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The Role of SGLT2 Inhibitors in Cardiovascular Outcomes for Heart Failure Patients with Reduced Ejection Fraction

Faraaz Zaveri[1*], Saria Naser[2]
[1]*Department of Cardiology, Texila American University, Nicaragua*
[2]*Department of General Medicine, Soochow University, China*

Abstract

This review article examines the effect of sodium-glucose cotransporter-2 (SGLT2) inhibitors on cardiovascular (CV) outcomes in patients with heart failure with reduced ejection fraction (HFrEF). The SGLT2 inhibitors, while being developed for type 2 diabetes management, are showing great promise in reducing hospitalization for heart failure and major adverse cardiovascular events: benefits shown in major trials like Dapagliflozin in patients with Heart failure and reduced Ejection fraction (DAPA-HF) and Empagliflozin outcome trial in patients with chronic Heart Failure and a Reduced Ejection fraction (EMPEROR-Reduced). The review underlines the therapeutic implications of SGLT2 inhibitors in both diabetic and nondiabetic patients with HFrEF for improving survival rates, the risk of hospitalization, and renal function preservation. These trials had an in-depth methodology and results review, after which a discussion on the clinical implications took place to decide on the wide application of SGLT2 inhibitors in managing HFrEF independent of their diabetes status.

Keywords*: Cardiovascular Outcomes, Dapagliflozin, Empagliflozin, Heart Failure, Hfref, SGLT2 Inhibitors.*

Introduction

Heart failure with reduced ejection fraction remains one of the major chronic public health burdens throughout the world, affecting millions and causing prominent morbidity and mortality. The current management of HFrEF is based on evidence-based therapies focused on beta-blockers, angiotensin-converting enzyme inhibitors, and mineralocorticoid receptor antagonists. Despite these, the prognosis for many patients with heart failure with reduced ejection fraction remains poor, indicating an unmet need for novel treatment options. [1].

SGLT2 inhibitors represent new classes of drugs that have been initially developed as antihyperglycemic agents but showed outstanding cardiovascular benefits among patients with T2DM. The benefits they confer on the prevention of hospitalization for heart failure in the improvement of overall cardiovascular outcomes in diabetic populations have led to their potential benefits being investigated in patients with HFrEF, independent of diabetes status. [2]. This review discusses large trials and studies involving the cardiovascular effects of SGLT2 inhibitors, including dapagliflozin and empagliflozin, among patients with HFrEF.

Materials and Methods

The objective of this review was to evaluate clinical data from the pivotal cardiovascular outcome trials of SGLT2 inhibitors, including the DAPA-HF trial and EMPEROR-Reduced study. Both trials tested SGLT2 inhibitors in both patients without and with type 2 diabetes with HFrEF.

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****Corresponding Author: drfaraazzaveri@outlook.com***

Study Design

The DAPA-HF was a multicenter, randomized, double-blind, placebo-controlled study that involved 4,744 patients with HFrEF (LVEF ≤ 40%). Participants were randomly assigned in a 1:1 ratio to dapagliflozin 10 mg or placebo, on top of standard heart failure therapy. The primary composite endpoint was a decrease in hospitalization for heart failure or cardiovascular death over a median follow-up of 18.2 months.

This finding is supported by results from the EMPEROR-Reduced trial, which randomized 3,730 patients with chronic heart failure with reduced ejection fraction (LVEF ≤40%) to empagliflozin 10 mg or placebo. The primary endpoint was a composite of hospitalization for heart failure and cardiovascular death evaluated over the median follow-up of 16 months. Baseline characteristics of patients included in the DAPA-HF and EMPEROR-Reduced trials are shown in Table 1.

Table 1. Baseline Characteristics of Patients Included in the DAPA-HF and EMPEROR-Reduced Trials

Characteristic	DAPA-HF	EMPEROR-Reduced
Age (years)	66	67
LVEF (%)	31	32
Diabetes (%)	42	49
Hypertension (%)	68	72
Previous MI (%)	34	40

Data Sources

The review was done by collecting and collating all the peer-reviewed clinical trials, meta-analyses, and review articles published between 2015 and 2021. Data were mined from PubMed, clinical trial registries, and leading cardiology journals. Methodology, participant characteristics, endpoints, and statistical analyses were evaluated for the trials.

Results

Results of the DAPA-HF Trial

In the current trial, dapagliflozin significantly reduced the composite risk of heart failure hospitalization and cardiovascular death. [3]. The primary composite outcome occurred in 16.3% of patients receiving dapagliflozin versus 21.2% receiving placebo (HR 0.74, 95% CI 0.65–0.85; p<0.001). Importantly, hospitalization for heart failure was reduced, showing a relative risk reduction of 30% with dapagliflozin compared to placebo, HR 0.70, 95% CI 0.59–0.83.

Dapagliflozin decreased the risk of cardiovascular death by 18%, HR 0.82, 95% CI 0.69–0.98. The benefits of dapagliflozin were preserved for the majority of pre-specified subgroups, including those patients without diabetes, illustrating that it has cardiovascular benefits irrespective of the glycemic status. [4].

Results from EMPEROR-Reduced Trial

Similarly, the results of the EMPEROR-Reduced trial are in agreement with the above-described results, documenting that empagliflozin significantly reduced the risk of the primary composite endpoint-that is, hospitalization for heart failure or cardiovascular death compared with placebo, as follows: 19.4% versus 24.7%; HR 0.75, 95% CI 0.65–0.86; p<0.001. As shown, this reduction was primarily driven by a decrease in hospitalization for heart failure, as assessed by a reduction in risk by 31% with empagliflozin, HR 0.69, 95% CI 0.59–0.81. The heart failure hospitalization rates across different treatments are illustrated in Figure 1.

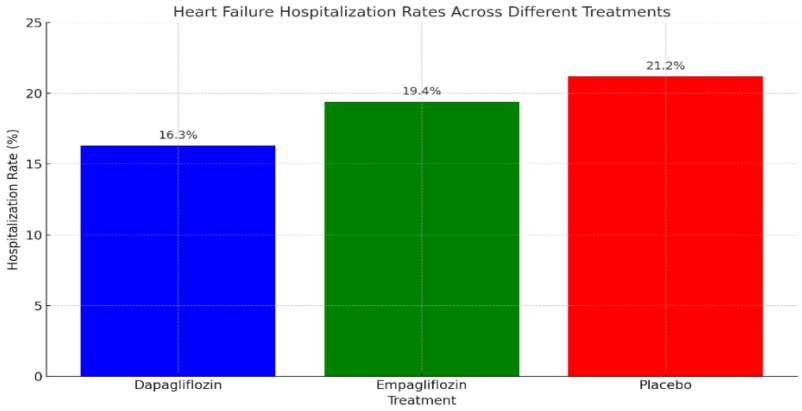

Figure 1. Heart Failure Hospitalization Rates Across Different Treatments

Although the trial did not meet a statistically significant reduction for cardiovascular death alone, the overall cardiovascular benefit of empagliflozin was supported by improvements in symptoms of heart failure and health-related quality of life, as measured by the KCCQ. [5]. The primary outcomes of the DAPA-HF and EMPEROR-Reduced trials are compared in Table 2, detailing the impact on hospitalizations and mortality.

Table 2. Primary Outcomes in the DAPA-HF and EMPEROR-Reduced Trials, Comparing the Impact of Dapagliflozin, Empagliflozin, and Placebo on Heart Failure Hospitalizations, Cardiovascular Deaths, and All-cause Mortality

Outcome	**Dapagliflozin (%)**	**Empagliflozin (%)**	**Placebo (%)**
Heart Failure Hospitalization	16.3	19.4	21.2
Cardiovascular Death	18	17.1	22
All-Cause Mortality	26.3	25.1	30.2

Moreover, Figure 2 compares cardiovascular outcomes between dapagliflozin, empagliflozin, and placebo, showing the percentage reduction in key outcomes.

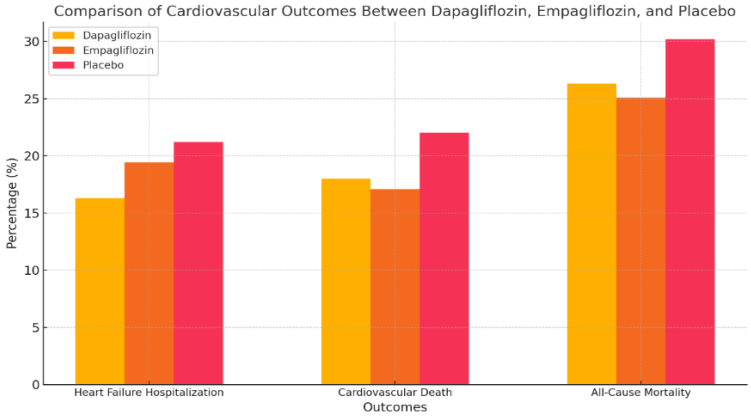

Figure 2. Comparison of Cardiovascular Outcomes Between Dapagliflozin, Empagliflozin, and Placebo, Showing Percentage Reduction in Heart Failure Hospitalization, Cardiovascular Death, and All-Cause Mortality

Renal Outcomes

The second tested renal outcomes as secondary endpoints. Both dapagliflozin and empagliflozin attenuated the decline in renal function-the rate of eGFR decline was reduced in both. [6]. Dapagliflozin lowered the risk of

worsening renal function by 30% in the DAPA-HF trial, while empagliflozin slowed the rate of renal function decline by 50% relative to placebo in the EMPEROR-Reduced trial.

Discussion

The DAPA-HF and EMPEROR-Reduced results are considered a landmark development in the management of HFrEF. These findings support the integration of SGLT2 inhibitors into the standard GDMT for HFrEF, regardless of the presence of diabetes. The resultant decrease in heart failure hospitalizations and cardiovascular events certainly speaks to the strong cardioprotective features of SGLT2 inhibitors.

The exact mechanisms through which SGLT2 inhibitors exert these protective effects remain under investigation. Proposed mechanisms include reductions in plasma volume, improved cardiac energy metabolism, and modulation of renal function. Importantly, the diuretic effects of SGLT2 inhibitors, combined with their ability to reduce preload and afterload, likely contribute to the favourable cardiovascular outcomes observed in these trials.

Conclusion

SGLT2 inhibitors have emerged as part of the cornerstone in managing patients with HFrEF, offering significant reductions in heart failure-related hospitalizations and improvements in cardiovascular outcomes. Evidence from the DAPA-HF and EMPEROR-Reduced studies is quite convincing for establishing both dapagliflozin and empagliflozin within the standard armamentarium in HFrEF, independently of the diabetes status. Future studies should further elucidate mechanisms underlying these benefits and their potential applications in wider heart failure populations.

Conflict of Interest

The authors declare no conflict of interest.

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