Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

ScriptSwitch™ Rapid Update 1 – March 2018

Type 2 diabetes: observational study investigates cardiovascular outcomes and amputation risks with sodium glucose co-transporter 2 inhibitors

Several randomised controlled trials (RCTs) have previously reported reductions in the risk of cardiovascular (CV) events with sodium-glucose co-transporter 2 (SGLT2) inhibitors. However, an analysis of two RCTs published last year also reported an approximate doubling in the risk of lower limb amputation with the SGLT2 inhibitor canagliflozin. The recently published EASEL* cohort study reports an association between treatment with an SGLT2 inhibitor and both of these outcomes within a real-world setting. In light of this additional evidence for an increased risk of amputation, it is perhaps an opportunity to reiterate recent advice about the need for careful foot care in patients receiving SGLT2 inhibitors.

Reference: Udell JA, Yuan A, Rush T *et al.* Cardiovascular Outcomes and Risks After Initiation of a Sodium Glucose Co-Transporter 2 Inhibitor: Results From the EASEL Population-Based Cohort Study Circulation. 2017. https://doi.org/10.1161/CIRCULATIONAHA.117.03122

**EASEL: Evidence for cArdiovascular outcomes with Sodium glucose co-transporter 2 inhibitors in the rEal worLd*

What do we know already?

- The SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) are a newer class of oral anti-diabetic agent that inhibit the reabsorbtion of glucose and sodium in the kidney, resulting in glycosuria and natriuresis. As well as effects on blood glucose (*circulating glycated haemoglobin reduced by about 0.7-1.0%*), SGLT2 inhibitors also exert other non-glycaemic effects, including blood pressure-lowering (*reductions of ~5 mmHg systolic and 2 mmHg diastolic*), weight loss (*~2-3 kilograms*), and reduced albuminuria (*~30-40% reductions*) (see *review*).
- In the NICE guideline on type 2 diabetes (T2D), SGLT2 inhibitors are an option:
    - for some adults if metformin is contraindicated or not tolerated
    - for first intensification of therapy in combination with metformin
    - for second intensification of therapy with metformin and either pioglitazone or a sulphonylurea.
- 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 outcomes. Up until recently, metformin was the only antidiabetic treatment known to improve CV and mortality outcomes, as demonstrated in the UKPDS 34 trial.
- In 2015, the EMPA-REG OUTCOME RCT reported a reduced risk of CV-related events in patients at high CV risk who received empagliflozin, and also lower rates of both CV-related and all-cause deaths (*see Oct-15 KINES*). Lower risks of hospitalisation for heart failure and death from any cause have been reported in CVD-REAL, an observational study of people using SGLT2 inhibitors compared with other T2D medicines.
- In 2017, analysis of CANVAS and CANVAS-R RCTs also reported a reduction in the risk of CV-events in patients receiving canagliflozin. However, treatment was associated with an approximately doubled risk of lower limb amputation (primarily of the toe or metatarsal) (*see Aug-17 KINES*). This led to additional warnings in the Summaries of Product Characteristics for SGLT2 inhibitors, and a safety update from the MHRA.

What does this evidence add?

- EASEL is the first population-based study to demonstrate a lower risk of major adverse CV events (MACE) in people with T2D with established cardiovascular disease (CVD) initiated on SGLT2 inhibitor therapy. It is also the first observational study to identify the higher risk (also approximately doubled [0.17 *vs.* 0.09 events per 100 person-years]) of lower limb amputation within clinical practice. Due to the low number of amputation events, it was not possible to derive risk estimates for the individual SGLT2 inhibitors.
- It has been hypothesised that reductions in hospitalisations for heart failure may, in part, relate to SGLT2 inhibitor effects on plasma volume contraction and weight loss. The EASEL investigators suggest this is supported by the attenuation of CV benefits seen in EASEL following discontinuation of SGLT2 inhibitors, with the haemodynamic and cardiometabolic effects of treatment being time-dependent and therefore potentially sensitive to prompt attenuation. They note the similarity to the early CV benefits seen in EMPA-REG OUTCOME and CANVAS trials.
- Limitations of this study include those inherent to observational studies, such as risk of residual bias. We note the study was funded by Janssen (the Marketing Authorisation Holder for canagliflozin), with Janssen employees listed amongst authors.

- MHRA advice recommends carefully monitoring people taking canagliflozin who have risk factors for amputation, such as poor control of diabetes and problems with the heart and blood vessels. Further, it suggests considering stopping canagliflozin if people develop foot complications, such as infection, skin ulcers, osteomyelitis or gangrene. All people receiving an SGLT2 inhibitor should be advised about the importance of routine foot care and adequate hydration.

Study details

Participants:

- EASEL was a population-based cohort study using data from the US Department of Defense Military Health System, which includes the records of about 10 million active or retired service personnel and dependents. It is regarded as being generally representative of many demographic and clinical characteristics of the US population.

Intervention and comparison:

- EASEL compared two comparator cohorts: adults aged 18 years or older with T2D and established CVD who, on top of standard care therapy (metformin), were:
    - new users of SGLT2 inhibitors, or
    - new users of non-SGLT2 inhibitors (*dipeptidyl peptidase-4 inhibitors, glucagon-like peptides-1 receptor agonists, thiazolidinediones, sulphonylureas, insulin and other anti-hyperglycaemic agents*)
- If a patient was a new user of both SGLT2 and non-SGLT2 agents, they would be classified as a SGLT2 inhibitor user, and the other therapy considered a baseline or concomitant therapy.
- First exposure (the index date) to one of the non-metformin antidiabetic drugs had to occur between Jan-13 and Mar-16, and be at least one year after the start of the observation of the patient in the database. Patients were followed from the index date to the outcome of interest, death, disenrollment or the last observation in the database. The median follow-up time was 1.6 years for the intention-to-treat (ITT) cohort and 0.67 years for the 'on-treatment' cohort (*this latter cohort included patients where the outcomes of interest were observed while exposed to the index therapy plus 7 days, to consider immediate biologic effects*).
- To reduce confounding, propensity score matching was used to match 12,269 new users of SGLT2 inhibitors to an equal number of new users of non-SGLT2 inhibitors; baseline characteristics of the matched groups were reported to be well balanced. Of patients using SGLT2 inhibitors, 7,333 (58.1%) were initiated on canagliflozin, 3,341 (26.4%) empagliflozin and 1,955 (15.5%) dapagliflozin.
- Among the matched cohort, the mean age was 65.8 years, 44.1% were female, the mean duration of T2D was 5.6 years and the mean duration of CVD was 4.4 years. Approximately 14.1% had a history of atrial fibrillation, 22.8% a history of congestive heart failure, 10.7% ischaemic stroke and 16.6% myocardial infarction (MI). At baseline, 80.7% were treated with metformin and 19.7% with insulin.

Outcomes and results:

- The primary outcome was a composite of all-cause mortality (ACM) and hospitalisation for heart failure (HHF). In addition, a composite of MACE incorporating ACM, nonfatal MI and nonfatal stroke, and a composite of MACE and HHF, as well as the individual components were evaluated.
- The incidence rate of the primary composite outcome (ACM and HHF) for patients in the ITT cohort was 1.73 *vs.* 3.01 per 100 person-years (Hazard Ratio [HR] 0.57, 95% Confidence Interval [CI] 0.50 to 0.65) among new users of SGLT2 inhibitors and non-SGLT2 inhibitors, respectively.
- Compared with non-SGLT2 inhibitors, initiation of an SGLT2 inhibitor was associated with a lower rate of ACM (1.29 *vs.* 2.26 events per 100 person-years; HR 0.57, 95% CI: 0.49 to 0.66; p < 0.0001) and HHF (0.51 *vs.* 0.9 events per 100 person-years; HR 0.57, 95% CI: 0.45 to 0.73; p < 0.0001).
- The events curves (*Figure 2 in the paper*) indicated that treatment benefit started early and persisted over the study period for the primary outcome, and ACM and HHF outcomes individually.
- The rate of MACE was also lower in patients newly initiated on an SGLT2 inhibitor compared with non-SGLT2 inhibitors (2.31 *vs.* 3.45 events per 100 person-years; HR 0.67; 95% CI: 0.60 to 0.75; p < 0.0001). The rate of the individual endpoints of nonfatal MI and nonfatal stroke were not significantly different. When ACM, nonfatal heart failure and atherothrombotic endpoints were considered in a single composite outcome, the rate of MACE and HHF was significantly lower among patients newly initiated on an SGLT2 inhibitor compared with non-SGLT2 inhibitor (2.72 *vs.* 4.11 per 100 person-years; HR 0.66; 95% CI:0.60 to 0.74; p < 0.0001).
- Treatment effects in the 'on-treatment' group were consistent with the findings of the ITT cohort.
- After excluding patients with a previous history of lower limb amputation, 53 new lower limb amputations were observed in the ITT cohort and 26 in the on-treatment cohort. The rate of lower limb amputation was approximately two-fold higher in the ITT cohort in patients following initiation of SGLT2 inhibitors *vs.* non-SGLT2 inhibitors (35 *vs.* 18 events; 0.17 *vs.* 0.09 events per 100 person-years; HR 1.99, 95% CI: 1.12 to 3.51; p = 0.018). The risk was similar in the on-treatment cohort with 17 *vs.* 9 events, respectively (0.14 *vs.* 0.07 events per 100 person-years; HR 2.01, 95% CI: 0.89 to 4.53; p = 0.09).

Level of evidence: Level 2 according to SORT criteria.
Study funding: Janssen R&D (*also involved in study design and analysis; employees listed amongst authors*).