Gliflozin monotherapy for type 2 diabetes: a review of NICE Technology Appraisal 390

The marketplace for medications for type 2 diabetes is becoming crowded with the incorporation, in the last decade, of DPP-4 inhibitors, GLP-1 agonists and, lastly, SGLT2 inhibitors (SGLT2i). The potential market worldwide for these drugs is millions of people, and the pharmaceutical companies are understandably jostling for position. Due to the FDA requirement for post-licensing studies to assess cardiovascular safety for new diabetes medications, we know about the potential benefit of the newer drugs, and their side effects.

SGLT2i act on the sodium-glucose co-transporters in the proximal renal tubules to prevent glucose reabsorption and thus induce glycosuria. They do not cause hypoglycaemia. Due to their mechanism of action their efficacy declines with creatinine clearance. They should only be initiated in adults with type 2 diabetes with an eGFR >60mmol/mol. They result in an improvement in HbA1c at 24–26 weeks of between -4.3 and -12.8mmol/mol (-0.39 and -1.17%) compared to placebo.1 They reduce weight by 0.97–3.9kg over placebo,1 and reduce blood pressure (possibly due to their diuretic effect2,3) by 3.5–5.3/1.3–2.5mmHg.1

The SGLT2i are well tolerated. Their main side effect is of increased uro-genital infections, mostly in women. These respond adequately to conventional treatment and usually are one off. They also cause polyuria.

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The recommendations
This appraisal compared the differences between SGLT2i, and against other oral diabetes medications. The conclusions for this appraisal were based on a review of clinical and economic evidence from the pharmaceutical companies and an assessment group from the University of Warwick. The assessment group identified seven relevant trials, three of them in Japanese and/or Chinese populations. Mindful of application to the NHS, it is worth noting that most people in the trials were 50–60 years old, within five years of diabetes diagnosis, with an HbA1c of 59–68mmol/mol (7.5–8.4%), and BMI 25–34kg/m2.1

The committee concluded that:
• There is no cost-effective difference between SGLT2i. It was noted canagliflozin 300mg lowered HbA1c more than the others. This is postulated to be due to SGLT1 activity which decreases absorption of glucose in the gut.
• SGLT2i are cost-effective when compared to DPP-4 inhibitors. They are as effective (empagliflozin) or more effective (canagliflozin and dapagliflozin) in reducing HbA1c, and result in greater weight loss.
• SGLT2i are not cost-effective compared to sulphonylureas. There is no difference in HbA1c reduction, though there is greater weight loss.
• SGLT2i are not cost-effective compared to pioglitazone. They are less effective for HbA1c reduction, though more effective for weight loss.

Therefore the recommendations for monotherapy in type 2 diabetes are: metformin first, if not tolerated consider sulphonylureas or pioglitazone. If those are not suitable and a DPP-4 inhibitor is considered, an SGLT2i is an acceptable alternative.

The positives
We have had one post-licensing trial suggesting the benefit of SGLT2i. With great fanfare, in summer 2015, the EMPA-REG OUTCOME study6 was published, showing reductions in cardiovascular mortality (3.7% vs 5.9%), all-cause mortality (5.7% vs 8.3%) and hospitalisation for heart failure (2.7% vs 4.1%) in the empagliflozin group vs placebo. The latest EMPA-REG paper was published in June this year, suggesting slower progression of kidney disease and lower rates of clinically relevant renal events when empagliflozin instead of placebo was added to standard care.3

Whether this is an SGLT2i class effect or not remains to be seen.8,9 There are several trials comparing SGLT2 vs placebo that should shed light on the subject in the coming years. CANVAS, CANVAS-R and CREDENCE compare canagliflozin vs placebo; the primary endpoint being cardiovascular death and non-fatal myocardial infarction and stroke for the first, progression of albuminuria for the second, and progression of renal disease and death for the latter. The reports are expected between 2017 and 2019. Dapagliflozin is compared to placebo in the DECLARE trial; the primary endpoint is also cardiovascular death and non-fatal myocardial infarction or stroke, and the trial is due to report in 2019.

The negatives
There is an increased risk of euglycaemic diabetic ketoacidosis (DKA), with numerous cases published in the last two years.10,11 Most of the cases are in people with type 1 diabetes (an unlicensed indication for use), in patients
with impaired pancreatic function, or post-surgery. However, some of the patients who developed euglycaemic DKA had no identifiable risk factors, or they were on low carbohydrate diets. Ogawa and Sakaguchi propose that this is due to decreased plasma glucose resulting in decreased insulin secretion and stimulation of free fatty acids, leading to ketone bodies. Additionally, SGLT2i stimulate glucagon (though it is not known if this is directly or as a result of low insulin). Because of the severity of this condition and the challenge of diagnosing DKA in euglycaemic patients, it is something that deserves careful consideration. Following the alert, cessation of treatment in patients who have developed DKA or are at risk has been recommended.

There is an increased risk of thrush and uro-genital infections, particularly in women, that responds to conventional therapy. These can lead to delirium or require hospital admission. To prevent them and the effect of volume depletion it is advised to drink plenty when on gliflozins. This increased intake, together with the osmotic effect of excreted glucose, causes polyuria. This can impact on quality of life, particularly in patients with decreased mobility and risk of falls.

In people older than 75 years, there is similar efficacy although there is concern over the diuretic effect. The incidence of volume depletion-related adverse events was 4.9%, 8.7% and 2.6%, with canagliflozin 100 and 300mg and non-canagliflozin, respectively.

The SGLT2i have been on the European market only since November 2013 (dapagliflozin), January 2014 (canagliflozin) and August 2014 (empagliflozin) and there are potentially long-term complications or adverse reactions yet to be discovered. So far, no concerns of malignancy or pancreatitis have been reported. The recent 200% RR of foot amputations detected in the CANVAS study (canagliflozin vs placebo) — albeit 6 in 1000 vs 3 in 1000 — raises concern. It has been suggested that might be due to peripheral volume contraction because of a diuretic effect. The study has been authorised to continue since this has not been confirmed in the parallel CANVAS-R, but both the FDA and the EMA have issued alerts and have begun an independent review.

Summary
With any analysis of new diabetes drugs, there are scant outcome measures and HbA1c is used as a surrogate. We know that in people with diabetes, well-being is more than just a number and polypharmacy is an issue. Choosing a therapeutic agent is always a complex decision that needs to be individualised taking into account the specific comorbidities, lifestyle and patient preferences. It is good practice according to the General Medical Council, and also common sense, to involve the patient in the process of decision making. The excellent feedback from the patient representative on the NICE committee and the data from trials suggest that, given tolerability, posology, lack of hypoglycaemia and weight loss, this is a group of drugs that patients will be willing to try. But they also need to be told about the above-mentioned risks. Where the SGLT2i will fit in the overall treatment of type 2 diabetes remains to be seen; nonetheless, their availability as monotherapy is a positive addition to our armamentarium.

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Declaration of interests
There are no conflicts of interest declared.

References