# Frequently asked questions

# SGLT2 inhibitors – a novel approach to managing hyperglycaemia

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## Clinical relevance

The advent of a new class of glucose-lowering agent presents clinicians with further options in the management of hyperglycaemia in type 2 diabetes. The prospect of adding a class of drugs that work independently of insulin is attractive and offers a novel additive glucose-losing effect, with a minimal risk of hypoglycaemia other than when used in combination with sulphonylureas and insulin. In people with type 2 diabetes who are determined to avoid injectable therapies, this class of agents provides an alternative or additional oral therapy for those with suboptimal glycaemic control. It is likely that sodium–glucose cotransporter 2 (SGLT2) inhibitors will be considered for use with standard oral hypoglycaemic agents as well as insulin.

Given the continuing pressure on controlling prescribing costs in diabetes and the lack of long-term data it remains to be seen what part SGLT2 inhibitors will eventually play in future diabetes clinical practice in the UK. However, an oral preparation that lowers glucose and weight will be of interest to many of the people with type 2 diabetes who we treat.

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Author details can be found at the end of the article.

**It has long been recognised that an extract of bark from certain fruit trees (pear, apple and cherry) can reduce blood glucose levels owing to the presence of phlorizin, which belongs to a group of flavonoids called the dihydrochalcones (Ehrenkranz et al, 2005). Phlorizin is a sodium–glucose cotransporter 1 (SGLT1) and 2 (SGLT2) inhibitor. Its use results in sodium, glucose and fluid loss mediated through SGLT1 inhibition in the small intestine and sodium and glucose loss with SGLT2 inhibition in the kidneys. However, its poor absorption, dehydrating properties and bitter taste have confined it to experimental rather than clinical use (Ehrenkranz et al, 2005). An understanding of phlorizin has led to the development of synthetic analogues that have now become available for clinical management of type 2 diabetes, as is described via the "frequently asked questions" below.**

## Q What is the role of the kidney in glucose regulation?

The role of the kidneys in maintaining normoglycaemia, through the filtration and reabsorption of glucose as well as gluconeogenesis, is well established. Every day, 180 litres of plasma is filtered through the kidneys and, in normoglycaemic individuals, this translates to approximately 180 g of glucose. Under normal conditions the ability of the kidneys to reabsorb glucose from the glomerular filtrate is very effective, with less than 0.5 g/day of filtered glucose ultimately appearing in the urine. Glucose and sodium reabsorption from the renal tubules increases in a linear relationship with rising levels of glucose in the glomerular filtrate (up to 350 mL/min/1.73 $m^2$) until SGLT2 capacity is exceeded and glycosuria occurs (generally around blood glucose levels of 11 mmol/L; Gerich, 2010).

## Q What is the physiological function of SGLT2?

Glucose reabsorption in the renal tubules is governed by sodium–glucose cotransporters (SGLTs), which move glucose into the renal epithelial cells. SGLT2 is a high-capacity, low-affinity transporter predominantly expressed in the kidney, where it is exclusively found in the brush border membrane of the S1 segment of the proximal tubule. The function of SGLT2 is to facilitate the reabsorption of filtered glucose and sodium as they pass the proximal convoluted tubule – a mechanism that maintains electrolyte and fluid balance in the body. The majority of the glucose is reabsorbed from the glomerular filtrate by SGLT2. The remainder of the glucose is reabsorbed from the filtrate in the distal S3 segment of the renal proximal tubule by the high-affinity, low-capacity transporter SGLT1 (Lee et al, 2007; Gerich, 2010).

However, while SGLT2 is predominantly expressed in the kidney, SGLT1 is also highly expressed in the small intestine, where it is involved in the transport of glucose across the brush-border membrane. In the renal tubule an electrochemical gradient generated by the $Na^+/K^+$ ATPase located in the basolateral membrane drives the movement of sodium ions across the luminal membrane and provides

**Page points**

1. Observations from case reports have added credibility to the concept of sodium–glucose cotransporter 2 (SGLT2) inhibition as a mechanism for treating hyperglycaemia in type 2 diabetes.
2. Dapagliflozin is the first agent in the SGLT2 inhibitor class to have been launched in the UK.
3. An extensive clinical trial programme for dapagliflozin assessed the drug's efficacy and tolerability in a number of specific populations with type 2 diabetes.

the driving force for glucose cotransport (Lee et al, 2007).

SGLT2 receptors account for 90% of the total glucose reabsorbed. Having been reabsorbed, glucose is then transported to the microvascular system under the passive action of facilitated-diffusion glucose transporters (GLUTs; Lee et al, 2007).

## Q Are genetic mutations of SGLT2 recognised in humans?

Renal glycosuria has long been recognised as a cause of concern for patients and physicians at routine medical examinations. The appearance of glucose in the urine with entirely satisfactory glucose handling led to the term "familial renal glycosuria" being created. There are, in fact, several mutations of the SGLT2 gene leading to differing degrees of SGLT2 receptor non-responsiveness, and resulting in varying levels of glucose loss in the urine. Although these variants are rare and SGLT2 inhibition is significantly less than that seen in people treated with therapeutic agents developed to inhibit SGLT2 activity (described below), people with SGLT2 mutations appear to have a normal lifespan (List et al, 2009). Some can experience polyuria and nocturia but, in general, most are asymptomatic (Gerich, 2010).

Such case reports of people with rare gene mutations suggest that the glucose and sodium loss does not increase mortality risk (Gerich, 2010). While the evidence, owing to the nature of case reports, should be interpreted with caution, these observations have added credibility to the concept of SGLT2 inhibition as a mechanism for treating hyperglycaemia in type 2 diabetes.

## Q What SGLT2 inhibitors are available or in development? And what are the clinical benefits?

The development of inhibitors of SGLT2 has been underway for many years and there are a number of agents in the class. At the time of writing, there is only one available in the UK – dapagliflozin. This agent is described in detail below, while two others in advanced stages of development are also considered briefly.

### Dapagliflozin

Dapagliflozin, a selective inhibitor of SGLT2, is the first agent in the class to have been launched in the UK (Bristol-Myers Squibb and AstraZeneca, 2012). It recently received a recommendation for use from NICE (2013; described in more detail below). The usual dose of dapagliflozin is 10 mg daily. However, in people with severe liver impairment an initial dose of 5 mg is recommended (Bristol-Myers Squibb–AstraZeneca EEIG, 2013).

An extensive clinical trial programme for dapagliflozin assessed the drug's efficacy and tolerability in a number of specific populations with type 2 diabetes, including: monotherapy for those inadequately controlled with diet and exercise, in a placebo-controlled trial (Ferrannini et al, 2010); dual therapy for people inadequately controlled with metformin, in a placebo-controlled trial (Bailey et al, 2010) and in a head-to-head comparison with glipizide (Nauck et al, 2011); dual therapy for people inadequately controlled with glimepiride, in a placebo-controlled trial (Strojek et al, 2011); and add-on therapy for people inadequately controlled with insulin (with or without oral antidiabetes drugs), in a placebo-controlled trial (Wilding et al, 2012). In the placebo-controlled trials, dapagliflozin was associated with statistically significant reductions in $HbA_{1c}$ from baseline compared with placebo at 24 weeks, while in the active comparator study, the drug met non-inferiority criteria for $HbA_{1c}$ reduction over 52 weeks in comparison with glipizide (Bristol-Myers Squibb–AstraZeneca EEIG, 2013). In the latter study, baseline-adjusted reductions in $HbA_{1c}$ levels after 52 weeks of treatment were 6 mmol/mol (0.52%) in both the dapagliflozin and the glipizide groups.

With regard to glucose excretion, a 12-week study of people with type 2 diabetes who were treated with dapagliflozin 10 mg daily revealed an average 24-hour excretion of glucose in the urine of 70 g (List et al, 2009). This equates to a daily energy loss of 280 kcal. In terms of effects on body weight, when dapagliflozin 10 mg was added to metformin, glimepiride or insulin in clinical trials, a statistically significant body weight reduction was observed at 24 weeks. In

**Page points**

1. Canagliflozin was granted approval for use by the US Food and Drug Administration in March 2013, and it has also been submitted for European approval.
2. Canagliflozin has been studied in nine phase III clinical trials involving over 10 000 people with type 2 diabetes.
3. Empagliflozin has recently been filed for approval in Europe and the US.
4. Empagliflozin is being investigated in an ongoing phase III research programme that plans to enrol in excess of 14 500 people through more than 10 clinical trials.

longer-term trials, when added to metformin, these effects were sustained at 52 weeks (–4.5 kg compared with glipizide) and 102 weeks (–3.07 kg compared with placebo; Bristol-Myers Squibb–AstraZeneca EEIG, 2013).

In addition to glucose lowering and weight loss, blood pressure reductions were noted among study participants (Bristol-Myers Squibb–AstraZeneca EEIG, 2013). The mechanism for this relates to the sodium-loss effect of SGLT2 inhibitors (Gerich, 2010).

## Canagliflozin

Canagliflozin was granted approval for use by the US Food and Drug Administration in March 2013 (Johnson & Johnson, 2013), and it has also been submitted for European approval (European Medicines Agency, 2013). It has been studied in nine phase III clinical trials involving over 10 000 people with type 2 diabetes, as a monotherapy and in combination with other diabetes agents including metformin, sulphonylureas, pioglitazone and insulin (Johnson & Johnson, 2013). The trials demonstrated significant reduction in $HbA_{1c}$ levels with canagliflozin compared with placebo, and non-inferiority to glimepiride and sitagliptin in active-comparator trials (Janssen Pharmaceuticals, 2013). Statistically significant weight losses were noted with canagliflozin in both a monotherapy and a combination-therapy setting (Janssen Pharmaceuticals, 2013).

## Empagliflozin

Empagliflozin has also recently been filed for approval in Europe and the US (Eli Lilly and Company and Boehringer Ingelheim, 2013a). Empagliflozin is being investigated in an ongoing phase III research programme that plans to enrol in excess of 14 500 people through more than 10 clinical trials. Phase III data that have already been presented – at the *American Diabetes Association 73rd Scientific Sessions* – on empagliflozin added to metformin, with or without a sulphonylurea, showed significant improvements in blood glucose control and weight reductions in people with type 2 diabetes. Similar results were demonstrated when empagliflozin was used as add-on to basal insulin (Eli Lilly and Company and Boehringer Ingelheim, 2013b).

## Q What are the side effects and limitations?

Focusing on dapagliflozin (the class's only currently available agent in the UK), in a pre-specified pooled analysis of 12 placebo-controlled studies, there were 1193 participants treated with a 10 mg daily dose and 1393 treated with placebo. The analysis revealed an increase in reports of vulvovaginitis, balanitis and related genital infections (including candidiasis) in people who received dapagliflozin 10 mg compared with placebo (4.8% versus 0.9%). Most infections were mild to moderate, and individuals responded to an initial course of standard treatment. The infections rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and participants with a prior history were more likely to have a recurrent infection (Bristol-Myers Squibb–AstraZeneca EEIG, 2013).

In these trials, there was also a slight increase in rates of urinary symptoms interpreted as urinary tract infection with the SGLT2 inhibitor compared with placebo (4.3% at a 10 mg daily dose versus 3.7%; Johnsson et al, 2013). These infections were more frequent in females, and participants with a prior history were more likely to have a recurrent infection (Bristol-Myers Squibb–AstraZeneca EEIG, 2013). Most identified infections were those considered typical for people with diabetes, were mild to moderate and responded to standard antimicrobial treatment. Discontinuations from the trials attributable to urinary tract infection were rare (Johnsson et al, 2013).

A few study participants complained of osmotic symptoms, which resulted at most in an additional urinary void on a daily basis. Dapagliflozin, compared with placebo, was associated with a slightly higher rate of volume-depleted effects, such as hypotension and dehydration (0.8% at a 10 mg daily dose versus 0.4%; Bristol-Myers Squibb–AstraZeneca EEIG, 2013). As these are agents that promote fluid and sodium urinary loss, it is advisable to discontinue SGLT2 inhibitors in individuals who become dehydrated and compromised in terms of fluid balance.

**Page points**

1. Since sodium–glucose cotransporter 2 (SGLT2) inhibitors depend on kidney function for their action, renal impairment is an important consideration in making prescribing decisions
2. The advent of a class of glucose-lowering agents that works independently of insulin provides a novel approach to reducing hyperglycaemia.
3. NICE, in its recently published technology appraisal for dapagliflozin, recommended its use as a treatment option for adults with type 2 diabetes as dual therapy in combination with metformin (if it is used as described for dipeptidyl peptidase-4 inhibitors in NICE Clinical Guideline 87), and in combination with insulin with or without other oral antidiabetes drugs.

The slight increase in urinary frequency and the aforementioned infections is likely to be a class effect.

Since SGLT2 inhibitors depend on kidney function for their action, renal impairment is another important consideration in making prescribing decisions. In the trials of dapagliflozin, there was a small increase in haematocrit (2.15% at 24 weeks) with a 0.5 mmol/L reduction in urate at 2 years but no other persistent alteration of electrolytes (Bailey et al, 2011). Dapagliflozin is not recommended in people with moderate-to-severe renal impairment (creatinine clearance <60 mL/min or estimated glomerular filtration rate <60 mL/min/1.73 $m^2$; Bristol-Myers Squibb–AstraZeneca EEIG, 2013).

The overall incidence of cancers in the phase III trials of dapagliflozin was not increased with this agent. However, there was a non-statistically significant increase in the rates of bladder, prostate and breast cancer. There were no such findings in preclinical studies and the relatively short interval between treatment initiation and data collection makes a causal relationship very unlikely. Dapagliflozin is not recommended for use with pioglitazone, an agent for which observational data have shown a small increase in the risk of bladder cancer (Bristol-Myers Squibb–AstraZeneca EEIG, 2013).

## Q Where do SGLT2 inhibitors fit into the treatment of type 2 diabetes?

The advent of a class of glucose-lowering agents that works independently of insulin provides a novel approach to reducing hyperglycaemia. Its effect in terms of reducing overall glucose load in hyperglycaemia is perhaps analogous to the fluid load reduction with diuretics seen in heart failure.

With the large number of glucose-lowering agents available it is becoming more difficult to define clear treatment algorithms. Individual regimens need to be fashioned for different people depending on their own wishes, their occupation or domestic situation, their $HbA_{1c}$ level, their driving status, their microvascular and macrovascular risk, their weight, their life expectancy and their related and unrelated co-morbidities.

The licence for dapagliflozin, the only currently available SGLT2 inhibitor in the UK, includes monotherapy (where intolerance to other oral hypoglycaemic agents exists) as well as add-on to other glucose-lowering medicinal products including insulin (Bristol-Myers Squibb–AstraZeneca EEIG, 2013). It is an oral glucose-lowering agent with weight-reducing properties and a minimal associated risk of hypoglycaemia unless used with sulphonylureas and insulin (Bristol-Myers Squibb–AstraZeneca EEIG, 2013). Aside from cost (just under £37 for 4 weeks' treatment at the time of writing [British National Formulary, 2013]) – an important practical consideration is the relative ineffectiveness of the agent for people with type 2 diabetes who have concomitant renal impairment (as noted above, it is not recommended for use in people with moderate-to-severe renal impairment). This is not a risk *per se* but results in reduced efficacy since the action of this class of glucose-lowering agent is dependent on reasonable renal function (Bristol-Myers Squibb–AstraZeneca EEIG, 2013). In addition, people with diabetes do need to be warned about the risks of candidal infections and possible urinary tract infections and should be advised to report these to their healthcare professional if they occur. It may be prudent to avoid use of these agents in those with recurrent infections until more experience is gained in their use within clinical practice.

Finally, NICE – in its recently published technology appraisal for dapagliflozin – recommended its use as a treatment option for adults with type 2 diabetes as dual therapy in combination with metformin (if it is used as described for dipeptidyl peptidase-4 inhibitors in NICE Clinical Guideline 87 [NICE, 2009]), and in combination with insulin with or without other oral antidiabetes drugs (NICE, 2013). ■

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