Sodium-glucose cotransporter-2 inhibitors and cardiovascular outcomes: insights from the CVD-REAL study

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Cardiovascular disease remains the leading cause of mortality among patients with type 2 diabetes mellitus (1). The increased risk of cardiovascular morbidity and mortality in this patient population is not only caused by the increased blood glucose levels, but rather more due to the presence of other associated risk factors such as obesity, hypertension and dyslipidemia, also known as metabolic syndrome. This was proven when results from many studies revealed that the absolute glycemic control on its own is not associated with significant reduction in the risk of cardiovascular events (2-5).

A new class of antidiabetic medications, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, has recently gained popularity because of their potential favorable effect on reducing the risk of cardiovascular events in type 2 diabetic patients (6). This class of medications exerts their effect by inducing therapeutic glucosuria through blocking glucose reabsorption from the proximal tubules of the kidney (7), and thus is independent of the pancreatic beta-cell mass and insulin sensitivity (8-10). A recent large multicenter randomized trial, The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG Outcome Trial) showed reduction in the risk of the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke with empagliflozin compared to placebo (6). The most plausible explanation for such benefit is believed to be the reduction in the risk of heart failure hospitalization which was consistent in patients with and without baseline heart failure (11). The osmotic diuresis induced by SGLT-2 inhibitors results in significant extravascular more than intravascular electrolyte-free water clearance, with subsequent relief of volume overload without significant impact on the blood volume or tissue perfusion (12-14). This can also explain the favorable cardio-renal effects observed with empagliflozin in multiple studies (15-17). Other proposed theories for the reduction of heart failure with empagliflozin includes a potential beneficial effect on the metabolic syndrome through weight reduction (18,19), and modest reduction in systolic BP (13,16), as well and cardiac oxygen demand (20).

However, whether this beneficial effect is a class effect and if it implies to patients without established cardiovascular disease remained uncertain. Kosiborod *et al.* conducted a propensity-matched observational study using data from medical claims, primary care/hospital records, and national registries in six countries (The United States, Germany, Sweden, Norway, Denmark, and the United Kingdom), and including 309,056 patients newly initiated on either SGLT-2 inhibitors versus other glucose-lowering drugs (21). In this Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) study, the authors compared the risk of heart failure hospitalization, death, and the combined end-point of heart failure hospitalization or death between both groups. The study showed that treatment with SGLT-2 Inhibitors was

associated with lower risk of heart failure hospitalization, all-cause death as well as the composite of heart failure hospitalization and death (HR 0.61, 0.49 and 0.54, respectively), with no significant heterogeneity by country and with consistent results among multiple sensitivity analyses. The authors concluded that the favorable outcomes with the SGLT-2 inhibitor empagliflozin in the EMPA-REG Outcome Trial is likely to be a class effect and to extend to a broader diabetic patient population.

The strengths of the CVD-REAL study include being a real-world practice data with a well-conducted propensity score matching between both groups. Furthermore, the authors performed multiple sensitivity analyses within each country, for each outcome, as well as using an intent-to-treat analysis and after stepwise removal of other glucose lowering medications to confirm their primary results.

While the CVD-REAL study enriches the literature with extremely helpful information about the potential cardiovascular benefits of SGLT-2 inhibitors, its results should be cautiously interpreted and implemented into clinical practice. The design of the study depended on robust propensity score matching to eliminate potential bias, however in the absence of prospective randomization, the presence of confounding factors cannot be completely excluded. Furthermore, the accuracy of data collected in routine practice has always been a concern when interpreting the results of observational studies. While prospective randomized clinical trials utilize clear outcome definitions and data-reporting methodology to minimize potential sources of bias, retrospective observational studies rely on data collected in daily routine practice. The CVD-REAL study utilized the primary discharge diagnosis codes from administrative and electronic medical records to measure their pre-specified outcomes. In routine clinical practice, the primary admission or discharge diagnoses might be subjective based on the opinion of the admitting/discharging physician. This is clearly observed on daily basis especially in patients with heart failure who usually present with overlapping clinical diagnoses such as those with underlying pulmonary disease or renal disorder. Thus, utilizing diagnosis codes for measuring the outcomes in the CVD-REAL study is the best that can be obtained in observational studies, but might not be a representative of highly accurate data.

The CVD-REAL study represents real-world data and points towards class rather than a drug effect of SGLT-2 inhibitors on cardiovascular outcomes. Further randomized controlled trials are indicated to confirm these results before switching the practice towards using SGLT-2 inhibitors in the majority of diabetic patients. A meta-analysis evaluated the cardiovascular outcomes with SGLT-2 inhibitors versus placebo or active drugs and demonstrated no clear evidence that cardiovascular outcomes would differ with various types of this class (22). However, another meta-analysis including only placebo-controlled randomized clinical trials showed that the beneficial effect on all-cause mortality and cardiovascular mortality with SGLT-2 inhibitors was mainly derived by empagliflozin and specifically the EMPA-REG outcome trial, but was not observed with other SGLT-2 inhibitors, with even a suggestion of a potential harm with dapagliflozin, raising a concern that the benefits with empagliflozin may not be a class effect (23). The safety of SGLT-2 inhibitors is another area that requires further evaluation, especially after recent safety FDA announcements regarding an increased risk of leg and foot amputations with canagliflozin in the ongoing CANagliflozin cardioVascular Assessment Study (CANVAS) (24), as well as an increased risk of acute kidney injury associated with canagliflozin and dapagliflozin (25). Ongoing randomized controlled clinical trials on multiple drug types in this group should provide further insight on the safety and efficacy of SGLT-2 inhibitors (24,26,27).

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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