Expect the Unexpected: SGLT-2 Inhibitors in the Treatment of Type 2 Diabetes and/or Heart Failure

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In the review, Santos-Ferreira et al. [1] discuss different aspects of the association between two frequent comorbidities, type 2 diabetes (T2D) and heart failure (HF). There is an abundance of data suggesting that patients with T2D and HF have an increased risk of cardiovascular (CV) and all-cause mortality, as well as reduced quality of life [2, 3]. While guidelines for individual treatments of T2D and HF are well established, recent findings from CV trials investigating glucose-lowering agents in T2D patients have revealed improved outcomes when treatments for both conditions are concurrently optimized.

Recently, few novel classes of glucose-lowering agents have been introduced. The results from the studies with sodium-glucose cotransporter 2 (SGLT2) inhibitors – a novel class of agents that inhibit glucose reabsorption in the proximal renal tubule [4] – yielded the greatest surprise. These agents are the main focus of the review article by Santos-Ferreira et al. [1], where three completed large CV outcome trials investigating SGLT2 inhibitors in patients with T2D and established atherosclerotic CV disease or multiple risk factors were elaborated in detail. The first one of these studies, EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), investigated the effects of

empagliflozin on CV outcomes in patients with T2D and established atherosclerotic disease [5] and found a 35% relative risk reduction in the exploratory endpoint of HF hospitalization. A similar effect was observed in the CANVAS study program (integrated data from 2 trials, CANVAS [Canagliflozin Cardiovascular Assessment Study] and CANVAS-R [Canagliflozin Cardiovascular Assessment Study – Renal]) [6], where canagliflozin significantly reduced the exploratory endpoint of HF hospitalization versus placebo in patients with and without history of HF. A post-hoc analysis found that canagliflozin reduced the overall risk of HF events, with no clear difference in effects on HF with reduced ejection fraction (HFrEF) versus HF with preserved EF (HFpEF) events [7]. In the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58) trial, dapagliflozin significantly reduced the risk of composite outcome of HF hospitalization or CV death versus placebo, and this was driven by a lower rate in HF hospitalization. This benefit was consistent in patients with and without recognized atherosclerotic disease, as well as in those with and without a prior HF history [8].

A meta-analysis of above-mentioned three trials confirmed individual findings, demonstrating consis-

tent beneficial effect of SGLT2 inhibitors on the reduction of HF hospitalization by 31%, regardless of atherosclerotic disease or prior history of HF [9]. Similar data was found in the real-world studies CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) [10] and the ongoing EMPRISE (Non-Interventional Study on the Effectiveness and Safety of Empagliflozin Compared with DPP-4 Inhibitors in Patients with Type 2 Diabetes in the United States) [11] trial, confirming the beneficial effect of SGLT-2 inhibitors on the prevention of HF hospitalization in patients with T2D, independent of atherosclerotic disease.

As noted in the review [1], the data from all these trials with SGLT2 inhibitors have changed the current understanding of the treatment paradigms of T2D and CV diseases, and HF in particular. Empagliflozin, as first-in-class SGLT2 inhibitor to demonstrate the beneficial effect on HF hospitalization, was recommended in the 2016 ESC guidelines for the diagnosis and treatment of HF [12] and Guidelines for CV prevention [13], for HF onset delay among patients with T2D. The recommendation was extended to other SGLT-2 inhibitors in the 2019 expert consensus report from the ESC Heart Failure Association [14]. In 2018, the consensus statement of the American Diabetes Association and European Association for the Study of Diabetes (ADA/EASD) included SGLT-2 inhibitors as the preferred treatment of T2D in patients with known HF or at risk of HF [15]. In addition, SGLT-2 inhibitors have been recommended as a second-line therapy, after metformin, or in patients in whom metformin is contraindicated or not tolerated.

Prior published data hold promise that SGLT-2 inhibitors have favorable effect in the prevention of HF among patients with T2D, across a wide spectrum of CV risk. However, whether SGLT-2 inhibitors could be beneficial in the treatment of HF, with or without T2D, is currently being investigated in several trials. The first completed trial, DAPA-HF (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction), reported a significant 26% risk reduction in the primary endpoint of CV mortality/HF hospitalization/urgent HF visit, in patients with HFrEF (LVEF $\leq 40\%$) and elevated natriuretic peptides, with similar results in patients with and without T2D [16]. Ongoing clinical trials, EMPEROR-Reduced ([Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction]), DELIVER ([Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure], and EMPEROR-Preserved [Empagliflozin Outcome Tri-

al in Patients with Chronic Heart Failure with Preserved Ejection Fraction]), will confirm the potential benefit of SGLT2 inhibitors in patients with HFpEF and/or HFrEF, irrespective of T2D status.

Overall, in trials reported thus far, SGLT2 inhibitors have been well tolerated. Genital mycotic infections, most frequently reported adverse event, are usually mild and could be effectively treated [5, 6]. Diabetic ketoacidosis may rarely occur, usually in patients with concomitant insulin therapy. However, reinitiating SGLT-2 inhibitors following ketoacidosis is not recommended because of an increased risk of recurrence [5, 6]. In the CANVAS Program, a greater risk of bone fractures and lower limb amputations was seen with canagliflozin compared to placebo. The risk was higher in patients with previous amputations or peripheral arterial disease [6]. However, this was not seen with other SGLT2 inhibitors. Furthermore, a meta-analysis of the three large CV outcome trials suggested that an increased risk of these events was evident only in the CANVAS trial. Further research is warranted to determine if the observed risk is associated with SGLT2 inhibitor treatment and, if so, whether this is a class or individual agent effect. In DAPA-HF, among the high-risk HFrEF patients with or without T2D, no significant excess in serious adverse events was noted with dapagliflozin versus placebo [16].

In conclusion, the review “SGLT 2 Inhibitors in Heart Failure and Type 2 Diabetes: Hitting Two Birds with One Stone?” [1] provides relevant and accurate overview of existing data on SGLT2 inhibitors as novel class of glucose-lowering agents with convincing evidence in the prevention of HF in patients with T2D. Current guidelines for the treatment of T2D suggest that SGLT2 inhibitors should be used as second-line agents for glucose reduction and CV protection, after metformin. The first trial of patients with prevalent HF found that the risk of worsening HF or death from CV causes was lower in those who received dapagliflozin compared to placebo, regardless of the presence of T2D. Ongoing clinical trials will investigate the potential benefit of SGLT2 inhibitors in patients with both HFpEF and HFrEF, with or without T2D.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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