Canagliflozin: SGLT2 inhibitor for treating type 2 diabetes

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Canagliflozin is a sodium-glucose transporter protein inhibitor under development for the treatment of type 2 diabetes mellitus; it reduces circulatory glucose by facilitating its urinary excretion. In this Drug profile, Richard Donnelly discusses the need for drugs with a mode of action independent of insulin and considers the efficacy and tolerability of canagliflozin in clinical trials, to date, as well as its potential place in management.

Type 2 diabetes (T2DM) is increasing in prevalence: over 2.6 million people are affected in the UK alone,[1] and global predictions from the International Diabetes Federation estimate there will be >0.5 billion patients with diabetes worldwide by the year 2030. Furthermore, two-thirds of these patients will die prematurely from cardiovascular (CV) complications.[2]

T2DM now accounts for 95% of diabetes, which is increasingly diagnosed at an earlier age and, on average, reduces life expectancy by at least 10–15 years.[2,3] Thus, the goal of treatment is to reduce CV risk and the morbidity associated with microvascular complications via reductions in blood pressure, glucose and lipids.[4]

Existing antihyperglycaemic drugs work primarily either by improving beta-cell secretion of insulin (*eg* sulfonylureas and the new incretin agents) or by improving peripheral and hepatic insulin sensitivity (*eg* metformin and pioglitazone). Ancillary mechanisms, *eg* promoting satiety and decreasing glucagon release (incretin-based drugs), may also contribute to the antihyperglycaemic effects. More recently, however, the role of the kidney in glucose homeostasis and as a therapeutic target has received considerable attention.[5]

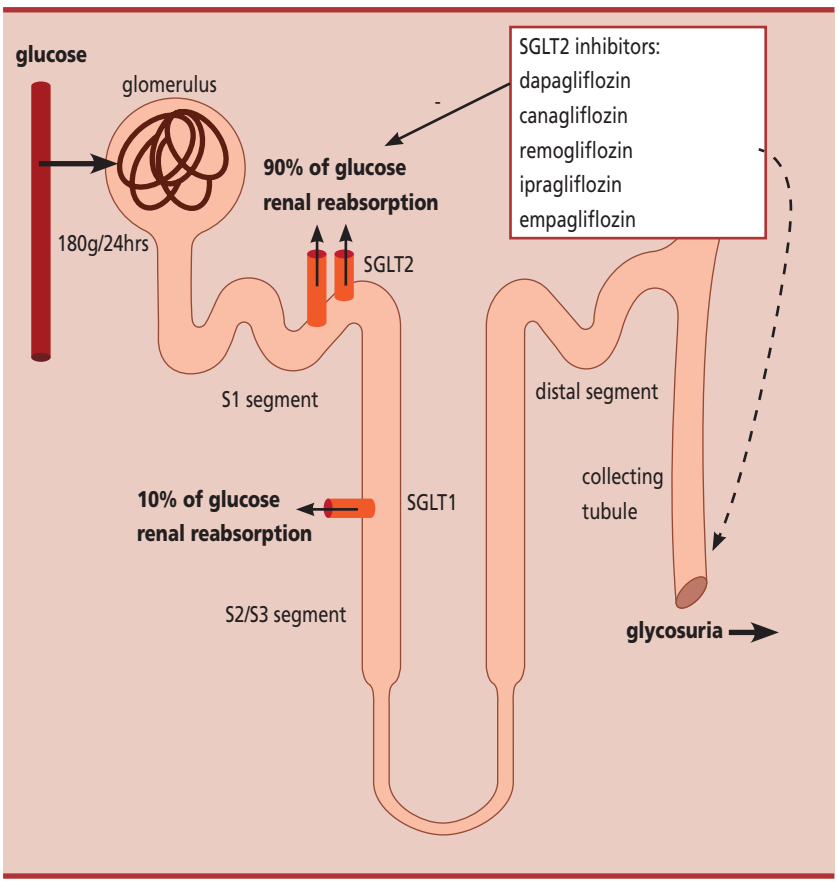

Figure 1. Glucose reabsorption from the kidneys is mediated by SGLT2 (90%) and SGLT1 (10%); inhibitors of SGLT2 lower RTG and increase urinary glucose excretion, therefore reducing circulatory glucose levels

Sodium-glucose co-transporters

In healthy individuals, glucose is filtered at the glomerulus but entirely reabsorbed into the circulation in the proximal renal tubule via sodium-coupled and glucose transporters (see Figure 1). Only at higher plasma glucose concentrations (*eg* >11mmol/litre) does the reabsorption pathway become saturated and glucose is then excreted in the urine.

There is inter-individual variability in the renal threshold for

glucose excretion (RTG), but in T2DM there seems to be an up-regulation of glucose reabsorption in the proximal tubule. The maximal transport rate for glucose is approximately 300mg/min for healthy subjects but up to 20% higher in patients with poorly controlled T2DM.[5]

Six sodium-glucose co-transporters have been identified in the kidney (SGLT1–SGLT6). SGLT2 is a low-affinity high-capacity transporter expressed mainly in the early (S1) segment of the proximal renal tubule and mediates most (90%) of the glucose reabsorption in the kidneys. SGLT1 is expressed in the small intestine and the distal (S3) segment of the proximal tubule where it accounts for <10% of glucose reabsorption (see Figure 1).

Inhibitors of the SGLT2 transporter therefore lower RTG, increase urinary glucose excretion, reduce circulating glucose levels and potentially facilitate weight loss via urinary excretion of calories (1g of glucose = 4kcal).[6]

Thus, SGLT2 inhibitors provide a novel insulin-independent mode of action for the treatment of T2DM. Interestingly, there is no reason why these drugs might not be equally effective in patients with type 1 diabetes as an adjunct to insulin therapy, but to date (largely because of commercial reasons) the clinical trials of SGLT2 inhibitors have been conducted exclusively in patients with T2DM.

Canagliflozin

Canagliflozin is a potent selective once-daily orally-administered SGLT2 inhibitor.[7] Clinical studies with canagliflozin have shown dose-dependent reductions in RTG in healthy subjects[8] and significant reductions in HbA_{1c} and body weight in patients with T2DM.[9,10]

For example, in a 12-week double-blind placebo-controlled active-comparator study in 451 patients with T2DM and suboptimal control on metformin (HbA_{1c} 7.6–8%), addition of canagliflozin 300mg once daily produced baseline-corrected reductions in HbA_{1c} of -0.92% compared with -0.22% for placebo and -0.74% with addition of sitagliptin 100mg once daily (see Figure 1).[9] Body weight was reduced by 2.3kg in the canagliflozin group, and there were very few instances of hypoglycaemia.

Canagliflozin is effective either as monotherapy[10] or in combination with other antihyperglycaemic drugs including insulin.[11] In a systematic review, the effects of canagliflozin on HbA_{1c} and body weight were comparable to those of dapagliflozin (Forxiga).[12] Furthermore, treatment with canagliflozin is associated with small but consistent reductions in systolic and diastolic blood pressure, *eg* 6/2mmHg.[13]

Because the rate of urinary glucose excretion is proportional to the glomerular filtration rate (GFR), as well as the circulating glucose concentration, the glucose-lowering efficacy of SGLT2 inhibitors would be expected to be less in patients with renal impairment. In a randomised double-blind placebo-controlled trial in 269 patients with T2DM and stage 3 chronic kidney disease (eGFR ≥30 and <50ml/min/1.73m^2), canagliflozin 100mg and 300mg produced HbA_{1c} reductions (baseline corrected) respectively of -0.33% and -0.44% after 26 weeks, compared with placebo (-0.03%).[13]

Thus, canagliflozin shows moderate but sustained efficacy even in patients with moderately impaired renal function (eGFR in the range 30–50ml/min/1.73m^2). In contrast, the European licence

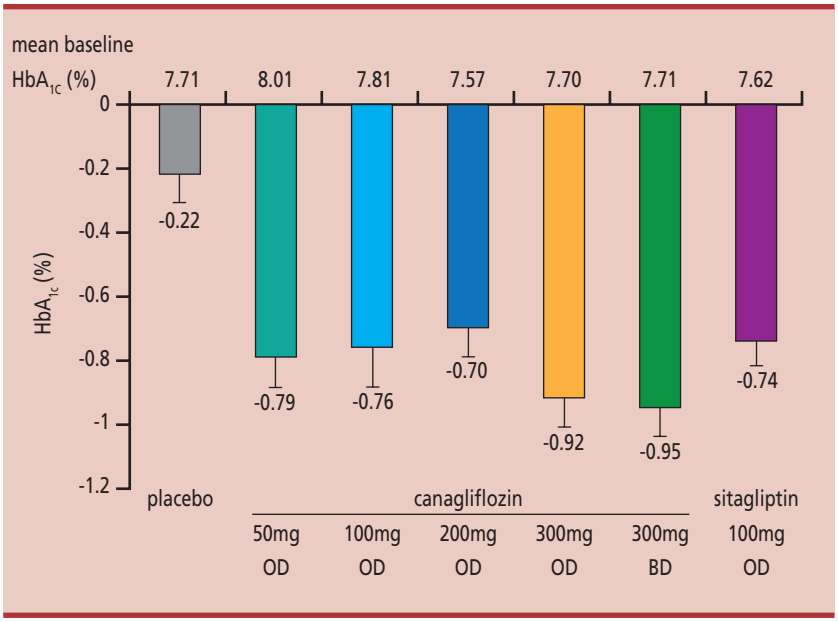

Figure 2. Reduction of HbA_{1c} from baseline at 12 weeks in patients with T2DM on metformin with the addition of either placebo, canagliflozin or sitagliptin[9]

for dapagliflozin restricts its use to patients with an eGFR >60ml/min/1.73m^2.

The major side-effect to emerge with canagliflozin and other SGLT2 inhibitors is an increase in genital mycotic infections (balanitis in men and vulvovaginal candidiasis in women). Genital infections were reported in 13–25% of female subjects across several canagliflozin treatment groups (*vs* 3% of women on placebo),[9] and these were mostly mycotic infections and vulvovaginal candidiasis.

In some trials, there has been a small increase in urinary tract infections, together with symptoms of headache and symptoms suggestive of hypovolaemia (*eg* postural dizziness or orthostatic hypotension).[9,13] The emerging profile of canagliflozin is summarised in Tables 1 and 2.

Likely place in the treatment algorithm

Following the experience with rosiglitazone – *ie* HbA_{1c} was reduced but it later transpired that mortality from CV disease was increased – regulatory authorities have rightly demanded greater evidence of CV safety at the time of licensing new treatments for T2DM.

The CANVAS trial (CANagliflozin cardioVascular Assessment Study) is a major CV outcome study that is ongoing. The study will evaluate the effects of canagliflozin compared to placebo on CV events including CV death, myocardial infarction and stroke in patients with T2DM in whom HbA_{1c} is not well controlled at the beginning of the study and who have a history of previous CV events or, by virtue of co-existing risk factors, are at high CV risk. The study duration for individual patients may be up to nine years (clinicalTrials.gov/show/NCT01032629).

- reduction in body weight
- modest but significant BP-lowering
- no significant changes in plasma electrolytes
- small increase in haematocrit and reduction in serum uric acid levels

Table 1. Nonglycaemic effects of canagliflozin

Although there are clinical trials in progress to demonstrate the efficacy and safety of canagliflozin in a wide range of patients with T2DM, *eg* those with newly diagnosed diabetes as well as those on dual or triple therapy or insulin, it is likely that the clinical and cost-effectiveness of the drug will be greatest in obese patients with high CV risk. Reductions in blood pressure, body weight and HbA_{1c} may have a favourable overall effect on CV risk.

Thus, at least initially, I suspect that canagliflozin will be used as add-on to metformin or dual (metformin plus sulphonylurea) therapy, or in combination with insulin, in patients who are obese and failing to achieve HbA_{1c} goals.

References

1. Diabetes UK. *Diabetes in the UK: key statistics on diabetes*. www.diabetes.org.uk/documents/reports.
2. Ford ES. *Diabetes Care* 2011;34:1337–43.
3. The Emerging Risk Factors collaboration. *NEJM* 2011;364:829–41.
4. Preiss D, *et al. Br Med J* 2011;343:d4243.
5. DeFronzo RA, *et al. Diab Obes Metab* 2012;14:5–14.
6. Chen LH, *et al. Diab Obes Metab* 2013;15(5):392–402.
7. Nomura S, *et al. J Med Chem* 2010;53:6355–60.
8. Sha S, *et al. Diab Obes Metab* 2011;13:669–72.
9. Rosenstock J, *et al. Diabetes Care* 2012;35:1232–8.
10. Stenlof K, *et al. Diabetologia* 2012;55 (Suppl. 1):S312–3.
11. Devineni D, *et al. Diab Obes Metab* 2012;4: 539–45.
12. Clar C, *et al. BMJ Open* 2012;2:e001007.
13. Yale J-F, *et al. Diab Obes Metab* 2013;15(5):463–73.

Declaration of interests

Richard Donnelly has received speaker fees and honoraria from several pharmaceutical companies including Janssen.

Glucose-lowering effect
- versatile (mono or combination therapy, including insulin)
- prevention of micro- and macrovascular complication (CANVAS CV outcome trial)
- decrease in glucotoxicity
- modest but reduced efficacy in patients with stage 3 CKD (eGFR 30-50ml/min/1.73m^2)
- low risk of hypoglycaemia (urinary glucose excretion decreases as plasma glucose decreases).

Insulin-independent mode of action
- ability to work at all stages of T2DM
- combination with other classes of antihyperglycaemic drugs
- stable glycaemic control in combination with other drugs and insulin

Osmotic diuresis
- decrease in blood pressure, benefiting CV risk reduction

Loss of calories in the urine
- sustained weight loss
- mitigation of weight gain from other classes of antihyperglycaemic drugs

Table 2. Potential clinical benefits of canagliflozin