Original Article

Sglt2 Inhibitors And The Clinical Conundrum Of Heart Failure With Preserved Ejection Fraction

Prof C. Sridhar[1], Prof C. Krithika[2]

[1]Prof & Head of the Department (Retd) Department of Medicine Tamilnadu Medical service
[2]Registrar & Professor Meenakshi Academy of Higher Education & Research, Chennai
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Abstract

The terminology, Heart Failure with Preserved Ejection Fraction (HFpEF) denotes a specific subset of a wider spectrum of cardiac failure. Neurohormonal blockade using Angiotensin converting enzyme inhibitors, Angiotensin receptor blockers, Angiotensin receptor neprilysin inhibitors, Mineralocorticoid receptor antagonists and beta blockers have been the mainstay of the treatment of heart failure thus far. However, the Sodium Glucose cotransporter inhibitors (SGLT2i) have recently found favor with the cardiologists for their pleiotropic effects on the heart leading to considerable prognostic benefits in heart failure patients. Initial studies have convincingly demonstrated the benefit of these drugs in heart failure with reduced ejection fraction (HFrEF). But the benefit of SGLT2i in HFpEF is yet to be determined conclusively. This review article is a therefore a narrative on the cardiac pharmacology of the SGLT2 inhibitors and their evolving role in the management of HFpEF based on evidence from recent trials and studies.

Introduction

SGLT2 inhibitors or gliflozins have recently caused a paradigm shift in the management of heart failure by virtue of their positive effects on the heart. The compound phlorizin was the first gliflozin to be discovered in 1835 although its glucosuric properties were detected much later in the 1980s. The gliflozins actually act upon the SGLT2 receptors present in the proximal convoluted tubules of the kidney and prevent the reabsorption of glucose and sodium, leading to glucosuria and natriuresis. This causes a reduction of hyperglycemia and the recognition of this property, led to the approval of the first gliflozin Canagliflozin by the FDA, for management of diabetes, in the year 2013.

Gliflozins in Heart Failure

The adverse cardiac effects caused by yet another anti hyperglycemic drug Rosiglitazone earlier, led the FDA to mandate that all newly launched anti diabetic drugs must be subjected to stringent cardiovascular safety trials to ensure their safety in the vulnerable diabetic population. Accordingly, the launch of the gliflozins was followed by a slew of cardiovascular safety outcome trials of these drugs in diabetic patients, including the EMPA-REG outcome trial, the CANVAS trial, the CREDENCE trial, the DECLARE-TIMI 58 trial and the VERTIS CV trials. These landmark trials demonstrated that the SGLT2 inhibitors were not only remarkably safe for the heart but in addition were significantly cardio protective.

Consequent to this unexpected discovery, several Randomized Control Trials were undertaken to study the beneficial effects of the gliflozins on both diabetic as well as the non-diabetic population. These studies confirmed that gliflozins produced significant benefits in heart failure across the entire spectrum of left ventricular ejection fractions.

Heart Failure

By definition, heart failure is a clinical syndrome with various symptoms and signs caused by either a structural or functional abnormality of ventricular filling or emptying. The American Heart Association, in its 2022 guidelines[1], stratified the stages of heart failure and accordingly, Stage A heart failure includes patients who are asymptomatic and without structural heart disease but have cardiac risk factors like diabetes, hypertension, obesity and metabolic syndrome. Stage B heart failure or pre heart failure patients are those without symptoms but with structural heart disease or elevated filling pressures or cardiac biomarkers. Stage C patients are symptomatic patients with evidence of structural heart disease. Stage D includes patients with advanced cardiac failure who are refractory to guideline directed medical therapy (GDMT) and require repeated hospitalizations for heart failure management.

An alternative method to classify heart failure based on Ejection Fractions (EF) is often used to determine the therapeutic and prognostic considerations. Fundamentally, the term heart failure with reduced ejection fraction (HFrEF) is used to denote heart failure with LVEF <40%. Heart failure with preserved ejection fraction (HFpEF) refers to heart failure with EF >50% along with raised filling pressures. In between these two groups, is the category of heart failure with mildly reduced ejection fraction (HFmrEF) which implies that the LVEF is between 41-50% along with raised filling pressures. Both the AHA 2022 guidelines[1] and the ESC 2021 guidelines[2] segregate heart failure into the above three categories. However, the AHA specifies yet another category of patients who initially had an LVEF <40% (HFrEF) but later improved to >40%, and these patients are said to have heart failure with improved ejection fraction (HFimpEF).

Mechanism of action of SGLT2 inhibitors in cardiac disease

The key mechanisms involved in the cardiac actions of SGLT2 inhibitors are probably multidimensional. Conventionally, diuresis, weight loss and increased hematocrit have been postulated as important factors for the cardiac benefits of these drugs. By inhibiting the SGLT2 receptors, the gliflozins cause glucosuria, natriuresis and a mild anti-hypertensive effect as well. This however does not explain the effect of SGLT2i, in patients without diabetes who remain normoglycemic. The anti-hypertensive effects were initially thought to be due to natriuresis but since these effects persist even with declining GFR, other mechanisms like improved endothelial function, altered sympathetic activity and reduced arterial stiffness are perhaps operative. SGLT2-inhibitor therapy may induce weight loss due to an increased glucagon-insulin ratio causing enhanced lipid mobilization and reduction in mortality.

Additionally, several novel mechanisms have been proposed for the myocardial effects of the gliflozins. This includes improved myocardial energetics in the form lesser mitochondrial oxidative metabolism of glucose and enhanced utilization of more oxygen efficient ketone bodies. Improved cardiac ionic homeostasis is yet another mechanism in which SGLT2-inhibitor therapy leads to a reduction in cardiac cytosolic sodium by inhibiting sodium-hydrogen exchanger 1, thereby reversing calcium overload. This altered myocardial calcium handling causes more efficient myocardial contractility.

Altered adipokine regulation causes a decrease in leptin which has been implicated in several cardiac disorders and an increase in cardioprotective adiponectin leading to a reduction in epicardial fat and enhanced cardiac work efficiency.

SGLT2i therapy may also induce autophagic clearance of damaged organelles by upregulation of adenosine monophosphate-activated protein kinase (AMPK), sirtuin-1 (SIRT1) and hypoxia-inducible factors (HIF-1alfa). Eventually this leads to reduced oxidative stress and inflammation and improvement of cardiovascular health.

Adverse effects of SGLT2 inhibitors

The most common adverse effect observed with SGLT2i therapy are genital mycotic infections which are more common in women. Additionally, polyuria, urinary tract infections, pyelonephritis and rarely serious urosepsis may also occur. Intravascular volume depletion may lead to hypotension and impaired renal function or Acute Kidney

Injury, particularly in the elderly and in patients on diuretics. Euglycemic ketoacidosis has been reported in the elderly or the fasting patients and electrolyte disturbances may add to the complications. Fournier's gangrene has also been reported, although rarely.

Evidence based SGLT2 inhibitor therapy in HFpEF

Several randomized control trials including the DAPA-HF, published online in September 2019 and the EMPEROR REDUCED trial published in August 2020 indicated the benefit of SGLT2i therapy in patients with HFrEF. The ESC 2021 guidelines[2] and the AHA 2022[1] guidelines on heart failure, endorsed this evidence by issuing Category of Recommendation 1 (COR-1) for SGLT2i therapy in HFrEF, level of evidence (LOE-A). However, in case of HFpEF, the AHA issued COR-2a, LOE-B-R based on the outcome of the EMPEROR PRESERVED trial which was published in August 2021. The ESC 2021 did not offer any recommendations for SGLT2i therapy in HFpEF.

The SOLOIST-WHF[3] trial was designed to study the effect of Sotagliflozin (SGLT1 & SGLT2 inhibitor) in diabetic patients with recent worsening heart failure. A total of 1222 diabetic patients, were randomized to Sotagliflozin or placebo just before or immediately after discharge, following an admission for recently worsening heart failure. The study sample included all categories of heart failure and the randomization was stratified based on LVEF (< 50% or > 50%). The study was originally planned to include 1100 patients with EF >50%, to evaluate whether the benefits of SGLT2i, extend to patients with HFpEF, but since the study was terminated early due to loss of funding, only 256 patients with EF >50% were enrolled. It was therefore difficult to draw conclusions on the effect of Sotagliflozin in HFpEF. However, Sotagliflozin significantly reduced the primary end point of the total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure [hazard ratio, 0.67; 95% confidence interval [CI], 0.52 to 0.85; P<0.001] in diabetic patients with recent worsening heart failure.

The EMPERIAL study[4] (Effect of Empagliflozin on exercise ability and heart failure symptoms in patients with chronic heart failure) published online in December 2020, was done to assess the effect of Empagliflozin on exercise ability as well as patient outcomes in HFrEF (EMPERIAL reduced) and HFpEF (EMPERIAL preserved), irrespective of their diabetic status. This was the first study to assess the efficacy of SGLT2i in HFpEF. The primary end point which was a change in the 6-min walk test at 12 weeks was statistically insignificant and hence the secondary end points, including the KCCQ-TSS score and the Chronic Heart failure Questionnaire self-administered standardized format (CHQ-SAS) dyspnea score, were considered to be of exploratory nature. The primary outcome was neutral in both the EMPERIAL reduced and EMPERIAL preserved studies. However, the effect of empagliflozin on KCCQ-TSS in EMPERIAL reduced was similar to the effect of dapagliflozin on KCCQ-CSS in the DAPA-HF trial. This probably suggests the possibility of future improvement in mortality and HF hospitalization.

The EMPEROR PRESERVED[5] was a double-blind trial which enrolled 5988 patients with class II-IV heart failure and an EF > 40%. The study participants were randomized to receive Empagliflozin 10 mg or placebo in addition to Guideline Directed Medical therapy. The primary outcome, which was a composite of cardiovascular death or hospitalization for heart failure occurred in 13.8% of the empagliflozin group and 17.15% of the placebo group (hazard ratio 0.79; 95% CI, 0.69 to 0.90; p<0.001). This conclusively demonstrated the beneficial effects of Empagliflozin in patients with heart failure and preserved ejection fraction, irrespective of the presence or absence of diabetes.

The PRESERVED HF[6] trial, published in November 2021 was done to assess whether the SGLT2i dapagliflozin produced any improvement in the symptoms, physical limitations and exercise function in patients with HFpEF irrespective of their diabetic status. The study enrolled 324 patients with a median LVEF of 60% and were randomized to either Dapagliflozin or placebo.

Dapagliflozin was found to meet the primary end point of improvement in the Kansas City Cardiomyopathy Questionnaire Clinical Summary score (KCCQ-CS) at 12 weeks after starting treatment and an improvement in the physical limitations score and the 6-minute walk test (6MWT). These clinical benefits of dapagliflozin were

statistically significant and was consistent across all the prespecified subgroups regardless of the presence or absence of diabetes and irrespective whether the EF was above or below 60%.

The **DELIVER**[7] **ClinicalTrials**.gov number, NCT03619213 (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) was a phase 3, international, multicenter, double blind, randomized controlled trial that was designed to evaluate the effects of Dapagliflozin in patients with higher left ventricular ejection fraction. This study published online in August 2022, randomly assigned 6263 patients with or without diabetes, who had heart failure with a LVEF more than 40%, to receive either Dapagliflozin 10 mg once a day or a placebo, in addition to guideline directed medical therapy. Approximately 34% of the study sample had an EF of 41-49%, 36% had an EF between 50-59% and 30% had an EF > 60%. The primary endpoint was a composite outcome of worsening heart failure or cardiovascular death. During a follow up of just over two years, the primary outcome was 16.4% in the dapagliflozin group and 19.5% in the placebo group (Hazard ratio, 0.82; 95% CI, 0.73 to 0.92, p< 0.001). The incidence of worsening heart failure was11.8% in the dapagliflozin group and 14.5% in the placebo group (hazard ratio, 0.79; 95% CI, 0.69 to 0.91). The occurrence of cardiovascular death was 7.4% and 8.3%, respectively in the two groups (hazard ratio, 0.88; 95% CI, 0.74 to 1.05). In simple terms, this implied a 18% reduction in the incidence of the primary outcome, a 21% decrease in the incidence of worsening heart failure and a 12% decrease in cardiovascular death in the dapagliflozin group.

The results were quite similar in patients with or without diabetes and also in patients with LVEF above or below 60%. It was therefore concluded that Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients diagnosed to have Heart failure with preserved ejection fraction and heart failure with mildly reduced ejection fraction. Besides the incidence of adverse events were similar in the dapagliflozin group and the control group.

The effects of Dapagliflozin in HFrEF has already been demonstrated in the DAPA-HF study and the DELIVER trial proves its efficacy in heart failure patients with EF over 40%. It also corroborates the findings of the EMPEROR PRESERVED trial that demonstrated the benefits of Empagliflozin in patients with HFpEF. The EMPEROR preserved suggested a possible attenuation of the benefit from SGLT2i therapy at the higher end of the EF range. The DELIVER trial however did not find any heterogeneity in treatment effects in patients who had an ejection fraction of more than 60% or less than 60%.

Finally, Hufang Zhou et al[8]., in a systematic review and meta-analysis of 12 RCTs including 10,883 patients reported that the gliflozins significantly improve cardiovascular outcomes in patients with HFpEF and with a low risk of serious adverse reactions.

Future guidelines may thus incorporate appropriate use of SGLT2i in HFpEF, paving the way for a broader use in heart failure, regardless of the ejection fraction and irrespective of the presence or absence of diabetes.

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