

# THE ROLE OF SGLT2 INHIBITORS IN TYPE 2 DIABETES

The advent of SGLT2 inhibitors, a new class of glucose lowering agent, currently represented by dapagliflozin (Forxiga) and canagliflozin (Invokana), offers a new mechanistic paradigm for treatment. Here, the authors consider the prescribing rationale and precautions, with an emphasis on the pharmacodynamic and kinetic properties of these agents.

**Andrew V Bailey**

Clinical Pharmacist, DIMEC, Med IC 4, Keele University Science Park

**Caroline Day**

Visiting Fellow, School of Life and Health Sciences, Aston University, Birmingham

## Background

Costing about 11% of global healthcare budgets, diabetes currently affects an estimated 382 million adults worldwide, a figure that is expected to escalate above 590 million within 25 years.<sup>1</sup> Type 2 diabetes mellitus (T2DM) accounts for about 95% of all diabetes, typically characterised by progressive hyperglycaemia with insulin resistance and a gradual loss of pancreatic  $\beta$ -cell function. Treatment aims to control hyperglycaemia and other metabolic and cardiovascular risk factors to reduce the associated microvascular and macrovascular complications.<sup>2,3</sup>

If lifestyle measures fail to achieve adequate glycaemic control, pharmacological intervention becomes necessary. The actions and limitations of established glucose-lowering agents have been discussed in a previous issue of this journal.<sup>4</sup>

The progressive nature of T2DM usually requires combinations of differently acting agents to maintain glycaemic control when monotherapy is inadequate.<sup>3-6</sup> However, choices are often limited by lifestyle requirements (e.g. driving) or comorbidities (e.g. obesity, impaired renal function or heart disease), and combinations found in daily practice are not always the most advantageous. Consider, for example, the potential advantages of tolbutamide or gliclazide in an older adult, due to shorter half-life and inactive metabolites; or use of a meglitinide such as repaglinide for a person with unpredictable meal times or poor renal function, where a rapid onset but short duration of action is more appropriate.<sup>5</sup>

Now a new option is available: the sodium glucose transporter-2 (SGLT2) inhibitor class, currently comprising dapagliflozin and canagliflozin.

## Mechanism of action

SGLT2 inhibitors act independently of insulin to eliminate excess glucose in the urine (i.e. increase glycosuria). They do this by inhibiting the SGLT2 transporter in the kidney, which normally reabsorbs most of the glucose from the renal filtrate.

Glycosuria has long been a diagnostic feature of poor glycaemic control; SGLT2 inhibitors act to potentiate this effect, thereby enhancing elimination of excess glucose. The caloric loss associated with this glycosuria assists weight loss, and a modest osmotic diuresis can facilitate a small decrease in blood pressure. The term “glucuretic” may therefore usefully describe the effects of SGLT2 inhibitors (by analogy with diuretic for fluid elimination). Since SGLT2 inhibitors do not stimulate insulin secretion or action, and their effect diminishes as blood glucose levels fall, they do not cause hypoglycaemia.<sup>6,7,8</sup>

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Of the 12 isoforms of SGLT responsible for glucose absorption and reabsorption, SGLT1 and SGLT2 are of importance here. SGLT1 is responsible for dietary glucose and galactose absorption but has a much lower capacity than SGLT2 for glucose absorption. SGLT1 is found predominantly in the gut, but is also located in S2-3 of the convoluted tubule, whereas SGLT2 is expressed solely in the S1 segment of the proximal convoluted tubule (Figure 1).<sup>9,10</sup> Thus, SGLT2 is responsible for the majority of renal glucose reabsorption and its inhibition by dapagliflozin and canagliflozin induces the “glucuretic” effect. Intestinal uptake of dietary glucose is essentially unimpaired, while active renal SGLT1 sites (with lower capacity) reabsorb any remaining glucose – thus guarding against hypoglycaemia. This “glucuretic” action is independent

of both insulin and glucose but requires adequate renal perfusion to achieve clinically meaningful outcomes.

Dapagliflozin and canagliflozin exert the majority of their actions on SGLT2, but their selectivity for the receptor varies: dapagliflozin has a 1200-fold affinity for SGLT2 over SGLT1, compared to the 250-fold affinity demonstrated by canagliflozin.<sup>11</sup> This may have implications when considering side effects, glycaemic control and weight loss (see Clinical outcomes).

## Prescribing a SGLT2 inhibitor

T2DM is a progressive disease, thus therapies need constant up-titration and alteration to optimise glycaemic control; a personalised therapeutic approach ensures that treatments accommodate the requirements of patients as much as possible. So what about SGLT2 inhibitors?

Both dapagliflozin (10mg od) and canagliflozin (100mg or 300mg od) are licensed in Europe for the treatment of T2DM in adults ( $\geq 18$  yrs), either as monotherapy (when lifestyle modifications are inadequate and/or metformin is inappropriate/not tolerated) or in combination with other antidiabetic agents including insulin. Both licenses recommend lowering doses of co-prescribed insulin secretagogues (e.g. sulphonylureas) to reduce risk of hypoglycaemia.<sup>12,13</sup> Despite its licensed indication, a recent NICE technology appraisal for dapagliflozin has not recommended triple therapy (addition to metformin and sulphonylurea); at the time of going to press, no such appraisal is available for canagliflozin.<sup>14</sup>

Contraindications include excipient hypersensitivity, and both manufacturers recommend cessation of treatment during pregnancy and while breastfeeding.<sup>12,13</sup> Considerations before prescribing are summarised in Table 1. SGLT2 inhibitors are not indicated for the treatment of T1DM.

## Clinical outcomes

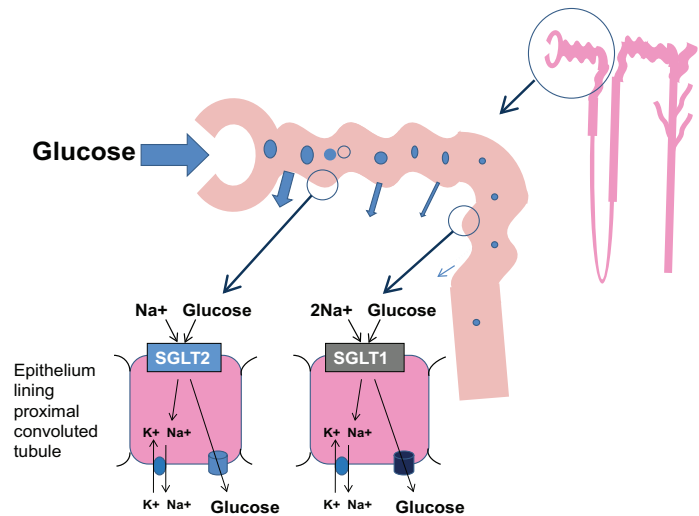
In clinical trials with an average baseline HbA1c of about 7.5-8.5%, SGLT2 inhibitors reduced HbA1c by 0.5-1.5% without inducing hypoglycaemia. This was accompanied by weight loss of 2-3kg, reflecting calorie loss via renal glucose excretion (loss of 80-85g glucose per day) with initial changes due to altered fluid balance plateauing at around 6 months.<sup>15</sup> SGLT2 inhibitor treatment induces an osmotic diuresis – voiding up to an extra 400ml/day, with unchanged natriuria – and a decrease in systolic blood pressure (2-5mmHg).<sup>15</sup>

## SGLT2 inhibitors and renal impairment

The ability of SGLT2 inhibitors to generate glycosuria is dependent on adequate renal filtration and an eGFR  $\geq 60$ ml/min/1.73m<sup>2</sup> or CrCl  $\geq 60$ ml/min. There are no data to indicate that renal impairment produces consequential toxic levels of active drug and/or metabolites and SGLT2 inhibitors may be prescribed in mild renal impairment (see Table 1). Consistently

**FIGURE 1: SGLT MEDIATED GLUCOSE EXCRETION IN THE RENAL TUBULE**

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**TABLE 1: PRIORITISATION IN THE PRESCRIPTION PROCESS**

Desired clinical outcome	HbA1c, decreased BP, calorie considerations (weight loss)
Patient situation	Compliance to medications, tablet burden, lifestyle, co-morbidities
Susceptibility to genitourinary infection	Age, mental state, hygiene, previous medical history
Interactions	Consider patient's prescription against Table 2
Blood pressure	Is the patient at risk of a non-synergistic SGLT2i induced drop?
Renal function	Monitor prior to commencing SGLT2i (eGFR $> 60$ ml/min) and at least annually thereafter; more frequently depending on the patient
Bloods	Particularly K <sup>+</sup> , haematocrit, HbA1c
Patient Counselling	Symptoms of acute volume depletion, UTIs, hypoglycaemia (if insulin secretagogue co-prescribed) Contact pharmacist before purchasing herbal products Take SGLT2i before breakfast
Black triangle drugs	Monitor for and report suspected adverse reactions to MHRA

slight increases in haematocrit have been detected. Due to enhanced diuresis, SGLT2 inhibitor treatment should be avoided in patients who are volume depleted/dehydrated (at chronic risk or acutely e.g. vomiting).<sup>12,13</sup>

## SGLT2 inhibitors and antihypertensive therapy

The diuretic effect of an SGLT2 inhibitor could be used synergistically with antihypertensive agents,

aiding further control of blood pressure and its complications. Caution should be exercised with the concomitant use of drugs affecting the renin, angiotensin and aldosterone system due to their effects on renal perfusion.<sup>16</sup>

All  $\beta$ -adrenoceptor antagonists – including, but to a lesser extent, the cardioselective  $\beta$ -adrenoceptor antagonists – effect carbohydrate metabolism and mask symptoms of hypoglycaemia (including tachycardia).<sup>16</sup> As SGLT2 inhibitors may be preferred in patients with frequent hypoglycaemic episodes, it may be inadvisable to co-prescribe these drugs.

### SGLT2 inhibitors and hepatic impairment

Although no dose adjustments are required in mild to moderate hepatic insufficiency, a 5mg dose of dapagliflozin could be prescribed in severe hepatic impairment, whereas canagliflozin would have to be stopped.

### SGLT2 inhibitors and genito-urinary infections

Due to the glycosuria, the incidence of genital mycotic infections is raised in patients taking an SGLT2 inhibitor. Patients with a history of infection are more susceptible; however, in clinical trials most infections were mild/moderate and responded to initial self treatment. Both vulvovaginal candidiasis (10.4-11.4% vs 3.2% in placebo [dose dependent]) and balanitis (3.7-4.2% vs 0.6% in placebo [dose dependent]) were reported with canagliflozin. Vulvovaginal candidiasis, balanitis and related genital infections were also reported with dapagliflozin (4.8% vs 0.9% in placebo).<sup>12,13</sup>

Urinary tract infections (UTIs) were slightly more common with dapagliflozin in trial patients (4.3% vs 3.7% in placebo). UTIs were similarly more common in trial patients taking canagliflozin (4.3-4.9% vs 4.0% in placebo [dose dependent]).<sup>12,13</sup> In both cases, the majority of infections were classed as being mild/moderate, responding to standard treatment and seldom necessitating SGLT2 inhibitor cessation.

When prescribing a SGLT2 inhibitor, patients should be made aware of the symptoms of genito-urinary infections so that they can self-treat when symptoms first appear and thus avoid fulminant expression. They should also be advised to consult their pharmacist before starting treatment if they have difficulty distinguishing between a UTI and genito-urinary infection.

### SGLT2 inhibitors and interactions

Drug interactions are often not mentioned; however, they are a vital consideration in the prescription process. Potentiating hypoglycaemia with insulin secretagogues is not discussed here, as this additive effect should be considered when optimising glycaemic control. Note,

**TABLE 2: INFORMATION SUMMARY INCLUDING INTERACTIONS**

Formulation	Dapagliflozin	Canagliflozin
Description	Yellow, film-coated, biconvex	White, film-coated, 17mm long
Strengths	5mg & 10mg tablets	100mg & 300mg caplets
Identification	5, 1427 on reverse - circular 10, 1428 on reverse - diamond	100, CFZ on reverse 300, CFZ on reverse
Dosing	10mg od (max), 5mg available	100mg od, 300mg od (max)
Half life	12.9hrs	10.6 - 13.1hrs
<b>Interactions</b>		
Diuretics	May add to diuretic effect of loops and thiazides; hypotension, dehydration. Monitor K <sup>+</sup> , particularly with K <sup>+</sup> sparing diuretics	
Insulin and its secretagogues	Increased risk of hypoglycaemia, monitor and alter doses/titrate accordingly	
Rifampicin (other UGT inducers: barbiturates, ritonavir, carbamazepine, St. John's wort)	22% decrease dapagliflozin AUC (drug exposure) with rifampicin, but no clinical effect on glycaemia	51% decrease canagliflozin AUC (drug exposure) with rifampicin, thus may reduce canagliflozin efficacy
Cholestyramine	Standard chelation based interaction impairing absorption	
Digoxin	No interaction of clinical significance	20% rise in digoxin AUC (drug exposure) and 36% rise in C <sub>max</sub> Avoid concomitant use
Renin, angiotensin & aldosterone modifiers	Monitor effect on renal perfusion and diuresis, K <sup>+</sup>	
CYP inducers eg phenytoin	Nil	Decreased exposure - reduces efficacy Avoid concomitant use
Herbal (UGT inhibitors: milk thistle, valerian)	Theoretical SGLT2i increase, but no data available	

however, that insulin secretagogue doses may have to be lowered when prescribing with a SGLT2 inhibitor, or at least up-titrated according to response.

Interactions for consideration include those with potassium sparing drugs and cytochrome (CYP) P450 isoenzyme inducers such as phenytoin. Special attention is warranted in the concomitant use of digoxin and canagliflozin (Table 2). Frequently discussed in isolation are coumarins; neither dapagliflozin nor canagliflozin had any effect on international normalised ratios (INR) with warfarin.

No studies have been conducted demonstrating the effects of herbal products on SGLT2 inhibitors'

plasma concentrations. *Silybum marianum* (milk thistle – for menopause) and *Valeriana officinalis* (valerian – for sleep aid) are hepatic glucuronosyltransferase (UGT) inhibitors, presenting a theoretical possibility of increased SGLT2 inhibitor plasma concentrations and thus further excess glucose excretion, potentially leading to hypoglycaemia. Nicotine is a UGT inducer, on which no studies have been conducted. These considerations are important as both dapagliflozin and canagliflozin are “black triangle” drugs; data are still being collected by the MHRA.<sup>16</sup>

### Patient counselling

All diabetic patients should be counselled on recognition and response to hypoglycaemic symptoms and the benefits of good glycaemic control reinforced.<sup>1</sup> When patients are prescribed a SGLT2 inhibitor, they should be made aware of the symptoms of UTIs and genital mycotic infections and advised to consult their pharmacist before commencing self-treatment, especially if they have difficulty distinguishing the symptoms. They should also be advised to discuss the purchase of herbal products with their pharmacist.

The SPCs advise taking a SGLT2 inhibitor before breakfast; however, the pharmacokinetic data suggest absorption is unaltered by food.<sup>12,13</sup>

### Other considerations

Considerations for older adults ( $\geq 65$  yrs) include increased risk of volume depletion, falls and raised susceptibility to UTIs. It may also be worth considering canagliflozin's increased affinity for SGLT1, potentially resulting in raised intestinal glucose levels in the presence of gut flora.

Tablet burden and compliance with treatment are of increasing concern with conditions requiring polypharmacy. Fixed dose combinations (FDC) should be considered; they are often no more costly than prescribing the individual drugs (provided that one drug is branded).<sup>4</sup> Marketing authorisation has recently been granted for FDCs of dapagliflozin plus metformin (Xigduo) and canagliflozin plus metformin (Vokanamet). If a patient has mostly once daily medications, a SGLT2 inhibitor may be a useful option instead of twice daily sulphonylureas, for example.

### Conclusion

SGLT2 inhibitors present a new, insulin independent treatment for hyperglycaemia in T2DM via a novel “glucuretic” mechanism that does not cause hypoglycaemia. This new class can be considered in patients either as monotherapy or as an adjunctive pharmacotherapy. These “black triangle” drugs additionally aid weight loss (3-5kg) and decrease systolic blood pressure (2-5mmHg). When prescribing a SGLT2 inhibitor, particular attention

## KEY POINTS

### Dapagliflozin and canagliflozin:

- 1 Have an insulin independent mechanism of action
- 2 Do not cause hypoglycaemia as monotherapy
- 3 Reduce HbA1c (0.5-1%), weight (2-3kg) and systolic blood pressure (2-4mmHg)
- 4 Cause a mild diuresis
- 5 Are contraindicated, due to reduced efficacy, in patients with eGFR  $< 60$  ml/min

should be given to renal function (eGFR  $\geq 60$  ml/min), risk of volume depletion and susceptibility to genitourinary infection.

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