Sodium-glucose co-transporter 2 (SGLT-2) inhibitors: The triple crown of medicines?

The role of SGLT-2 inhibitors, such as empagliflozin, is now well established for people with type 2 diabetes and those with heart failure, regardless of diabetes status. However, increasing evidence demonstrates a wide range of benefits of this class of medicines across metabolic, cardiovascular and renal health outcomes. Funding restrictions are a limitation in some cases, but the strong consensus from both international guidelines and local experts is that a SGLT-2 inhibitor should be considered for any patient with type 2 diabetes, heart failure or chronic kidney disease.

KEY PRACTICE POINTS

- In people with type 2 diabetes, SGLT-2 inhibitors promote metabolic improvements and reduce the risk of adverse cardiovascular and renal outcomes. Treatment with a SGLT-2 inhibitor has also been demonstrated to improve prognostic outcomes in people with heart failure and protect against disease progression in people with chronic kidney disease, independent of diabetes status.
- Empagliflozin is the only SGLT-2 inhibitor funded in New Zealand and is available alone and in a combination formulation with metformin (i.e. empagliflozin + metformin). Treatment is funded with Special Authority approval for patients with type 2 diabetes who have a HbA_{1C} above target despite treatment with other funded blood glucose-lowering medicines and patients with heart failure with reduced ejection fraction.
- Test renal function before initiating empagliflozin. In patients with an eGFR of < 30 mL/min/1.73 m^2, the maximum daily dose of empagliflozin is 10 mg and treatment with the empagliflozin + metformin combination formulation is contraindicated (although concomitant metformin can be prescribed separately if eGFR is ≥ 15 mL/min/1.73 m^2, with appropriate dose reduction). Initiation of empagliflozin is not recommended if the patient's eGFR is < 20 mL/min/1.73 m^2.
  - The blood glucose-lowering effectiveness of empagliflozin decreases with increasing renal impairment. Treatment is generally ineffective for glycaemic control in patients with an eGFR of < 30 mL/min/1.73 m^2; other blood glucose-lowering medicines are usually required.
- In patients with type 2 diabetes prescribed sulfonylureas or insulin, a dose reduction may be required when initiating empagliflozin to prevent hypoglycaemia. Also consider reducing doses of concurrent antihypertensive or diuretic medicines in patients with risk factors for volume depletion, e.g. age ≥ 75 years.
- Monitor renal function annually, or more frequently if deterioration is anticipated. If eGFR decreases to < 30 mL/min/1.73 m^2 during treatment, the empagliflozin + metformin combination formulation is contraindicated but empagliflozin alone can be continued for cardiorenal benefits until renal replacement therapy, at a maximum daily dose of 10 mg, with the addition of other blood glucose-lowering medicines as required for glycaemic control. Concomitant metformin can also be prescribed separately if eGFR is ≥ 15 mL/min/1.73 m^2, with appropriate dose reduction.
- Key adverse effects associated with SGLT-2 inhibitors include genitourinary infections, ketoacidosis and volume depletion
  - Educate patients about potential adverse effects and self-care measures to reduce risk, e.g. regular genital hygiene, sick day management, maintaining fluid and electrolyte intake

SGLT-2 inhibitors reduce metabolic, cardiovascular and renal risk

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors were initially developed for glycaemic control in people with type 2 diabetes, but have since demonstrated considerable efficacy for improving cardiovascular and renal outcomes in people with cardiovascular risk factors independent of their blood glucose-lowering activity.[1] The cardiovascular and renal benefits of SGLT-2 inhibitors have also been established in people with chronic kidney disease (CKD) and heart failure, irrespective of diabetes status, supporting the value of SGLT-2 inhibitors in people with one or more of these conditions.[1]

SGLT-2 inhibitors prevent glucose reabsorption and promote glucosuria

SGLT-2 is a transport protein located in the proximal convoluted tubule of the kidney that uses the sodium concentration gradient across the luminal membrane to facilitate glucose reabsorption.[2] Approximately 90% of the glucose filtered by the kidneys is reabsorbed by SGLT-2.[2] As a result, SGLT-2 inhibitors decrease glucose reabsorption, inducing sustained glucosuria that reduces blood glucose levels.[3]

The blood glucose-lowering effect of SGLT-2 inhibition is proportional to the filtered glucose load, therefore is greater in people with type 2 diabetes.[3] As the mechanism is independent of insulin, treatment is associated with a low risk of hypoglycaemia.[3] Energy loss due to glucosuria (approximately 200 – 300 kcal/840 – 1250 kJ per day) promotes weight loss and induces a fasting-like metabolic state that reduces insulin resistance, promotes lipid metabolism and stimulates hepatic ketogenesis.[4, 5]

SGLT-2 inhibitors also provide cardiovascular and renal protection

The cardiovascular and renal protective effects of SGLT-2 inhibitors are mediated through several mechanisms.[3] SGLT-2 inhibitor-induced natriuresis and osmotic diuresis reduce plasma volume and blood pressure, decreasing ventricular pre- and after-load.[3] Increased lipolysis and ketogenesis optimise cardiac metabolism, which may be particularly beneficial in pathological states characterised by cardiac energy depletion, e.g. heart failure.[3] SGLT-2 inhibitors also improve cardiac oxygen delivery, reduce sympathetic hyperactivity and promote reverse cardiac remodelling.[2]

A key mechanism involved in the nephroprotective effects of SGLT-2 inhibitors is a reduction in intraglomerular pressure, which is mediated by tubuloglomerular feedback in response to increased sodium delivery to the distal renal tubule.[3] This reduces physical renal stress and the hyperfiltration of glucose and albumin, providing protection against the development and progression of CKD.[2, 5] Additional renal protective mechanisms of SGLT-2 inhibitors include reducing renal oxygen demand, improving renal metabolic efficiency, upregulating pathways that promote vascular health and modulating inflammatory processes.[2]

SGLT-2 inhibitors also induce urinary potassium excretion, reducing the risk of hyperkalaemia associated with medicines that inhibit the renin-angiotensin-aldosterone system (RAAS), e.g. angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs).[5] In people with type 2 diabetes and cardiovascular risk factors or CKD, treatment with a SGLT-2 inhibitor has been reported to reduce the risk of serious hyperkalaemia, with and without concurrent RAAS inhibitor treatment, and without increasing the risk of hypokalaemia.[6]

Clinical applications of SGLT-2 inhibitors

The clinical benefits of SGLT-2 inhibitors have been established in people with type 2 diabetes and in people with heart failure or CKD, regardless of their diabetes status.[2]

Type 2 diabetes: Promoting glycaemic control, metabolic improvements and reducing cardiorenal risk

In people with type 2 diabetes, treatment with a SGLT-2 inhibitor reduces HbA_{1C}, systolic and diastolic blood pressure and body weight (associated with decreases in visceral, subcutaneous and ectopic liver adipose tissue with extended treatment).[7–9] SGLT-2 inhibitors have also been found to reduce the risk of adverse cardiorenal outcomes in people with type 2 diabetes with established, or at high risk of, atherosclerotic cardiovascular disease.[10]

Read the evidence

According to the New Zealand Society for the Study of Diabetes Management Algorithm for Type 2 Diabetes, the use of a SGLT-2 inhibitor as a second-line blood glucose-lowering medicine is associated with a mean reduction in HbA_{1C} of 6 – 13 mmol/mol.[7] A 2020 meta-analysis reported a mean HbA_{1C} reduction of approximately 6 mmol/mol* when a SGLT-2 inhibitor was added to metformin, alone or in combination with other blood glucose-lowering medicines, in people with type 2 diabetes over a median study duration of 26 weeks.[11] Over the same median study duration, treatment with a SGLT-2 inhibitor has also been demonstrated to reduce mean body weight by 1.85 kg and mean systolic and diastolic blood pressure by 2.89/1.44 mmHg.[8] In addition to body weight reduction, decreases in visceral, subcutaneous and ectopic liver adipose tissue, body mass index (BMI) and waist circumference have been reported in people with type 2 diabetes treated with a SGLT-2 inhibitor for > 16 weeks.[9]

* This result was reported as a reduction in percentage HbA_{1C} of 0.55%.[11] In New Zealand laboratories, HbA_{1C} has been reported as a molar proportion of total haemoglobin, i.e. in mmol/mol, instead of a percentage since 2011.[12] A reduction in percentage HbA_{1C} of 1% is equivalent to a reduction of 11 mmol/mol.[13]

A 2019 meta-analysis of people with type 2 diabetes and either established atherosclerotic cardiovascular disease (ASCVD) or significant cardiovascular risk factors reported a 23% overall reduction in the risk of cardiovascular mortality or hospitalisation for heart failure with SGLT-2 inhibitor treatment.[10] Overall reductions in the risk of hospitalisation due to heart failure (31%) and adverse renal outcomes (worsening renal function, end-stage kidney disease or mortality due to renal causes; 45%) were also observed.[10] Subgroup analysis identified that the risk reduction for hospitalisation due to heart failure and adverse renal outcomes was similar in both groups, however, a reduction in the risk of cardiovascular mortality was only observed in people with established ASCVD (20%).[10] Treatment in people with ASCVD was also associated with a reduction in the risk of major adverse cardiovascular events (MACE; 14%) and myocardial infarction (15%), suggesting additional cardiovascular benefit in this group.[10]

For further information on the use of SGLT-2 inhibitors in type 2 diabetes, see: bpac.org.nz/2021/diabetes-management.aspx

Heart failure: Reducing hospitalisation and cardiovascular mortality

In people with heart failure, SGLT-2 inhibitors have been demonstrated to reduce the risk of hospitalisation due to heart failure and mortality due to a cardiovascular cause, independent of left ventricular ejection fraction.[14]

Read the evidence

A 2022 meta-analysis found that SGLT-2 inhibitor treatment reduced the risk of first hospitalisation due to heart failure by 28% and cardiovascular mortality by 13%, with equivalent efficacy in people with reduced and preserved or mildly reduced left ventricular ejection fraction.[14] The effect of SGLT-2 inhibitor treatment on the composite outcome of cardiovascular mortality or first hospitalisation due to heart failure was consistent across 13 clinically-relevant patient subgroups, including diabetes status, left ventricular ejection fraction and baseline eGFR.[14] Only New York Heart Association (NYHA) functional class was identified to modulate the effect; risk reduction was greater in people with NYHA class II heart failure relative to NYHA class III or IV (28% versus 14%).[14]

For further information on the use of SGLT-2 inhibitors in heart failure, see: bpac.org.nz/2025/heart-failure-part-2.aspx

CKD: Reducing disease progression and improving cardiovascular outcomes

SGLT-2 inhibitors reduce the risk of CKD progression and adverse cardiovascular outcomes in people with CKD, particularly those with co-morbidities, e.g. type 2 diabetes.[15–17]

Read the evidence

A 2024 Cochrane review found that SGLT-2 inhibitor treatment reduced the risk of all-cause mortality (15%), cardiovascular mortality (17%), kidney failure (30%) and composite kidney outcomes (32%) relative to placebo in people with CKD and diabetes.[15] There is also evidence of benefit in people without diabetes; a 2020 meta-analysis identified a comparable reduction in CKD progression (~37%) in people with and without diabetes that was independent of baseline eGFR.[16] Overall, SGLT-2 inhibitors reduce the risk of cardiovascular mortality, heart failure, MACE, disease progression, acute kidney injury and all-cause mortality in people with CKD.[17]

For further information on the use of SGLT-2 inhibitors in CKD, see: bpac.org.nz/2026/ckd.aspx

Empagliflozin is currently the only funded SGLT-2 inhibitor in New Zealand

Two SGLT-2 inhibitors are approved for use in New Zealand: empagliflozin (funded with Special Authority approval) and dapagliflozin (not funded).[18] Empagliflozin is the most widely used in clinical practice, however, dapagliflozin could be considered in patients who are unable to tolerate empagliflozin (and are able to self-fund treatment).

For further information on dapagliflozin, refer to the New Zealand Formulary (NZF)

Empagliflozin is **indicated*** for patients with:[18]

- Type 2 diabetes
  - As monotherapy or in combination with other blood glucose-lowering medicines; ***OR***
  - To reduce the risk of cardiovascular death in patients with established cardiovascular disease (in conjunction with other measures)
- Heart failure (NYHA class II – IV), independent of left ventricular ejection fraction
- CKD

Empagliflozin is also available in a combination formulation with metformin (i.e. empagliflozin + metformin) for patients with type 2 diabetes.[18]

* Not funded for all indications, see below

Special Authority criteria for empagliflozin

Empagliflozin (with or without metformin) is funded with Special Authority approval for patients with type 2 diabetes who have a HbA_{1C} above target despite treatment with other funded blood glucose-lowering medicines and patients with heart failure with reduced ejection fraction (Table 1).

The Special Authority criteria for empagliflozin were amended in September, 2026, to widen access for patients with type 2 diabetes. For further information, see: pharmac.govt.nz/news-and-resources/consultations-and-decisions/2026-08-widened-access-to-diabetes-medicines

Discuss self-funding empagliflozin with patients who are likely to benefit

Some patients who are not eligible for funded empagliflozin are also likely to benefit from treatment, including those with:

- Type 2 diabetes who do not meet Special Authority criteria
- Type 2 diabetes who are currently prescribed a funded GLP-1 receptor agonist (not eligible for funded empagliflozin at the same time, unless they also have heart failure with reduced ejection fraction)
- Heart failure with preserved or mildly reduced ejection fraction
- Non-diabetic kidney disease

For further information on patients with type 2 diabetes who are likely to benefit from self-funding empagliflozin, see: bpac.org.nz/2021/diabetes.aspx

Consider discussing the option to self-fund treatment with these patients, unless there are contraindications or significant cautions. This can be a challenging conversation to negotiate, as those who are unable to meet the financial burden of self-funding treatment may find this distressing. However, it is important that patients are aware of all their options in order to make an informed decision about their health care.

Best Practice Tip: For patients who are self-funding empagliflozin, consider ways to reduce cost for them, e.g. use of a disability allowance if applicable, checking costs of tablets of different strengths and between pharmacies.

Table 1. Special Authority criteria for funded treatment with empagliflozin or empagliflozin + metformin.[19]

Type 2 diabetes
Patient has **either**: 1. Type 2 diabetes **AND** a HbA_{1C} of > 53 mmol/mol, despite the regular use of at least one blood glucose-lowering medicine (e.g. metformin, vildagliptin, insulin) for three months; ***OR*** 2. Previously received an initial approval for a GLP-1 receptor agonist **AND** is changing funded treatment to a SGLT-2 inhibitor **AND** Funded empagliflozin (alone or in a combination formulation with metformin) **is not** prescribed in combination with a funded GLP-1 receptor agonist, unless for the treatment of heart failure
Heart failure with reduced ejection fraction (HFrEF)
Patient has heart failure and **all of** the following characteristics: 1. Is in NYHA functional class II, III or IV 2. Has a documented left ventricular ejection fraction (LVEF) of ≤ 40% ***OR*** an echocardiogram (ECHO) is not reasonably practicable, and, in the opinion of the clinician, the patient will benefit from treatment 3. Is receiving concomitant optimal standard funded chronic heart failure treatment N.B. Funded treatment with both empagliflozin and a GLP-1 receptor agonist is not available, unless the patient is receiving empagliflozin (alone or in a combination formulation with metformin) for the treatment of heart failure with reduced ejection fraction and the GLP-1 receptor agonist for type 2 diabetes.

Prescribing empagliflozin

Key prescribing and monitoring information for empagliflozin (with and without metformin) is presented in Table 2. Empagliflozin is ineffective for glycaemic control in patients with an eGFR of < 30 mL/min/1.73 m^2; treatment can be continued for cardiorenal protection, however, other blood glucose-lowering medicines are usually required for glycaemic control.[18] A transient reduction in eGFR may occur following initiation; this is usually small (average reduction of 3 – 5 mL/min/1.73 m^2) and is not a reason to discontinue treatment.[20]

Available formulations of empagliflozin:

- Empagliflozin (Jardiance): 10 mg or 25 mg
- Empagliflozin + metformin (Jardiamet): 5 mg or 12.5 mg empagliflozin with 500 mg or 1 g metformin

Discuss the risk of adverse effects with patients

SGLT-2 inhibitors have a favourable safety profile and treatment is generally well-tolerated.[1] Key adverse effects include genitourinary infections, ketoacidosis and volume depletion; risk can be reduced with patient education and appropriate early management.[20, 21]

For a complete list of adverse effects associated with empagliflozin, refer to the NZF

Increased risk of genitourinary infections

Increased urinary glucose excretion associated with SGLT-2 inhibitor treatment promotes the growth of microorganisms in the anogenital region, increasing the risk of genitourinary infections, particularly in conjunction with poor genital hygiene.[22] **Genital mycotic infection** risk is increased approximately three-fold in patients prescribed SGLT-2 inhibitors, with a higher incidence in females than males.[23]

SGLT-2 inhibitors as a class are not thought to increase the risk of **urinary tract infections (UTIs)** relative to placebo.[20, 23] However, limited evidence suggests that dapagliflozin, specifically, may be associated with an increased risk, particularly at higher doses.[20, 23] Patients prescribed SGLT-2 inhibitors may also have a higher baseline risk of UTIs because of their underlying disease pathology, e.g. diabetes, or concurrent use of other medicines.[23]

Fournier's gangrene (necrotising fasciitis of the perineum and genitalia) is a rare but serious condition that has been reported in people taking SGLT-2 inhibitors.[22] It can develop if bacterial infection of the deep soft tissue occurs, e.g. via mucous membranes or a break in the anogenital skin; untreated genitourinary infections may increase risk.[22, 23] Fournier's gangrene is potentially life-threatening, as the infection can spread rapidly.[22] In New Zealand, cases have been reported in patients with and without type 2 diabetes prescribed empagliflozin; males are more often affected.[24] Other risk factors for Fournier's gangrene include excessive alcohol consumption, immunosuppression and obesity.[25] A causal relationship between SGLT-2 inhibitors and Fournier's gangrene has not been confirmed; while the risk of genitourinary infections is increased in patients prescribed a SGLT-2 inhibitor, they are no more likely to develop Fournier's gangrene as a complication.[23]

Preventing genitourinary infections

When initiating empagliflozin, educate patients about the risk of genitourinary infections and genital hygiene measures to reduce this risk, including regular cleaning (at least once daily, or twice daily for females) and keeping the genital area dry, particularly after passing urine.[18] Also encourage sufficient fluid intake to prevent urinary stasis.[20] Advise patients to seek prompt medical attention if they develop symptoms or signs of a genital infection and to regularly check the genital area for inflammation and changes in skin integrity.[18] Explain that urgent medical attention is required if they develop symptoms of Fournier's gangrene, e.g. pain, tenderness, redness or swelling in the genital or perineal area, fever or malaise.[22]

Patient information sheets about Fournier's gangrene in English, te reo Māori and Samoan are available from: medsafe.govt.nz/consumers/educational-material.asp

Managing genitourinary infections that develop during treatment

Genitourinary infections that develop while a patient is taking empagliflozin can be managed with standard antimicrobial treatment.[26] Treat symptomatic genital mycotic infections with a topical or oral antifungal medicine; collect a swab for fungal culture if the diagnosis is uncertain or the infection does not respond to empiric treatment.[26] If a UTI is suspected, ideally collect a urine sample for microscopy, culture and sensitivity analysis prior to initiating empiric antibiotic treatment, which can then be adjusted if necessary once the results are available.[26] Patients with suspected Fournier's gangrene require urgent secondary care referral.[18]

Empagliflozin can usually be continued alongside antimicrobial treatment, unless the infection is severe or associated with complications.[18, 23] In most cases, empagliflozin can be re-initiated following resolution of the infection, with monitoring for symptoms or signs of recurrence.[23]

For further information on the management of UTIs, see: bpac.org.nz/2025/uti.aspx

Ketoacidosis can occur regardless of diabetes status

SGLT-2 inhibitors increase the risk of ketoacidosis by promoting lipolysis and ketogenesis.[27] Ketoacidosis can occur with

Table 2. Key empagliflozin and empagliflozin + metformin prescribing and monitoring information.[7, 18] N.B. For full prescribing information, refer to the NZF for individual monographs.

	Empagliflozin (Jardiance)	Empagliflozin + metformin (Jardiamet)
Contraindications	■ Type 1 diabetes	**Additional contraindications for combination formulation treatment** ■ Severe hepatic impairment ■ Severe renal impairment (eGFR < 30 mL/min/1.73 m^2) or unstable renal function N.B. Metformin alone is only contraindicated if eGFR is < 15 mL/min/1.73 m^2 (avoid in unstable impairment). However, the minimum daily dose of metformin in the empagliflozin + metformin combination formulation (1 g) exceeds the maximum daily dose for patients with an eGFR of < 30 mL/min/1.73 m^2 (500 mg). ■ Tissue hypoxia, e.g. recent myocardial infarction ■ Alcoholism ■ History of lactic acidosis
Cautions	■ Risk of ketoacidosis ■ Risk of hypotension or volume depletion, e.g. aged ≥ 75 years ■ Complicated urinary tract infections (temporarily withhold treatment) ■ Concomitant treatment with lithium carbonate	**Additional cautions for combination formulation treatment** ■ Risk factors for lactic acidosis, e.g. metformin dose > 2 g daily, older age ■ May impair vitamin B_{12} absorption
Before starting	Assess renal function (serum creatinine). If eGFR is < 30 mL/min/1.73 m^2, consider the addition of another blood glucose-lowering medicine if required for glycaemic control. Initiation is not recommended if eGFR is < 20 mL/min/1.73 m^2.	Assess renal function (serum creatinine). Treatment with the empagliflozin + metformin combination formulation is contraindicated if eGFR is < 30 mL/min/1.73 m^2.
	■ Ensure the patient is sufficiently hydrated ■ If the patient is already taking insulin and/or a sulfonylurea and their HbA_{1C} is ≤ 75 mmol/mol, a dose reduction may be required to prevent hypoglycaemia following initiation of empagliflozin. A 15 – 20% reduction in total daily insulin or a 50% reduction in sulfonylurea dose is a recommended starting point. If HbA_{1C} is < 64 mmol/mol, consider switching premixed or basal plus one insulin regimens to insulin alone, or withdrawing sulfonylureas if dose is ≤ 80 mg of gliclazide or ≤ 5 mg of glipizide per day. ■ Consider reducing dose(s) of existing antihypertensive or diuretic medicines	
Dosing	**Type 2 diabetes** 10 mg, once daily; can be increased to 25 mg, once daily, if necessary and tolerated N.B. If eGFR is < 30 mL/min/1.73 m^2, maximum daily dose is 10 mg. **Heart failure** 10 mg, once daily **CKD** 10 mg, once daily	**Type 2 diabetes** One tablet, twice daily; initiate at 5 mg empagliflozin (10 mg daily dose) with the dose of metformin (i.e. 500 mg or 1 g) that is closest to that prescribed as monotherapy. Maximum daily dose is 25 mg empagliflozin and 2 g metformin.
Monitoring	■ Test renal function at least annually and before and after initiating medicines that may reduce renal function. If eGFR deteriorates to < 30 mL/min/1.73 m^2, reduce dose to 10 mg, once daily, and consider adding another blood glucose-lowering medicine, if required. If eGFR deteriorates to < 20 mL/min/1.73 m^2, treatment can be continued until renal replacement therapy (i.e. dialysis or kidney transplantation), if tolerated. ■ Monitor volume status and adjust doses of concomitant diuretic and antihypertensive medicines, if required ■ In patients prescribed concomitant lithium carbonate, increase frequency of serum lithium monitoring; lithium dose adjustment may be required	**Additional monitoring for combination formulation treatment** ■ Test renal function at least twice yearly in older patients and at least 3 – 6 monthly in patients with an eGFR of < 60 mL/min/1.73 m^2. Also test renal function if deterioration is suspected; the empagliflozin + metformin combination formulation is contraindicated if eGFR deteriorates to < 30 mL/min/1.73 m^2, however, the two medicines can be prescribed separately with appropriate dose reductions. ■ Check serum vitamin B_{12} if deficiency is suspected, e.g. patient develops symptoms of anaemia or peripheral neuropathy

For further information about initiating empagliflozin in patients prescribed **lithium**, see: medsafe.govt.nz/profs/PUArticles/March2023/Starting-empagliflozin-or-dapagliflozin-in-patients-on-lithium.html

or without increased blood glucose levels (euglycaemic ketoacidosis).[27] Patients with type 2 diabetes are at increased risk, however, euglycaemic ketoacidosis has also been reported in patients without diabetes prescribed SGLT-2 inhibitors for heart failure.[28] Risk factors include acute illness or infection, surgery, insulin deficiency, inappropriate insulin dose reduction, severe dehydration, reduced caloric intake, low carbohydrate diet, excessive alcohol consumption and a history of ketoacidosis.[27] The symptoms of ketoacidosis may be non-specific, e.g. nausea, vomiting, malaise, abdominal pain, excessive thirst, shortness of breath, dizziness, confusion.[27]

Preventing ketoacidosis

Educate patients prescribed empagliflozin about the risk of ketoacidosis and the symptoms that indicate an urgent need to have their ketone levels checked (in primary or secondary care), independent of their blood glucose levels, e.g. frequent urination, thirsty with a dry mouth, "fruity" smelling breath.[7] Advise patients to temporarily withhold empagliflozin if they develop an acute illness and to resume treatment when they have recovered and are eating and drinking normally; provide a written sick day plan.[7] Also explain that they may need to temporarily discontinue treatment before medical procedures that require them to change their eating or drinking patterns, e.g. colonoscopy, bariatric surgery.[7]

A patient handout with at-home sick day management advice is available from: healthed.govt.nz/products/kidney-health-at-home-sick-day-advice-he2647

For further information on the peri-procedural management of patients prescribed SGLT-2 inhibitors, see: t2dm.nzssd.org.nz/Section-81-SGLT2-inhibitors

Elevated capillary ketones are an indication for acute secondary care referral

Test capillary ketone levels in patients prescribed empagliflozin who present with symptoms of ketoacidosis, even if their blood glucose level is not elevated.[7] Acute secondary care referral is indicated for patients with a capillary ketone level > 1.5 mmol/L.[7]

Some patients may be at increased risk of volume depletion

As SGLT-2 inhibitors induce osmotic diuresis, polyuria is a common adverse effect.[26] Polyuria is usually mild and transient; increased urine output is most significant following treatment initiation and typically decreases over time.[26] However, patients aged ≥ 75 years and those with heart failure (particularly with an eGFR of < 60 mL/min/1.73 m^2 or who are prescribed concurrent loop diuretics) are more susceptible to volume depletion as a result of osmotic diuresis, potentially associated with orthostatic hypotension and dizziness.[18, 29]

Reducing the risk of volume depletion

Consider reducing doses of concurrent diuretic or antihypertensive medicines when initiating empagliflozin, particularly in patients with risk factors for volume depletion.[7] Ongoing monitoring of volume status is recommended, as further dose adjustments may be required in response to diuresis.[18]

Encourage patients to maintain adequate fluid and electrolyte intake to prevent dehydration and to temporarily withhold empagliflozin if they become unwell with vomiting or diarrhoea, as per their sick day plan (see: "Preventing ketoacidosis").[20]

Discontinuing SGLT-2 inhibitor treatment

Treatment with a SGLT-2 inhibitor is usually continued long-term. The clinical benefits do not persist following discontinuation; in people with heart failure treated with empagliflozin, increases in fasting plasma glucose, body weight, systolic blood pressure and N-terminal pro-hormone B-type natriuretic peptide were observed within 30 days of withdrawal.[30] Treatment discontinuation was also associated with clinical deterioration and an increased risk of hospitalisation for heart failure and cardiovascular mortality.[30]

The decision to permanently withdraw SGLT-2 inhibitor treatment, e.g. due to adverse effects, should take into consideration both the risks associated with continuing treatment and the potential harms of discontinuation, as well as the patient's preferences.[26]

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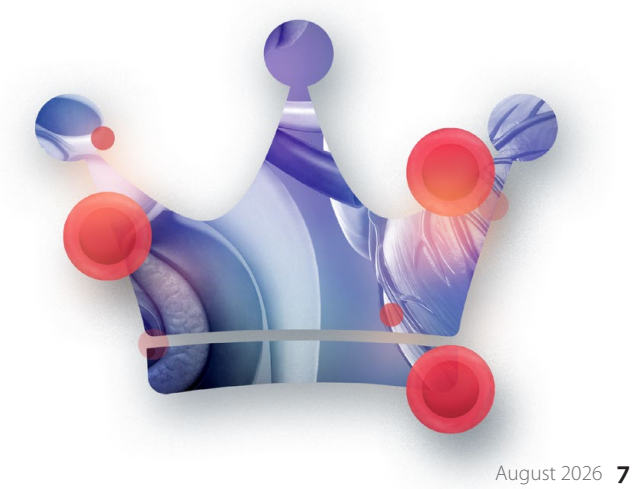

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