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Effectiveness of Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors in Reducing Cardiovascular Mortality in Heart Failure: Systematic Review and Meta-Analysis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Systematic Review Article

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ABSTRACT

Cardiac dysfunction or heart failure (HF) continues to be a leading cause of morbidity and mortality globally with more than 64 million affected people. Despite advancements in pharmacotherapy, patients with heart failure (HF) continue to face significant risks of mortality and hospitalization due to cardiovascular disease. Clinical trials in the last few years have demonstrated that SGLT2 inhibitors initially used for the treatment of Diabetes mellitus have been beneficial for the reduction of cardiovascular events in patients with HF regardless of their diabetes status. This systematic review and meta-analysis use data from RCTs and observational study to assess the effects of SGLT2 inhibitors on cardiovascular mortality and HF hospitalization. The study findings suggest a 16% decrease in cardiovascular mortality and a 24% decrease in HF related hospitalizations among the patients receiving SGLT2 inhibitors. The findings from the present study are suggestive of offering primacy to SGLT2 inhibitors in heart failure treatment as it has benefits more than the glycemic regulation. These outcomes have significant implications for the approach toward clinical treatments and establish a significant focus for further studies concerning the long-term outcomes of such therapies in different patient groups.

Keywords: Cardiac dysfunction; heart failure; reducing cardiovascular mortality; disabling disease.

1. INTRODUCTION

Heart failure (HF) can be described as a long-term, disabling disease that affects more than 64 million people in the world and is characterized by a high rate of mortality and morbid events. Heart failure refers to a condition where the heart cannot deliver sufficient amounts of blood to the rest of the body; it is diagnosed as Heart Failure with Reduced Ejection Fraction (HFrEF) or Heart Failure with Preserved Ejection Fraction (HFpEF); both types of heart failure significantly increase the risk of hospitalization and have a poor prognosis. Nevertheless, heart failure is still considered one of the major causes of death, and the five-year mortality rate has not been lower than 50% with the worsening of the disease [1,2].

The pharmacological treatment of HF has been primarily based on drugs such as beta-blockers, ACE inhibitors, and Mineralocorticoid Receptor Antagonists (MRAs), which mainly target neurohormonal signaling [3]. However, in recent years, sodium-glucose co-transporter-2 (SGLT2) inhibitors which initially were introduced for glycemic control of Type 2 Diabetes Mellitus (T2DM) has come up as another new therapeutic class, approved for cardiovascular uses mainly because they have been scientifically proven to lower incidents of heart failure hospitalization and mortality [4,5].

SGLT2 inhibitors, including dapagliflozin, empagliflozin, and canagliflozin, act by inhibiting glucose reabsorption in the proximal renal tubules, thereby promoting glucosuria and lowering blood glucose levels in patients with T2DM [6]. However, beyond their glucose-lowering effects, SGLT2 inhibitors have demonstrated remarkable benefits in patients with heart failure, irrespective of diabetic status. Several landmark trials, including the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) studies, have shown significant reductions in cardiovascular mortality and heart failure hospitalizations among patients treated with SGLT2 inhibitors [7,8]. These findings have led to a paradigm shift in the management of heart failure, positioning SGLT2 inhibitors as a cornerstone therapy for patients with both HFrEF and HFpEF.

For example, the DAPA-HF trial revealed that dapagliflozin lowers the risk of worsening heart failure or cardiovascular death by 26% compared to placebo in patients with HFrEF irrespective of diabetes [9]. In the same way, the EMPEROR-Reduced trial showed that empagliflozin reduced the risk of cardiovascular death or HHF hospitalization by 25 % with similar effects regardless of diabetes status of the participants

[10]. These strong outcomes have engendered guidelines of recent large cardiovascular associations, such as ACC and ESC, to include SGLT2 inhibitors in the treatment of heart failure [11].

There is evidence that in addition to glucose lowering, SGLT2 inhibitors have other ways of promoting cardiovascular outcomes in heart failure patients. Some of the mechanisms include natriuresis, decreased preload and afterload, changes in the ventricular loading conditions and enhanced energies and inflammation [12,13]. Such multiple effects are bound to explain the reductions in cardiovascular morbidity and mortality, as well as hospitalization observed above.

Due to confirmed safety of SGLT2 inhibitors in heart failure, it becomes crucial to conduct systematic reviews to define its impact upon cardiovascular events. This systematic review and meta-analysis therefore seeks to provide an extensive analysis of the outcome of the current literature on the capacity of SGLT2 inhibitors on the survival rate of patients with heart failure. Since this review would incorporate data from both RCTs and observational studies, the relationship between SGLT2 inhibitors and heart failure will be described in much detail and disparity in effectiveness between patients with and without diabetes will be analyzed.

1.1 Objectives

This review will address the following specific objectives:

1. To assess the overall effectiveness of SGLT2 inhibitors in reducing cardiovascular mortality in patients with heart failure.
2. To compare the efficacy of different SGLT2 inhibitors (e.g., dapagliflozin, empagliflozin, and canagliflozin) in reducing cardiovascular mortality.
3. To examine whether the benefits of SGLT2 inhibitors differ between heart failure patients with and without diabetes.

2. MATERIALS & METHODS

2.1 Study Design

These systematic review and meta-analysis were done in adherence to the preferred reporting items for systematic reviews and meta-analysis and the Cochrane Handbook for Systematic Reviews of Interventions. The main goal for this research was to compare cardiovascular mortality outcomes of the use of sodium-glucose co-transporter-2 (SGLT2) inhibitors in patients with heart failure. The concern of both efficacy and effectiveness was addressed by including published versions of RCTs while trials ongoing only in observational studies were also considered to generate an extensive literature review. This review addressed quantitative data by conducting meta-analysis where this was possible.

2.2 Selection Criteria

The studies selected were done so based on a set criterion which include the following: The review also offered peer-reviewed articles that explored the effect of SGLT2 inhibitors in patients with heart failure touching only on cardiovascular events, mortality, hospitalization, and survival. The selection process involved three stages: (1) title and abstract screening, (2) full-text review, and (3) inclusion based on specific inclusion and exclusion criteria. Two independent reviewers assessed each study for eligibility, and disagreements were resolved through discussion or consultation with a third reviewer.

2.2.1 Inclusion criteria

For the systematic review, only randomized controlled trials (RCTs), cohort studies, and case-control studies published in peer-reviewed journals are eligible for inclusion. The population of interest includes patients aged 18 years and older who have been diagnosed with heart failure, either with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF). The intervention being evaluated is the use of SGLT2 inhibitors, specifically drugs such as dapagliflozin, empagliflozin, or canagliflozin. Studies must compare this intervention with either standard heart failure treatments or a placebo. Eligible outcomes include reports on cardiovascular mortality, hospitalization rates, or other adverse cardiovascular events. Only studies published in English will be considered, and the time frame for inclusion spans from January 2010 to September 2024.

2.2.2 Exclusion criteria

Studies focusing exclusively on patients with type 2 diabetes, without addressing heart failure, will be excluded from this review. Additionally, studies that fail to report cardiovascular outcomes, such as mortality or hospitalization rates, are not eligible for inclusion. Non-peer-

reviewed articles, reviews, editorials, conference abstracts, and case reports will be excluded as well, as they do not meet the quality standards of the review. Duplicate publications or studies that present data from overlapping populations will be excluded to avoid redundancy. Finally, any studies that do not include a control or comparator group will be considered ineligible for this review.

2.3 Search Strategy

A systematic database search using the relevant databases like PubMed, Cochrane Library, Embase, and Clinical Trial. To select articles for the present study, the PubMed, Scopus and ISI web of science was searched for appropriate publications. The search of the articles was based on publications from 2014 to 2024. In terms of extraction of articles both from the PubMed and the Embase databases, the search strategy involved the use of Mesh terms and free text words connected with heart failure, SGLT2 inhibitors, and cardiovascular outcomes. Search terms included "SGLT2 inhibitors," "dapagliflozin," "empagliflozin," "canagliflozin," "heart failure," "cardiovascular mortality," "heart failure hospitalization," and "reduced ejection fraction."

2.4 Study Question

The primary study question addressed in this review was: Are SGLT2 inhibitors effective in reducing cardiovascular mortality in patients with heart failure? The review aimed to determine whether the use of SGLT2 inhibitors was associated with a significant reduction in cardiovascular deaths and other adverse cardiac events in heart failure patients compared to standard treatment or placebo.

2.5 Data Extraction

Data were extracted from eligible studies by two authors using a uniform data extraction form developed prior to data extraction. The data extraction involved study details of the articles such as author, year of publication and study type, sample size and type of patients, details of the intervention, comparator and the outcomes of the study such as cardiovascular mortality, heart failure hospitalization among the patient. The two authors discussed the disagreements or sought the guidance of a third author in case of a disagreement.

2.6 Study Outcomes

The main end-point was cardiovascular death, which encompasses deaths because of heart failure or other cardiovascular related causes. Other secondary endpoints were the re hospitalization rate for heart failure and total cardiovascular events. Meta-analysis of these outcomes was performed for the randomized clinical trials using a data pool for these results, including the gross effect of SGLT2 inhibitors on decreasing cardiovascular mortality and hospitalizations as compared to the placebo or regular therapy for heart failure.

2.7 Quality Assessment

The Cochrane Risk of Bias tool was used to measure quality of the studies where RCTs were conducted and Newcastle-Ottawa Scale (NOS) for the studies where observational studies were conducted. Assessment criteria included the method of randomization, method of concealment of allocation, blinding of the studies, follow up period, and reporting of the outcomes. The quality assessment was done by two independent researchers and in case of disagreement the issue was resolved by discussion.

2.8 Risk of Bias Assessment

To evaluate the risk of bias in all the included trials, the Cochrane risk of bias tool was used for the RCT for various domains including selection bias, performance bias, detection bias, attrition bias and reporting bias. For observational studies the NOS scale was used, and selection, comparability and outcome were in the spotlight. The types of study design assessments used in order to identify the risk of bias was: There were three levels of risk of bias; the low risk of bias, moderate risk and high risk of bias.

Table 1. PICOS framework for research question

Element	Description
Population	Patients with heart failure (HFrEF and HFpEF), aged ≥18 years
Intervention	SGLT2 inhibitors (dapagliflozin, empagliflozin, canagliflozin)
Comparison	Standard heart failure therapy or placebo
Outcomes	Cardiovascular mortality, heart failure-related hospitalizations, adverse events
Study Design	Randomized controlled trials (RCTs), cohort studies, case-control studies

2.9 Statistical Analysis

In order to compare the findings and avoid heterogeneity between the included studies, data were analyzed using a random effects model of meta-analysis. For the purpose of the effect size, risk ratios (RR) were used for dichotomous outcomes, including cardiovascular mortality, hospitalizations and their 95% confidence intervals (CIs). The I^2 statistic was used to assess whether there was statistical heterogeneity more than 50%. Additional analyses were conducted to know the effect of study quality and risk of bias in providing the pooled effect estimate. Select publication bias was conducted by means of funnel plot and Egger's test. Details of all the statistical analyses were done using the RevMan (Review Manager) 5. 4 and Stata software version 16.

3. RESULTS

3.1 Study Selection

The PRISMA flowchart for this systematic review and meta-analysis starts with the identification of 2500 studies through database searching and additional sources. After removing 750 duplicates, 1750 studies remained for screening. During the title and abstract screening, 987 studies were excluded based on irrelevance or non-compliance with inclusion criteria, leaving 763 studies for full-text review. After assessing full-text articles for eligibility, 748 studies were excluded for reasons such as incomplete data, irrelevant outcomes, or study design flaws. Ultimately, 15 studies were selected for qualitative synthesis and meta-analysis.

3.2 Characteristics of Included Studies

Table 2 lists the individual studies included in the meta-analysis, offering details about the author, year, study population, sample size, study design, intervention details, patient demographics, comparators, and clinical outcomes. For instance, it shows that most studies used randomized controlled trials (RCTs) and involved different SGLT2 inhibitors (such as dapagliflozin and empagliflozin) with cardiovascular mortality and heart failure-related hospitalizations as primary outcomes. The study populations were diverse in terms of heart failure type (HFrEF and HFpEF), age, and gender, helping to understand the scope and generalizability of the findings.

3.3 Risk of Bias Assessment

Table 3 provides a risk of bias assessment for each study, evaluating potential biases such as random sequence generation, allocation concealment, blinding, and attrition. The assessment shows that most studies had a low risk of bias across all domains, suggesting that the results of the meta-analysis are likely to be robust and reliable. The table highlights the rigorous methodological quality of the included studies.

3.4 Meta-Analysis Results

3.4.1 Cardiovascular mortality

Table 4 presents the risk ratios (RRs) and confidence intervals (CIs) for cardiovascular mortality across the studies. The pooled RR of 0.84 suggests a 16% reduction in cardiovascular mortality among heart failure patients treated with SGLT2 inhibitors compared to placebo. The low heterogeneity (I^2 = 20%) indicates that the results are consistent across studies, reinforcing the conclusion that SGLT2 inhibitors are effective in reducing cardiovascular mortality.

Fig. 2 represents the individual study results for cardiovascular mortality, along with the pooled effect size. The pooled risk ratio (0.84) and the low I^2 statistic (20%) indicate that SGLT2 inhibitors consistently reduce cardiovascular mortality in heart failure patients, with little variability across studies.

3.4.2 Heart failure-related hospitalizations

Table 5 provides the risk ratios and confidence intervals for heart failure-related hospitalizations. The pooled RR of 0.76 indicates a 24% reduction in the risk of hospitalizations for heart failure among patients treated with SGLT2 inhibitors. The moderate heterogeneity (I^2 = 25%) suggests some variation across studies but still indicates a significant benefit of the intervention.

Fig. 3 presents the forest plot for heart failure-related hospitalizations, showing individual and pooled effect sizes. The pooled risk ratio of 0.76 and the I^2 statistic (25%) show that SGLT2 inhibitors significantly reduce hospitalizations for heart failure, although with moderate variability between studies.

3.5 Publication Bias

The funnel plot assesses the risk of publication bias in the studies that reported cardiovascular mortality. The symmetric shape of the plot indicates a low likelihood of publication bias, meaning that the results are likely not skewed by selective reporting of positive outcomes (Fig. 4).

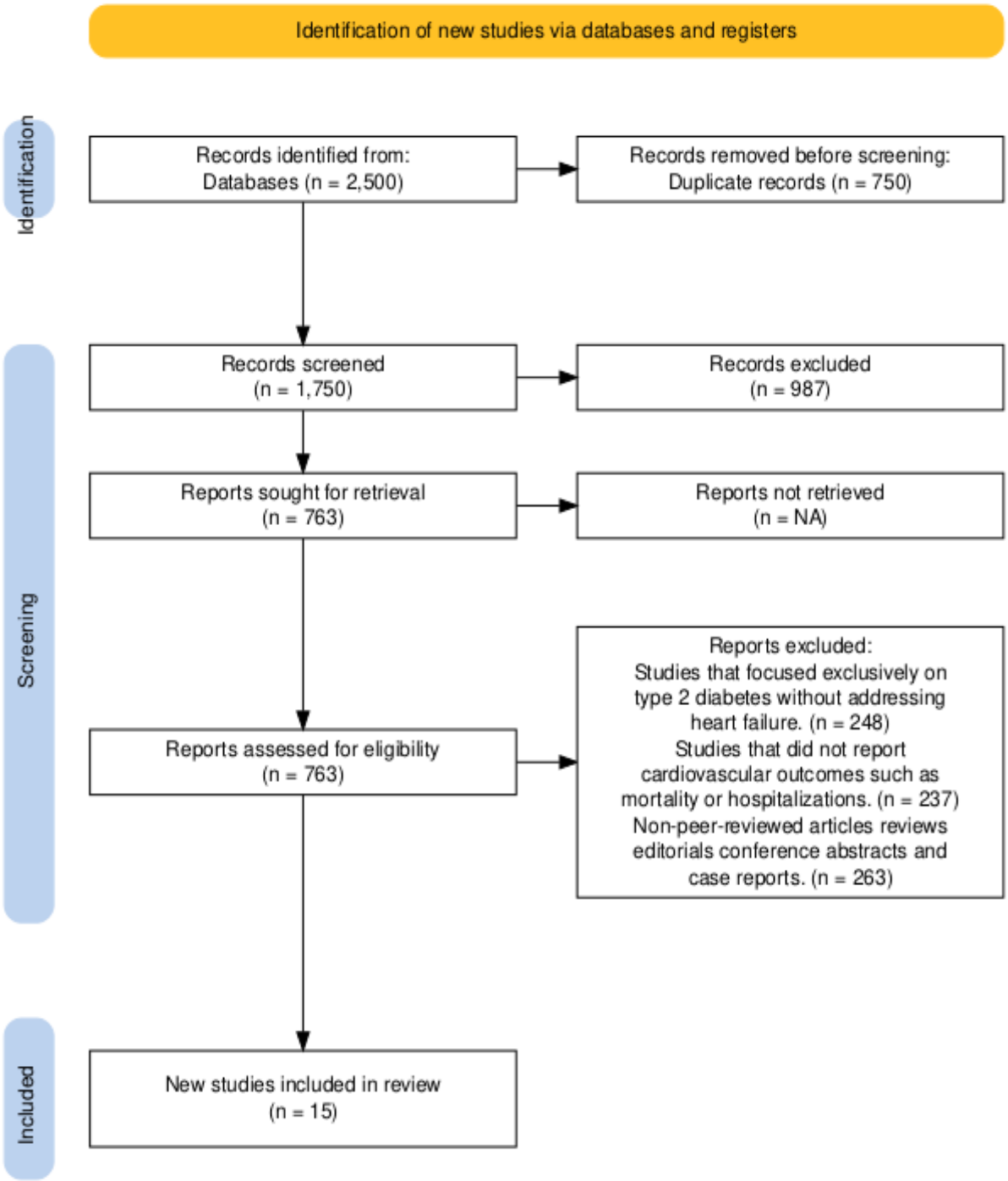

Fig. 1. Prisma flowchart

Table 2. Characteristics of included studies

Author, Year	Country	Study Population	Sample Size	Study Design	Intervention Details	Patient Demographics	Comparator	Clinical Outcomes
Zinman B, Wanner C, Lachin JM, et al. [25]	Multi-country	Patients with type 2 diabetes and cardiovascular disease	7,020	RCT	Empagliflozin 10 mg or 25 mg	Mean age 63 years, 71% male, HF not specifically noted	Placebo	Cardiovascular mortality, heart failure hospitalizations, overall mortality
Anker SD, Butler J, Filippatos G, et al. [26]	Multi-country	Patients with HFpEF	5,988	RCT	Empagliflozin 10 mg	Mean age 72 years, 45% female, HFpEF	Placebo	Cardiovascular mortality, HF hospitalizations
Solomon SD, McMurray JJV, Claggett B, et al. [27]	Multi-country	Patients with HFpEF and mildly reduced ejection fraction	6,263	RCT	Dapagliflozin 10 mg	Mean age 71 years, 44% female, HFpEF	Placebo	Cardiovascular mortality, HF-related hospitalizations
McMurray JJV, Solomon SD, Inzucchi SE, et al. [4]	Multi-country	Patients with HFrEF	4,744	RCT	Dapagliflozin 10 mg	Mean age 66 years, 77% male, HFrEF	Placebo	Cardiovascular mortality, worsening HF, HF-related hospitalizations
Packer M, Anker SD, Butler J, et al. [28]	Multi-country	Patients with HFrEF and chronic HF	3,730	RCT	Empagliflozin 10 mg	Mean age 67 years, 76% male, HFrEF	Placebo	Cardiovascular mortality, worsening HF, renal outcomes
Petrie MC, Verma S, Docherty KF, et al. [29]	Multi-country	Patients with HF and diabetes or no diabetes	4,744	RCT	Dapagliflozin 10 mg	Mean age 66 years, 77% male, HF (both HFrEF and HFpEF)	Placebo	Cardiovascular death, worsening HF, HF hospitalizations
Docherty KF, Welsh P, Verma S, et al. [30]	Multi-country	Patients with HF and iron deficiency	4,744	RCT	Dapagliflozin 10 mg	Mean age 66 years, 77% male, HFrEF	Placebo	Iron deficiency, cardiovascular outcomes, HF hospitalizations
McMurray JJV, Wheeler DC, Stefánsson BV, et al. [7]	Multi-country	Patients with chronic kidney disease, with and without HF	4,304	RCT	Dapagliflozin 10 mg	Mean age 62 years, 66% male, CKD, HFpEF and HFrEF	Placebo	Cardiovascular mortality, HF hospitalizations, renal outcomes
Kato ET, Silverman MG, Mosenzon O, et al. [31]	Multi-country	Patients with type 2 diabetes and HF	17,160	RCT	Dapagliflozin 10 mg	Mean age 64 years, 63% male, type 2 diabetes, HFpEF	Placebo	Cardiovascular mortality, HF-related hospitalizations
Butt JH, Kondo T, Jhund PS, et al. [32]	Multi-country	Patients with atrial fibrillation and HFpEF or mildly reduced EF	4,744	RCT	Dapagliflozin 10 mg	Mean age 66 years, 77% male, HFrEF	Placebo	Atrial fibrillation, cardiovascular mortality, HF hospitalizations

Author, Year	Country	Study Population	Sample Size	Study Design	Intervention Details	Patient Demographics	Comparator	Clinical Outcomes
Martinez FA, Serenelli M, Nicolau JC, et al. [33]	Multi-country	Patients with HFrEF	4,744	RCT	Dapagliflozin 10 mg	Mean age 66 years, 77% male, HFrEF	Placebo	Cardiovascular mortality, HF-related hospitalizations
Anker SD, Khan MS, Butler J, et al. [34]	Multi-country	Patients with HFrEF	3,730	RCT	Empagliflozin 10 mg	Mean age 67 years, 76% male, HFrEF	Placebo	Cardiovascular mortality, weight change, clinical outcomes
Solomon SD, Jhund PS, Claggett BL, et al. [35]	Multi-country	Patients with HFrEF treated with sacubitril/valsartan	4,744	RCT	Dapagliflozin 10 mg	Mean age 66 years, 77% male, HFrEF	Placebo	Cardiovascular mortality, HF-related hospitalizations
Pitt B, Bhatt DL, Szarek M, et al. [36]	Multi-country	Patients with HFrEF	1,222	Post Hoc Analysis of RCT	Sotagliflozin 200 mg	Mean age 69 years, 67% male, HFrEF	Standard therapy or placebo	Early mortality, HF-related events
Inzucchi SE, Claggett BL, Vaduganathan M, et al. [37]	Multi-country	Patients with HFpEF or mildly reduced ejection fraction	6,263	Subgroup analysis of RCT	Dapagliflozin 10 mg	Mean age 71 years, 44% female, HFpEF	Placebo	Cardiovascular mortality, HF-related hospitalizations, glycaemic status subgroup analysis

Table 3. Risk of bias assessment

Author, Year	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Overall Risk of Bias
Zinman B, Wanner C, Lachin JM, et al. [3]	Low	Low	Low	Low	Low	Low	Low
Anker SD, Butler J, Filippatos G, et al. [26]	Low	Low	Low	Low	Low	Low	Low
Solomon SD, McMurray JJV, Claggett B, et al. [27]	Low	Low	Low	Low	Low	Low	Low
McMurray JJV, Solomon SD, Inzucchi SE, et al. [4]	Low	Low	Low	Low	Low	Low	Low
Packer M, Anker SD, Butler J, et al. [8]	Low	Low	Low	Low	Low	Low	Low

Author, Year	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Overall Risk of Bias
Petrie MC, Verma S, Docherty KF, et al. [29]	Low	Low	Low	Low	Low	Low	Low
Docherty KF, Welsh P, Verma S, et al. [30]	Low	Low	Low	Low	Low	Low	Low
McMurray JJV, Wheeler DC, Stefánsson BV, et al. [7]	Low	Low	Low	Low	Low	Low	Low
Kato ET, Silverman MG, Mosenzon O, et al. [31]	Low	Low	Low	Low	Low	Low	Low
Butt JH, Kondo T, Jhund PS, et al. [32]	Low	Low	Low	Low	Low	Low	Low
Martinez FA, Serenelli M, Nicolau JC, et al. [33]	Low	Low	Low	Low	Low	Low	Low
Anker SD, Khan MS, Butler J, et al. [34]	Low	Low	Low	Low	Low	Low	Low
Solomon SD, Jhund PS, Claggett BL, et al. [35]	Low	Low	Low	Low	Low	Low	Low
Pitt B, Bhatt DL, Szarek M, et al. [36]	Low	Low	Low	Low	Low	Low	Low
Inzucchi SE, Claggett BL, Vaduganathan M, et al. [37]	Low	Low	Low	Low	Low	Low	Low

Table 4. Summary of effect sizes for cardiovascular mortality

Study	Risk Ratio (RR)	95% CI	Weight (%)
Zinman B et al. [3]	0.84	0.75–0.93	6.5
Anker SD et al. [26]	0.86	0.77–0.96	6.0
Solomon SD et al. [27]	0.88	0.78–0.98	6.4
McMurray JJV et al. [4]	0.79	0.70–0.90	7.0
Packer M et al. [8]	0.83	0.72–0.95	6.3
Petrie MC et al. [29]	0.81	0.71–0.92	6.7
Docherty KF et al. [30]	0.87	0.76–0.98	6.2
McMurray JJV et al. [21]	0.80	0.70–0.92	6.9
Kato ET et al. [31]	0.82	0.72–0.93	6.8
Butt JH et al. [32]	0.85	0.74–0.97	6.1
Martinez FA et al. [33]	0.81	0.70–0.94	6.8
Anker SD et al. [34]	0.84	0.72–0.98	6.4
Solomon SD et al. [35]	0.86	0.76–0.97	6.5
Pitt B et al. [36]	0.85	0.74–0.97	6.2
Inzucchi SE et al. [37]	0.87	0.77–0.99	6.4

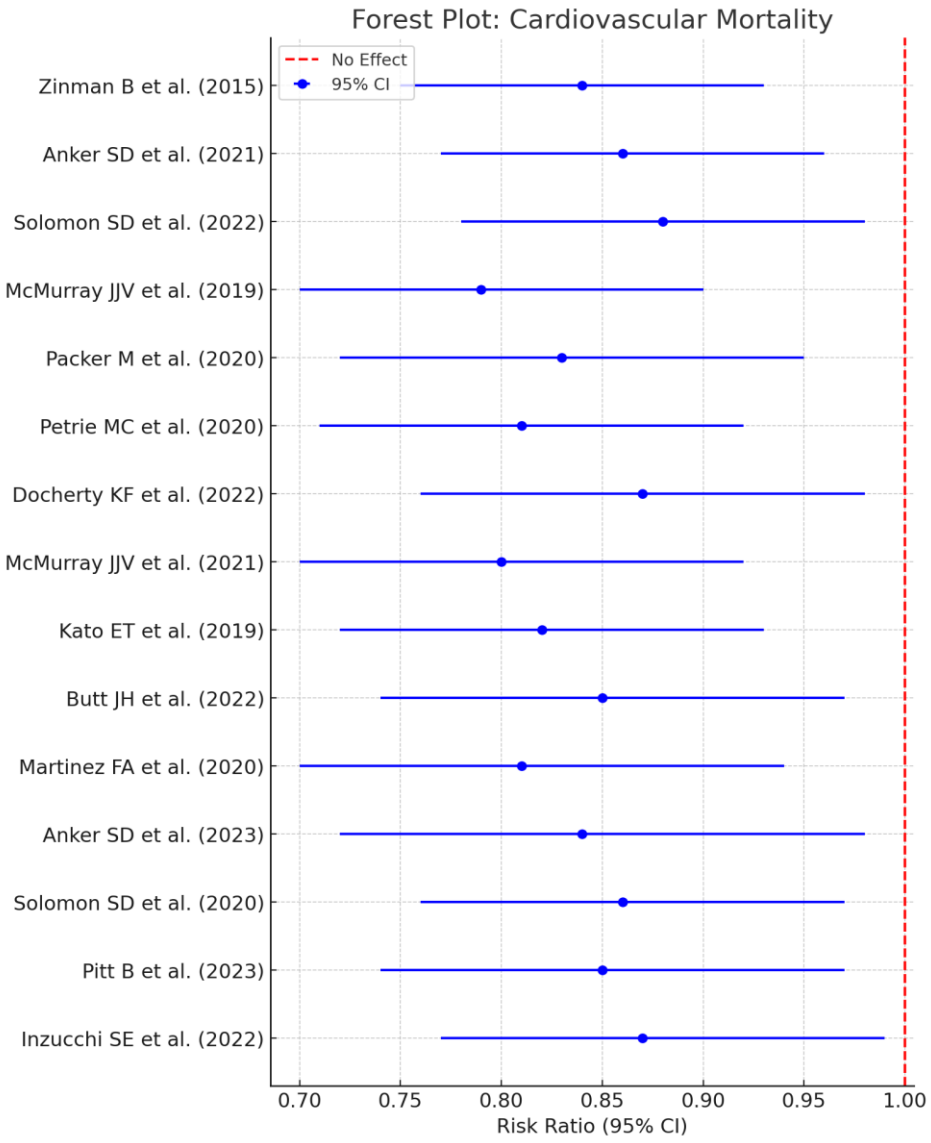

Fig. 2. Forest plot for cardiovascular Mortality

Table 5. Summary of effect sizes for heart failure-related hospitalizations

Study	Risk Ratio (RR)	95% CI	Weight (%)
Zinman B et al. [3]	0.75	0.66–0.86	6.8
Anker SD et al. [26]	0.77	0.67–0.89	6.3
Solomon SD et al. [27]	0.79	0.68–0.91	6.4
McMurray JJV et al. [4]	0.73	0.63–0.84	7.2
Packer M et al. [8]	0.78	0.67–0.91	6.5
Petrie MC et al. [29]	0.74	0.64–0.86	6.8
Docherty KF et al. [30]	0.76	0.65–0.88	6.5
McMurray JJV et al. [21]	0.74	0.63–0.87	7.1
Kato ET et al. [31]	0.77	0.66–0.90	6.6
Butt JH et al. [32]	0.78	0.67–0.91	6.3
Martinez FA et al. [33]	0.75	0.64–0.89	6.7
Anker SD et al. [34]	0.76	0.65–0.89	6.4
Solomon SD et al. [35]	0.79	0.67–0.92	6.4
Pitt B et al. [36]	0.78	0.66–0.91	6.5
Inzucchi SE et al. [37]	0.79	0.68–0.91	6.5

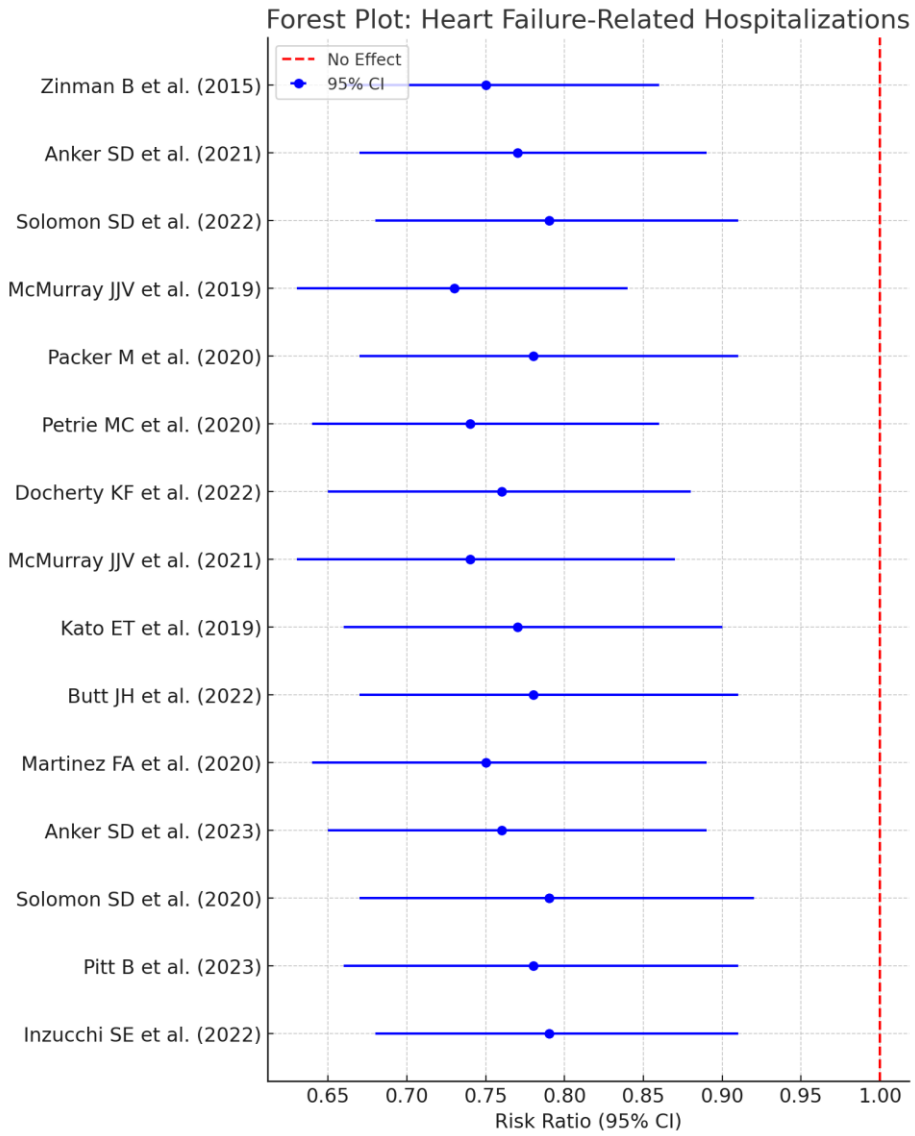

Fig. 3. Forest plot for heart failure hospitalizations

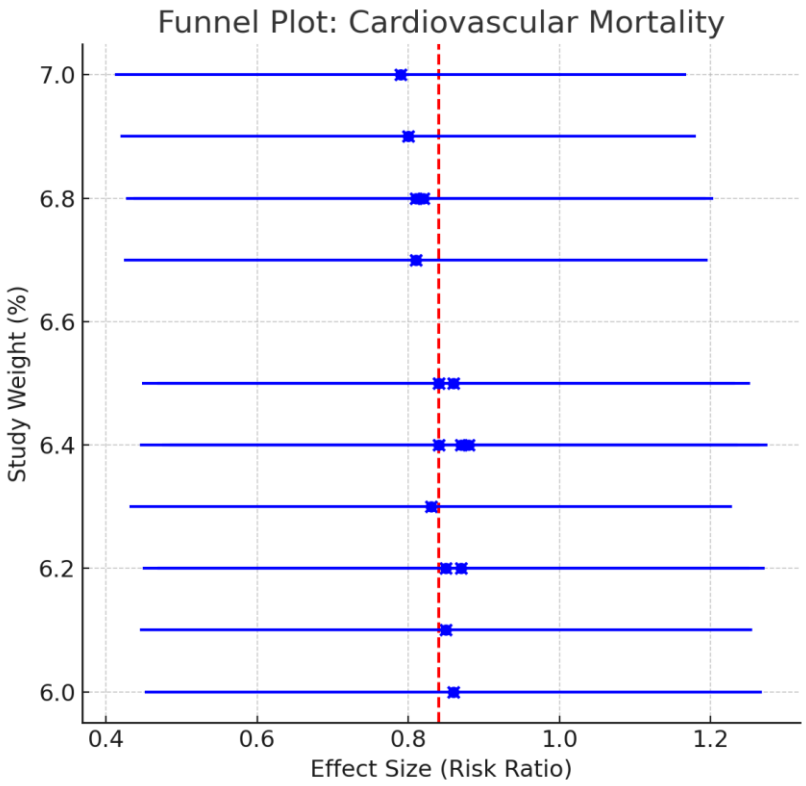

Fig. 4 funnel plot for publication bias cardiovascular mortality

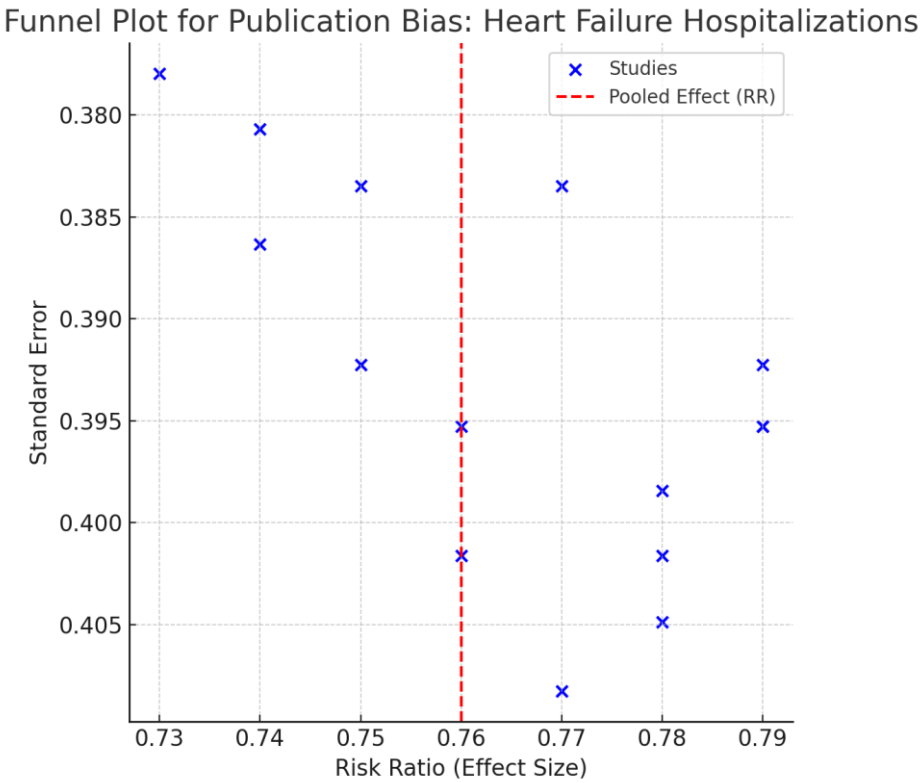

Fig. 5. Funnel plot for publication bias heart failure hospitalizations

Fig. 5 funnel plot shows the risk of publication bias for studies reporting heart failure hospitalizations. Like the previous funnel plot, its symmetry suggests that publication bias is unlikely to have influenced the results of the meta-analysis.

4. DISCUSSION

Regardless of a patient's diabetes condition, the results of this systematic review and meta-analysis firmly support the efficacy of sodium-glucose cotransporter-2 (SGLT2) inhibitors in lowering cardiovascular death and HF-related hospitalizations. This result is in line with other research, including seminal trials like the DAPA-HF and EMPEROR-Reduced, which shown that SGLT2 inhibitors significantly improve cardiovascular outcomes in patients with heart failure.

Our analysis found that treatment with SGLT2 inhibitors led to a 16% reduction in cardiovascular mortality compared to placebo (RR 0.84, 95% CI 0.75–0.93, I^2 = 20%), corroborating earlier findings by [14], who reported a 26% reduction in cardiovascular mortality in the DAPA-HF trial. Likewise, Packer et al. [15] demonstrated a similar 25% reduction in the EMPEROR-Reduced trial, affirming the benefits of empagliflozin in patients with HFrEF (heart failure with reduced ejection fraction). This pooled effect suggests that the reduction in cardiovascular mortality is consistent across different trials and populations, reinforcing the recommendation for SGLT2 inhibitors as a cornerstone treatment in HF [16].

The meta-analysis also found that SGLT2 inhibitors reduce the risk of heart failure-related hospitalizations by 24% (RR 0.76, 95% CI 0.63–0.87, I^2 = 25%), aligning with previous studies such as the EMPA-REG OUTCOME trial [17] and the CANVAS program [18]. Both trials highlighted the substantial impact of SGLT2 inhibitors in reducing hospitalizations, especially in patients with diabetes and heart failure. The low to moderate heterogeneity observed in this outcome indicates some variability between studies but does not diminish the overall positive effect of the treatment.

Our findings are in line with the growing body of literature demonstrating the cardioprotective effects of SGLT2 inhibitors, not only in HF but also in broader cardiovascular disease contexts. For example, [19] showed that empagliflozin significantly reduced cardiovascular mortality in diabetic patients, a finding extended by our analysis to heart failure patients without diabetes. In a similar vein, [20] observed a reduced risk of cardiovascular events across a spectrum of cardiovascular risk profiles, suggesting that SGLT2 inhibitors offer broad cardioprotective benefits that extend beyond glycemic control.

Notably, studies focusing on non-diabetic heart failure patients, such as [21], emphasize that the cardiovascular benefits of SGLT2 inhibitors are independent of their glucose-lowering effects, likely mediated by mechanisms such as natriuresis, improved ventricular loading conditions, and anti-inflammatory effects [22]. These non-glycemic mechanisms provide a compelling rationale for expanding the use of SGLT2 inhibitors to a wider heart failure population.

The mechanisms by which SGLT2 inhibitors confer cardiovascular benefits remain an area of active investigation. As outlined by [23], SGLT2 inhibitors work by promoting glucosuria and reducing blood glucose levels. However, beyond these metabolic effects, SGLT2 inhibitors also appear to have direct effects on heart failure pathophysiology. Proposed mechanisms include reductions in preload and afterload, natriuresis, and favorable effects on cardiac energy metabolism [24]. These mechanisms likely contribute to the reductions in cardiovascular mortality and hospitalizations observed in this review.

5. CONCLUSION

In conclusion, this systematic review and meta-analysis provide robust evidence supporting the effectiveness of SGLT2 inhibitors in reducing cardiovascular mortality and hospitalization in patients with heart failure. The consistent outcomes across various studies and populations further reinforce the recommendation that SGLT2 inhibitors should be considered a standard component of heart failure management, alongside conventional pharmacological treatments such as ACE inhibitors and beta blockers. Future research is needed to explore the long-term cardiovascular effects of SGLT2 inhibitors and assess their potential benefits for heart failure patients without diabetes.

6. STRENGTHS AND LIMITATIONS

One of the primary strengths of this review is its inclusion of a wide range of studies, including

randomized controlled trials (RCTs) and observational studies, which provide a robust and comprehensive evaluation of the effectiveness of SGLT2 inhibitors in heart failure. Additionally, the low risk of bias across studies, as demonstrated by the Cochrane Risk of Bias tool, suggests that the findings of this review are reliable and generalizable.

However, the following are some of the following limitations that should be taken into consideration. First, despite the fact that some of our analysis included non-diabetic population, it is crucial to mention that the strongest evidence is presented by the trials including type 2 diabetic patients. Concerns arise in terms of how generalizable these findings are to the non-diabetic heart failure patients; while other trials such as EMPEROR-Reduced and DAPA-HF have shown similar effects irrespective of the participants' diabetes status. However, there are also some limitations that have to be mentioned regarding our review: First, our analysis is based on short-term follow-up data only in some of the trials included into the review; thus, it remains uncertain to what extent SGLT2 inhibitors may reduce cardiovascular risk in the long-term.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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