# Sodium–glucose cotransporter 2 inhibitors: Emerging evidence and changes in guidance

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## Article points

1. Sodium–glucose cotransporter 2 (SGLT2) inhibitors are recommended by NICE as part of a stepwise treatment algorithm for type 2 diabetes.
2. In addition to their glucose- and weight-lowering effects, emerging evidence suggests that, as a class, SGLT2 inhibitors protect against cardiovascular (CV) and renal outcomes and death, particularly in people with established CV disease.
3. These benefits come at a cost of increased risk of genitourinary infections and diabetic ketoacidosis, and reports of increased rates of fracture and amputation require further exploration.

## Key words

– Antidiabetes drugs
– SGLT2 inhibitors
– Type 2 diabetes

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**Sodium–glucose cotransporter 2 (SGLT2) inhibitors work by selectively inhibiting renal glucose reabsorption, and promoting urinary glucose excretion, to reduce blood glucose levels via an insulin-independent mode of action. Several large cardiovascular (CV) outcome trials of SGLT2 inhibitors have been published, which were initially set up to rule out any undue CV risk from these medications. These trials, along with a large observational study, have produced interesting and important data on both CV risk, renal outcomes and drug side effects. In this review, these emerging data and changes to clinical guidance are analysed, and the author discusses how healthcare professionals can make best use of these promising agents for people living with diabetes.**

In healthy individuals, virtually all glucose filtered by the renal glomeruli is reabsorbed into the circulation within the proximal convoluted tubule, and almost no glucose is excreted into the urine. This glucose reabsorption from the glomerular filtrate is mediated by sodium–glucose cotransporter (SGLT) proteins present in the renal tubules, via a process that is independent of insulin (Cefalu and Riddle, 2015). Around 90% of filtered renal glucose is reabsorbed in the first segment of the proximal convoluted tubule by SGLT2, and the remaining 10% is removed in the distal segment by SGLT1 (Gerich, 2010).

## SGLT2 inhibitors

SGLT2 inhibitors block this reabsorption of glucose, thereby leading to rapid glycosuria and caloric loss (Torimoto et al, 2017). Given that this mechanism is independent of insulin, SGLT2 inhibitors would be expected to act independently of pancreatic beta-cell function and insulin resistance, and should not lose potency as beta-cell function declines.

The amount of glucose excreted in the urine depends on both the level of hyperglycaemia and the glomerular filtration rate. SGLT2 inhibitors all require normal renal function to have their maximum effect on glucose-lowering.

Several randomised, placebo-controlled trials of SGLT2 inhibitors in people with type 2 diabetes have been published, with study durations ranging from 12 to 104 weeks, and with SGLT2 inhibitors administered as monotherapy or in addition to other glucose-lowering therapies, including insulin. These have shown significant reductions in $HbA_{1c}$ levels (Scheen, 2015). A recent meta-analysis of 58 studies of eight different SGLT2 inhibitors showed that these agents reduced mean $HbA_{1c}$ levels by 8.6 mmol/mol (0.79%) when used as monotherapy and by 6.7 mmol/mol (0.61%) when used as add-on treatment, as well as inducing a mild weight loss of approximately 2 kg, compared with placebo (Vasilakou et al, 2013). In addition, the use of various SGLT2 inhibitors is associated with mean reductions in systolic and diastolic blood pressure of 4.0 mmHg and 1.6 mmHg, respectively, compared with baseline (Baker et al, 2014).

There are currently three SGLT2 inhibitors available to be prescribed in the UK: dapagliflozin, canagliflozin and empagliflozin. Another, ertugliflozin, is in phase III trials, and

ipragliflozin and luseogliflozin are both available in Japan only.

Investigators have recently reported that sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, can be used in combination with insulin by people living with type 1 diabetes, and results in reduced $HbA_{1c}$ with no severe hypoglycaemia, albeit with a higher rate of diabetic ketoacidosis (DKA; Garg et al, 2017). Additionally, investigators have demonstrated that dapagliflozin may be used in addition to insulin to improve glycaemic control in people with inadequately controlled type 1 diabetes (Dandona et al, 2017). While licences may ultimately be sought for these indications, there are currently no licences for the use of SGLT2 inhibitors in people with type 1 diabetes.

The three SGLT2 inhibitors available in the UK are pharmacokinetically similar: they are rapidly absorbed after oral administration, have a long elimination half-life that allows for once-daily dosing, are extensively metabolised by the liver and have no clinically relevant drug–drug interactions (Mosley et al, 2015). They are all available as monotherapy and as fixed-dose combinations with metformin.

## Current guidance on SGLT2 inhibitors in the management of type 2 diabetes

The NICE guideline on the management of type 2 diabetes in adults, NG28, helps healthcare professionals decide how to use these agents, and recommends their use in a process of stepwise intensification (NICE, 2015). NICE also advises that metformin be used as a first-line therapy, adding that sustained-release forms of metformin may be offered if standard metformin is not tolerated. If no metformin preparation is tolerated, or is contraindicated, then a dipeptidyl peptidase-4 (DPP-4) inhibitor, pioglitazone, a sulfonylurea or an SGLT2 inhibitor may be used as monotherapy.

The guideline also recommends that, at first intensification (if $HbA_{1c}$ has risen to 58 mmol/mmol [7.5%]), metformin may be combined with a DPP-4 inhibitor, pioglitazone, a sulfonylurea or an SGLT2 inhibitor (NICE, 2015). The choice of agents then remains broadly the same for second intensification, although licences for their use in these combinations may vary, and NICE recommends trying to maintain an $HbA_{1c}$ of 53 mmol/mol (7.0%).

NICE has published a Technology Appraisal (TA390) on the three currently available SGLT2 inhibitors as monotherapies for type 2 diabetes (NICE, 2016). In turn, this advice has been incorporated into an update of the full NG28 guideline, within the initial therapy section. The treatment algorithm has also been amended to include new information on SGLT2 inhibitors, in the box on action to take if metformin is contraindicated or not tolerated, as follows (NICE, 2015; updated May 2017):

- *As monotherapy when diet and exercise alone do not provide adequate glycaemic control in people for whom the use of metformin is considered inappropriate due to intolerance or contraindications;*
- *when a DPP-4 inhibitor would otherwise be prescribed; and*
- *when a sulfonylurea or pioglitazone is not appropriate.*

The NICE guideline broadly aligns with that of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), which promotes a pragmatic, stepwise approach to medication escalation (Inzucchi et al, 2015). The ADA/EASD guidance recognises that, while SGLT2 inhibitors are approved as monotherapy if metformin is inappropriate, they are mainly used in combination with metformin and/or other agents. Currently, updated SIGN guidance for the management of type 2 diabetes is in draft form for consultation, but a broadly similar approach to that of NICE is anticipated.

## Cardiovascular outcome trials and SGLT2 inhibitors

In 2008, the Food and Drug Administration (FDA) mandated that all new diabetes pharmaceutical agents submitted to be licensed in the US should undergo trials for cardiovascular (CV) risk. Required outcomes included CV death, myocardial infarction (MI) and stroke, and could include hospitalisation for acute coronary syndrome and urgent revascularisation procedures (FDA, 2008). However, the FDA did not include heart failure as one of the required outcomes,

### Page points

1. The three sodium–glucose cotransporter 2 (SGLT2) inhibitors currently available in the UK are dapagliflozin, canagliflozin and empagliflozin. All three are pharmacokinetically similar and are available as monotherapy or in fixed-dose combinations with metformin.
2. NICE recommends SGLT2 inhibitors as monotherapy when metformin, a sulfonylurea and pioglitazone are not appropriate, and as combination therapy at first and second treatment intensification.

**Page points**

1. Cardiovascular outcome trials of empagliflozin and canagliflozin have both shown reductions in the risk of major adverse cardiac events and, in the case of empagliflozin, cardiovascular death.
2. Results from the observational CVD-REAL study suggest that these benefits are a class effect.
3. However, it remains unknown whether the benefits extend to people at lower cardiovascular risk at baseline.

opting instead for a composite measure of major adverse cardiac events (MACE), typically a combination of MI, stroke, and CV death.

This 2008 guidance resulted in profound changes in the ways new antidiabetes drugs are evaluated and brought to market, leading to a number of large and very expensive CV outcome trials (CVOTs). Because of the significant number of participants required to produce sufficient statistical power, the trials have meant that many more patient outcomes have been published than is usual in regular licensing studies, and with them more side effects and complications have become apparent.

The effects of SGLT2 inhibitors on the risk of CV disease (CVD) are being monitored in several CVOTs:

- Canagliflozin: CANVAS, CANVAS-R and CREDENCE.
- Dapagliflozin: DECLARE-TIMI.
- Empagliflozin: EMPA-REG OUTCOME.
- Ertugliflozin: VERTIS CV.

Results of CANVAS and EMPA-REG have been published, and data from DECLARE-TIMI and Vertis CV are due to be published in 2019.

In addition to these CVOTs, CVD-REAL, a large, observational study of people with type 2 diabetes newly initiated on SGLT2 inhibitors and compared with other hypoglycaemic agents, has been published.

## EMPA-REG OUTCOME

This study enrolled over 7000 people with type 2 diabetes, all of whom were at high risk of CV events (Zinman et al, 2015). When added to standard care, empagliflozin resulted in a 14% relative risk reduction (RRR) in the primary composite outcome of CV death, non-fatal MI and non-fatal stroke, a 38% RRR in CV death and a 32% RRR in death from any cause, compared with placebo. Empagliflozin has since received a licence in the US, but not in Europe, for "improving survival in adults with type 2 diabetes and CVD".

## CANVAS

The CANVAS programme pooled data from the CANVAS and CANVAS-R (CANVAS-Renal) studies. A total of 10 142 people with type 2 diabetes and high CV risk (66% with established CVD and 34% with two or more risk factors for CVD) were evaluated. Treatment with canagliflozin resulted in a significant 14% RRR in the primary endpoint, a composite of CV death, non-fatal MI and non-fatal stroke (Neal et al, 2017).

## CVD-REAL

In this observational study, 309 056 people living with type 2 diabetes from five different countries were followed, of whom half were newly initiated on SGLT2 inhibitors (Kosiborod et al, 2017). Using data from clinical practice, the researchers compared rates of heart failure and death between recipients of SGLT2 inhibitors and other glucose-lowering drugs, in participants with and without prior CVD. SGLT2 inhibitors were associated with a 39% lower risk of hospitalisation for heart failure (HHF), a 51% lower risk of death from any cause and a 46% lower risk of the composite endpoint of HHF and death from any cause. The results were consistent regardless of the type of SGLT2 inhibitor used, which varied from country to country.

## Potential mechanisms behind cardioprotective effects

Taking the data from these studies into account, SGLT2 inhibitors as a class appear to protect against CV outcomes and death, with the most significant effects seen in people with pre-existing CVD. To date, empagliflozin is the only SGLT2 inhibitor with evidence of a significant reduction in the risk of CV death.

There has been speculation over how the benefits of SGLT2 inhibitors in heart failure are mediated, as this particular effect cannot be explained by the drugs' effects on glycaemic control or osmotic diuresis. Instead, the effects on heart failure are hypothesised to be mediated by sodium–hydrogen exchange in both the kidney and heart (Packer et al, 2017).

However, investigators have recently pointed out that not all of these effects may be directly applicable to a typical UK general practice population, of whom only around 16% have

the same high CV risk as the participants in EMPA-REG (McGovern et al, 2017).

## SGLT2 inhibitors and renal disease

Due to their mechanism of action, SGLT2 inhibitors are dependent on renal filtration of glucose. Therefore, good renal function is required to achieve maximal hypoglycaemic effect, with an estimated glomerular filtration rate (eGFR) of ≥60 mL/min/1.73 $m^2$ needed for initiation of these therapies (Electronic Medicines Compendium [EMC], 2017a; 2017b; 2017c). Traditionally, renal function (creatinine clearance rate and eGFR) is monitored every 6 months, but prescribers may wish to increase the frequency to every 3 months in the presence of traditional and non-traditional risk factors for chronic kidney disease.

If eGFR falls below 60 mL/min/1.73 $m^2$, dapagliflozin should be discontinued, as it is not thought to have a significant hypoglycaemic effect below this level. Canagliflozin and empagliflozin may be continued at their lower daily doses (100 mg and 10 mg, respectively), provided eGFR does not drop below 45 mL/min/1.73 $m^2$, whereupon they should also be discontinued (EMC, 2017a; 2017b; 2017c). These prescribing considerations are summarised in *Table 1*.

Clinicians using SGLT2 inhibitors need to be aware that, although the individual drugs have been trialled separately, most cause hyperfiltration, which leads to transient reductions in eGFR, which return to baseline by 24 weeks. (Trujillo and Nuffer, 2017). Neither canagliflozin nor dapagliflozin are recommended to be taken with loop diuretics (EMC, 2017a; 2017b). People aged ≥75 years and those with moderate renal impairment may be at an increased risk of volume depletion-related adverse effects, such as postural dizziness and hypotension (Bays, 2013).

It has been speculated that SGLT2 inhibitors would leave people with type 2 diabetes at increased risk of acute kidney injury (AKI); however, a recent matched control study did not demonstrate this (Nadkarni et al, 2017).

### Renoprotective effects

Two studies have examined progression of renal disease in people using SGLT2 inhibitors as part of larger outcome trials: EMPA-REG OUTCOME (a secondary analysis) and CANVAS-R. The CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy [Clinicaltrials.gov identifier: NCT0206579]) will report separately on canagliflozin when completed, and will assess progression of renal impairment and incidence of renal or CV death in people with existing renal impairment.

The effect of empagliflozin on progression of chronic kidney disease in the EMPA-REG cohort was examined as a pre-specified secondary objective. Empagliflozin was associated with a significant 38% reduction in the risk of the primary renal endpoint (a composite of incident or worsening nephropathy; doubling of serum creatinine level plus an eGFR of ≤45 mL/min/1.73 $m^2$; initiation of renal replacement therapy; or death from renal disease) compared with placebo (Wanner et al, 2016). Rates of adverse events, including AKI, were similar in the empagliflozin and placebo groups, regardless of renal function at baseline.

The CANVAS-R data have not yet been fully published; however, a 40% reduction in the composite renal outcome (a 40% reduction in eGFR, development of end-stage renal disease or death from renal causes) was reported in the original analysis of CV outcomes (Neal et al, 2017).

**Table 1. Prescribing considerations for the three sodium–glucose cotransporter 2 inhibitors licensed in the UK.**

| Drug | Administration | Prescribing considerations (eGFR presented in mL/min/1.73 $m^2$) |
|---|---|---|
| Dapagliflozin | Once daily | Not recommended if eGFR <60<br>Reduce dose in severe hepatic impairment |
| Canagliflozin | Once daily | Do not initiate if eGFR <60<br>Reduce dose if eGFR falls below 60<br>Stop if eGFR falls below 45<br>Not recommended in severe hepatic impairment |
| Empagliflozin | Once daily | Do not initiate if eGFR <60<br>Reduce dose if eGFR falls below 60<br>Stop if eGFR falls below 45<br>Not recommended in severe hepatic impairment |

eGFR=estimated glomerular filtration rate.

**Page points**

1. SGLT2 inhibitors are associated with an increased risk of genitourinary infections due to increased levels of glucose in the urine.
2. Diabetic ketoacidosis is a rare but significant side effect, which should be suspected in any symptomatic user, even if blood glucose levels are normal.
3. There is also evidence of an increased risk of fractures, amputation and bladder cancer, and clinicians should exercise caution in people at high risk of these complications until further research has been conducted.

## What is the overall safety profile of SGLT2 inhibitors?

### Genitourinary infections

Adverse events related to the presence of glucose in the urine, including genital mycotic infections and lower urinary tract infections, can occur with SGLT2 inhibitors (Gerich, 2010; Monami et al, 2014). These are more commonly observed in women (up to 20–30% of women may be affected) than in men (Cefalu and Riddle, 2015). The extent to which these side effects may affect long-term adherence to treatment remains unclear, although reports from the randomised trials suggest that in most cases, the symptoms did not lead to discontinuation.

### Bone health and amputations

People with type 1 diabetes and type 2 diabetes have an increased fracture risk (Sundararaghavan et al, 2017). Early clinical trials have suggested an approximate 30% increase in risk of bone fractures in people with type 2 diabetes who receive canagliflozin (Taylor et al, 2015). Fractures occurred as early as 12 weeks after the start of treatment, were often related to minor trauma, such as falls, and were more likely to affect the arms than the lower extremities (Janssen Pharmaceuticals, 2017). It is thought that increased serum phosphate levels caused by SGLT2 inhibition may have a negative effect on bone. In the CANVAS study, the rate of all fractures was higher with canagliflozin than with placebo (15.4 vs 11.9 per 1000 person-years), and there was a similar trend with respect to low-trauma fracture events (Neal et al, 2017). However, there was evidence of heterogeneity in these findings between CANVAS and CANVAS-R, with significant differences observed only in CANVAS.

In addition, there was a higher risk of amputation of the toes, feet or legs with canagliflozin compared with placebo (6.3 vs 3.4 per 1000 person-years), with 71% of the affected participants having their highest amputation at the level of the toe or metatarsal (Neal et al, 2017). In response to this, the European Medicines Agency (EMA, 2017) has issued a warning about toe amputations for all SGLT2 inhibitors. This apparent increased risk has also been borne out by reports to the FDA, which concluded that the frequency of reports of amputation as an adverse event with canagliflozin was significantly higher than for non-SGLT2 inhibitor drugs, and even compared with dapagliflozin and empagliflozin (Fadini and Avogaro, 2017).

### Diabetic ketoacidosis

Following a number of reports, the EMA (2016) has reviewed data to evaluate the risk of euglycaemic DKA and has recommended that the Product Information of SGLT2 inhibitors be updated to list DKA as a rare adverse reaction (affecting up to 1 in 1000 people). However, a recent meta-analysis found that people with type 2 diabetes taking SGLT2 inhibitors did not have a significantly higher risk of DKA than controls (Monami et al, 2017). Nevertheless, prescribers should ensure that people taking SGLT2 inhibitors do indeed have type 2 diabetes and not misdiagnosed type 1 diabetes (SGLT2 inhibitors are not licensed for use in people with type 1 diabetes), and healthcare professionals should consider the possibility of ketoacidosis in people who have symptoms consistent with the condition, even if their blood glucose levels are not high (EMA, 2016).

### Bladder cancer

It should be noted that, although there is a licence for the combination of dapagliflozin and pioglitazone, this combination is not recommended by NICE (2016), as dapagliflozin has an additional label warning for bladder cancer. Consequently, in the US, dapagliflozin is not recommended for use in people with active bladder cancer (AstraZeneca Pharmaceuticals, 2017).

## Current and future roles of SGLT2 inhibitors

SGLT2 inhibitors are emerging as important and useful agents in the management of type 2 diabetes. They are well tolerated and have a useful impact on both diabetes and its associated CV risk factors. The risk of hypoglycaemia is much lower with SGLT2 inhibitors than with sulfonylureas, and is comparable to that reported with metformin, pioglitazone and sitagliptin, although there is additional risk of hypoglycaemia

when added to sulfonylurea or insulin therapy. Increased renal glucose elimination also assists weight loss and can help to reduce blood pressure.

SGLT2 inhibitors would appear to have positive effects on heart failure, via an as yet unknown mechanism, although the maximal effect is in people with pre-existing CVD. Only empagliflozin has had a positive effect on CV mortality. Given all these demonstrated and emerging benefits, SGLT2 inhibitors are a potentially attractive management option for primary care teams, especially if weight and CV risk are part of the underlying treatment considerations. It is likely that their use will continue to widen, although healthcare professionals will want to understand significant differences in side effects between the available agents. ■


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***"Given all these demonstrated and emerging benefits, SGLT2 inhibitors are a potentially attractive management option for primary care teams, especially if weight and cardiovascular risk are part of the underlying treatment considerations."***