Empagliflozin and Heart Failure
What Can We Learn From EMPRISE?

The world of diabetes mellitus entered a new era when, in 2008, the US Food and Drug Administration guidance recommended rigorous evaluations of cardiovascular safety for new glucose-lowering therapies. The findings of the cardiovascular outcome trials (CVOTs) are now fueling a fundamental shift in the management of type 2 diabetes mellitus from the relatively narrow focus on glycemic control to a much broader paradigm of comprehensive cardiovascular risk reduction. This move is appropriate and, as evidenced by the results of the CVOTs, much needed because there are important differences across the classes of antihyperglycemic agents with regard to their cardiovascular effects.

The CVOTs with dipeptidyl peptidase-4 inhibitors revealed that although dipeptidyl peptidase-4 inhibitors are neutral for the outcome of major adverse cardiovascular events, they may in some cases increase the risk of hospitalization for heart failure (HHF). Conversely, several glucagon-like peptide 1 receptor analogs have demonstrated favorable effects on major adverse cardiovascular events, and one (liraglutide) had an effect on cardiovascular death. The sodium-glucose co-transporter 2 inhibitors (SGLT2is) have consistently demonstrated a significantly lower risk of HHF, and recently completed CVOTs have shown benefits with regard to the progression of chronic kidney disease. In the EMPA-REG OUTCOME study (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), patients with type 2 diabetes mellitus and known atherosclerotic cardiovascular disease were randomized to receive empagliflozin or placebo. It is important to point out that placebo implied active non-SGLT2i-based therapy to lower glucose, such that glycemic differences between groups could be minimized in an attempt to study the glucose-independent effects of the active therapy. Although EMPA-REG OUTCOME demonstrated a modest, but statistically significant, 14% relative risk reduction in major adverse cardiovascular events, there was a robust reduction in cardiovascular (38%) and all-cause (32%) mortality and a 35% reduction in HHF with empagliflozin. The mortality and heart failure benefits appeared early after treatment initiation and were observed regardless of a history of heart failure and across the spectrum of estimated glomerular filtration rate (≥30 mL·min⁻¹·1.73 m⁻²). Subsequent large CVOTs of 2 other SGLT2is, namely canagliflozin and dapagliflozin (the CANVAS Program [Canagliflozin Cardiovascular Assessment Study] and DECLARE-TIMI 58 study [Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events–Thrombolysis in Myocardial Infarction 58], respectively), confirmed the heart failure prevention benefits of SGLT2is as a class in a broader population of patients with and without established atherosclerotic cardiovascular disease. Nonetheless, questions remain about the effect of SGLT2is in the much broader, truly primary prevention...
population without established atherosclerotic cardiovascular disease, because even the most representative randomized controlled trials (RCTs) use stringent inclusion and exclusion criteria, and their external validity and applicability to routine clinical practice are limited.

In this regard, the emergence of real-world evidence (RWE) studies that can answer a variety of clinically relevant questions using the data collected via the natural course of clinical care from a variety of sources (medical claims, registries, and electronic health records) has the potential to provide additional, complementary information to that of the RCTs. Specifically, despite their methodological limitations, including an inability to eliminate residual confounding factors, RWE studies can provide external validity for trial data by extending insights to patients not studied in trials, including those at low risk, and other underrepresented patient populations (eg, women, ethnic and racial groups, individuals from certain geographic regions). In addition, RWE studies allow flexibility in evaluating both individual compounds and entire classes of medications, as well as the choice of active comparators, providing comparative-effectiveness and safety data that are highly relevant to clinical practice but would likely never be assessed in CVOTs. These attributes of RWE studies have captured the attention of the regulators, including the US Food and Drug Administration, which recently issued a guidance document outlining certain principles of incorporating RWE into its decision making. It is important to point out, however, that RWE studies are not replacements for RCTs.

Several comparative-effectiveness RWE studies of SGLT2is have recently been published, some focusing on the entire class and some on individual agents. These include the CVD-REAL 1 and 2 studies (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors), which demonstrated significantly lower risk of HHF and all-cause mortality in patients initiating SGLT2is versus other glucose-lowering agents across 12 countries and hundreds of thousands of patients, most at low cardiovascular risk. Similar results were seen in real-world studies comparing canagliflozin with other glucose-lowering agents across 12 countries and hundreds of thousands of patients, most at low cardiovascular risk. Similar results were seen in real-world studies comparing canagliflozin with other glucose-lowering compounds.

In this issue of Circulation, Patorno et al provide results from the first real-world analysis dedicated to comparing empagliflozin with sitagliptin. The EMPRISE program (Empagliflozin Comparative Effectiveness and Safety) included real-world data from 3 data sets in the United States: 2 commercial databases (Optum Clininformatics and IBM MarketScan) and 1 federal database (Medicare). Within these collective data sources, the authors identified 18,880 and 201,839 patients with

Figure. Schematic representation of the EMPRISE (Empagliflozin Comparative Effectiveness and Safety) study design and results.

In the EMPRISE real-world evidence study, new users of either empagliflozin or sitagliptin were propensity-matched and included most patients without established atherosclerotic vascular disease, because even the most representative randomized controlled trials (RCTs) use stringent inclusion and exclusion criteria, and their external validity and applicability to routine clinical practice are limited.

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diabetes mellitus in whom empagliflozin or sitagliptin was initiated between 2014 and 2016. The groups were propensity-matched on 140 baseline characteristics to yield 16443 matched patients in the empagliflozin and sitagliptin groups. The primary outcome was HHF in the primary position. Overall, only 25% of the population had known cardiovascular disease, and 5% had a history of heart failure; the mean follow-up period was 5.3 months. For the primary outcome, initiation of empagliflozin was associated with a 50% lower risk of HHF compared with sitagliptin (hazard ratio, 0.50 [95% CI, 0.28–0.91]). This remained consistent when a broader outcome of HHF was evaluated (HHF as a discharge diagnosis in any position).

Several strengths of the present analysis merit attention. Analyses were restricted to new users of either therapy and excluded SGLT2i and dipeptidyl peptidase-4 inhibitor users in the year before the study inclusion criteria, thus minimizing immortal time bias,11 and analyses were constructed to limit the potential time-lag bias. Furthermore, the authors have extensively tried to account for unmeasured confounding, which remains the Achilles’ heel of such studies. To this aim, they performed high-dimensional propensity score matching that accounts for an additional 100 covariates beyond the 140 included in the initial matching, which did not affect the overall point estimate. A “falsification end point” evaluating an expected null finding of flu vaccination was not different between groups. Multiple sensitivity analyses produced consistent results. Overall, these findings suggest that empagliflozin may reduce HHF among a broader group of patients than those included in the EMPA-REG OUTCOME trial (Figure) and thus provide an important contribution to the growing avalanche of data suggesting robust cardiovascular benefits of SGLT2is.

Several limitations of the EMPRISE results must be considered. First, the follow-up was short (mean, 5.3 months), reflecting the relatively recent introduction of empagliflozin in the United States. Second, despite extensive matching and strategies to attenuate confounding, a possibility of residual bias by indication can never be fully excluded in this or any other observational analysis. Third, data on mortality, major adverse cardiovascular events, and renal outcomes, as well as key safety end points (amputations, fractures, diabetic ketoacidosis, etc), are not yet available. Real-world studies are often relied on primarily for safety (versus efficacy) signals; hence, this information from EMPRISE and other RWE studies of SGLT2is is much needed. Finally, the present analysis is limited to the United States and its healthcare system and (for now) includes a relatively modest number of patients and events.

Recent experience clearly demonstrates that large-scale, pharmacoepidemiological comparative-effectiveness studies in type 2 diabetes mellitus are feasible, can include high-quality data, can be methodologically rigorous (despite potential limitations that apply to all observational studies), and can provide consistent and reproducible results, effectively complementing the findings from RCTs. EMPRISE provides additional, valuable data to this growing field and has several key points for physicians and patients (Figure): (1) the robust reduction in HHF noted in EMPA-REG OUTCOME is also observed consistently in the real-world setting; (2) EMPRISE, when added to the collective wisdom of the previous RCTs and real-world data, provides further support for the notion that the HHF benefits of SGLT2is appear to extend across a broad-based population of primary and secondary prevention patients; and (3) although EMPRISE makes a potential case for choosing empagliflozin over sitagliptin for preventing HHF, these findings should be interpreted with caution given the inherent limitations of observational studies. Several mechanisms (including hemodynamic, natriuretic, and metabolic) have been postulated to mediate the benefits of SGLT2is on HHF,12 with experimental data suggesting that these benefits may occur independently of glycemia.13

In conclusion, clinicians are reminded that SGLT2is have emerged as powerful cardiovascular therapies and, as echoed in a recent American College of Cardiology consensus pathway,14 should become a part of the cardiovascular specialists’ toolbox,15 in part because of their robust effects on the prevention of HHF. Whether these therapies will emerge in the treatment of established heart failure is currently being investigated in dedicated heart failure studies in patients with reduced and preserved ejection fraction (with or without concomitant diabetes mellitus).

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