

# Do we need another SGLT2 inhibitor?

Rachel Livingstone, Miles Fisher, Gerry McKay

The overall risk of cardiovascular disease is doubled in patients with type 2 diabetes and life expectancy is reduced by an average of seven years.<sup>1</sup> The high incidence of cardiovascular events associated with diabetes, including strokes and amputations, is a major cause of illness and an economic burden. There are multiple modifiable risk factors for cardiovascular disease in patients with type 2 diabetes, including hyperglycaemia, hypertension, dyslipidaemia, smoking and obesity, which combined contribute to increased morbidity and mortality.<sup>1</sup> There is good evidence in the real-world setting that a multifaceted approach to management improves patients' cardiovascular outcomes.<sup>2</sup> Management of glycaemia as part of this approach remains challenging despite numerous newer therapeutic options, and many patients still do not achieve optimal control (HbA<sub>1c</sub> <7.0% [53mmol/mol]). Many of the current treatments lose their effectiveness over time, partially due to progressive beta-cell dysfunction, meaning that patients often require multiple glucose-lowering medications and many eventually require insulin therapy, which is associated with weight gain and hypoglycaemia.

Several new classes of drugs have been introduced into routine clinical care in the last decade. When the first drug in class is launched there is interest in the mechanism of action. For subsequent members of the class the focus is more on comparative efficacy, safety and side effect profile. For example, rosiglitazone was launched as an insulin sensitiser and data for pioglitazone showed different effects on lipids and a better long-term cardiovascular safety profile. Sitagliptin was the first DPP-4 inhibitor, lowering blood glucose via the incretin effect. Of the subsequent members in the class the only clear difference is with linagliptin, which has a different route of excretion so does not require dose reduction in patients with renal impairment.

## SGLT2 inhibitors

Sodium glucose co-transporter 2 (SGLT2) inhibitors are a novel insulin-independent therapeutic option for patients with type 2 diabetes. They act by inhibiting SGLT2 in the kidneys, reducing the re-absorption of glucose in the proximal convoluted tubule and increasing glucose excretion in the urine. Weight reduction is a favourable outcome of SGLT2 inhibitor therapy, and the glucose excreted in the urine equates to a net loss of 200–300 calories per day. Another advantage of SGLT2 inhibitors is the observed reduction in systolic blood pressure which may be attributable to chronic osmotic diuresis, glycosuria causing an increase in 24-hour urine volumes of 107–400ml.<sup>3</sup> Dapagliflozin, canagliflozin and empagliflozin, which received licensing authorisation in 2014, are all licensed for use by the European Medicines Agency, and have been shown to be effective in glycaemic control. Given that they may also help modify other cardiovascular risk factors, including weight loss and blood pressure reduction, are there any appreciable differences among them or is it a class effect?

## Dapagliflozin

Dapagliflozin is an oral, selective SGLT2 inhibitor which has been the most widely studied. Pharmacokinetic and pharmacodynamic studies in various populations have demonstrated predictable dose-proportional parameters. Glycosuria is dose dependent and varies between 18–62g daily.<sup>4</sup> Plasma concentrations of dapagliflozin and its metabolites are incrementally increased by declining renal function. It has been shown that steady-state plasma concentrations of dapagliflozin were 4%, 6% and 9% higher in individuals with mild, moderate and severe renal impairment respectively compared to normal renal function.<sup>5</sup>

Dapagliflozin has shown to be beneficial as monotherapy for the management of type 2 diabetes with a significant reduction in HbA<sub>1c</sub> relative to placebo (-0.56%), a reduction similar to metformin monotherapy.<sup>6</sup> It also reduced fasting plasma glucose, an effect superior to that seen with metformin. Dapagliflozin has also been studied as add-on therapy to metformin, as well as to glimepiride, pioglitazone, sitagliptin and insulin, and significantly improved HbA<sub>1c</sub> by 0.5–0.7%.<sup>7</sup>

Dapagliflozin monotherapy resulted in a loss of 2.5kg in body weight compared to 1.2kg in metformin groups.<sup>7</sup> When used in combination or as additional therapy to other hypoglycaemic agents, dapagliflozin results in a similar favourable outcome on weight, and the combination of metformin and dapagliflozin has the greatest benefit (3.3kg).<sup>7</sup>

Dapagliflozin causes a reduction in systolic blood pressure of 2–9mmHg with no increase in the heart rate or increase in syncopal episodes. In a pooled analysis of 12 placebo controlled studies, treatment with 10mg daily of dapagliflozin resulted in a reduction in systolic blood pressure of 4.4mmHg and diastolic blood pressure of 0.5mmHg compared to placebo group at 24 weeks.<sup>3</sup>

No studies have demonstrated a significant improvement in lipid profile using dapagliflozin. A small increase in HDL cholesterol with dapagliflozin (1.8–4.4% compared with 0.4% placebo), and a small reduction in triglycerides (2.4–6.2% vs 2.1% with placebo) have been demonstrated. However, these improvements are likely to be related to the weight loss associated with therapy, rather than as a direct effect of dapagliflozin.<sup>8</sup>

Dapagliflozin is not recommended in moderate to severe renal impairment, end-stage renal disease or in patients receiving dialysis. This is not because of safety concerns but because of a lack of efficacy. A study into dapagliflozin and placebo in patients with moderate renal impairment (eGFR 30–59ml/min/1.73m<sup>2</sup>) showed no significant difference in HbA<sub>1c</sub> results between interventions. This, therefore, illustrates that the efficacy of SGLT2 inhibitors requires adequate filtered load of glucose through renal tubules.<sup>7</sup>

## Canagliflozin

Canagliflozin at both 100mg and 300mg daily dosing has been shown to achieve significant HbA<sub>1c</sub> reductions in comparison to placebo and to selected active comparators. As

monotherapy it demonstrated a reduction in HbA<sub>1c</sub> of 0.91% and 1.17% in 100mg and 300mg daily dosing respectively. It was also shown to significantly reduce fasting blood glucose as well as post-prandial glycaemic parameters.<sup>9</sup> The beneficial effect on post-prandial glucose may be related to delayed intestinal glucose absorption via SGLT1 inhibition in addition to renal glucose excretion via SGLT2 inhibition.

Canagliflozin 100mg in addition to metformin has been shown to be non-inferior to metformin and sitagliptin or glimepiride combinations. However, canagliflozin 300mg is superior to both combinations, with an additional reduction in HbA<sub>1c</sub> of 0.73%. Studies also demonstrated favourable outcomes as an add-on therapy to insulin, with an improvement in both fasting glucose levels and HbA<sub>1c</sub>.<sup>7</sup> Canagliflozin has also been studied in patients with stage 3 chronic kidney disease (eGFR >30 and <50ml/min/1.73m<sup>2</sup>). At both doses it was well tolerated and produced a lower but still significant reduction in HbA<sub>1c</sub> relative to placebo (0.3% and 0.41% in 100mg and 300mg respectively). These patients did, however, have increases in serum urea (6–9% vs 2%) and creatinine (9–10% vs 4%) compared to placebo which occurred in the first three weeks of treatment and returned to baseline over time.<sup>10</sup>

Canagliflozin monotherapy, both at 100 and 300mg doses, was associated with significant reduction in body weight from baseline compared with placebo (2.2% and 3.3% respectively). When used as add-on therapy, with metformin, sitagliptin and sulphonylurea individually, there was also a significant reduction in body weight. In addition to this, canagliflozin and insulin combination also resulted in weight reduction with 1.9kg and 2.4kg weight loss with 100 and 300mg respectively.<sup>7</sup>

Similarly, canagliflozin had positive effects on blood pressure, and this improved with the higher dose of canagliflozin. At 300mg daily of canagliflozin, there was a 5.1mmHg improvement in systolic blood pressure compared to sitagliptin, and this was sustained over time.

There are varying effects on lipid profile observed with canagliflozin. There was an increase in HDL levels relative to placebo, with mean percentage increases ranging from 0.8–6.8% with 100mg and 0.9–8.4% with 300mg daily. This improvement in HDL was statistically significant in comparison to placebo. Canagliflozin has also been demonstrated to increase LDL cholesterol levels, and it has been suggested that this could be an increase of up to 8.15mg/dl (0.21mmol/L) in LDL cholesterol with 300mg daily of canagliflozin. This increase in LDL cholesterol could translate into a 4–5% increase in the incidence of major cardiovascular events over a five-year period. This estimate assumes that other cardiovascular risk factors remain stable over five years, whereas canagliflozin has beneficial effects on blood pressure, weight loss, glycaemic control and increases in HDL cholesterol and this may counteract the changes in LDL cholesterol.<sup>7</sup> Some studies also reported reductions in fasting triglyceride levels; however, the difference was small and often not significant.

### Empagliflozin

Empagliflozin is a potent and selective SGLT2 inhibitor. In pre-clinical studies, empagliflozin was shown to have the highest selectivity for SGLT2 over SGLT1 (>2500 fold), followed by dapagliflozin (>1200 fold) and canagliflozin

(>250 fold).<sup>11</sup> Studies are ongoing but results so far have been promising, and it has been studied as monotherapy, and as-add on therapy to metformin and other oral agents as well as insulin. Empagliflozin significantly decreased HbA<sub>1c</sub> (-0.72%), fasting plasma glucose and body weight (-1.2kg) relative to placebo in patients with type 2 diabetes. In patients with inadequate diabetes control on oral hypoglycaemic agents or insulin, the addition of empagliflozin was shown to have statistically significant reductions in HbA<sub>1c</sub> (0.65% and 0.6% respectively).<sup>7</sup> Additionally, empagliflozin significantly reduced mean daily blood glucose levels, body weight, and systolic blood pressure. The weight loss effects are superior to those seen with metformin and sitagliptin, and mean weight reduction for empagliflozin is 2.1kg vs 0.9kg with metformin.<sup>12</sup> The reduction in systolic blood pressure was significant in comparison to placebo, and a greater reduction was seen in hypertensive patients (>140mmHg systolic). The average reduction in systolic blood pressure was 2.6mmHg and 3.3mmHg with 10mg and 25mg empagliflozin respectively. There was no associated increase in heart rate and the changes in blood pressure did not correlate with weight loss or glycaemic improvement, thus suggesting that the antihypertensive effects of empagliflozin are independent of its ability to cause weight loss and improve glycaemic control.<sup>13</sup>

### Summary

SGLT2 inhibitors have been shown to have benefits on glycaemic control, as well as on cardiovascular risk factors including weight loss, blood pressure reduction and some effects on lipid profile. They can be used in addition to other oral hypoglycaemic agents, or in addition to insulin, and the main side effects are genital mycotic infections and urinary tract infection, which can be easily treated with conventional treatment and respond well to this. Although there are slight differences in the licences for each drug, from current available data there are no clear clinical differences in the class among the three available drugs. Direct head-to-head comparisons are lacking, so it is unknown at present if slight changes in selectivity will translate into differences in efficacy, safety or side effect profile. Longer-term data and cardiovascular outcomes are awaited. Several other SGLT2 inhibitors are in development, and it is hard to see any major clinical differences emerging with these newer drugs, so at present we have no great need for another SGLT2 inhibitor.

**Rachel Livingstone**,<sup>1</sup> BScMedSci (Hons), MB ChB, MRCP(UK), Core Medical Trainee

**Miles Fisher**,<sup>1</sup> MD, FRCP, Consultant Physician

**Gerry McKay**,<sup>1</sup> BSc (Hons), FRCP, Consultant Physician  
<sup>1</sup>Glasgow Royal Infirmary, Glasgow, UK

### Declaration of interests

Professor Fisher has received honoraria for talks and advisory work from AstraZeneca/Bristol-Myers Squibb, Janssen and Boehringer/Lilly. Professor McKay has received honoraria for talks and advisory work from AstraZeneca/Bristol-Myers Squibb and Boehringer/Lilly.

### References

References are available at [www.practicaldiabetes.com](http://www.practicaldiabetes.com).

## References

1. National Institute for Health and Care Excellence. Type 2 diabetes. National clinical guideline for management in primary and secondary care (update). July 2014. [www.nice.org.uk/guidance/cg87/resources/cg66-type-2-diabetes-full-guideline2](http://www.nice.org.uk/guidance/cg87/resources/cg66-type-2-diabetes-full-guideline2) [accessed 2 February 2015].
2. Gaede P, et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;358:580–91.
3. Sjoström D, et al. Pilot analysis of the effect of the SGLT2 inhibitor dapagliflozin on blood pressure in patients with type 2 diabetes mellitus: a pooled analysis of placebo controlled trials. *Eur Heart J* 2012;33:S680.
4. Kasichayanula S, et al. Clinical pharmacokinetics and pharmacodynamics of dapagliflozin, a selective inhibitor of sodium-glucose co-transporter type 2. *Clin Pharmacokinetics* 2014;53:17–27.
5. Kasichayanula S, et al. The influence of kidney function on dapagliflozin exposure, metabolism and pharmacodynamics in healthy subjects and in patients with type 2 diabetes mellitus. *Br J Clin Pharmacol* 2013;76:432–44.
6. List JF, et al. Sodium-glucose co-transport inhibition with dapagliflozin in type 2 diabetes. *Diabetes Care* 2009;4:650–7.
7. Hasan F, et al. SGLT2 inhibitors in the treatment of type 2 diabetes. *Diabetes Res Clin Pract* 2014;104:297–322.
8. Food and Drug Administration. FDA Briefing Document NDA 202293. Dapagliflozin tablets 5 and 10mg. In: DoMae Products (ed). Silver Spring: FDA, 2011.
9. Stenlof K, et al. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes mellitus inadequately controlled by diet and exercise. *Diabetes Obes Metab* 2013;12:1232–8.
10. Yale F, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab* 2013;5:463–73.
11. Seman L, et al. Empagliflozin (B110773), a potent and selective SGLT2 inhibitor, induces dose dependant glycosuria in healthy subjects. *Clin Pharmacol Drug Dev* 2013;2:152–61.
12. Ferrannini E, et al. Long term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel group, randomised, 78 week open label extension study in patients with type 2 diabetes. *Diabetes Care* 2013;12:4015–21.
13. Hach T, et al. The sodium glucose co-transporter-2 (SGLT2) inhibitor empagliflozin lowers blood pressure independent of weight or HbA<sub>1c</sub> change. *Diabetologia* 2012;55:S317.