONS

SGLT-2 inhibitor and sick day management – patient instructions

Illness can cause blood sugar levels to rise. High blood sugar levels increase the risk of dehydration and can lead to other medical complications. When you are unwell:

- Check your blood sugar levels every 4 to 6 hours. If you do not already do this at home ask the diabetes clinic staff to teach you.
- If blood sugar levels are greater than 15 mmol/L for 24 hours, see your GP as soon as possible.
- Drink 1 to 2 glasses of water or sugar-free drink every hour to avoid dehydration.

Illnesses listed below can cause dehydration. STOP TAKING SGLT-2 INHIBITOR OR SGLT-2 INHIBITOR COMBINATIONS IF YOU HAVE:

- Nausea or vomiting
- Stomach pain (associated with vomiting)
- Diarrhoea
- Inability to eat or drink.

If illness continues for more than a few days, you should discuss with your GP whether you need a test for ketones.

You can start taking your medication again when you are feeling well and able to eat and drink normally.

NOTE: If you are on insulin, it is important to continue taking this at your normal doses. See your GP if you have any concerns.

Abbreviation: SGLT-2 = sodium-glucose cotransporter-2.

adequate hydration. If fluid restriction has been recommended, this too may need review.

Genitourinary infections

Similarly to patients with untreated hyperglycaemia, those with SGLT-2 inhibitor-induced glycosuria have an increased risk of urogenital infections. Analysis of 21 RCTs of dapagliflozin or canagliflozin versus placebo found ORs of 3.50 (95% CI 2.46 to 4.99) for genital tract infections and 1.34 (95% CI 1.03 to 1.74) for urinary tract infections (UTIs).[6] A review of four trials of empagliflozin showed an increased risk of genital tract infections but not UTIs.[18]

As in the general population, women have a higher UTI risk than men, but of note is the greatly increased risk of genital tract infection in men who are uncircumcised versus those who are circumcised (5.7% versus 0.7% in pooled canagliflozin trials).[19] Some clinicians have a higher threshold for prescribing SGLT-2 inhibitors in uncircumcised men. Others advise daily cleaning of the penile glans following foreskin retraction, a practical suggestion that has not been assessed for efficacy. Notably, genital tract infections are treated as usual; it is their frequency that is increased and not necessarily their severity.[6]

Ketoacidosis

Clinicians are increasingly recognising the association between SGLT-2 inhibitor use and ketoacidosis. A distinctive feature of ketoacidosis associated with SGLT-2 inhibitors is that it can occur even when the patient is euglycaemic. A Victorian public hospital series found a ketoacidosis rate of 1.02 per 1000 in SGLT-2 inhibitor users versus 0.69 per 1000 in nonusers.[16] The mechanism may relate to SGLT-2 inhibitors stimulating pancreatic glucagon secretion while reducing glycaemic stimulation of insulin through glycosuria.[20,21] When glucagon relatively exceeds insulin, lipolysis and ketogenesis are stimulated.[22] Glycosuria prevents the hyperglycaemia typical of ketotic states, accounting for the occasionally euglycaemic nature of ketoacidosis that occurs with SGLT-2 inhibitors.[22]

SGLT-2 inhibitor-related ketoacidosis is often precipitated by infection, inflammation or fasting states.[23] Surgery, which combines inflammation with fasting, is thus a major risk factor. The Australian Diabetes Society recently recommended withholding SGLT-2 inhibitor medications for three days before surgery.[2] However, this strategy risks preoperative hyperglycaemia, with a consequent need in some patients for increased monitoring and medication adjustment, such as commencing or increasing insulin doses.

Full sick day management guidelines are shown in Box 2.

Glucose-lowering medications

Depending on the patient's current HbA_{1c} and glycaemic target, a reduction in medications that can cause hypoglycaemia, namely sulfonylureas and insulin, might be considered. In practice, if the HbA_{1c} is more than 1.5 percentage points above target (e.g. more than 8.5% [69 mmol/mol] with a target of 7.0% [53 mmol/mol]) without hypoglycaemic events, no reduction may be necessary. If the HbA_{1c} is within 1.5 percentage points or below the target, sulfonylurea doses can be halved or ceased, and insulin may be pre-emptively reduced or the patient advised to reduce by up to 25% if they experience hypoglycaemia.

Other concerns

The EMPA-REG OUTCOME, DECLARE-TIMI 58 and CREDENCE trials did not find any increased risk of osteoporosis, fractures, or amputations.[10-12] This alleviates concern about these complications raised by an earlier trial.[9]

Phase 3. First follow-up consultation

At the first follow-up visit after commencement of an SGLT-2 inhibitor, it is important to assess for side effects. We recommend conducting this review between two and four weeks after the patient starts taking the SGLT-2 inhibitor. Given the variable response to agents in this class, it is important to ensure there has been no increase in hypoglycaemia, particularly in patients taking insulin. Hypotension and dehydration should be sought with a brief examination and postural blood pressure measurement. Any suggestion of genital infection warrants examination, especially of the

glans in uncircumcised men.

An eGFR drop of up to 8 mL/min/1.73 m^2 after a few weeks of SGLT-2 inhibitor use is consistent with their renal actions and should be expected.[8] This drop can be viewed as comparable to that seen with ACE inhibitors, an on-treatment effect related to changed intraglomerular pressure that resolves on medication cessation. However, further monitoring of renal function is warranted as a larger eGFR drop could indicate dehydration or a UTI.

Phase 4. Unmet target

Despite the glycaemic efficacy and related benefits of SGLT-2 inhibitors, patients may not reach their HbA_{1c} target, even after successful initiation and three to four months of use for the full effects of the medications to manifest. If adherence is confirmed, it is important to use the available algorithms to prescribe additional or alternative therapy.[5,13] Options include escalating to a combination of an SGLT-2 inhibitor and DPP-4 inhibitor or commencing insulin. Data exist supporting the safety and efficacy of concurrent SGLT-2 inhibitor and GLP-1 receptor agonist therapy.[24] However, this is not currently subsidised by the PBS. Depending on the HbA_{1c} and comorbidities, specialist advice may be indicated at this stage.

Conclusion

SGLT-2 inhibitor medications should be considered in all eligible patients with type 2 diabetes whose HbA_{1c} is not at their individualised target, especially patients with prevalent atherosclerotic cardiovascular disease, heart failure or renal impairment, in preference to other classes. However, major precautions and contraindications should be considered, patients should be appropriately counselled on avoiding and mitigating side effects, and the prescribing practitioner should actively assess for side effects. The practical advice outlined above should help GPs to prescribe SGLT-2 inhibitor medications safely and effectively and ensure their patients reap the full benefits of these new agents. MT

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