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SGLT2-Inhibitors - significant role in Heart Failure treatment

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Abstract

Heart failure (HF), which has a high morbidity and mortality rate, is nevertheless a common and crippling ailment, especially in older populations. The complicated pathophysiology of heart failure (HF), which includes oxidative stress, endothelial dysfunction, fibrosis, and inflammation, is frequently not sufficiently treated despite advances in medication. Inhibitors of the sodium-glucose co-transporter 2 (SGLT2) have become a key treatment for HF in patients with varying left ventricular ejection fractions (LVEF). SGLT2 inhibitors have been shown in recent clinical trials to considerably lower hospitalization rates for heart failure, cardiovascular mortality, and all-cause mortality. The mechanisms of SGLT2 inhibitors, such as better ventricular loading, increased heart metabolic efficiency, and decreased inflammation and necrosis, are covered in this review. Additionally, we provide an overview of four important clinical trials—DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER—highlighting their effectiveness in lowering unfavorable cardiovascular outcomes for patients with heart failure who have preserved (HFpEF), slightly reduced (HFmrEF), or reduced (HFrEF). The results validate the need of SGLT2 inhibitors in all-inclusive HF treatment plans by highlighting their adaptability and safety in a range of clinical contexts.

Keywords Heart failure, SGLT2 inhibitors, EF

Introduction

Despite the advancements in the pharmacological management of heart failure (HF), the condition is becoming more common in aging populations and is associated with high rates of morbidity and death. The intricate pathophysiology of heart failure involves multiple harmful pathways, such as oxidative stress, endothelial dysfunction, fibrosis, and inflammation, which may not be sufficiently addressed by current pharmacotherapy.[1]

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors, also referred to as anti-hyperglycemic medications, are now a major treatment for heart failure (HF) over the whole spectrum of left ventricular ejection fraction (LVEF).[3]

Recent groundbreaking results from clinical trials assessing the use of SGLT2 inhibitors in heart failure patients have demonstrated considerable reductions in the risk of heart failure hospitalization, cardiovascular mortality, and all-cause mortality. The immense enthusiasm these findings have aroused has led to an extraordinary shift in the therapy of heart failure, with SGLT2 inhibitors now recognized as necessary elements of comprehensive treatment regimens.[2]

Materials and methods

We used the resources from medical databases, including Pubmed and Google Scholar, to construct the work. We looked for articles on the topics we were interested in in the first step. Then, we checked them for accuracy in terms of study technique, content, and conflicts of interest. We thus obtained a collection of eight articles with the highest impact factors. The most recent multi-environmental papers, including meta-analyses, were chosen.

Description of the state of knowledge

SGLT2 inhibitors work by blocking a sodium-glucose co-transporter located in the proximal convoluted tubule of the nephron. Improved ventricular loading conditions, increased cardiac metabolic efficiency, and decreased necrosis and local inflammation are some of the suggested advantageous mechanisms of SGLT2 inhibition in heart failure.[2]

The pleiotropic effects of SGLT2 inhibition in heart failure are associated with multiple factors. To begin with, increased glycosuria and natriuresis, which result in osmotic diuresis and volume control, have been postulated as one of the earliest processes reported. This suggests that a reversal of the detrimental cardiac remodeling process may be occurring in the greater proportion of patients who show a moderate or significant reduction in natriuretic peptides at the long-term follow-up. The enhancement of endothelial function and arterial stiffness has led to the hypothesis that SGLT2 inhibition has a blood pressure-lowering effect. [1]

The role of SGLT2i as a fundamental therapy for HFrEF is supported by current guideline recommendations in combination with angiotensin-converting enzyme inhibitors (ACEi),

angiotensin II receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), β-blockers, and mineralocorticoid receptor antagonists.[2]

With a median follow-up of 3.1 years, 7,020 individuals with established cardiovascular disease were included in the EMPA-REG OUTCOME study, which evaluated cardiovascular outcomes with empagliflozin. When compared to placebo, empagliflozin significantly reduced the primary composite endpoint of major adverse cardiovascular events (cardiovascular mortality, nonfatal stroke, nonfatal myocardial infarction; MACE-3) by 14% (12.1% vs. 10.5%; hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.74–0.99). This reduction was mainly due to a 38% substantial decrease in cardiovascular death.[4]

HFrEF

Dapa-HF and EMPEROR-Reduced were two extensive randomised trials that examined dapagliflozin and empagliflozin in HFrEF patients.

The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial was the first to evaluate the efficacy of an SGLT-2 inhibitor in treating patients with HFrEF. The trial included 4,744 participants with stable, chronic heart failure (HF) and LVEF of less than 40%, who were monitored for a total of eighteen months. The main composite outcome of cardiovascular death, hospitalizations related to heart failure, and urgent heart failure visits was found to be considerably lower with dapagliflozin than with a placebo (16.3% vs. 21.2%; HR, 0.74; 95% CI, 0.65–0.85).[5]

Following this groundbreaking work was the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trial, which evaluated the effectiveness of empagliflozin in a cohort similar to that of DAPA-HF but with a reduced mean LVEF of up to 27% instead of up to 31%. The experiment involved 3,730 individuals, with a median follow-up of 16 months. Empagliflozin significantly reduced the composite outcome of hospitalizations for heart failure and cardiovascular death when compared to a placebo, resulting in a 21% relative risk reduction (19.4% vs. 24.7%; HR, 0.75; 95% CI, 0.65–0.86).[6]

HFmrEF and HFpEF

The Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) trial was the first to specifically assess the efficacy

of SGLT-2 inhibitors (empagliflozin) in patients with HF with mildly reduced (HFmrEF) and HFpEF, regardless of the patient's diabetes status. The study comprised 5,988 people with LVEF >40% and NYHA II and III symptoms in total. Empagiflozin significantly reduced the risk of heart failure hospitalizations by 27%, which in turn decreased the major composite endpoint of cardiovascular death and heart failure hospitalizations by 19% (13.8% vs. 17.1%; HR, 0.79; 95% CI, 0.69–0.90). The results were similar to those of EMPEROR-Reduced.[7]
The Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial evaluated the efficacy of dapagliflozin in treating patients with HFmrEF and HFpEF. There were 6,263 patients in all, with a median follow-up duration of 2.3 years. When dapagliflozin was compared to a placebo, the major composite result was significantly lower (16.4% vs. 19.5%; HR, 0.82; 95% CI, 0.73–0.92). A notable 21% drop in HF hospitalizations and urgent visits (11.8% vs. 14.5%; HR, 0.79; 95% CI, 0.69–0.91) was the main cause of this decrease.[8]

Conclusion

SGLT2 inhibitors, which were first created to treat patients with type 2 diabetes mellitus, have a pleiotropic mechanism of action that makes them an appealing and secure therapy choice in a number of situations. [2]
A breakthrough in the treatment of HF has been made possible by the effectiveness of SGLT2 inhibitors, such as dapagliflozin and empagliflozin, not only in HFrEF but also in HFmrEF and HFpEF.
No matter the level of clinical setting acuteness, eGFR, LVEF, or diabetes condition, SGLT2 inhibitors are a valuable adjunct to HF treatment. In clinical heart failure situations, SGLT2 inhibitors are generally well-tolerated and efficacious medications.[9]

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