The CANVAS trial programme raises more questions than answers

Miles Fisher

ow that we have the results of several cardiovascular outcomes trials, mandated by the US Food and Drug Administration (FDA), clear differences are starting to emerge among the different classes of newer antidiabetes drugs, and differences are also emerging within each class of antidiabetes drug.

The first three cardiovascular outcomes trials with DPP-4 inhibitors all demonstrated non-inferiority but not superiority for the primary composite outcome of MACE (major adverse coronary events, i.e. cardiovascular death, non-fatal myocardial infarction, non-fatal stroke; SAVOR, EXAMINE) or MACE plus hospitalisation for unstable angina (TECOS). Within the class, saxagliptin in SAVOR-TIMI51 and alogliptin in EXAMINE2 were associated with some increases in heart failure hospitalisation (HFH) that were not seen with sitagliptin in TECOS.3

Of the GLP-1 receptor agonists the results of the ELIXA trial were neutral,4 confirming non-inferiority for MACE but not superiority. By contrast, the LEADER trial with lixisenatide demonstrated significant reductions in MACE, with a significant reduction in cardiovascular deaths as a component of the primary composite endpoint, but no effect on HFH.5 For exenatide, the SUSTAIN-6 trial also demonstrated a significant reduction in MACE, with a significant reduction in strokes as a component of the composite.6

SGLT2 inhibitors and CANVAS

The results of the EMPA-REG OUTCOME cardiovascular outcome trial with empagliflozin, which demonstrated significant reductions in MACE, cardiovascular death, total mortality and HFH,7 have focused the attention of diabetologists and cardiologists on this newest class of antidiabetes drugs. Indeed, the reduction in heart failure has stimulated studies in patients with established heart failure including subjects without diabetes.8,9 The cardiovascular benefits in the CANVAS trial programme were not so clear cut as those in EMPA-REG OUTCOME, and important adverse events were observed.10 This may be disappointing compared to the results of EMPA-REG OUTCOME, but perhaps these results were not unexpected.

On the positive side, non-inferiority was confirmed and there was a statistically significant reduction in MACE with canagliflozin, with additional significant reductions in HFH. On the disappointing side, there were no statistically significant reductions in any of the components of the primary outcome, and nor was there a statistically significant reduction in total mortality. On the negative – and worrying – side, lower extremity amputations were increased with canagliflozin, including so-called minor and major amputations, and fractures were also increased.

Study designs

There were clear differences in the study design and statistical procedures between EMPA-REG OUTCOME and CANVAS that may explain some of the differences in the results. EMPA-REG OUTCOME randomised 7020 subjects in a 1–1–1 ratio to empagliflozin 10mg or empagliflozin 25mg or placebo, with a median duration of treatment of 2.6 years and a median observation time of 3.1 years. Some interim data from the trial were added to the results of the phase 3 development programme for the FDA new drug application, and the final analysis was of all the subjects in EMPA-REG OUTCOME. Overall, this was a straightforward study design and analysis.

For the CANVAS trial programme, a more complicated approach was adopted. CANVAS was initially set up as a cardiovascular outcomes trial with 4330 subjects randomised 1–1–1 to canagliflozin 100mg or 300mg, or placebo. Unmasked interim cardiovascular data from CANVAS were included in the data submitted to the FDA for approval. The original intention had been to keep the data blinded at the time of submission and to expand the CANVAS study by the addition of 14 000 further subjects.11 Instead, as the CANVAS data had been unblinded, a parallel study with 5813 subjects was established with a primary renal outcome and secondary cardiovascular outcomes (CANVAS-R).12 The cardiovascular results of CANVAS-R were then analysed jointly with CANVAS in an integrated cardiovascular analysis.

Although the subjects that were recruited to CANVAS and CANVAS-R were similar, the time that individuals were in the study was very different: CANVAS subjects were followed for 5.6 years and CANVAS-R for 2.1 years, with a mean follow up of 3.6 years. The combined trial programme was much smaller than had been previously intended, reducing statistical power, and we can only guess what the results for the components of the primary outcome or for cardiovascular death would have been with a larger study.

Amputations in the CANVAS trial programme

In the CANVAS trial programme, the risk of amputations was doubled in subjects treated with canagliflozin compared to placebo. This included minor amputations (toe or transmetatarsal) and major amputations (ankle, below knee, above knee). The highest risk of amputation was in subjects with previous amputation or with diagnosed peripheral vascular disease, but it was also doubled in subjects without a previous amputation and without a diagnosis of peripheral vascular disease. The CANVAS investigators report that the increase in amputations is a new
finding for which the mechanism is unknown. This increase in the CANVAS trial programme had already been the subject of safety warnings from the European Medicines Agency (EMA) and the FDA, and the knowledge that the increase is doubling of risk will mean that canagliflozin should be contraindicated in patients with previous amputation or peripheral vascular disease.

It is uncertain if other SGLT2 inhibitors have the same effect. Amputations were not specifically reported in the EMPA-REG OUTCOME trial. Amputations will have been recorded as serious adverse events, however, and it should be relatively easy to interrogate the EMPA-REG OUTCOME database for this information. Hopefully, ongoing cardiovascular trials with other SGLT2 inhibitors (DECLARE-TIMI with dapagliflozin, VERTIS CV with ertugliflozin) will report amputations in the main publication.

Fractures with canagliflozin
In the CANVAS trial programme, the rate of all fractures was significantly increased by 26%, and a similar, but non-significant, increase was seen in low trauma fractures. In comparison, the rate of fractures was similar with empagliflozin and placebo in EMPA-REG OUTCOME. On further analysis the increase in fractures was only seen in the CANVAS trial and not in CANVAS-R. The investigators acknowledge that an increase in fractures with canagliflozin has previously been demonstrated and comment that there is no clear explanation for the difference in fracture risk between the two trials. As mentioned previously, the time in the study was much longer for subjects in CANVAS than in CANVAS-R, and it may take a more prolonged exposure to canagliflozin to increase the risk of fractures.

Implications for clinical practice
The possible cardiovascular effects of canagliflozin in the CANVAS trial programme are similar to, but not identical to, the effects of empagliflozin in EMPA-REG OUTCOME. The adverse effects, however, are different and canagliflozin is associated with a doubling in the rate of amputations and an increase in fractures that was not seen with empagliflozin. These are important and serious outcomes, so it is difficult to think of a patient phenotype where the use of canagliflozin would be preferable to the use of empagliflozin. EMPA-REG OUTCOME included only subjects with established cardiovascular disease, whereas in the CANVAS trial programme a third of subjects was recruited on the basis of increased cardiovascular risk. The subgroup of subjects without cardiovascular disease in the CANVAS trial programme showed no reduction in MACE with canagliflozin, so even in this group of patients empagliflozin would seem to be a safer option.

Clinicians will need to consider if individual patients with previous amputations or peripheral vascular disease who are currently receiving canagliflozin should be switched to another SGLT2 inhibitor, or to a different drug class.

Conclusions
As health care professionals looking after people with type 2 diabetes, we should be extremely grateful to the American interventional cardiologist Steve Nissen. In 2007, he analysed the results of the rosiglitazone phase 3 development programme and concluded that rosiglitazone was associated with a significant increase in non-fatal myocardial infarctions and a non-significant increase in cardiovascular mortality. This controversial publication changed the safety requirements of the FDA and the EMA for new diabetes therapies, and as a consequence the phase 3 development programmes of new antidiabetes drugs have included patients at higher cardiovascular risk, who are much more representative of the general diabetes population, including older patients, patients with existing cardiovascular disease and patients with chronic kidney disease. For most new drugs this has also included a dedicated, randomised, controlled cardiovascular outcomes trial and, as we have seen, the results of these studies are profoundly changing clinical practice.

Miles Fisher, MD, FRCP
Consultant Physician, Glasgow Royal Infirmary, Honorary Professor, University of Glasgow, Glasgow, UK

Declaration of interests
Professor Fisher has received payment for lecturing and advisory board membership from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, MSD and Pfizer.

References