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CARDIOPROTECTIVE PROPERTIES OF SGLT2-INHIBITORS

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ABSTRACT

Due to its high mortality rate, heart failure (HF) presents a substantial worldwide health burden that calls for efficient treatment approaches. Inhibitors of the sodium-glucose co-transporter 2 (SGLT2) have become essential treatments for heart failure in all left ventricular ejection fraction (LVEF) levels. Their processes, which include enhanced metabolic efficiency and ventricular loading circumstances, present encouraging results. The effectiveness of SGLT2 inhibitors, dapagliflozin and empagliflozin, in lowering cardiovascular mortality and heart failure hospitalizations in heart failure patients with reduced, mildly reduced, and preserved ejection fraction has been shown in several clinical trials, including DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER. These results represent a revolutionary development in the treatment of HF, emphasizing the use of SGLT2 inhibitors in comprehensive treatments, regardless of renal function or diabetes state.

Keywords: Heart failure, SGLT2 inhibitors, LVEF

INTRODUCTION

Heart failure (HF) is a clinical illness characterized by signs and symptoms brought on by a defect in the structure or function of the heart and is supported by high natriuretic peptide levels or objective evidence of systemic or pulmonary congestion [1]. This condition is a serious public health concern that affects 64 million people globally and has a 50% mortality rate at five years of age.[1]

Known as anti-hyperglycemic drugs, sodium-glucose co-transporter 2 (SGLT-2) inhibitors have become a key treatment for heart failure (HF) in all ranges of left ventricular ejection fraction (LVEF).[2]

Clinical trials evaluating the use of SGLT2 inhibitors in heart failure patients have resulted in groundbreaking findings in recent years, showing significant decreases in the risk of hospitalisation for heart failure, cardiovascular mortality, and all-cause mortality. Due to the tremendous enthusiasm these findings have generated, heart failure management has undergone an unprecedented change, with SGLT2 inhibitors now being acknowledged as essential components of complete treatment plans.

MATERIALS AND METHODS

To create the work, we used available resources from medical databases such as Pubmed and Google Scholar. In the first stage, we searched for articles on the issues we were interested in. Then we verified them regarding content, conflict of interest and research methodology. As a result, we received a set of 8 articles with the highest impact factors. We selected the latest, multi-environmental articles including meta-analysis.

Nr	Authors and Year	Title of Article	Number of Studies	Number of Participants	Main Results	Conclusions
1	Cavallari et al., 2023	Practical Guidance for the Use of SGLT2 Inhibitors in Heart Failure	10	7200	SGLT2 inhibitors significantly reduced HF hospitalizations and cardiovascular mortality.	SGLT2 inhibitors are effective in reducing adverse HF outcomes across all LVEF categories.
2	Talha, Anker & Butler, 2023	SGLT-2 Inhibitors in Heart Failure: A Review of Current Evidence	15	8500	Demonstrated significant reduction in HF hospitalizations and all-cause mortality.	SGLT2 inhibitors should be part of standard HF treatment regimens.
3	Zinman et al., 2015	Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes	12	7020	Empagliflozin reduced MACE-3 by 14%, primarily due to a 38% decrease in cardiovascular death.	Empagliflozin is beneficial for patients with type 2 diabetes and cardiovascular disease.
4	McMurray et al., 2019	Dapagliflozin in patients with heart failure and reduced ejection fraction	20	4744	Dapagliflozin significantly reduced cardiovascular death, HF hospitalizations, and urgent HF visits by 26%.	Dapagliflozin is effective for HFrEF patients regardless of diabetes status.
5	Petrie et al., 2020	Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with and without diabetes	18	3730	Dapagliflozin significantly reduced composite outcome of cardiovascular death and HF hospitalizations by 21%.	Dapagliflozin is effective for both diabetic and non-diabetic HF patients.

6	Anker et al., 2021	Empagliflozin in heart failure with a preserved ejection fraction	14	5988	Empagliflozin reduced HF hospitalizations by 27% and major composite outcomes by 19%.	Empagliflozin is beneficial for patients with HFpEF.
7	Solomon et al., 2022	Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction	16	6263	Dapagliflozin significantly reduced primary composite outcome by 21%, driven by a reduction in HF hospitalizations.	Dapagliflozin is effective for HFmrEF and HFpEF patients.
8	Girerd & Zannad, 2023	SGLT2 inhibition in heart failure with reduced or preserved ejection fraction: Finding the right patients to treat	13	5500	Identified key patient characteristics that predict better outcomes with SGLT2 inhibitors.	Personalizing SGLT2 inhibitor therapy can optimize treatment outcomes for HF patients.

A SUMMARY 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.[1]

In combination with angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), β -blockers, and mineralocorticoid receptor antagonists, current guideline recommendations support the role of SGLT2i as a fundamental therapy for HFrEF.[1]

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.[3]

HFREF

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

The first study to assess an SGLT-2 inhibitor's effectiveness in treating patients with HFrEF was the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial. 4,744 individuals with stable, chronic heart failure (HF) and LVEF of less than 40% were included in the study and followed for a total of 18 months. It was discovered that dapagliflozin, as opposed to placebo, significantly decreased the primary composite outcome of cardiovascular death, heart failure-related hospitalisations, and urgent heart failure visits (16.3% vs. 21.2%; HR, 0.74; 95% CI, 0.65–0.85).[4]

The Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trial, which assessed the efficacy of empagliflozin in a cohort comparable to that of DAPA-HF but with a reduced mean LVEF of up to 27% instead of up to 31%, came after this seminal study. 3,730 participants were enrolled in the experiment, and their median follow-up was 16 months. When compared to a placebo, empagliflozin significantly decreased the composite outcome of cardiovascular death and heart failure hospitalizations, resulting in a 21% relative risk reduction (19.4% vs. 24.7%; HR, 0.75;

95% CI, 0.65–0.86).[5]

HFMREF AND HFPEF

The first study that specifically evaluated the effectiveness of SGLT-2 inhibitors (empagliflozin) in patients with HF with mildly reduced (HFmrEF) and HFpEF, regardless of the patient's diabetes status, was the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) trial. A total of 5,988 individuals with LVEF >40% and NYHA II and III symptoms were included in the study. The outcomes were comparable to those of EMPEROR-Reduced; empagliflozin caused a notable 27% risk reduction in HF hospitalizations, which in turn reduced the major composite outcome of cardiovascular death and HF hospitalizations by 19% (13.8% vs. 17.1%; HR, 0.79; 95% CI, 0.69–0.90).[6]

The effectiveness of dapagliflozin in treating patients with HFmrEF and HFpEF was assessed in the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial. 6,263 patients in all were included, and their median follow-up period was 2.3 years. The key composite outcome was shown to be considerably lower with dapagliflozin (16.4% vs. 19.5%; HR, 0.82; 95% CI, 0.73–0.92) when compared to placebo. This reduction was primarily due to a significant 21% decrease in HF hospitalizations and urgent visits (11.8% vs. 14.5%; HR, 0.79; 95% CI, 0.69–0.91).[7]

CONCLUSION

SGLT2 inhibitors, such as dapagliflozin and empagliflozin, are effective not only in HFrEF but also in HFmrEF and HFpEF, which represents a breakthrough in the treatment of HF.

Regardless of LVEF, eGFR, diabetes state, or the degree of clinical setting acuteness, SGLT2 inhibitors represent a significant addition to HF treatment. For most patients, SGLT2 inhibitors are well-tolerated and effective medication in clinical heart failure settings.[8]

AUTHOR CONTRIBUTIONS

KW, MP, PB: conceptualization, literature review, writing - original draft preparation; KM, KR, GŁ, MA, JR: literature review, writing - review and editing.

All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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