Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

ScriptSwitch™ Rapid Update 3 – August 2017

Type 2 diabetes: potential cardiovascular benefits with the SGLT2 inhibitor canagliflozin but with a greater risk of amputation

Following publication of similar evidence for empagliflozin, cardiovascular (CV) outcomes data for a second sodium-glucose co-transporter 2 (SGLT2) inhibitor, canagliflozin, have now been published in the CANVAS studies. Here, people with type 2 diabetes (T2D) at elevated risk of CV disease who were treated with canagliflozin had a 14% lower risk of CV events compared with those receiving placebo – a similar finding to that for empagliflozin, adding weight to CV benefits being a possible class effect of the SGLT2 inhibitors.

In this analysis canagliflozin was associated with an approximately doubled relative risk of lower limb amputation (primarily of the toe or metatarsal). To date this safety signal has only been reported for canagliflozin, although advice from the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) cautions the risk could apply to other SGLT2 inhibitors.

When considering the use of SGLT2 inhibitors, prescribers should also be aware other cautions relating to renal impairment (*efficacy of SGLT2 inhibitors is dependent on renal function*) and their use in patients at risk of volume depletion – both issues of greater concern in the aging patient. The MHRA has also issued safety advice on the risk of diabetic ketoacidosis.

Reference: Neal B, Perkovic V, Mahaffey KW *et al*. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017 Jun 12. doi: 10.1056/NEJMoa1611925

What do we know already?

- The SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) are a relatively new class of oral anti-diabetic agents. NICE has published guidance on their use as monotherapies (TA390) and combination therapies (TA315; TA336; TA418), and in May 2017, the NICE T2D guideline (NG28) was updated to state that SGLT2 inhibitors may be appropriate for some adults where metformin is contraindicated or not tolerated. The NICE algorithm for blood glucose lowering therapy has also been revised.
- Whilst CV morbidity and mortality are well-established risks of T2D, reductions in surrogate markers, such as HbA1c, do not necessarily translate into benefits for these important outcomes.
  - Up until recently, metformin was the only antidiabetic treatment known to improve CV and mortality outcomes in T2D, as demonstrated in the UKPDS 34 trial.
  - In 2015, the EMPA-REG OUTCOME study reported that patients treated with the SGLT2 inhibitor empagliflozin had a reduced risk of CV-related events versus placebo (a 14% relative risk reduction). The empagliflozin treatment group also had significantly lower rates of death from CV causes (a 38% relative risk reduction), hospitalisation for heart failure (35% reduction) and death from any cause (32% reduction). The observational CVD-REAL study has also recently reported lower risks of hospitalisation for heart failure and death from any cause in patients using SGLT2 inhibitors compared with other T2D medicines.
  - Regarding glucagon-like peptide-1 (GLP-1) mimetics, reductions in CV events have been reported for liraglutide (LEADER trial), but not for lixisenatide (ELIXA study). Three non-inferiority studies of 'gliptins (saxagliptin [SAVOR-TIMI 53], sitagliptin [TECOS] and alogliptin [EXAMINE]), did not show lowered rates of CV events. (*Also, see the August 2016 KINES covering the LEADER trial [Log-in required]*)

What does this evidence add?

- This latest analysis combines data from the CANVAS and CANVAS-R randomised placebo controlled studies of canagliflozin. Over a mean-follow-up of 188 weeks, compared with placebo, patients treated with canagliflozin had a 14% reduction in the primary outcome (*a composite of death from CV causes, nonfatal myocardial infarction [MI], or nonfatal stroke*). This is in line with the findings seen with empagliflozin in the EMPA-REG OUTCOME study. In contrast to empagliflozin, death from CV causes and death from any cause were not significantly different between canagliflozin and placebo-treated patients.
- There was a relative doubling in the risk of amputation in the canagliflozin group. This was expected, having previously been reported by the regulatory agencies whilst the CANVAS study was ongoing. The latest MHRA advice is to carefully monitor people taking canagliflozin who have risk factors for amputation, such as poor

control of diabetes and problems with the heart and blood vessels. The MHRA also recommends considering stopping canagliflozin if people develop foot complications, such as infection, skin ulcers, osteomyelitis or gangrene. People receiving an SGLT2 inhibitor should also be advised about the importance of routine foot care and adequate hydration.

Study details

- The CANVAS program, which comprised two sister trials, was designed to assess CV safety and efficacy of canagliflozin and to evaluate the balance of benefits with risks, such as genitourinary infection, diabetic ketoacidosis and fracture.
- CANVAS was initiated in December 2009 with the goal of showing CV safety during approval by the Food and Drug Administration (FDA). CANVAS-Renal (CANVAS-R) commenced in 2014 and was designed as a second CANVAS-like, double-blind placebo-controlled trial to be analysed jointly with CANVAS to meet a post-approval CV commitment to regulatory agencies.
- The 2 trials were conducted in 667 centres in 30 countries and were scheduled to close when at least 688 CV events had been observed and the last randomised participant had undergone ~78 weeks of follow-up.
- The primary goal of the CANVAS program was to test for the non-inferiority of canagliflozin *vs.* placebo with regards to CV safety. CV safety was to be shown if the upper boundary of the 95% confidence interval (CI) of the hazard ratio (HR) with canagliflozin as compared with placebo for the primary outcome (*defined below*) was less than 1.3, and superiority was to be shown if the upper boundary was less than 1.0.

Participants:

- The two trials involved a total of 10,142 participants (64.2% were men and 35.8% women) with T2D (glycated haemoglobin ≥ 7.0% and ≤ 10.5%).
- The mean age of participants was 63.3 years, the mean duration of diabetes was 13.5 years and the mean estimated glomerular filtration rate (eGFR) was 76.5 ml/min/1.73m^2. 65.6% of participants had a history of CV disease.

Intervention and comparison:

- Randomisation was undertaken centrally (web-based), with allocation concealment. Participants in CANVAS were randomly assigned in a 1:1:1 ratio to canagliflozin 100 mg, 300 mg or placebo. In CANVAS-R, participants were randomly assigned in a 1:1 ratio to canagliflozin 100 mg (with the option of increasing to 300 mg from week 13) or placebo. Use of drugs for glycaemic management or control of other risk factors was guided by best practice.

Outcomes and results:

- 9,734 (96%) participants completed the trials (i.e. were alive and could be assessed for safety and efficacy outcomes, or had died before final follow up.). Mean follow-up was 188.2 weeks; median follow up was 126.1 weeks. 29.2% of participants assigned canagliflozin and 29.9% assigned placebo discontinued their treatment prematurely.
- The primary outcome was a composite of death from CV causes, non-fatal MI, or non-fatal stroke. Secondary outcomes were death from any cause, death from CV causes, progression of albuminuria, and the composite of death from CV causes and hospitalisation for heart failure.
- Significantly fewer participants in the canagliflozin group than in the placebo group had a primary outcome event (26.9 *vs.* 31.5 participants with an event per 1,000 patient-years; HR 0.86, 95% CI: 0.75 to 0.97; p < 0.001 for non-inferiority [*the primary hypothesis test for this study*]; p = 0.02 for superiority). However, while each component of the primary outcome showed point estimates of effect suggesting benefit, the individual components did not reach statistical significance. Furthermore, superiority was not shown for death from any cause (p = 0.24); as such, estimates for other fatal secondary outcomes were not considered to be significant.
- Progression of albuminuria occurred less frequently among those assigned to canagliflozin *vs.* placebo (89.4 *vs.* 128.7 participants with an event per 1,000 patient-years; HR 0.73, 95% CI: 0.67 to 0.79). Regression of albuminuria also occurred more frequently among those assigned canagliflozin (HR 1.70, 95% CI: 1.51 to 1.91). Since most renal effects were based on changes in eGFR, more patient-oriented evidence is required to confirm the clinical significance of this effect – this is likely to be provided by the ongoing CREDENCE trial.
- Adverse effects leading to discontinuations did not differ between groups. In this analysis, adverse effects significantly more common in the canagliflozin group included: infections of the male genitalia (34.9 *vs.* 10.8 events per 1,000 patient years; p < 0.001); female genitalia (68.8 *vs.* 17.5; p < 0.001); volume depletion (26 *vs.* 18.5; p = 0.009); diuresis (34.5 *vs.* 13.3; p < 0.001); and fracture (15.4 *vs.* 11.9; p = 0.02). There was no increased risk of hypoglycaemia, hyperkalaemia, acute kidney injury, pancreatitis, malignancies or venous thromboembolism. Only a small number of events of diabetic ketoacidosis were observed (0.6 *vs.* 0.3 participants with an event per 1,000 patient-years; HR 2.33, 95% CI: 0.76 to 7.17).
- There was a higher risk of amputation of toes, feet or legs with canagliflozin than placebo (6.3 *vs.* 3.4 participants per 1,000 patient-years; p < 0.001; HR 1.97, 95% CI: 1.41 to 2.75), with 71% of affected patients having their highest amputation at the level of the toe or metatarsal.

Level of evidence: Level 1 (good quality patient-oriented evidence) according to SORT criteria.
Study funding: Trials sponsored by Janssen. MedErgy provided medical writing support, funded by the sponsor.