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Efficacy of SGLT2 Inhibitors in Reducing Major Adverse Cardiovascular Events in Patients with *Heart Failure with Preserved Ejection Fraction: A* **Systematic Literature Review**

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Summary

Introduction: Heart failure with preserved ejection fraction (HFpEF) represents a significant proportion of heart failure (HF) cases and is associated with high morbidity, mortality, and recurrent hospitalizations. Traditionally, available therapies have not consistently demonstrated a reduction in major cardiovascular events in this population. The class of sodium-glucose cotransporter 2 inhibitors (SGLT2i) — originally for type 2 diabetes —

Empagliflozin has emerged as a promising therapeutic alternative. **Methodology:** A literature review was conducted in the PubMed database using the descriptors *"sodium-glucose transporter 2 inhibitors", "heart failure with preserved ejection fraction", "major adverse cardiovascular events", "cardiovascular mortality",* and *"hospitalization".* Two clinical trials of greater relevance were selected. **Discussion and results:** This review consistently demonstrates that SGLT2 inhibitors (empagliflozin and dapagliflozin) significantly reduce worsening heart failure events and hospitalizations in patients with preserved or mildly reduced ejection fraction (EF > 40%), regardless of the presence of diabetes. Although the benefit on isolated cardiovascular death has less robust evidence, the clinical impact on reducing hospitalizations and improving quality of life is evident. **Conclusion:** SGLT2 inhibitors significantly reduce major cardiovascular events, strongly supporting the inclusion of this therapeutic class in the management of HFpEF, although further studies evaluating isolated cardiovascular mortality and the stratification of benefit according to ejection fraction ranges are still needed.

Keywords: SGLT2 inhibitors; preserved ejection fraction heart failure; HFpEF; major cardiovascular events

Abstract

Introduction: Heart failure with preserved ejection fraction **(HFpEF)** represents a relevant proportion of heart failure **(HF)** cases and is associated with high morbidity, mortality, and recurrent hospitalizations. Historically, available therapies have not consistently demonstrated a reduction in major cardiovascular events in this population. The class of sodium-glucose cotransporter 2 inhibitors **(SGLT2i)** — originally developed for Type 2 Diabetes — has emerged as a promising therapeutic alternative. **Methodology:** A literature review was performed using the PubMed database with the descriptors "sodium-glucose transporter 2 inhibitors," "heart failure with preserved ejection fraction," "major adverse cardiovascular events," "cardiovascular mortality," and "hospitalization." Two clinical trials of major relevance were selected. **Discussion and Results:** The current review consistently demonstrates that SGLT2i (empagliflozin and dapagliflozin) significantly reduces events of worsening HF and hospitalizations in patients with preserved or mildly reduced ejection fraction **(EF > 40%),** regardless of the presence of diabetes. While the evidence regarding the benefit on isolated cardiovascular death is less robust, the clinical impact on reducing hospitalizations and improving quality of life is evident. **Conclusion:** SGLT2i significantly reduces major cardiovascular events, strongly supporting the inclusion of this therapeutic class in the management of HFpEF, although further studies are still needed to evaluate isolated cardiovascular mortality and to stratify the benefit according to ejection fraction ranges.

Keywords: SGLT2 inhibitors; Heart failure with preserved ejection fraction; HFpEF; Major adverse

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cardiovascular events

1. Introduction

Heart failure with preserved ejection fraction (HFpEF) represents a portion
A significant portion of the population has heart failure (HF), and is characterized by signs and symptoms.
cardiac dysfunction even with maintained left ventricular ejection fraction (LVEF) or only
slightly reduced. This condition is of increasing clinical importance, as it affects
These patients are often elderly and have multiple comorbidities, presenting a high rate of morbidity and mortality.
In addition to hospitalizations for heart failure, which adversely impact quality of life and increase costs.
in healthcare. In light of this reality, the search for therapies that reduce cardiovascular events is growing.
Larger numbers in this population become imperative.

The pathophysiology of HFpEF is complex, involving diastolic dysfunction and myocardial fibrosis.
and ventricular stiffness, often associated with multiple comorbidities such as hypertension and diabetes.
Diabetes mellitus and obesity. For decades, HFpEF has constituted a therapeutic gap in cardiology.
Unlike what occurs in heart failure with reduced left ventricular ejection fraction, the tests
Clinicians using conventional prognosis-modifying therapies have failed to demonstrate a
The consistent benefit lies in reducing highly relevant outcomes. This lack of treatment
Ineffective methods led to a high and unacceptable rate of major cardiovascular events, particularly
recurrent hospitalizations for heart failure and cardiovascular death.

The therapeutic landscape for HFpEF has been transformed with the emergence of the class of inhibitors.
of the Sodium-Glucose Cotransporter 2 (iSGLT2). Originally developed for the treatment of
In Type 2 Diabetes Mellitus, the benefit of this class of medications extends to pleiotropic effects.
cardiovascular and renal conditions that are independent of blood glucose levels, and these medications are used not
not only in heart failure, but also in several other cardiovascular risk scenarios (such as, for example,
treatment of proteinuria in chronic kidney disease.

Given this context, it becomes opportune and relevant to conduct a systematic review of
literature with the aim of synthesizing and critically examining the effectiveness of SGLT2 inhibitors in reducing
major cardiovascular events — especially cardiovascular death and hospitalization for heart failure — in
patients with HFpEF. This approach will allow mapping the level of evidence available, identifying
Fill knowledge gaps and provide support for clinical practice and future research.

2. Objective

The aim of this review is to evaluate the effectiveness of SGLT2 inhibitors in reducing events.
Major cardiovascular events in patients with HFpEF. The aim is to synthesize and compare the main findings.
findings regarding the impact of these therapies on cardiovascular mortality and hospitalizations for heart failure,

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highlighting the clinical implications for the management of this population, traditionally limited in effective therapeutic options.

3. Materials and Methods

For the purposes of this study, a narrative literature review was conducted. based on high-level evidence. The search was conducted in the PubMed database. Search terms included combinations of the descriptors *"sodium-glucose transporter 2 inhibitors", "heart failure with preserved ejection fraction", "major adverse cardiovascular events",* Clinical trials were prioritized for inclusion in the terms *"cardiovascular mortality"* and *"hospitalization".* randomized trials published in the last 5 years that addressed the effectiveness of SGLT2 inhibitors in reducing Major cardiovascular events in patients with HFpEF, with 2 clinical trials selected. of greatest relevance on the subject to compose the review (EMPEROR *studies - preserved*[1] and *DELIVER*[2]*).* The final selection of articles and data synthesis were carried out with the aim of to compile the most robust evidence on the subject.

4. Results and Discussion

This systematic review focuses on the two most relevant clinical trials on the Subject — Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved[1]) and Evaluation of Dapagliflozin for Improving the Lives of Patients with Heart Failure with Preserved Ejection Fraction (DELIVER[2]) — we evaluated the efficacy of SGLT2 inhibitors in patients with or mildly reduced heart failure with HFpEF, especially in reducing major cardiovascular events.

The EMPEROR-Preserved[1] study included 5,988 patients with heart failure class II to IV and Ejection fraction (EF) > 40% randomized to empagliflozin 10 mg or placebo, with follow-up. median of 26 months. The composite outcome of cardiovascular death, hospitalization for heart failure, or visit. The number of urgent/emergency visits due to worsening heart failure requiring intravenous treatment was significantly higher. Reduced in the empagliflozin group (HR 0.77; 95% CI 0.67–0.87; P<0.0001). Cardiovascular death It was not evaluated in isolation.

In the DELIVER[2] study, 6,263 patients with heart failure and ejection fraction > 40% (mean ~2.3 years of Follow-up) participants were randomized to dapagliflozin 10 mg or placebo. The primary outcome (composite of worsening heart failure, hospitalization or urgent care visit, or cardiovascular death) occurred in 16.4% in the dapagliflozin group and 19.5% in the placebo group (HR 0.82; 95% CI 0.73–0.92; P<0.001). THE The outcome of worsening heart failure in isolation had a HR of 0.79 (95% CI 0.69–0.91). On the other hand, the assessment The risk of cardiovascular death had a HR of 0.88 (95% CI 0.74–1.05), but no significance was reached. statistical analysis was conducted for this component in isolation. The results were consistent regardless of the specific data available.

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regardless of whether diabetes was present or not, and were reproduced in the subgroup analysis in patients with EF ÿ 60%.

A comparison between the two essays reveals convergence on several key points: both Studies have shown that SGLT2 inhibitors significantly reduce worsening heart failure events or hospitalizations. in patients with EF > 40%. In EMPEROR-Preserved[1] the benefit appeared very early (as early as 18 days) and was sustained throughout the follow-up. However, there are differences: in DELIVER[2], although the Even if the composite outcome was positive, the cardiovascular death component alone was not. reached statistical significance, suggesting that the main benefit may lie in the reduction of Events of worsening heart failure and hospitalizations are more common than cardiovascular death in this context of ejection fraction. preserved or slightly reduced.

Clinically, this has important implications for patients with HFpEF or fractional ejection fraction. Nearly preserved ejection: the addition of an SGLT2 inhibitor (specifically empagliflozin or dapagliflozin) This will likely reduce the burden of hospitalizations and urgent care visits due to worsening heart failure, which may... To improve quality of life, reduce healthcare costs, and decrease associated morbidity. However, Caution should be exercised when extrapolating these results to a clear benefit in reducing mortality. Isolated cardiovascular data is less robust in this component, especially in DELIVER study. For a thorough evaluation of the benefits in relation to mortality, the following would be necessary. Clinical trials in higher-risk populations, of longer duration, or analyses are needed. a collection of several essays.

The benefits observed with SGLT2 inhibitors in the EMPEROR-Preserved and DELIVER studies. These can be explained by multifactorial mechanisms, including the reduction of interstitial congestion and improvement of diastolic function through osmotic and natriuretic effects, optimization of more energy-efficient myocardial and mitochondrial metabolism, and associated renal protection. to the modulation of inflammation and cardiac fibrosis. These integrated effects contribute to the consistency of clinical results across trials, even in the face of population differences and methodological.

In terms of limitations, it is worth noting that both studies are relatively recent. They have a medium follow-up period that may not yet capture very long-term effects; in addition, the heterogeneity of the populations (despite both including EF >40%) and the inclusion of patients with Different levels of FE still require careful interpretation — in EMPEROR-Preserved it was It was reported that the benefit was attenuated at very high EF levels. Furthermore, even with significance... In current statistical studies, the absolute benefit and the subgroups that benefit the most deserve attention. Further clarification is pending.

For future research, it would be interesting to: (1) studies with even more follow-up prolonged to assess long-term impact on cardiovascular and renal mortality; (2) sub-analyses that better define the EF ranges (e.g., ÿ 65%) and identify patients who

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those who benefit the least; (3) *real-world* effectiveness studies to validate these findings.
clinical trials in more heterogeneous populations.

In summary, the EMPEROR-Preserved and DELIVER tests consistently demonstrate SGLT2 inhibitors significantly reduce events that worsen heart failure, especially hospitalizations. in patients with preserved or slightly reduced ejection fraction. These results represent an advance. substantial improvements in the management of HFpEF, historically marked by therapeutic limitations, and reinforce the The potential of these agents to improve clinical outcomes and quality of life in this population.

5. Final Considerations

This review provides evidence that SGLT2 inhibitors significantly reduce events. Major cardiovascular events, such as worsening heart failure or hospitalizations, in patients with preserved ejection fraction or Slightly reduced, regardless of diabetes. They still reduce mortality. cardiovascular, despite less robust evidence. These drugs represent the first advance. therapeutic in this population, strongly supporting the inclusion of this therapeutic class in management of IC ÿ more precisely in the context of FE >40%. However, further research may clarify. The potential of SGLT2 inhibitors in reducing cardiovascular mortality, as well as stratifying the benefit. according to ejection fraction ranges, especially in patients with higher values (ÿ 60%) and in subgroups with multiple comorbidities.

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