Journal of the Saudi Heart Association

Volume 37 | Issue 1 Article 2

2025

Effectiveness of Empagliflozin in Treating Patients with Heart Failure with Preserved Ejection Fraction: A Systematic Review

Recommended Citation

Al-Saud, Sara Abou (2025) "Effectiveness of Empagliflozin in Treating Patients with Heart Failure with Preserved Ejection Fraction: A Systematic Review," *Journal of the Saudi Heart Association*: Vol. 37 : Iss. 1 , Article 2.
Available at: https://doi.org/10.37616/2212-5043.1412

Effectiveness of Empagliflozin in Treating Patients With Heart Failure With Preserved Ejection Fraction: A Systematic Review

Sara Abou Al-Saud

Department of Cardiac Sciences, College of Medicine, King Saud University, P.O. Box 7805, Riyadh 11472, Saudi Arabia

Abstract

Aim: **The goal of this systematic review is to determine the effectiveness of empagliflozin in managing patients with heart failure with preserved ejection fraction (HFpEF) as compared with a placebo.**

Methods: **Web of Science, Cochrane, PubMed, and Scopus databases were searched for articles from 2000 to 2023. Reference lists of articles were manually screened. Trials that recruited patients with HFpEF and reported the effects of empagliflozin were included. Endnote X9 software was used for the study screening process.**

Results: **1029 non-duplicate articles were identified from the literature and 9 were selected for inclusion in this review. The included papers were all randomized controlled trials (RCTs). According to the findings, empagliflozin reduces the risk of cardiovascular mortality, hospitalization for heart failure, and urgent heart failure visit to the hospital, as compared to placebo treatment. Empagliflozin was also associated with improved quality of life and lower occurrence of severe adverse events. Additionally, there were no significant differences between the treated and placebo groups, regarding the occurrence of adverse events or ability to exercise. The effect of empagliflozin was found to be better in Mineralocorticoid Receptor Antagonists (MRA) non-users and non-diabetic HFpEF patients. The effectiveness of empagliflozin was unaffected by age or gender.**

Conclusion: **Empagliflozin treatment for HFpEF patients appears to be both safe and efficient when compared to a placebo, according to data of moderate quality.**

Keywords: Empagliflozin, Heart failure, Diastolic dysfunction, SGLT2 inhibitors, Clinical trial, Treatment outcomes

1. Introduction

Heart failure is a chronic condition that progresses over time, often requiring more intensive management during episodes of clinical deterioration. These episodes can often be managed in outpatient settings such as offices, clinics, or emergency facilities [1]. It is a serious medical condition affecting an estimated 64 million individuals globally, with significant economic implications [2,3]. Patients may present with either reduced or preserved ejection fraction.

Heart failure with preserved ejection fraction (HFpEF) affects approximately half of all heart failure patients and is associated with high morbidity and mortality rates [4]. Unlike heart failure with reduced ejection fraction (HFrEF), which can be treated with therapies targeting neurohormonal overactivity [5], treatment options for HFpEF are limited. While neprilysin inhibitors and mineralocorticoid-receptor antagonists offer some benefits, these effects have been modest and restricted to specific patient subgroups [6,7].

Recent innovations, particularly sodium-glucose cotransporter 2 (SGLT2) inhibitors and vericiguat, have shown promising outcomes across the heart failure spectrum [8]. SGLT2 inhibitors have demonstrated efficacy in managing type 2 diabetes

Received 27 August 2024; revised 24 October 2024; accepted 4 December 2024.
Available online 8 February 2025

E-mail address: saboualsaud@ksu.edu.a.

https://doi.org/10.37616/2212-5043.1412

mellitus [9] and have consistently outperformed placebo in reducing heart failure hospitalizations and mortality rates, regardless of heart failure presence [10]. Specifically, in diabetic patients, SGLT2 inhibitors have reduced the incidence of heart failure admissions and overall mortality by 23 % [11].

Evidence from recent randomized controlled trials (RCTs) and meta-analyses indicates that SGLT2 inhibitors can improve cardiovascular outcomes in HFpEF patients [12]. Cheema et al. [13] analyzed multiple SGLT2 inhibitors—including empagliflozin—and found a significant reduction in heart failure hospitalization and cardiovascular death. Similarly, Banerjee et al. [14] reported improved cardiovascular outcomes associated with empagliflozin and other SGLT2 inhibitors. Other studies also supported these findings, highlighting the collective effectiveness of various SGLT2 inhibitors [15,16]. However, studies by Fukuta et al. [12] and Zhou et al. [16] specifically focused on patients with preserved ejection fraction.

Crucially, these reviews did not compare the effectiveness of individual SGLT2 inhibitors, making it difficult to discern the specific benefits of empagliflozin, despite evidence suggesting its unique effects in diabetes management [3,9–11]. An RCT by Posch et al. [17] noted that sotagliflozin outperformed empagliflozin in certain metabolic parameters among type 2 diabetes patients. Therefore, to address this gap, this review focuses solely on empagliflozin and its impact on patients with heart failure and preserved ejection fraction.

1.1. Research question

Is empagliflozin safe and effective in managing patients with HFpEF?

2. Materials and methods

This systematic review did not have a formal protocol registered. However, we followed standard practices for systematic reviews as outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review process adhered to the established Cochrane recommendations and the PRISMA statement for systematic reviews [18,19]. We implemented the PRISMA guidelines by conducting a comprehensive literature search, defining clear inclusion and exclusion criteria, performing quality assessments, and extracting data in a systematic manner.

Abbreviations

HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
MRA	Mineralocorticoid Receptor Antagonists
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized controlled trials
SGLT2	Sodium-glucose cotransporter 2

3. Literature search

A manual and electronic search of publications from digital dissertation databases, including Scopus, Web of Science, PubMed, and the Cochrane CENTRAL Register for Controlled Trials, was conducted for articles published from 2000 to 2023. The search was restricted to human-only articles in English that used the terms “Empagliflozin” and “heart failure with preserved ejection fraction” OR “HFpEF” as keywords or MeSH terms. Additionally, the reference lists of the resulting articles were thoroughly checked for further relevant studies. The search strategy for each database is summarized in Table 1.

3.1. Inclusion criteria

Trials included in this review studied the long-term effects (>1 month) of empagliflozin compared with a placebo in managing HFpEF patients.

3.2. Exclusion criteria

The following were excluded from this review:

- Systematic reviews
- Case studies
- Non-journal articles

Table 1. Search strategies.

Database	Search Strategy
Web of science	(Empagliflozin AND (HFpEF OR “heart failure with preserved ejection fraction”))
PubMed	(Empagliflozin [tiab]) AND HFpEF OR (“heart failure with preserved ejection fraction") *Filters applied: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review, from 2000 - 2024.*
Cochrane	Year range: Jan 2000 to November 2023 Empagliflozin AND (“heart failure with preserved ejection fraction” OR HFpEF) in title abstract keyword
Scopus	TITLE-ABS- ((empagliflozin AND (HFpEF OR “heart failure with preserved ejection fraction”)))

Table 2. Study description table.

Author	Study Design	Region	Sample Size	Definition of Preserved EF	Follow up Period	Objective/Theme of the Study
Anker et al., [22]	RCT	Global	5988	>40 %	3 months	Determining how empagliflozin affects heart failure outcomes in HFpEF patients.
Butler et al., [26]	RCT	Global	5988	>40 %	52 weeks	To assess the impact of empagliflozin on HFpEF patients' quality of life
Ferreira et al., [27]	RCT	Global	5988	>40 %	3 months	Empagliflozin's impact on HFpEF patients who take and those who don't utilize MRA
Böhm et al., [30]	RCT	Global	5988	>40 %	1.5 months	To assess the interaction between age and empagliflozin effects in patients with HFpEF.
Anker et al., [23]	RCT	Global	5988	>40 %	33 months	To provide empagliflozin effects reports based on DELIVER endpoints that were predetermined.
Abraham et al., [25]	RCT	Global	5988	>40 %	3 months	To assess how empagliflozin affects patients with HFrEF and HFpEF's capacity for exercise.
Butler et al., [28]	RCT	Global	5988	>40 %	26 months	To determine whether sex has an impact on how empagliflozin works for HFpEF patients.
Packer et al., [24]	RCT	Global	1200	>40 %	3 months	To provide information on how empagliflozin affects all categories of patients with HFpEF
Filippatos et al., [29]	RCT	Global	5988	>40 %	1.5 months	To evaluate the impact of empagliflozin on HFpEF patients' baseline diabetic status.

NOTE: HFpEF- heart failure with preserved ejection fraction, MRA- Mineralocorticoid Receptor Antagonists, DELIVER-Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction Heart Failure.

- Meta-analyses
- Conference proceedings
- Editorials and commentaries
- Additionally, studies that did not address the effects of empagliflozin in managing HFpEF patients or were animal studies were excluded.

3.3. Quality assessment

An independent assessment of the included trials' quality was conducted using the Cochrane tool for risk of bias assessment (Figs. 2 and 3) [20] (see Table 2). Four domains were used to measure the risk of bias: randomization, blinding, intention-to-treat analysis, and attrition. This assessment was performed by multiple reviewers, and discrepancies were resolved through discussion.

3.4. Data extraction

Data were extracted by multiple reviewers using a pre-created study descriptor table. This approach ensured thoroughness and accuracy in data collection. In cases where discrepancies arose between reviewers, they were resolved through discussion and consensus. If consensus could not be reached, a third reviewer was consulted to provide an objective resolution. The following information was extracted: lead author, year of publication, type of study, study area, sample size, definition of preserved ejection fraction, follow-up time, and study objectives.

4. Results

4.1. Search results

The literature search identified 1029 non-duplicate articles. After screening titles and abstracts, 1015 were excluded for not meeting the exclusion criteria or failing to report on empagliflozin's effects. Of the remaining 14 articles, only nine fully met the inclusion criteria upon full review. The study selection process is illustrated in the PRISMA flowchart in Fig. 1.

4.2. Quality assessment results

Using the Cochrane risk of bias tool, all studies showed a low risk of selection bias. Four studies had an unclear risk of performance bias, eight had a low risk of detection bias, and one had an unclear risk. Additionally, four studies had an unclear risk of attrition bias, three had an unclear risk of reporting bias, two had a high risk of other biases, and four had an unclear risk of other biases (Fig. 2).

4.3. Data extraction results

All studies were published in 2021 and 2022 and involved a similar sample population of 5988 participants [22–24,26–30], except for Abraham et al. [25], which had a sample size of 315. The follow-up period ranged from 1.5 to 33 months.

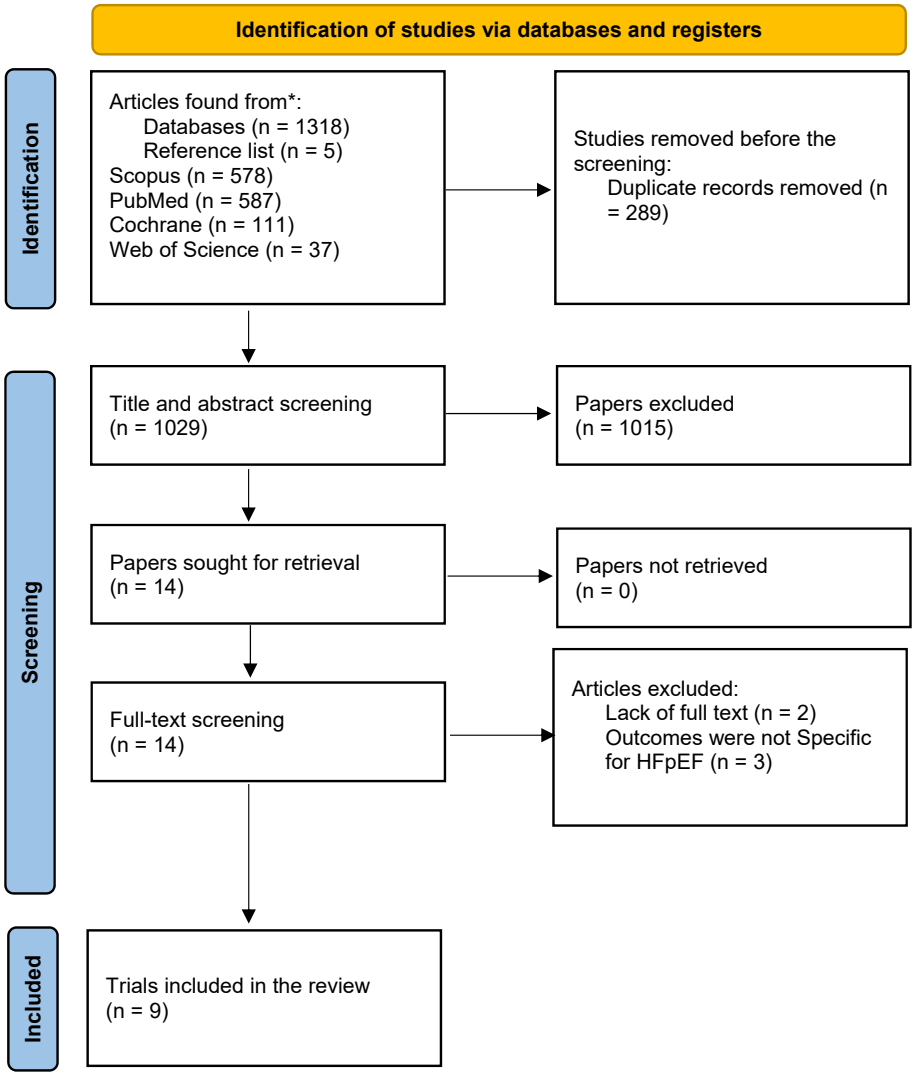

Fig. 1. The study selection process according to PRISMA

4.4. Analysis and consistent themes

Using thematic analysis as outlined by Braun & Clarke [21], dominant themes from the collected papers were highlighted and evaluated. All nine publications were included in the qualitative analysis. Key themes were categorized into quality of life, exercise capacity, prevention of cardiovascular mortality and heart failure-related hospitalizations, safety profile, and treatment effects across various subgroups.

4.5. Efficacy of empagliflozin on prevention of mortality and admissions due to heart failure

Anker et al. [22] recruited 5988 patients with HFpEF for their event-driven RCT (EMPEROR-Preserved trial) in 2021 across 622 centers in 23 countries. Eligible patients were randomized to receive 10 mg of empagliflozin daily or a placebo alongside their standard heart failure medications. After 3, 8, and 12 months of double-blind therapy, cardiovascular fatalities occurred in 415 patients (13.7 %) receiving empagliflozin and 511 (17.2 %) receiving placebo. Hospitalizations for heart failure were reported in 259 patients (9 %) in the empagliflozin group and 352 (12 %) in the placebo group.

In 2022, Anker et al. [23] evaluated the effects of a DELIVER-like definition on the results of the EMPEROR-Preserved trial. According to the DELIVER endpoint criteria, cardiovascular fatalities were 13.1 % for empagliflozin and 16.8 % for placebo ($p = 0.0001$). Considering urgent heart failure visits, the relative risk reduction (RRR) increased from 20 % to 26 %, with patients having an ejection fraction of 60 % showing a 28 % RRR compared to the overall 24 %. Deaths due to cardiovascular disease were 6.1 % in the empagliflozin group versus

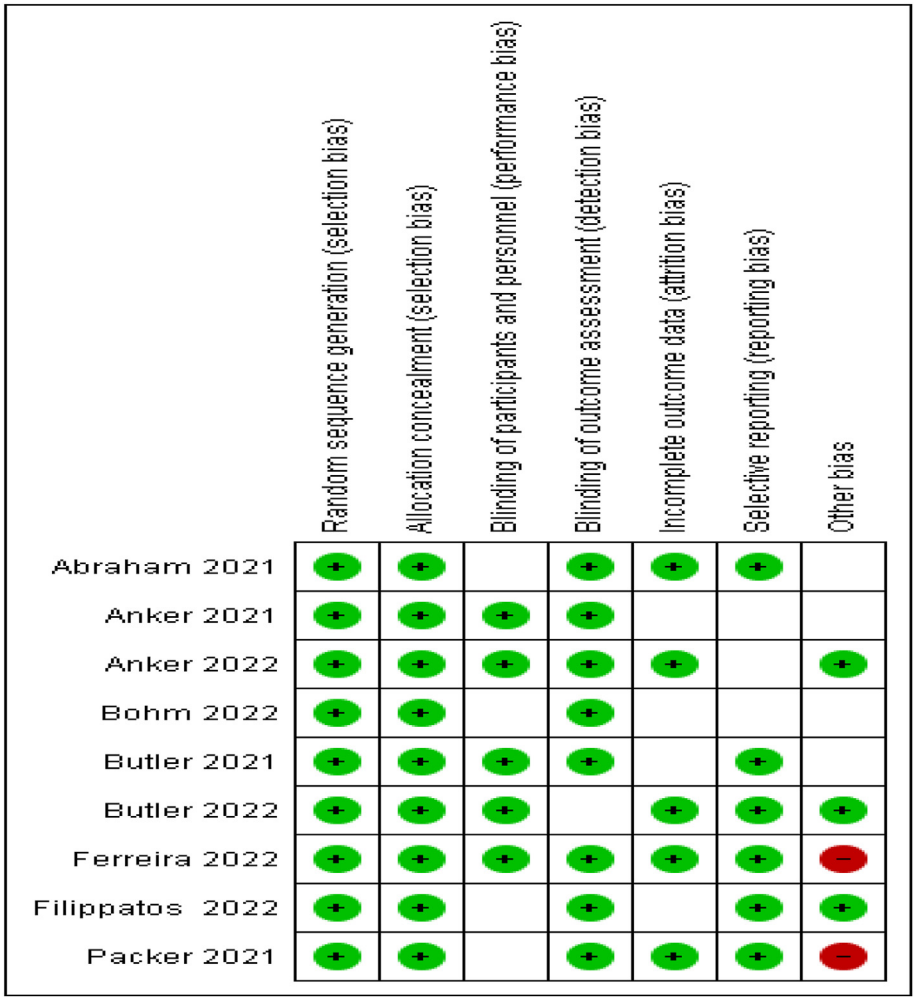

Fig. 2. Risk of bias summary.

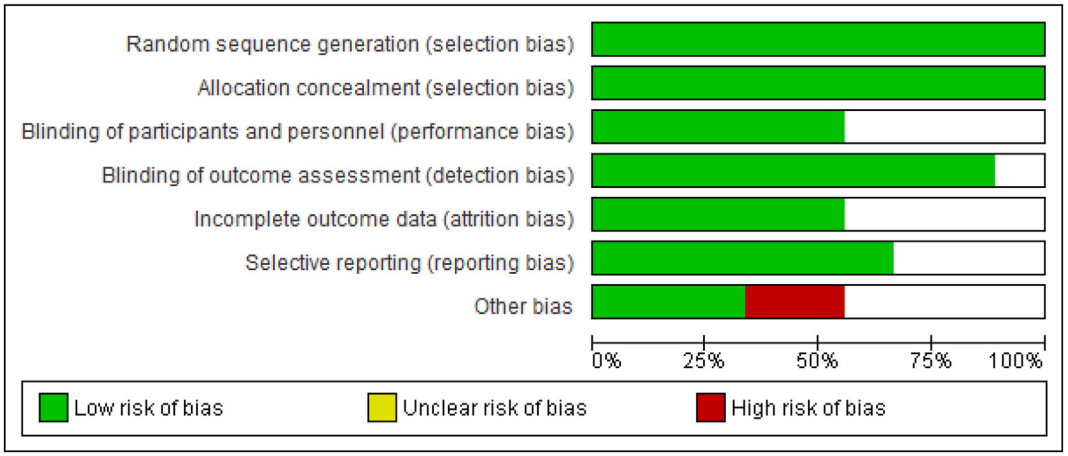

Fig. 3. Risk of bias graph.

7.2 % in the placebo group, with the RRR for the composite renal endpoint rising from 21.4 % to 40.2 % ($p = 0.037$) among patients with an ejection fraction of 60 %.

In a multicenter randomized controlled study by Packer et al. [24], empagliflozin was compared to placebo regarding outpatient and inpatient heart failure episodes. They prospectively gathered data

on worsening heart failure incidents. Empagliflozin reduced cardiovascular mortality, heart failure hospitalization, and urgent heart failure visits (432 patients with empagliflozin vs. 546 with placebo), with statistical significance achieved after 18 days. Empagliflozin also decreased critical care admissions (HR, 0.72 [95 % CI, 0.51−0.97]; P = 0.029) and admissions requiring inotropic medication or vasopressors (HR, 0.73 [95 % CI, 0.56−0.98]; P = 0.034). Patients on empagliflozin were 25 %−55 % more likely to improve in New York Heart Association functional class, with significant effects at 12 weeks sustained for at least two years. Additionally, empagliflozin users reported less frequent outpatient diuretic intensification (482 vs. 610) compared to the placebo group. The reduction in total heart failure admissions was similar across patients with ejection fractions between 40 % and 60 %, though effects were less pronounced at higher ejection fractions.

4.6. The safety profile of empagliflozin as compared with placebo

According to Anker et al. [22], 1543 patients in the placebo group and 1436 in the empagliflozin group experienced significant side events. Treatment discontinuation due to adverse events occurred in 571 patients (19.2 %) in the empagliflozin group and 551 patients (18.3 %) in the placebo group. Abraham et al. [25] reported no significant differences in overall rates of adverse events or those resulting in treatment termination (47.7 % for empagliflozin vs. 47.4 % for placebo), although severe adverse events were less common with empagliflozin (13.5 % vs. 17.3 %).

Packer et al. [24] found that empagliflozin patients had fewer emergency room or intensive care unit visits due to worsening heart failure (298 events in the placebo group vs. 174 in the empagliflozin group). After defining a worse heart failure event as cardiac death, admission for heart failure, or an emergency visit requiring intravenous treatment, there were 546 events in the placebo group compared to 432 in the empagliflozin group, indicating a 24 % reduced risk of worse heart failure events with empagliflozin.

4.7. Empagliflozin Compared with Placebo on Quality of Life and the Ability to Exercise in HFpEF Patients

In 2021, Butler et al. [26] used the Kansas City Cardiomyopathy Questionnaire (KCCQ-23) to assess the quality of life in HFpEF patients. The KCCQ scores were categorized into three areas: (1) Total Symptom Score (TSS), combining symptom incidence and burden; (2) Clinical Summary Score (CSS), combining physical constraint and TSS; and (3) Overall Summary Score (OSS), merging quality of life, social constraint, and CSS. Scores range from 0 to 100, with 100 being the highest. Patients on empagliflozin showed significant improvements in mean KCCQ scores at 10, 34, and 48 weeks compared to those on placebo: CSS increased by 1.04, 1.26, and 1.51 points; TSS by 1.78, 1.54, and 2.08 points; and OSS by 1.09, 1.54, and 1.59 points, respectively [26].

Abraham et al. [25] investigated the impact of empagliflozin on exercise ability in HFpEF patients, finding no significant difference in 6-min step counts between empagliflozin and placebo groups, and KCCQ scores were similar for both groups.

4.8. Impact of empagliflozin compared with placebo in different subgroups of HFpEF patients

In 2022, Ferreira et al. [27] examined the effects of empagliflozin in patients using mineralocorticoid receptor antagonists (MRA). Among 5988 patients, 2244 (37.5 %) were MRA users. MRA users showed higher incident rates, but there was no significant difference in the benefits of empagliflozin on the primary outcome between MRA users and non-users (HR: 0.74 [95 % CI: 0.61−0.88] vs. HR: 0.86 [95 % CI: 0.69−1.06]; P = 0.21). However, non-users experienced greater reductions in heart failure admissions (HR: 0.61 [95 % CI: 0.46−0.76] vs. HR: 0.91 [95 % CI: 0.67−1.20]; interaction P = 0.039). Empagliflozin also reduced the risk of hyperkalemia regardless of MRA use (MRA non-users: HR: 0.91 [95 % CI: 0.70−1.20]; MRA users: HR: 0.75 [95 % CI: 0.55−0.95]; interaction P = 0.28), with hyperkalemia events being nearly twice as common in MRA users [27].

In the EMPEROR-Preserved trial, Butler et al. [28] assessed the impact of sex on empagliflozin effects. Among 5988 patients, 2676 (44.7 %) were women. Women in the placebo group had a generally lower risk of adverse outcomes. Both sexes experienced similar reductions in cardiovascular mortality or heart failure admissions with empagliflozin (HR: 0.82 [95 % CI, 0.68−0.95] for men; HR: 0.75 [95 % CI, 0.61−0.92] for women). The relationship between empagliflozin and outcomes was consistent across all ejection fraction groups, with both genders showing significant increases in KCCQ Clinical Summary Scores (1.39 for men vs. 1.64 for women at 52 weeks) [28].

Filippatos et al. [29] investigated empagliflozin's effects in patients with and without diabetes, with

2938 (49 %) of the 5988 enrolled individuals having diabetes. Diabetic patients had a higher risk of the primary outcome, which included first heart failure admission or cardiovascular mortality. Empagliflozin reduced the risk of the primary outcome regardless of diabetes status (HR: 0.78 [95 % CI: 0.68−0.93] for diabetics vs. HR: 0.79 [95 % CI: 0.63−0.96] for non-diabetics), and both groups experienced fewer heart failure hospitalizations without an increased risk of hypoglycemia [29].

Bohm et al. [30] studied the impact of age on empagliflozin effects in HFpEF patients, grouping the 5988 patients into four age categories. Placebo users showed age-related increases in cardiovascular mortality (P trend = 0.03) and heart failure admissions (P trend = 0.003). All age groups experienced reductions in cardiovascular mortality and heart failure admissions with empagliflozin, with no significant age interactions (P interaction = 0.22 for ≥75 years; P interaction = 0.52 for >80 years). Empagliflozin also increased the KCCQ-Clinical Summary Score at week 52 and slowed declines in projected glomerular filtration rate without significant differences in adverse effects across age groups [30].

5. Discussion

This systematic review aimed to investigate the effectiveness of empagliflozin versus placebo in treating HFpEF patients. We summarized evidence from nine RCTs, marking this review as the first to comprehensively assess the impact of empagliflozin on HFpEF patients. Given the clinical significance of increased mortality associated with preserved ejection fraction in heart failure patients, this review contributes valuable insights.

The included trials demonstrated that empagliflozin significantly reduces cardiovascular death and heart failure hospitalizations compared to placebo. Importantly, consistent evidence of empagliflozin's efficacy was observed across predefined subcategories, including patients with and without diabetes [29].

Given that HFpEF patients tend to be older than HFrEF patients [31,32], the lack of substantial improvement in treatment outcomes from existing interventions has been noted [33]. Our results indicate that empagliflozin's effectiveness in improving heart failure outcomes is maintained across the entire age spectrum of HFpEF patients.

Exercise intolerance, which severely impacts quality of life in older patients with HFpEF, is another crucial aspect of patient care [34]. This review highlights that empagliflozin not only improves health-related quality of life for these patients but that this benefit persists for at least one year. However, no significant differences were found in exercise capacity between the empagliflozin and placebo groups.

Research indicates that women are more likely to experience HFpEF than men [35], potentially due to gender-specific differences in left ventricular remodeling [36]. Our findings suggest that both sexes benefit similarly from empagliflozin in terms of outcomes and health status.

Regarding safety, this study found no significant differences in adverse events between empagliflozin and placebo, reinforcing that empagliflozin is generally well-tolerated, with a lower incidence of serious adverse events.

5.1. Limitations

This review has several important limitations. First, some clinical outcomes were assessed in only a single trial, which limits the ability to conduct a comprehensive meta-analysis and diminishes the robustness of our conclusions. The review primarily relies on two major trials: the EMPERIAL trial [25] and the EMPEROR-Preserved trial [22−24,26−30], which may restrict the generalizability of our findings.

Furthermore, both trials were funded by Boehringer Ingelheim, the manufacturer of Jardiance® (empagliflozin). This potential conflict of interest necessitates careful interpretation of the results and highlights the need for additional independent studies to validate our findings.

6. Conclusion

In conclusion, while evidence from multiple trials indicates that empagliflozin is a safe and effective treatment for patients with HFpEF, the limitations regarding study diversity and potential funding biases necessitate careful interpretation. To firmly establish empagliflozin as the optimal therapy for this patient population, further independent, high-powered studies are essential. These studies should aim to explore efficacy across diverse demographic groups and treatment settings.

Author contributions

Conception and design of Study: SAA. Literature review: SAA. Acquisition of data: SAA. Analysis and interpretation of data: SAA. Research investigation and analysis: SAA. Data collection: SAA. Drafting of manuscript: SAA. Revising and editing the manuscript critically for important intellectual

contents: SAA. Data preparation and presentation: SAA. Supervision of the research: SAA. Research coordination and management: SAA. Funding for the research: SAA.

Funding body

This study was not funded by any external sources. The author conducted the research independently without financial support from governmental or non-governmental organizations.

Ethical statement

This review paper is based on published literature, and no new human or animal data were collected. All cited studies followed ethical guidelines as per their respective institutions.

Conflict of interest

No Conflict of Interest.

References

[1] Tyl B, Rodriguez CL, Gheorghiade MD, Aranda DE, Campbell MM, Ruschitzka DC, et al. Comparison of outcome adjudication by investigators and by a central end point committee in heart failure trials. Circulation: Heart Fail 2020;13(7). https://doi.org/10.1161/circheartfailure.119.006720.

[2] Ambrosy AP, Fonarow AL, Butler JD, Chioncel RD, Givertz LC, O'Connor ME. The global health and economic burden of hospitalizations for heart failure. J Am Coll Cardiol 2014;63(12):1123−33. https://doi.org/10.1016/j.jacc.2013.11.053.

[3] Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res 2022;118(17). https://doi.org/10.1093/cvr/cvac013.

[4] Virani SS, Alonso AD, Benjamin MS, Bittencourt DS, Callaway JS, Carson JL. Heart disease and stroke statistics—2021 update: a report from the American heart association. Circulation 2021;143(8). https://doi.org/10.1161/cir.0000000000000950.

[5] Vaduganathan M, McMurray MP, Pfeffer RM, Desai AB, Bhatt DS, Bozkurt AR. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet 2020;396(10244):121−8. https://doi.org/10.1016/S0140-6736(20)30748-0.

[6] Pitt B, Cohn MS, Bristow SB, Feldman PS, Hargrove JS, Combs GL. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370(15):1383−92. https://doi.org/10.1056/nejmoa1313731.

[7] Solomon SD, McMurray DB, O'Connor SM, Morrow TA, Pfeffer RJ, Packer AS. Angiotensin−neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019;381(17):1609−20. https://doi.org/10.1056/nejmoa1908655.

[8] Murphy SP, Ibrahim NE, Januzzi JL. Heart failure with reduced ejection fraction. JAMA 2020;324(5):488. https://doi.org/10.1001/jama.2020.10262.

[9] Hanefeld M, Forst T. Dapagliflozin, an SGLT2 inhibitor, for diabetes. Lancet 2010;375(9733):2196−8. https://doi.org/10.1016/s0140-6736(10)60749-0.

[10] Kato ET, Miller RD, Johnson AK, Sanders MG, Adams TP, Hart CML. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation 2019;139(22):2528−36. https://doi.org/10.1161/circulationaha.119.040130.

[11] Zelniker TA, Neal KA, Finkelstein FK, McMurray GE, Brunner PCH, Packer PD. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393(10166):31−9. https://doi.org/10.1016/s0140-6736(18)32590-x.

[12] Fukuta H, Hagiwara H, Kamiya T. Sodium-glucose cotransporter 2 inhibitors in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. IJC Heart Vasc 2022;42:101103. https://doi.org/10.1016/j.ijcha.2022.101103.

[13] Cheema HA, Hessel FL, Ibarra SML, Grayson TD, Koenig MM, Rosen DJ. Efficacy and safety of sodium-glucose cotransporter-2 inhibitors for heart failure with mildly reduced or preserved ejection fraction: a systematic review and meta-analysis of randomized controlled trials. Front Cardiovasc Med 2023;10(Oct). https://doi.org/10.3389/fcvm.2023.1273781.

[14] Banerjee M, Pal R, Nair K, Mukhopadhyay S. SGLT2 inhibitors and cardiovascular outcomes in heart failure with mildly reduced and preserved ejection fraction: a systematic review and meta-analysis. Indian Heart J 2023;75(2):122−7. https://doi.org/10.1016/j.ihj.2023.03.003.

[15] Treewaree S, Kulthamrongsri N, Owattanapanich W, Krittayaphong R. Is it time for class I recommendation for sodium-glucose cotransporter-2 inhibitors in heart failure with mildly reduced or preserved ejection fraction?: an updated systematic review and meta-analysis. Front Cardiovasc Med 2023;10. https://doi.org/10.3389/fcvm.2023.1046194.

[16] Zhou H, Kim YS, Lee JM, Brown SP, Liu FR, Davis TM. Effect of sodium-glucose cotransporter 2 inhibitors for heart failure with preserved ejection fraction: a systematic review and meta-analysis of randomized clinical trials. Diabetes Care 2022;9. https://doi.org/10.3389/fcvm.2022.875327.

[17] Posch M, et al. Metabolic, intestinal, and cardiovascular effects of sotagliflozin compared with empagliflozin in patients with type 2. Diabetes: Random Double-Blind Study 2022;45(9):2118−26. https://doi.org/10.2337/dc21-2166.

[18] Cumpston M, Lee JT, Chalmers GL, Wilson MW, Wilson KM, Hogg AR. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2021. https://doi.org/10.1002/14651858.ed000142.

[19] Page MJ, Moher PT, McDonald KC, Toledano AB, Cummings ML, Craig SH. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Br Med J 2021;372(71). https://doi.org/10.1136/bmj.n71.

[20] Higgins JPT, Sutherland RB, Horvat GW, Thompson ML, Wilson TF, Johnson BM. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343(343). https://doi.org/10.1136/bmj.d5928.

[21] Braun V, Clarke V. What can 'thematic analysis' offer health and wellbeing researchers? Int J Qual Stud Health Well-Being 2014;9(1):26152. https://doi.org/10.3402/qhw.v9.26152.

[22] Anker SD, Harms MR, McMurray JP, Bailey LRL, Hernandez RL, Kennedy AL. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385(16). https://doi.org/10.1056/nejmoa2107038.

[23] Anker SD, Zannad FM, Butler RK, Stevens DD, Carabello MH, Bailey LRL. Outcomes with empagliflozin in heart failure with preserved ejection fraction using DELIVER -like endpoint definitions. Eur J Heart Fail 2022. https://doi.org/10.1002/ejhf.2558.

[24] Packer M, Givens EL, Brown WH, Taylor TR, Henderson RW, Thomson PS. Effect of empagliflozin on worsening heart failure events in patients with heart failure and a preserved ejection fraction: the EMPEROR-preserved

trial. Circulation 2021. https://doi.org/10.1161/circulationaha.121.056824.

[25] Abraham WT, Franklin PSB, Griffith MT, Jelinek KE, Lee RPY, Lee GS. Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes. Eur Heart J 2021;42(6):700−10. https://doi.org/10.1093/eurheartj/ehaa943.

[26] Butler J, Zannetti MWM, Franks SF, O'Brien RA, Thomas TD, Horne CA. Empagliflozin, health status, and quality of life in patients with heart failure and preserved ejection fraction: the EMPEROR-preserved trial. Circulation 2021. https://doi.org/10.1161/circulationaha.121.057812.

[27] Ferreira JP, Garcia ML, Jensen AB, Roqué BH, Anker SD, Coresh RK. Mineralocorticoid receptor antagonists and empagliflozin in patients with heart failure and preserved ejection fraction. J Am Coll Cardiol 2022;79(12):1129−37. https://doi.org/10.1016/j.jacc.2022.01.029.

[28] Butler J, Mehra MS, Lambert ED, Davis TJ, Reilly MG, Taylor CD. Effects of empagliflozin in women and men with heart failure and preserved ejection fraction. Circulation 2022;146(14):1046−55. https://doi.org/10.1161/CIRCULATIONAHA.122.059755.

[29] Filippatos G, Virani SS, Ervin RM, Januzzi SJ, Schulz HE, O'Connell CA. Empagliflozin for heart failure with preserved left ventricular ejection fraction with and without diabetes. Circulation 2022;146(9):676−86. https://doi.org/10.1161/circulationaha.122.059785.

[30] Böhm M, Bui TK, Stewart SM, Alessi MF, Lanza SG, Hardy MR. Empagliflozin improves outcomes in patients with heart failure and preserved ejection fraction irrespective of age. J Am Coll Cardiol 2022;80(1):1−18. https://doi.org/10.1016/j.jacc.2022.04.040.

[31] Lam CSP, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail 2011;13(1):18−28. https://doi.org/10.1093/eurjhf/hfq121.

[32] Chen X, Savarese G, Dahlström U, Lund LH, Fu M. Age-dependent differences in clinical phenotype and prognosis in heart failure with mid-range ejection compared with heart failure with reduced or preserved ejection fraction. Clin Res Cardiol 2019;108(12):1394−405. https://doi.org/10.1007/s00392-019-01477-z.

[33] Wintrich J, Reed AK, Tressler ML, McGowan RJ, Linfield SF, Soper CE. Therapeutic approaches in heart failure with preserved ejection fraction: past, present, and future. Clin Res Cardiol 2020;109(9):1079−98. https://doi.org/10.1007/s00392-020-01633-w.

[34] Reddy YNV, Patel CM, Johnson JH, Herr BS, Lawrence DP, Stewart WG. Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity. Eur J Heart Fail 2020;22(6):1009−18. https://doi.org/10.1002/ejhf.1788.

[35] Scantlebury DC, Borlaug BA. Why are women more likely than men to develop heart failure with preserved ejection fraction? Curr Opin Cardiol 2011;26(6):562−8. https://doi.org/10.1097/hco.0b013e32834b7faf.

[36] Stolfo D, Glover EJ, Clark RH, Patel SG, Timm MR, Gonzalez JK. Sex-based differences in heart failure across the ejection fraction spectrum. JACC (J Am Coll Cardiol): Heart Fail 2019;7(6):505−15. https://doi.org/10.1016/j.jchf.2019.03.011.