CANVAS and EMPA-REG findings support cardiovascular safety of SGLT2 inhibitors

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In the last issue, David Morris provided a comprehensive overview of the three sodium–glucose co-transporter 2 (SGLT2) inhibitors in use in the UK (empagliflozin, canagliflozin and dapagliflozin; Morris, 2017; https://is.gd/morrisjdn). He described the cardiovascular (CV) and renal benefits seen in the EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial. Since writing his article, publication of the CANVAS (CANagliflozin cardioVascular Assessment Study) results has provided further evidence to address his query regarding whether the beneficial effect on CV outcomes and reduction in the incidence and progression of nephropathy may be a class effect.

SGLT2 inhibitors reduce the risk of heart failure and cardiovascular death

In 2008, the US Food and Drug Administration recommended that all new diabetes therapies should provide evidence that they do not cause an unacceptable increase in CV risk, i.e. they should be CV event-neutral. In 2012, the European Medicines Agency (EMA) followed suit (Schnell et al, 2016). The EMPA-REG OUTCOME trial (empagliflozin; Zinman et al, 2015) and now CANVAS (canagliflozin; Neal et al, 2017) not only show no increased CV risk; they also show that SGLT2 inhibitors can actually reduce the risk of heart failure and CV death.

The CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) trial, using real-world data from more than 300 000 patients across six countries, compared those recently initiated on a SGLT2 inhibitor (over 150 000 patients, with the majority prescribed canagliflozin and dapagliflozin) with those recently initiated onto another glucose-lowering medication (Kosiborod et al, 2017). SGLT2 inhibitors were associated with a 39% lower incidence of heart failure and a 51% lower rate of all-cause death. In addition to this – and in contrast to EMPA-REG and CANVAS – the majority of patients did not have established cardiovascular disease (CVD), so it appears that people with type 2 diabetes with or without established CVD may benefit from SGLT2 inhibitor therapy. These benefits are also seen in a remarkably short time (Kosiborod et al, 2017). Further evidence regarding dapagliflozin will be available when the DECLARE (Dapagliflozin Effect on CardiovascuLAR Events) trial reports in 2019.

As a class, SGLT2 inhibitors share several attractive features. They not only lower HbA_{1c}, they:

- Can facilitate weight loss.
- Produce a small reduction in blood pressure.
- Have low hypoglycaemia risk (as monotherapy or in combination with agents that in themselves have a low risk of hypoglycaemia), and so avoid the need for costly blood glucose monitoring.
- Do not require injection.
- Are taken once daily, which aids concordance.

They can be used as monotherapy or in combination with most other glucose-lowering agents, including insulin, in people at varying stages of type 2 diabetes. The additional CV and renal benefits suggest these agents may be very attractive indeed: "two (and more) for the price of one"!

CVD is the leading cause of morbidity and mortality in people with type 2 diabetes (Sarwar et al, 2010; Tancredi et al, 2015) so, justifiably, the focus has moved away from glucocentric management to a more holistic approach around reducing all risk factors for CVD. Indeed, there is little evidence to show that intensive glucose control reduces the risk of heart failure and CV-related death, and some evidence that it can be harmful (Udell et al, 2015) and increase heart failure admissions (Dormandy et al, 2005). Blood pressure and lipid control is thus just as important, if not more so, than HbA_{1c}. Using an agent that results in

"The EMPA-REG OUTCOME trial and CANVAS show that SGLT2 inhibitors can actually reduce the risk of heart failure and cardiovascular death. Caution is advised, however, as CANVAS and CANVAS-R showed increased risk for amputations."

HbA$_{1c}$ reduction as well as reducing CVD therefore makes sense in the management of type 2 diabetes.

Other class effects: increased amputation risk?

David's article discusses several other class effects: the increased risk of genital fungal infections and, to a lesser degree, urinary tract infections and the risk of diabetic ketoacidosis in vulnerable patients. However, the CANVAS trial results showed that the risk of lower limb amputation (particularly toes and mid-foot) was doubled in patients taking canagliflozin compared to the comparator (Neal et al, 2017). As the SGLT2 inhibitors seem to share many other features, will we see a similar problem arising with empagliflozin and dapagliflozin? There is no evidence so far to suggest this side-effect is common to all three drugs. Despite this, the EMA issued a recommendation that a warning be included in the prescribing information for all SGLT2 inhibitors that they may increase the risk of lower limb amputation (EMA, 2017).

In 2016, the US Food and Drug Administration issued a warning after the interim results from CANVAS and CANVAS-R showed the increased risk for amputations. There were 5.9 vs 2.8 amputations per 1000 patients in CANVAS, and 7.5 vs 4.2 amputations per 1000 in CANVAS-R (Neal et al, 2017). The larger number of amputations in the renal study should remind us that patients with renal disease have a higher risk of foot problems. The number of amputations overall, no matter what treatment they had, should reinforce the importance of ensuring all patients have a foot examination as part of their annual diabetes review and have access to podiatry and foot clinic services. Most importantly, patients should know how to look after their feet and how to access advice when they notice a problem.

Caution is advised

As healthcare professionals, we want to provide the best care for our patients. The SGLT2 inhibitors have many attractive features for patients (particularly the benefit of weight loss for those who are overweight and the low risk of hypoglycaemia for those who drive). Reducing CV events is a real plus. We do not want to cause harm, however, and the foot amputation issue should be taken into account when prescribing any SGLT2 inhibitor until, as the EMA concludes, more investigations are completed and hopefully confirm this is not a class effect.

All the above emphasises the importance of identifying appropriate treatments for individual patients; for example, a significant number of patients who developed diabetic ketoacidosis with SGLT2 agents had type 1 diabetes. These agents are licensed for people with type 2 diabetes only. A 2017 alert from the Medicines and Healthcare products Regulatory Agency about canagliflozin advised stopping it in people with lower extremity ulcers, osteomyelitis or gangrene. This sounds like good advice when prescribing any of the SGLT2 inhibitors.

As ever, making sure patients are well-informed, involved in choice of treatment, are aware of potential side-effects, and know where and when to get advice is essential. Healthcare professionals should also make use of the yellow card system to report concerns about medications. ■

Read more online

The SGLT2 inhibitors – where are we now?
Journal of Diabetes Nursing **21**: 162–7
Available at:
https://is.gd/morrisjdn

Real-world experience of SGLT2 inhibitors
Journal of Diabetes Nursing **20**: 314–8
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