The SGLT2 inhibitors – where are we now?

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Article points

1. Sodium–glucose cotransporter 2 (SGLT2) inhibitors are once-daily oral agents effective in treating hyperglycaemia in type 2 diabetes. Additional benefits include weight loss and a low risk of hypoglycaemia. There is also early evidence of favourable effects on cardiovascular and renal outcomes.
2. SGLT2 inhibitors carry an increased risk of fungal genital infection and, to a lesser extent, urinary tract infection, with women and individuals with a previous history at higher risk.
3. SGLT2 inhibitors should not be commenced if estimated glomerular filtration rate (eGFR) is <60 mL/min/1.73 m^2. They should be used cautiously with diuretics and be temporarily discontinued in any acute illness leading to volume depletion. They should be avoided in people with type 1 diabetes.

Key words

- SGLT2 inhibitors
- Type 2 diabetes

Authors

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Sodium–glucose cotransporter 2 (SGLT2) inhibitors are once-daily oral agents effective in treating hyperglycaemia in people with type 2 diabetes, with additional benefits including weight loss and a low risk of hypoglycaemia. This review provides a basic guide to the SGLT2 inhibitors licensed in the UK, including their mechanism of action, benefits, adverse effects and limitations, and place in treatment. Advice on avoiding the rare but serious adverse effect of diabetic ketoacidosis is also provided.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a relatively recent addition to the treatment options for type 2 diabetes, with dapagliflozin first licensed in the UK in November 2012. This article reviews their place in therapy in the light of accumulating evidence of their benefits and disadvantages.

Mechanism of action

Typically, in a healthy person, the kidney filters around 180 g of glucose per day into the urine; however, almost all of this is reabsorbed. Filtration occurs in the renal glomeruli, while reabsorption takes place in the proximal convoluted tubule (PCT) of the nephron, via the sodium–glucose cotransporters, of which two have been identified in the PCT: SGLT1 and SGLT2 (Marsenic, 2009).

SGLT2 is a high-capacity transporter located in the early part of the PCT and is responsible for absorbing around 90% of the filtered glucose load. SGLT1 is a high-affinity transporter located more distally in the PCT and is responsible for reabsorbing the remaining 10% of the filtered glucose (*Figure 1*). While SGLT2 is found almost exclusively in the kidney, SGLT1 also has a central role in absorbing glucose from the small intestine (Gerich, 2010; DeFronzo et al, 2012).

Inhibition of glucose transport at the SGLT sites in the kidney enables the elimination of glucose in the urine, which may be a route to improving glycaemic control in people with diabetes. However, SGLT1 inhibition induces diarrhoea owing to glucose malabsorption in the gut. Thus, the

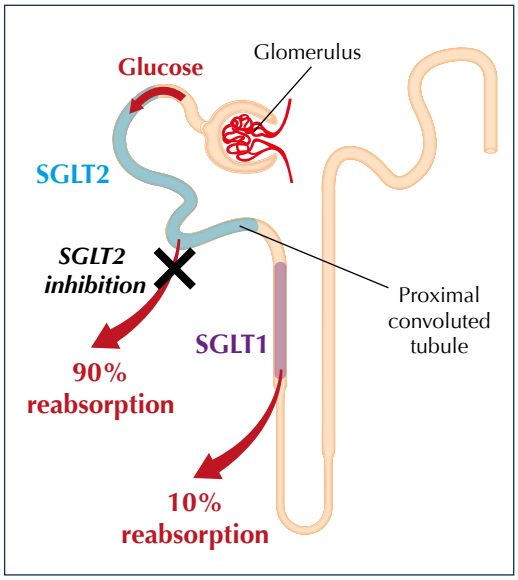

Figure 1. Position and function of the sodium–glucose cotransporter (SGLT) proteins within the kidney. SGLT2 inhibitors act by blocking the majority of glucose reabsorption into the bloodstream.

rationale has been to develop a selective inhibitor to avoid the side effects of SGLT1 inhibition whilst still targeting the major site of glucose reabsorption, SGLT2 (Nair and Wilding, 2010; DeFronzo et al, 2012).

When the reabsorptive capacity of SGLT1 and SGLT2 is exceeded, glucose appears in the excreted urine. This point is known as the renal threshold and typically occurs at a blood glucose concentration of around 10 mmol/L, although, owing to an adaptive response that leads to increased SGLT2 expression, the threshold rises to around 14 mmol/L in people with type 2 diabetes. A selective SGLT2 inhibitor effectively lowers the renal threshold to around 5 mmol/L, thus enhancing glycosuria; as a result, around 60–80 g of glucose is excreted per day in the urine (Gerich, 2010; Nair and Wilding, 2010; DeFronzo et al, 2012).

What can SGLT2 inhibitors offer people with diabetes?

Three SGLT2 inhibitors are currently available in the UK: dapagliflozin (Forxiga®; AstraZeneca), canagliflozin (Invokana®; Janssen) and empagliflozin (Jardiance®; Boehringer Ingelheim). The licences have a broad remit and can be used as monotherapy or in combination with other glucose-lowering medicines, including insulin, when diet and exercise do not provide adequate glycaemic control. The agents are available as monotherapy and as fixed-dose combinations with metformin. In addition, dapagliflozin is available as a fixed-dose combination with saxagliptin (*Table 1*).

The broad clinical and practical benefits of SGLT2 inhibitor treatment are listed in *Box 1*. The clinical benefits are discussed in more detail below.

Table 1. Available sodium–glucose cotransporter inhibitor preparations.

Medication	Available doses	Dose frequency
Dapagliflozin (Forxiga®)	5 mg 10 mg	Once daily
Dapagliflozin + metformin (Xigduo®)	5 mg/850 mg 5 mg/1000 mg	Twice daily, with food
Dapagliflozin + saxagliptin (Qtern®)	10 mg/5 mg	Once daily
Canagliflozin (Invokana®)	100 mg 300 mg	Once daily, before first meal of the day
Canagliflozin + metformin (Vokanamet®)	50 mg/850 mg 50 mg/1000 mg 150 mg/850 mg 150 mg/1000 mg	Twice daily, with food
Empagliflozin (Jardiance®)	10 mg 25 mg	Once daily
Empagliflozin + metformin (Synjardy®)	5 mg/850 mg 5 mg/1000 mg 12.5 mg/850 mg 12.5 mg/1000 mg	Twice daily, with food

HbA_{1c} reduction

Evidence from randomised controlled trials shows that all SGLT2 inhibitors are effective in improving glycaemic control, either as monotherapy or in combination with other antidiabetes agents, including metformin, sulfonylureas, pioglitazone, dipeptidyl peptidase-4 (DPP-4) inhibitors and insulin (Electronic Medicines Compendium [eMC], 2017a; 2017b; 2017c). Treatment typically reduces HbA_{1c} by 5–11 mmol/mol (0.5–1.0%), although greater reductions are seen with higher initial levels of HbA_{1c}. A meta-analysis of clinical trials revealed a mean HbA_{1c} reduction of 7 mmol/mol (0.64%) compared with placebo (Vasilakou et al, 2013).

Weight and blood pressure reductions

In addition to lowering HbA_{1c}, the daily elimination of 60–80 g of glucose in the urine equates to an energy loss of 240–320 kcal and induces a typical weight loss of 2–3 kg (eMC, 2017a; 2017b; 2017c). The glycosuria also results in osmotic diuresis that enables a small reduction in blood pressure (typically 4/2 mmHg), a useful secondary benefit given the frequent coexistence of hypertension in people with type 2 diabetes (Baker et al, 2014).

Low hypoglycaemia risk

An important safety feature of SGLT2 inhibitors is that, because their mode of action is not dependent on insulin secretion, they have a low risk of hypoglycaemia (similar to placebo in clinical trials). Hypoglycaemia really only arises

Box 1. Clinical and practical benefits of sodium–glucose cotransporter 2 inhibitor treatment.

- Consistent HbA_{1c} reductions.
- Weight loss.
- Small reductions in blood pressure.
- Well tolerated.
- Low risk of hypoglycaemia.
- Once-daily oral agent.
- Early evidence of cardiovascular benefit (for empagliflozin in people with established cardiovascular disease) and renoprotection.
- Flexibility to use with other antidiabetes agents.

when the individual is taking other treatments that themselves predispose to hypoglycaemia, such as sulfonylureas, repaglinide and insulin, and it is only in these circumstances that self-monitoring of blood glucose levels would be encouraged. To minimise the risk of hypoglycaemia when adding an SGLT2 inhibitor to either insulin secretagogues or insulin, it is advisable to reduce the dose of the latter treatments. It is the author's practice to halve the dose of sulfonylurea or cut the insulin dose by around 20% unless the patient's HbA_{1c} is running particularly high.

Possible cardiovascular and renal effects

The EMPA-REG OUTCOME study, reported in 2015, was a double-blind, randomised controlled cardiovascular outcome trial comparing once-daily empagliflozin 10 mg and 25 mg with placebo in over 7000 people with type 2 diabetes and established cardiovascular disease with controlled hypertension and hyperlipidaemia (Zinman et al, 2015). The results showed a significant 14% relative risk reduction (RRR) in the primary outcome, a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, in empagliflozin recipients compared with placebo (absolute risk reduction [ARR], 1.6%). Positive secondary outcomes included a 38% RRR for cardiovascular death (ARR, 2.2%); a 32% RRR for all-cause mortality (ARR, 2.6%); and a 35% RRR for hospitalisation for heart failure (ARR, 1.4%) with empagliflozin.

Thus, it would appear that empagliflozin provides cardiovascular protection in people with type 2 diabetes and established cardiovascular problems. The benefits of treatment appeared early after starting treatment, implying that they arose from a haemodynamic effect rather than an effect on atherosclerosis (for which benefits would be expected to emerge over a longer time frame). Whether or not these cardiovascular benefits are a class effect should become evident when the cardiovascular outcome trials for canagliflozin and dapagliflozin are reported in 2017 and 2019, respectively.

An additional benefit demonstrated in the EMPA-REG trial was a reduction in the incidence and progression of nephropathy with empagliflozin compared to placebo (RRR, 32%; ARR, 6.1%; Wanner et al, 2016). Empagliflozin stabilised renal function, with a 44% RRR in the doubling of serum creatinine level compared with placebo (ARR, 1.1%).

Further evidence of the renoprotective properties of SGLT2 inhibitors is found in the case of canagliflozin, with a reduced incidence and progression of albuminuria and a stabilisation of renal function compared with placebo in individuals with type 2 diabetes and chronic kidney disease (Yale et al, 2013). Dapagliflozin has also been reported to reduce albuminuria in people with diabetes and hypertension receiving renin–angiotensin system (RAS) blockers (Heerspink et al, 2016). The mechanism of action behind these renoprotective effects appears to be a reduction in intraglomerular pressure induced by afferent arteriole vasoconstriction (in contrast to the efferent arteriole vasodilation caused by RAS blockade).

Disadvantages and limitations of use

An overall list of people in whom SGLT2 inhibitors should be avoided is presented in *Box 2*. Specific clinical concerns are described in greater detail below.

Infection risk

The glycosuria induced by SGLT2 inhibitors predisposes to an increased risk of genital fungal infection and urinary tract infection (UTI; eMC, 2017a; 2017b; 2017c). Women and people with a previous history of these infections are at particular risk. For example, the incidence of vulvovaginitis and balanitis in individuals receiving dapagliflozin was 5.5%, compared with 0.6% in placebo recipients. Generally, these infections were easily treated with conventional antifungal therapy and rarely resulted in discontinuation of dapagliflozin. Similar results are seen with canagliflozin and empagliflozin. The occurrence of genital mycotic infection is a marker of increased risk of a future episode, and the decision whether to continue with the SGLT2 inhibitor should be discussed with the patient.

The increased risk of UTI is less pronounced. Again taking dapagliflozin as an example, the incidence of UTI was 4.7%, compared to 3.5% with placebo (eMC, 2017a). The majority of these

infections were mild to moderate in severity and were responsive to standard therapy. Again, similar results are seen with canagliflozin and empagliflozin (eMC, 2017b; 2017c).

Diuretic effects

Glycosuria induces an osmotic diuresis that may result in increased urination in people taking SGLT2 inhibitors. Associated with this is a slightly raised incidence of side effects related to volume depletion, such as postural hypotension (eMC, 2017a; 2017b; 2017c). It is important that patients and clinicians are aware of the need to temporarily discontinue SGLT2 inhibitors under circumstances of acute illness in which reduced blood volume is present, such as gastroenteritis. The manufacturers emphasise the need for caution when using SGLT2 inhibitors with diuretics, especially in older people, who are at higher risk of dehydration. In the case of dapagliflozin and canagliflozin, the use of loop diuretics is not recommended.

Use with renal impairment

The efficacy of SGLT2 inhibitors reduces with falling eGFR. The agents should not be commenced when the estimated glomerular filtration rate (eGFR) is below 60 mL/min/1.73 m^2. If eGFR falls below this level whilst on treatment, the manufacturers recommend that dapagliflozin should be stopped, but canagliflozin and empagliflozin may be continued down to an eGFR of 45 mL/min/1.73 m^2 at their lower dose, below which treatment should be discontinued (eMC, 2017a; 2017b; 2017c). Thus, eGFR should be monitored regularly in people taking SGLT2 inhibitors: at least annually and more frequently (at least two to four times per year) if renal function is approaching moderate impairment. It is the author's practice to include renal function tests routinely in 6-monthly diabetes blood tests.

Bladder cancer risk

Dapagliflozin is not recommended to be used in combination with pioglitazone because of a possible, small increased risk of bladder cancer (eMC, 2017a). It should be stressed, however, that no causal relationship has been established between dapagliflozin and bladder cancer.

Amputation risk

In the CANVAS (Canagliflozin Cardiovascular Assessment Study) trial, a higher incidence of lower limb amputation was observed with canagliflozin compared with placebo; therefore, until this is further understood, it may be appropriate to stop canagliflozin in patients developing lower extremity ulcers, osteomyelitis or gangrene (Medicines and Healthcare Products Regulatory Agency, 2016). While similar results have not been observed in studies of dapagliflozin and empagliflozin, the European Medicines Agency (EMA, 2017) has determined that a warning should be included in the prescribing information for all drugs in the class, stating that SGLT2 inhibitors may increase the risk of lower limb amputation, whilst it undertakes further investigation of this finding.

Fracture risk

In 2015 the US Food and Drug Administration (FDA) strengthened its warning over the relation between use of canagliflozin and risk of bone fracture (FDA, 2015). Taylor et al (2015) have reviewed the evidence concerning reduced bone mineral density and increased fracture risk associated with SGLT2 inhibition. While it is difficult to draw firm conclusions until further evidence is gathered, it may be appropriate to avoid SGLT2 inhibitors in people at high risk of fracture.

Risk of diabetic ketoacidosis

Over the last 2 years it has become apparent that SGLT2 inhibitors are associated with an increased risk of diabetic ketoacidosis (DKA; Rosenstock and Ferrannini, 2015; Erondu et al, 2015; Peters et al, 2015). The risk of DKA is low, affecting less than 1 in 1000 people, and the DKA tends to occur early in treatment. It may occur with only moderately elevated blood glucose levels (<14 mmol/L), in which case it is known as euglycaemic DKA. Reviews of DKA in people taking SGLT2 inhibitors revealed that a significant proportion of cases occurred in people with type 1 diabetes – for whom SGLT2 inhibitors are not licensed (Peters et al, 2015). Other situations that predisposed to DKA in people with type 2 diabetes were those of relative insulin deficiency, including acute illness, surgery, alcohol abuse and people with an underlying low reserve of insulin; for

Box 2. When should sodium–glucose cotransporter 2 inhibitors be avoided?

- Type 1 diabetes.
- Recurrent fungal genital infection/urinary tract infection.
- Volume depletion in acute illness (temporarily withdraw treatment).
- Avoid initiation if estimated glomerular filtration rate is <60 mL/min/1.73 m^2.
- Elevated haematocrit.
- Pregnancy, breastfeeding.
- Caution if used with diuretics (SPCs advise to avoid loop diuretics with dapagliflozin and canagliflozin).
- Caution with older people (SPCs advise to avoid dapagliflozin in people aged >75 years and empagliflozin in those aged >85 years.

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example, those with long-standing type 2 diabetes with failing beta-cell function and those with latent autoimmune disease in adults, who slowly progress to an absolute requirement for insulin therapy (Erondu et al, 2015).

The EMA (2016) has published recommendations aimed at minimising the risk of DKA from SGLT2 inhibitors. Patients should be advised on how to avoid DKA, when to suspect it and what action to take (*Box 3*). Clinicians need to test for raised ketones if DKA is clinically suspected, even if plasma glucose levels are not unduly raised, and if ketonaemia is confirmed the SGLT2 inhibitor needs to be stopped and the DKA corrected as an emergency.

Although this is a very serious complication, the EMA concluded that the benefits of SGLT2 inhibitors continue to outweigh the risks in people type 2 diabetes.

Box 3. Advice for patients on avoiding diabetic ketoacidosis (DKA) when taking sodium–glucose cotransporter 2 (SGLT2) inhibitors.

- Do not take SGLT2 inhibitors if you have type 1 diabetes.
- Maintain good fluid intake.
- Avoid very-low-carbohydrate diets.
- Temporarily stop SGLT2 inhibitors in cases of vomiting, severe illness and major surgery.
- Be alert for the symptoms of DKA (excessive thirst, excessive urination, rapid weight loss, nausea and vomiting, abdominal pain, difficulty breathing, abnormal fatigue and confusion).
- Seek medical help if you have symptoms of DKA, even if blood glucose levels are not unduly high.
- Stop SGLT2 inhibitor therapy if DKA is suspected and seek urgent medical advice.

Guidelines

The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) guideline algorithm for the treatment of type 2 diabetes places SGLT2 inhibitors as an option for second-line therapy in conjunction with metformin or as a third-line option in triple therapy (Inzucchi et al, 2015).

NICE has published technology appraisals on the SGLT2 inhibitors (NICE, 2013; 2014; 2015a), and more recently has clarified its position in the updated clinical guideline on the treatment of type 2 diabetes (NICE, 2015b). It adopts a similar position to the ADA/EASD guideline, stating that SGLT2 inhibitors may be considered as one of the options for add-on therapy to metformin (on an equal footing with DPP-4 inhibitors, sulfonylureas and pioglitazone), or as an option in triple therapy, including in combination with insulin.

The emphasis in both of these guidelines is a patient-centred approach to treatment.

Titration

The doses of canagliflozin and empagliflozin can be titrated up in people who need tighter glycaemic control. There is no specific guidance in the Summaries of Product Charateristics on the time intervals before dose increases for canagliflozin (100 mg to 300 mg) or empagliflozin (10 mg to 25 mg) but, in the author's view, these should be at least 1 month and may reasonably be 3 months or more, by which time a further HbA_{1c} test would be informative.

Conclusions: Place in therapy

SGLT2 inhibitors appear to be a valuable addition to the options for treating hyperglycaemia in people with type 2 diabetes. They are convenient, well-tolerated, once-daily oral agents that may be used at first intensification to add to metformin or at second intensification in triple therapy. The mechanism of action is distinctive and confers the option to use with virtually any other antidiabetes agent, including insulin, as well as the flexibility to use at different stages of the diabetes trajectory. Such benefits are illustrated in the case histories in *Boxes 4* and *5*.

The decision to choose an SGLT2 inhibitor as treatment will ultimately depend on the individual's profile and need. SGLT2 inhibitors may be a useful treatment choice if weight loss and/or low risk of hypoglycaemia are priorities. Used in combination with insulin, they may limit both the dose of insulin necessary and the associated weight gain. The availability of combination formulations of SGLT2 inhibitors with metformin or a DPP-4 inhibitor may be useful in reducing pill burden and might improve compliance.

SGLT2 inhibitors should only be used in people with adequate renal function, and their use may be curtailed by recurrent fungal genital infection or urinary tract infection. The early evidence of cardiovascular benefit and renoprotection may strengthen the case for using these agents in people with type 2 diabetes who have cardiovascular disease or diabetic nephropathy. ■

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Box 4. Case history 1.

George was a 56-year-old lorry driver diagnosed with type 2 diabetes 4 years previously, with known background (stage 1) diabetic retinopathy. His blood glucose was above target, with an HbA_{1c} of 64 mmol/mol (8.0%) despite lifestyle advice and dual therapy with twice-daily metformin 1000 mg and a dipeptidyl peptidase-4 inhibitor. Blood pressure and lipid levels were well controlled on losartan and atorvastatin. His estimated glomerular filtration rate was steady at 74 mL/min/1.73 m^2. His BMI was 29 kg/m^2.

Priorities for George in choosing an additional treatment to improve glycaemic control were to avoid weight gain, minimise the risk of hypoglycaemia and avoid insulin. After discussion, he was prescribed dapagliflozin 10 mg once daily.

After 6 months' treatment with dapagliflozin, George's HbA_{1c} had fallen to 54 mmol/mol (7.1%), and this was accompanied by a weight loss of 3 kg, with no significant adverse events reported.

Box 5. Case history 2.

Mary was a 61-year-old retired teacher with an 8-year history of type 2 diabetes taking a combination of twice-daily, modified-release metformin 1000 mg and a twice-daily biphasic insulin: 34 units with breakfast and 30 units with the evening meal. Her HbA_{1c} was poorly controlled, at 76 mmol/mol (9.1%), with self-monitored blood glucose (SMBG) readings typically at 10–15 mmol/L and never below 7 mmol/L. Her BMI was 31 kg/m^2 and her renal function test results were satisfactory.

In the past, Mary had been intolerant of glucagon-like peptide-1 receptor agonist therapy. After discussion, canagliflozin 100 mg once daily was added to her regimen, with initial reductions of insulin doses to 30 units with breakfast and 24 units with the evening meal to reduce the risk of hypoglycaemia. Subsequently, the canagliflozin was titrated up to 300 mg once daily.

After 9 months, Mary's HbA_{1c} had fallen to 61 mmol/mol (7.7%), with SMBG readings now mainly in single figures, and her insulin doses had not been increased. Mary had also lost nearly 4 kg in weight.

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