Comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors: SGLT2 inhibitors in the real world

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Patients with type 2 diabetes (T2DM) are at high risk for the development of cardiovascular (CV) disease and premature death (1). Heart failure is a CV outcome whose association with diabetes is being increasingly recognised (2). Heart failure is not only a common complication of T2DM but is also associated with a very poor prognosis. The 5-year survival rate for people with T2DM that develop heart failure has been reported to be less than 25% (3). The results from two randomised clinical trials of glucose lowering medications belonging to the sodium-glucose co-transporter 2 (SGLT-2) inhibitor class which showed a reduction in CV events, especially those related to heart failure, in high risk vascular patients with T2DM have therefore been enthusiastically received (4,5). Evidence is now also available to suggest that SGLT-2 inhibitors may have similar effects outside of the clinical trial setting. Furthermore, this so called "real world" data infer a SGLT-2 inhibitor class effect for CV protection in patients with T2DM across a range of background CV disease risk.

The SGLT-2 receptor mediates high-capacity glucose uptake in the early proximal tubule, and SGLT2 inhibitors, through their ability to promote glycosuria, have been developed as glucose lowering medications (6). As well as having a glucose lowering effect, SGLT-2 inhibitors also reduce blood pressure, promote weight loss and reduce uric acid levels. In the landmark CV safety trial of empagliflozin (EMPA-REG OUTCOME trial), 7,020 T2DM patients at high risk for CV events were randomised to receive empagliflozin versus placebo (4). The primary composite outcome of the trial, death from CV causes, nonfatal myocardial infarction, or nonfatal stroke, occurred in 10.5% of empagliflozin and 12.1% of placebo treated patients when followed for 3.1 years (HR =0.86; 95% CI: 0.72–0.99, P=0.04). This reduction in the primary endpoint was mainly accounted for by lower rates of death from CV causes (HR =0.62; 95% CI: 0.49–0.77; P<0.001). Other important benefit seen in empagliflozin treated patients included reductions in the rate for death from any cause (HR =0.68; 95% CI: 0.57–0.82; P<0.001).

In a follow-up study that specifically focused on heart failure outcomes in EMPA-REG, empagliflozin versus placebo treated patients had a significantly lower risk of hospitalisation for heart failure (HR =0.65; 95% CI: 0.50–0.85; P=0.002) and the combined endpoint of hospitalisation for heart failure or CV death (HR =0.66; 95% CI: 0.55–0.79; P<0.001) (7). The risk in the primary CV endpoint and the heart failure outcomes in empagliflozin treated patients reported in EMPA-REG were consistently lower in subgroup analysis exploring the effects of age, renal function, blockers of the renin-angiotensin system, lipid

lowering medications, diuretics and the presence of absence of heart failure at baseline (4,7).

Another SGLT-2 inhibitor, canagliflozin, has subsequently reported similar results to EMPA-REG, in the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program which integrated the data from two randomised controlled trials involving a total of 10,142 T2DM patients at high CV risk followed for 188 weeks (5). Unlike the EMPA-REG trial, the CANVAS program also contained participants (33%) without established CV disease. The primary outcome, a composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke was reduced by 14% in canagliflozin versus placebo treated patients (HR =0.86; 95% CI: 0.75–0.97; P=0.02). A sensitivity analysis suggested that the reduction in the primary outcome seen with canagliflozin was consistent across a wide range of prespecified subgroups, including those with a history of CV disease (yes/no) and history of heart failure (yes/no). The only exceptions to this was a history of beta blocker and diuretic use where canagliflozin was not associated with a significant reduction in the primary endpoint of the trial in patients who were not prescribed these classes of medications. Hospitalisation for heart failure was also reduced by 33% (HR =0.67; 95% CI: 0.52–0.87) and the combined endpoint of death from CV causes or hospitalisation for heart failure was reduced by 22% (HR =0.78; 95% CI: 0.67–0.91) in canagliflozin versus placebo treated patients, respectively.

The mechanisms explaining the improved CV outcomes for the above trials involving SGLT-2 inhibitors remain to be fully defined. Although SGLT-2 inhibitors improve HbA1c levels, and lower systolic blood pressure, weight, waist circumference and uric acid levels, other mechanisms are most likely responsible for the impressive CV protective effects of empagliflozin and canagliflozin. SGLT-2 inhibitors cause volume contraction from a sustained osmotic diuresis and natriuretic effect which could potentially play a prominent role in explaining the improved heart failure outcomes (6).

Other proposed mechanisms include a shift in cardiac fuel metabolism from fat and glucose oxidation to ketone bodies in SGLT-2 inhibitor treated patients. SGLT-2 inhibitors are known to increase ketone levels in the circulation and their use has been associated with the development of diabetic ketoacidosis. The mechanisms linking SGLT-2 inhibitors with increased circulating ketone body levels is not fully understood but may relate to alterations in the insulin to glucagon ratio and a decrease in the renal clearance of ketones bodies. As opposed to glucose or free fatty acids, ketones bodies are known to provide a more fuel efficient substrate for energy production which improves myocardial and most likely renal work efficiency and function (8,9).

The development and progression of chronic kidney disease (CKD) is a well-recognised risk factor for CV disease (10). SGLT-2 inhibitors have been shown to reduce albuminuria, glomerular filtration loss and progression to end-stage kidney disease (ESRD) (4,5,11). Whilst these benefits related to CKD may contribute to a reduction in CV disease in the long term, other factors most likely account for the relatively rapid separation in CV event rates seen, at least, for empagliflozin and placebo treated patients in the EMPA-REG trial (7).

Very recent studies have suggested that novel and direct cardiac effects of SGLT-2 inhibitors may in part explain their rapid CV protective effects. One study has shown that SGLT-2 inhibitors have favourable effects on ventricular repolarization heterogeneity which has previously been shown to be a predictor of CV mortality in T2DM (12). Furthermore, it has been suggested that SGLT-2 inhibitors may play a role in modulating sympathetic tone as the volume contraction induced by this class of medication is not accompanied by an increase in pulse rate. Indeed, in an experimental animal model, SGLT-2 inhibition was associated with the attenuation of high fat diet induced elevations of the sympathetic neuron protein tyrosine hydroxylase and the neurotransmitter noradrenaline in the heart and kidney (13).

Studies examining the effects of SGLT-2 inhibitors in the "real world" setting strongly suggest that the CV benefits of this class of medication observed in randomised controlled trials will apply to a broad range of patients with T2DM seen in routine clinical practice. These "real-world" studies have used data collected from patient's health care records from an unselected T2DM populations with a broad risk of CV risk profiles to negate the well-acknowledged limitations of randomised clinical trials that relate to generalisability. The largest of these so called "real-world" studies relating to the use of SGLT-2 inhibitors is the Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors (CVD-REAL) study which was published this year in the July edition of *Circulation* (14).

In the above study, the outcome of hospitalisation for heart failure and all cause-death for patients newly initiated on a SGLT-2 inhibitor versus other glucose lowering

medications was compared using medical claims, primary care/hospital records and national records in the United States, Norway, Denmark, Sweden, Germany and the United Kingdom. Inclusion criteria included new users of SGLT-2 inhibitors or other glucose lowering medications, established T2DM on or prior to the index date, being greater than 18 years old and having greater than 1 year of historical data available prior to the index date to allow for adequate risk adjustment and to make sure that participants were newly initiated on a glucose lowering medication. The time for participants who were newly initiated on either an SGLT-2 inhibitor or another glucose lowering medication was set as the date of first prescription or pharmacy dispensation of the above medications. Patients were followed from the index date until the outcome date or the censoring date.

The primary aim of the study was to compare the risk of hospitalisation for heart failure in T2DM patients who were newly initiated on SGLT-2 inhibitors versus other glucose lowering medications. Secondary aims were to compare the risk of all-cause death and the combined endpoint of hospitalisation for heart failure and all-cause death between the two treatment groups. The investigators initially identified 1,392,254 T2DM patients that started a new glucose lowering medication. As expected the vast majority were started on non-SGLT-2 inhibitor medications (n=1,226,221) with a far smaller number starting on the newer SGLT-2 inhibitor class of medication (n=166,033).

A non-parsimonious propensity score was developed for 'being initiated on an SGLT-2 inhibitor' within each country to minimize confounding by indication. Patients in SGLT-2 inhibitor and other glucose lowering group were then matched 1:1 by propensity score. This manoeuvre resulted in a total of 154,528 patients being matched in each group. The majority of non SGLT-2 medications prescribed were accounted for by insulin (34%), DPP-4 inhibitors (17%), sulfonylureas (17%) and GLP-1 receptor agonist (14%). Overall the total exposure time of patients to canagliflozin and empagliflozin were balanced with <7% of total exposure attributable to empagliflozin, however it should be noted that there were differences in exposure time for the various SGLT-2 inhibitors according to the outcome examined, as discussed below.

The mean age of the study participants was 57 years, 44% were women, 13% had established CV disease, 67% received statins, 80% antihypertensive medications, 74% were on blocker of the renin-angiotensin system and 79% were on metformin. Incidence rates for hospitalisation for heart failure, all-cause death, and the composite endpoint of hospitalisation for heart failure and all-cause death were calculated separately within each country. Hazard ratios and 95% CI for all outcomes derived for SGLT-2 inhibitor versus other glucose lowering medication treatment groups within each country were calculated using Cox proportional hazards models with a time-to-first event analysis used for all outcomes.

The outcome of hospitalizations for heart failure analysis was conducted using patient data from Denmark, Germany, Norway, Sweden, United Kingdom and the United States, with 42% of patients taking dapagliflozin, 53% on canagliflozin and 6% on empagliflozin. Mean duration of follow-up was 239 days for the SGLT-2 inhibitor group and 211 days for the other glucose lowering medication group. Starting a SGLT-2 inhibitor compared with another class of glucose lowering mediation was associated with a 39% reduction in the rate of hospitalization for heart failure (HR =0.61; 95% CI: 0.51–0.73; P<0.001).

The analysis of all cause death was conducted using patient data only from Denmark, Norway, Sweden, United Kingdom and the United States (this information was not available for the German Registry), with 51.0% of patients taking dapagliflozin, 42.3% on canagliflozin and 6.7% on empagliflozin. Mean duration of follow-up was 271 days in the SGLT-2 inhibitor and 251 days in the other glucose lowering medication group. Starting a SGLT-2 inhibitor compared with another class of glucose lowering mediation was associated with a 51% reduction in death from any cause (HR =0.49; 95% CI: 0.41–0.57; P<0.001). The composite endpoint of hospitalization for heart failure and death from any cause was also significantly reduced by 46% in new SGLT-2 inhibitor users compared with other glucose lowering medications (HR =0.54; 95% CI: 0.48–0.60; P<0.001).

Similar results to the above were demonstrated after multivariate adjustment, including history of heart failure, age, sex, frailty, history of myocardial infarction, history of atrial fibrillation, hypertension, obesity/body mass index, duration of diabetes mellitus, use of renin-angiotensin system inhibitors, β-blocker or α-blocker use, calcium channel, blocker use, loop diuretic use and thiazide diuretic use. An analysis based on an intent-to-treat approach, and stepwise removal of specific classes of other glucose lowering medications, including thiazolidinedione, which can cause fluid retention, did not significantly alter the above hazard ratios (15). Comparisons within geographic regions also found similar results to those of the overall study.

The results of a number of secondary studies form CVD-REAL have also just been released. Preliminary data from an analysis examining the effects of the absence or presence of pre-existing CV disease at baseline has confirmed the observation that even in patients without a history of CV disease, starting a SGLT-2 inhibitor is associated with a significantly lower risk of all-cause death, hospitalisation for heart failure and the combined outcome of hospitalisation for heart failure or all-cause death compared to similar patients with newly initiated on other glucose lowering medications (16). Another substudy, CV-REAL Nordic, examined CV mortality in patients from Sweden, Denmark and Norway as these countries had detailed national registries that allowed assessment of the cause of death (17). Over a median follow up of 0.9 years, CV mortality was reduced by 47% in patients newly initiated on an SGLT-2 inhibitor compared with other glucose lowering medications (HR =0.53; 95% CI: 0.40–0.70; P<0.0001). A further study using the CVD-REAL Nordic database has also found that the new initiation of dapagliflozin was associated with a lower risk of CV events, hospitalisation for heart failure and all-cause mortality compared with DPP-4 inhibitors (18). Unfortunately, information regarding the types of DPP-4 inhibitors prescribed was not presented in the study. This is an important point because although DPP-4 inhibitors have generally been reported to have a neutral effect on CV outcomes, the use of saxagliptin has been implicated with an increased risk for developing heart failure (19).

Although consistent CV protective results have been reported with SGLT-2 inhibitor use in the above studies, it is pertinent to highlight the limitations of "real-world" data. Regardless of sophisticated attempts to balance study groups through propensity matching in CVD-REAL, investigators were not blinded and patients were not randomised, therefore the influence of residual, unmeasured confounding cannot be excluded. For example, could seeing a doctor who prescribes an SGLT-2 inhibitor rather than a different class glucose lowering medication have beneficial effect on a patient's health that cannot be accounted for given the CVD-REAL study design? The issue of channelling bias also needs to be considered. This is a form of allocation bias where drugs with similar therapeutic indications are prescribed to patients with different baseline characteristics. In other words, the potential association between medications and outcomes is masked or enhanced by disease severity or disease state. The large magnitude of the benefits seen with SGLT-2 inhibitors over such a short time period reported in the CVD-REAL studies may possibly be explained to some extent by channelling bias.

Additional limitations to consider include the fact that outcome data in CVD-REAL was not collected in a systematic fashion and events of interest were not adjudicated on by an independent committee. It is therefore possible that different definitions of hospitalisation for heart failure may have influenced the results of the CVD-REAL study. Furthermore, associations and not causality can only be inferred from this type of real-world study. Although mechanisms linking SGLT-2 inhibitor use with favourable CV outcomes together with the safety and side-effect profile associated with this class of medication were not addressed in CVD-REAL, these aspects of SGLT-2 inhibitor use have been the subject of numerous other publications.

Despite the above limitations, the CVD-REAL dataset provides important supportive information regarding the CV benefits of SGLT-2 inhibitors. The results of CVD-REAL need to be interpreted in the context that two randomised controlled trial have now been published that demonstrate that the use of empagliflozin and canagliflozin reduce CV events, especially those related heart failure in high risk T2DM vascular patients. The CVD-REAL results infer that the benefits reported in the above clinical trials may possibly be applicable to a broad population of patients with T2D with and without established CV disease in real-world practice. The CVD-REAL results also suggest that there is a class-effect for SGLT-2 inhibitors, at least for empagliflozin, canagliflozin and dapagliflozin. The results of the Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) trial which will examine CV related outcomes in T2DM patients with and without established CV disease randomised to dapagliflozin or placebo are expected to be released in 2019. It is expected that the positive CV outcomes associated with the use of dapagliflozin reported in the observation CV-REAL study will be confirmed in the interventional DECLARE-TIMI trial (NCT01730534).

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Footnote

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