The Role of SGLT2 Inhibitors in the Management of Heart Failure

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Abstract: Sodium – glucose co-transporter 2 (SGLT2) inhibitors reduce blood glucose by inhibiting reabsorption of glucose from the proximal renal tubules. Initial studies showed that apart from reducing blood glucose they also reduce the combined endpoint of myocardial infarction, stroke, and cardiovascular death, hospitalization from heart failure, and occurrence of renal failure in patients with known cardiovascular disease or at high risk of developing cardiovascular disease. Recent studies have shown that these drugs also could be used in patients to treat heart failure or to slow the progression of renal failure, irrespective of whether the patients have diabetes or not. In this review, we discuss the clinical trial evidence for the use of SGLT2 inhibitors for the treatment of patients with heart failure with reduced ejection fraction and for the prevention of heart failure in patients with diabetes who are at high risk of cardiovascular events. The DAPA-HF study and the EMPERORREDUCED TRIAL have shown that Dapaglifozin and Empaglifozin could be used to treat patients with heart failure, with or without diabetes. SGLT2 inhibitors provide us with a new armamentarium for treatment of patients with a triad of diabetes, heart or renal disease. Their mechanism of action in prevention or treatment of patients with heart failure however still remains speculative.

Key words: Heart failure, Reduced ejection fraction, SGLT2 inhibitors, Diabetes, Renal disease.

Introduction: Cardiovascular diseases remain the leading cause of death worldwide, with heart failure (HF) being one of the significant causes of mortality in patients with type 2 diabetes mellitus (T2D) . Heart failure (HF) is a global health problem with a prevalence of ~26 million worldwide. Patients with HF are at a 40%-50% risk of mortality within five years of diagnosis and suffer from recurrent hospitalizations and poor quality of life. Type 2 diabetes mellitus (T2DM) is growing with a prevalence of over 400 million globally. The deleterious effects of T2DM can be separated into microvascular (neuropathy, nephropathy, retinopathy) and macrovascular (coronary disease, stroke, peripheral arterial disease) complications. While there is moderate to high quality evidence that glucose

control reduces the risk of microvascular complications, its beneficial effect on macrovascular complications are less apparent and appear to take longer to manifest. Cardiovascular diseases (CVD) account for approximately half of the deaths in T2DM.4 CVD, HF, and T2DM are all associated with chronic kidney disease (CKD), which together further worsen prognosisAccording to the Framingham study, the patients with T2D have a two- and five-fold higher risk of developing HF in men and women, respectively, compared to the healthy population. As a result, HF diminishes the quality of life and increases hospitalization, making this syndrome a growing public health matter. HF is present in about 20–40% of diabetic patients. The patients with HF are assessed mainly by echocardiography and their symptoms, and they are classified into three groups based on their ejection fraction (EF): reduced EF (EF < 40%; HFrEF); intermediate EF (EF between 40% and 49%; HFmrEF); and preserved EF (EF > 50%; HFpEF) . The people suffering from HFrEF often show dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and ankle swelling. The currently approved pharmacological treatments for HFare reported in 2023 . A new class of drugs, sodium-glucose co-transporter two inhibitors (SGLT2i), has been added to the treatment of HF. According to the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), all new glucose-lowering agents used in patients with or without T2D must demonstrate cardiovascular safety to prevent cardiovascular complications.

Main body: Biological mechanisms and efects of SGLT2 inhibitors in heart failure Te mechanisms of action of SGLT2 inhibitors in heart failure are still speculative although the drugs are shown to have several metabolic, hemodynamic, and organspecifc efects. In addition to glycosuria, SGLT2 inhibitors promote natriuresis and uricosuria. Other metabolic efects include increased insulin sensitivity and glucose uptake in muscle cells, decreased neoglucogenesis, and increased ketogenesis. Tese drugs also stimulate weight loss due to renal calorie loss in glycosuria and a favorable impact on body fat distribution. A rise in hematocrit was also seen with SGLT2 inhibitor therapy. Te hemodynamic efects are mediated by several mechanisms including osmotic diuresis, and plasma and interstitial fuid volume reduction, leading to a reduction in ventricular preload and afterload. Furthermore, unlike diuretics, SGLT2 inhibitors seem to exert a greater reduction of interstitial fuid compared with plasma volume which may prevent plasma volume depletion and subsequent hypoperfusion occasionally observed with diuretics. However these favorable metabolic and hemodynamic effects are

unlikely to be solely responsible for the prevention and treatment of heart failure. Another proposed mechanism for the benefcial efects of SGLT2 inhibitors is inhibition of the sodium-hydrogen exchanger (NHE1) activity which is up-regulated both in T2DM and heart failure. By inhibiting the NHE1 receptors, SGLT2 inhibitors may protect the heart from toxic intracellular Ca2+overload. SGLT2 inhibitors may also exert direct efects on myocardial metabolism, and decrease myocardial oxidative stress. Similar to T2DM, HF is characterized by a state of insulin resistance. In the insulin-resistant heart, free fatty acids (FFA) are favored as an energy source over glucose which results in decreased cardiac metabolic efciency (insufcient ATP production). By promoting a metabolic shift from FFA to glucose oxidation, SGLT2 inhibitors result in increased cardiac ATP production and prevent a decrease in cardiac function.

A benefit on ventricular remodeling was also demonstrated in patients with T2DM and coronary artery disease in the EMPA-HEART CardioLink-6 study, which showed a reduction in left ventricular (LV) mass index and improvement in diastolic function without changes in LV systolic function after 6 months of treatment with empaglifozin. Furthermore, a signifcant reduction in LV mass in patients with T2DM was observed with dapaglifozin in the DAPA-HF trial, suggesting a possibility of reverse LV remodeling. It is known that neurohormonal activation causes increased oxidative and other forms of cellular stress, which leads to dysfunction and loss of cardiomyocytes. Another postulated mechanism is that by inhibiting the energy surplus sensors SGLT2 inhibitors mimic cellular starvation and induce nutrient deprivation signals such as sirtuin 1 (SIRT1) which in turn inhibit activation of proinfammatory pathways, reduce cellular stress and promote autophagy. Tis helps in reversing mitochondrial dysfunction and slowing cardiomyocyte dysfunction and cell loss. Other hypotheses include cardiac anti-fbrotic efects, improved balance in adipokine secretion, benefcial efects on endothelial function, parameters of arterial stifness and vascular resistance as well as a reduction in sympathetic nervous system activity.

There are many clinical trials those demonstrate SGLT2I role on HF. For example: Empagliflozin Several CVOTs were designed to evaluate the use of SGLT2i in patients with high cardiovascular risk. The first SGLT2i cardiovascular trial was EMPA-REG OUTCOME, which studied 7020 patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD) over 3.1 years. The primary composite endpoint was major adverse cardiac events (MACE), such as cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction. These

showed a 14% reduction compared with the placebo group (HR, 0.86; 95% CI, 0.74–0.99; p = 0.04 for superiority). In addition, the empagliflozin group had a 32% risk reduction in death from all-causes, a 38% risk reduction in cardiovascular causes (HR, 0.62; 95% CI, 0.49–0.77), and a 35% relative risk reduction in hospitalization for heart failure. No significant differences were found in the myocardial infarction or stroke rates between the two groups. An increased rate of genital infection was observed among the patients receiving empagliflozin. Empagliflozin reduced the overall burden of cardiovascular complications and hospital admissions in patients with type 2 diabetes and atherosclerotic cardiovascular disease. The EMPEROR-REDUCED, a multicenter, randomized, double-blind, placebo-controlled trial, aimed to investigate the effect of empagliflozin in patients with established HF with an HFrEF. The study included 3730 patients with or without T2DM with a chronic HF for at least three months with a left ventricular ejection fraction (LVEF) ≤ 40%, treated with optimal medical therapy, result that relative risk reduction in hospitalization for heart failure.

Dapagliflozin Dapagliflozin is a selective inhibitor of SGLT2 that blocks the glucose reabsorption in the proximal tubule of the kidney, promotes glucosuria, and induces clinically significant changes in the glycemic parameters in T2DM patients. Dapagliflozin was evaluated in the DECLARE-TIMI 58 study, which enrolled 17,160 diabetic patients (HA1c level at least 6.5% but less than 12.0%) with or without (10,186 pts) established ASCVD and followed them for 4.2 years [30]. All of the eligible patients were 40 or older and had an estimated glomerular filtration rate (eGFR) of 60 mL/min. The patients were divided into two groups receiving dapagliflozin 10 mg or placebo. The primary efficacy outcomes were MACE and a composite of cardiovascular death or HFH. Compared to the EMPA-REG OUTCOME and CANVAS, the inclusion criteria for this study indicated that participants were at a lower risk for CVD . Dapagliflozin did not significantly reduce the primary composite outcome, including CV death, non-fatal MI, and non-fatal stroke (HR, 0.93; 95% CI, 0.84–1.03; p = 0.17), and hospitalization, but did result in a lower rate of cardiovascular death or HFH. DECLARE-TIMI 58 was the first SGLT2i study to include HFH. There was no significant difference in the various primary endpoints in the dapagliflozin group compared with the placebo group; however, only HFH was significantly reduced by dapagliflozin (HR, 0.73; 95% CI, 0.61–0.88). The secondary evidence of efficacy was renal composite and death from any cause. Dapagliflozin also reduced the incidence of HFH or CV

death by 17% (HR, 0.83; 95% CI, 0.75–0.95). In the baseline population, 3.9% of patients had HFrEF, 7.7% had HFpEF, and the remaining 88.4% had no history of HF. It was observed that dapagliflozin reduced the number of hospitalizations or cardiovascular deaths more in patients with HFrEF (HR 0.62, 95% CI, 0.45–0.86) compared with those with HFpEF (HR, 0.88; 95% CI, 0.76–1.02; p-interaction 0.046) [30,31]. However, this study reported only a 2% reduction in CV death with dapagliflozin, compared with a 38% reduction in Pharmaceutics 2022, 14, 1730 6 of 13 cardiovascular death with empagliflozin. In addition, dapagliflozin showed a lower rate of adverse renal events.

The CREDENCE study examined the effect of canagliflozin in 4401 people with T2D and chronic kidney disease with or without CVD over 2.6 years. The primary outcome was a composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal or cardiovascular causes. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group ($p = 0.00001$). HFH was reported in 4.0% of patients receiving canagliflozin, compared with 6.4% in the placebo group ($p < 0.001$). In addition, CV death or HFH occurred in 8.1% of canagliflozin patients compared with 11.5% of placebo patients.

Ertugliflozin VERTIS-CV is a multicenter, double-blind trial that followed up 8246 diabetic patients with established ASCVD for 3.5 years and who were randomly assigned to receive 5 mg or 15 mg of ertugliflozin or placebo. In this trial, ertugliflozin did not achieve superiority in reducing major CV or secondary composite renal events. The incidence of death from CV causes or HFH did not differ significantly between the trial groups. However, HFH was reduced by ertugliflozin, and it was reported that when ertugliflozin is used alone with the standard of care medication, it can decrease the risk of a sustained 40% decline in eGFR in patients with T2DM and established ASCVD. Overall, ertugliflozin reduced the risk for first HFH (HR, 0.70 [95% CI, 0.54–0.90]; $p = 0.006$) . Indeed, a subgroup analysis suggested a benefit for HFH and HFH/CV death with ertugliflozin vs. placebo among patients with a higher risk (presence of albuminuria, higher KDIGO class). The adverse events, such as urinary infections observed with ertugliflozin, were similar to the known risks of the medicines in the SGLT2 inhibitor class. In the patients with type 2 diabetes mellitus, ertugliflozin reduced the risk of first and total HFH and total HFH/CV death, further supporting the use of sodium-glucose cotransporter 2 inhibitors in the primary and secondary prevention of HFH.

Sotagliflozin Sotagliflozin is the most recent SGLT2i studied for safety and cardiovascular risk in diabetic patients. The SCORED study randomly enrolled 10,584 individuals with type 2 diabetes and chronic kidney disease, regardless of the presence of ASCVD (at least one major if age > 18 years, at least two minor if age ≥ 55 years), to receive sotagliflozin or placebo. A total of 31% of the participants had a history of HF. The trial stopped early, after 1.3 years, due to a loss of funding due to COVID-19. To maintain the statistical power, the investigators changed the primary endpoint to CV death, HF hospitalization, and urgent visits for HF for sotagliflozin vs. placebo: 11.3% vs. 14.4% (p = 0.0004). This achieved significance by 95 days of follow-up. Sotagliflozin is also able to reduce the gastrointestinal SGLT1 delay in glucose absorption and reduce postprandial glucose; this resulted in a 26% reduction in the primary outcome (HR, 0.74; 95% CI, 0.63–0.88).

Conclusion: SGLT2 inhibitors (empaglifozin, canaglifozin, dapaglifozin, ertuglifozin) are recommended to reduce the risk of HF hospitalization with or without T2DM patients with either established cardiovascular disease or at high cardiovascular risk Moreover, 2023 Focused Update addresses changes in recommendations for the treatment of HF because of this new evidence. Guidelines have given a Class I recommendation for dapaglifozin and empaglifozin for the treatment of HFrEF, HFmrEF, HFprEF, with or without T2DM so we it said that SGLT2I is currently best drugs to treat heart failure.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failureMullens W,
   Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, et al. Acetazolamide in acute decompensated heart failure with volume overload. N Engl
2. Trullàs JC, Morales-Rull JL, Casado J, Carrera-Izquierdo M, Sánchez-Marteles M, Conde-Martel A, et al. Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial
3. Eur Heart J, Straus SE, Farkouh ME, Austin PC, Taljaard M, Chong A, et al. Trial of an intervention to improve acute heart failure outcomes. Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med.

4. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE and Woerle HJ. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. The New England journal of medicine.
5. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC and Inzucchi SE. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial.
6. Eur Heart J. Gerstein HC, Miller ME, Byington RP, Goff DC, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F and Grimm RH. Effects of intensive glucose lowering in type
7. 7. 2 diabetes. The New England journal of medicine. 2008;358:2545-59. 19 24.
8. Major outcomes in high-risk hypertensive patients randomized to angiotensinconverting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Jama. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S and Wedel H.
9. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002;359:995-1003. 26. Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, Johnston CI, McNeil JJ, Macdonald GJ, Marley JE, Morgan TO and West MJ. A comparison of outcomes with angiotensin-converting--enzyme inhibitors and diuretics for hypertension in the elderly. The New England journal of medicine