

Sodium-Glucose Cotransporter-2 Inhibitors and Health-Related Quality of Life Outcomes in All Types of Heart Failure: A Systematic Review and Meta-Analysis

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DISCLOSURE: Authors have no financial interest or affiliation concerning materials discussed

SOURCE OF SUPPORT: None

Abstract

INTRODUCTION: Exercise intolerance in patients with heart failure (HF) leads to a lower quality of life. An increasing number of studies suggest that early initiation of guided-directed medical therapy (GDMT) leads to better outcomes. Sodium-glucose cotransporter-2 (SGLT-2) inhibitor is one of the cornerstones in HF treatment, but its effectiveness in improving quality of life remains uncertain.

METHODS: A comprehensive search of randomized controlled trials (RCT) was conducted. Outcome measures for cardiovascular death and HF symptoms using the Kansas City Cardiomyopathy Questionnaire - Total Symptom Score (KCCQ-TSS) in the early phase of treatment and at 8 months were analyzed using the Review Manager V5.4. The KCCQ-TSS ranges from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with HF. The treatment effect was shown as a win ratio, in which a value greater than 1 indicates superiority.

RESULTS: Five RCTs were included in the meta-analysis. There was improvement in HF symptoms based on the KCCQ-TSS (HR 3.39 [95%CI: 2.95-3.89]² = 68%, p<0.00001) with substantial heterogeneity. The major source of heterogeneity identified was the interval when the KCCQ-TSS was performed, hence a subgroup analysis that specifically monitored patients during the eighth month of treatment was done, which showed improvement in HF symptoms (HR 3.16 [95%CI: 2.98-3.36]² = 8%, p<0.00001) in SGLT-2 inhibitors compared to placebo.

Conclusion: The meta-analysis showed that initiation of SGLT-2 inhibitors resulted in improvement of HF symptoms which may lead to improvement of patients' quality of life. Therefore, SGLT-2 inhibitors in all types of HF are effective in promoting better quality of life.

KEYWORDS: Sodium-glucose cotransporter-2 inhibitor, heart failure, quality of life

INTRODUCTION

Heart failure (HF) is a global pandemic with increasing prevalence, especially in the ageing population.¹ The important key goals of HF therapy are to prevent progression of symptoms, prolong survival and more importantly, to improve quality of life.² Studies on patients with HF with reduced ejection fraction (HFrEF), defined as having left ventricular ejection fraction (LVEF) of <40%, have shown that poor quality of life is associated with poorer prognosis.³ The available validated tool to measure the quality of life is the Kansas City Cardiomyopathy Questionnaire (KCCQ). It is a simple and cost-effective tool recommended for quantifying the quality of care and characterizing a patient's HF-related status.⁴ The KCCQ clinical summary score (CSS) includes the physical function and symptom domains like the total symptom score (TSS) which quantifies symptom frequency and severity. The overall summary score (OSS) is

Published online: 29 May 2025
<https://doi.org/10.69944/pjc.69d1d8143d>
<https://pjc.philheart.org>
 ISSN: 0115-1029
 e-ISSN: 2815-2123
 Volume 53 Issue 1

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derived from TSS wherein physical function, quality of life and social function were included.⁵ In terms of HF-related quality of life, the KCCQ-TSS domain is considered an important parameter to determine symptomatic burden in HF.⁶

The different classes of HF were categorized based on the LVEF value. HFrEF has LVEF $\leq 40\%$, heart failure with mildly reduced ejection fraction (HFmrEF) has LVEF between 41%-49% and heart failure with preserved ejection fraction (HFpEF) has LVEF $\geq 50\%$. The categorization was also a way of identifying available treatment strategies.⁷ Pharmacotherapy is the cornerstone of treatment for HFrEF and should be implemented before considering device therapy. The general principles of pharmacotherapy in HF are modulation of renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system. Based on the European Society of Cardiology (ESC) 2021 treatment guidelines on HF, there are already Class I and IIB recommendations in the following medications for the treatment of patients with HFrEF and HFmrEF, respectively. These are 1) angiotensin-converting enzyme inhibitors (ACE-I) or an angiotensin receptor-neprilysin inhibitor (ARNI), 2) beta-blockers, 3) mineralocorticoid receptor antagonists (MRA) and 4) sodium-glucose cotransporter (SGLT-2) inhibitors. These available pharmacotherapies were recognized as the pillars of HF therapy.⁸ Patients under the spectrum of HFpEF focus more on treatment strategies to address the underlying disease process. There are already large randomized clinical trials (RCTs) available for HFpEF, however, data are still conflicting with regards to all-cause mortality and rate of rehospitalization. But one of the remarkable trials that showed significant outcomes is from the SGLT-2 inhibitor clinical trials.

SGLT-2 inhibitors are glucose-lowering agents initially developed for the treatment of diabetes mellitus type 2. The recent treatment guidelines already recommend use of SGLT-2 inhibitors in HFrEF and HFmrEF. In several large cardiovascular outcome trials, SGLT-2 inhibitors are already being recommended in patients with HFpEF, specifically in the DELIVER and EMPEROR-PRESERVED trials. These studies clearly demonstrated benefits in the treatment of HF.⁹⁻¹⁰ These are large clinical trials mainly focused on reducing mortality and prevention of recurrent hospitalizations. The studies on efficacy of SGLT-2 inhibitors in improving quality of life among patients with HF remain uncertain. This meta-analysis aims to determine the outcomes of HF symptoms and cardiovascular death in all types of HF.

Research Question

Among adult patients with HF, how effective are SGLT-2 inhibitors in improving quality of life?

Specific Objectives

The general objective of this meta-analysis is to determine the efficacy of SGLT-2 inhibitors versus placebo in all types of HF. Our specific objectives include evaluating HF patients on guidelines-directed medical therapy (GDMT) in terms of: a) quality of life in the early phase of treatment, b) quality of life in the maintenance phase of treatment and c) cardiovascular death.

MATERIALS AND METHODS

Criteria for considering studies for this review

Studies were selected based on the comparison of SGLT-2 inhibitors versus placebo in all patients with HF on GDMT. Studies were included if: 1) Subjects were diagnosed with chronic HF and acute HF (de novo or decompensated chronic HF) regardless of the ejection fraction. 2) Subjects who had elevated NT-proBNP on the initial visit. 3) Subjects on appropriate dose of medical therapy for HF [such as ACE-I, angiotensin receptor blocker (ARB), beta-blocker, oral diuretics, mineralocorticoid receptor antagonist (MRA), ARNI and ivabradine]. 4) KCCQ was used in assessing quality of life. 5) Cardiovascular death outcomes were assessed by death from acute myocardial infarction (arrhythmia, sudden death, HF, stroke, pulmonary embolism and peripheral artery disease), death resulting from a procedure to treat myocardial infarction [percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)] or death from an elective procedure to treat myocardial ischemia. Studies that were excluded from the meta-analyses were: 1) Abstracts without full-text publication, and 2) Absence of the above-mentioned clinical outcomes. There was no restriction on the language of reporting or period. Published and unpublished RCTs were included, whether it was single-blinded, double-blinded, or unblinded.

Information sources and search strategies for identification of studies

Three independent reviewers (B.D., B.B. and R.T.) conducted a systematic search and evaluation of studies on the efficacy of SGLT-2 inhibitor in all spectrums of HF published from inception up to December 2022, in the following scientific search engines: PubMed, Cochrane Library, Lancet and Clinical Trials. This meta-analysis was performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) 2020 statement. The search strategy used was "(sodium-glucose cotransporter-2 inhibitors) AND (heart failure)." The authors also sought unpublished trials and ongoing studies in national and international trial registers (ClinicalTrials.gov, ISRCTN Register, EU Clinical Trials Register and WHO ICTRP), dissertation and thesis databases, conference abstracts and other grey literature sources in relevant search. The comprehensive search was not restricted by any language or publication date filter.

Selection of studies

Three independent reviewers (B.D., B.B. and R.T.) independently performed a systematic process for selecting studies for inclusion in the review, wherein any duplicate records of the same report were removed. Abstracts and manuscript titles examined to be included were only those that met the criteria for assessment. Studies were included if there was an agreement between the three reviewers. During the study selection process, any discrepancies were resolved accordingly and consulted with a fourth expert investigator (F.G.).

Data collection

Review authors have planned relevant data to be collected in this meta-analysis and systematic review. A data collection

form was created, including the citation details, study design, total study duration, type and number of participants, study location, study inclusion and exclusion criteria, baseline patient characteristics, description of intervention and control, and relevant outcome of interest and results. This data collection form guaranteed some consistency in data abstraction and was deemed necessary in comparing data.

Data extraction and management

Three data extractors (B.D., B.B. and R.T.) independently extracted data using a data collection form created by the authors. Data in the studies were tabulated separately by study authors.

Assessment of risk-of-bias in included studies

Three independent reviewers (B.D., B.B. and R.T.) critically appraised each trial using the risk of bias review manager tool for the RCT. The domains include bias arising from the selection bias from randomization sequence and allocation concealment, performance bias from blinding the participants and personnel, detection bias from blinding of outcome, attrition bias from incomplete outcome data and reporting bias from selective bias. The overall risk of bias was further subdivided into “low risk of bias,” “some concerns,” or “high risk of bias.”

Data synthesis and analysis

Data synthesis and analysis were performed using Revman 5.4. All p values were two-sided and determined as statistically significant. The effect measure of choice for the outcome was reported as risk ratio for dichotomous data at 95% interval. The

Mantel-Haenszel method was used primarily for some studies with lower event rates.

The I^2 statistic was used to assess statistical heterogeneity across studies. An I^2 value of 30%-60% was reconsidered as moderate heterogeneity, 50%-90% substantial heterogeneity and 75%-100% considerable heterogeneity. A random-effects analysis model estimate was utilized. Evidence of publication bias was evaluated using a funnel plot to check for funnel plot asymmetry, which may indicate the presence of small-study effects or selective publication of positive findings.

Sources of heterogeneity were identified and discussed in this review. For the presence of significant heterogeneity on the random-effects model, a sensitivity analysis was done through the exclusion of studies not eligible based on sample size, methodological quality, population variance and intervention features. All the sources of heterogeneity were identified and discussed in this review.

RESULTS

Study Selection

Out of the 1,599 records identified in the database, 248 duplicates were removed and 1,166 articles were excluded after screening the titles and abstracts. Five full-text articles were assessed for eligibility and were all included in the meta-analysis (Figure 1). The studies were mainly designed to investigate SGLT-2 inhibitors in the treatment of all types of HF in terms of quality of life and cardiovascular death. There were

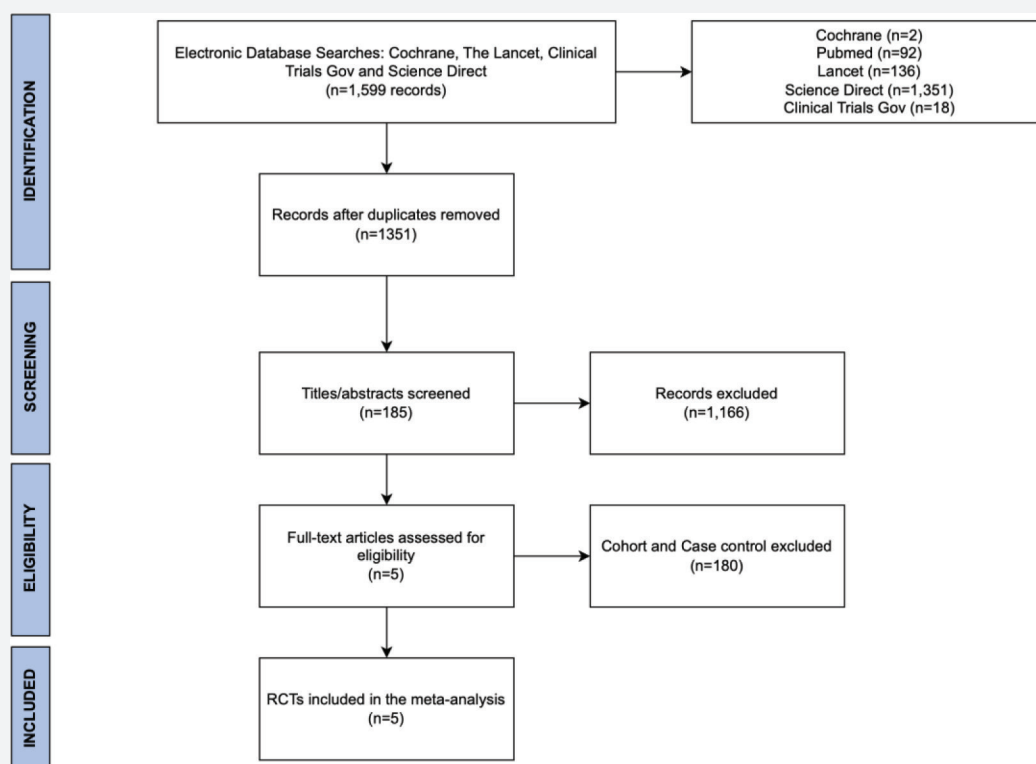


Figure 1. PRISMA Flow Diagram

Table 1. Review of Studies on SGLT-2 Inhibitors

Study	Design	Number of Participants	Type of Heart Failure	Intervention	Control	Follow-up period	Outcomes
DAPA-HF 2019 ¹¹	RCT	4,744	HFrEF	Dapagliflozin 10 mg once daily	Placebo	18.2 months	1)Worsening HF 2)CV mortality 3)KCCQ symptoms 4)Worsening renal function
DELIVER 2022 ⁹	RCT	6,263	HFmrEF, HFpEF	Dapagliflozin 10 mg once daily	Placebo	2.3 years	1)Worsening HF 2)CV mortality 3)KCCQ symptoms
EMPEROR PRESERVED 2021 ¹⁰	RCT	5,988	HFpEF	Empagliflozin 10 mg once daily	Placebo	26.2 months	1)Hospitalization 2)CV mortality 3)KCCQ symptoms 4)Change in eGFR
EMPEROR REDUCED 2020 ⁵	RCT	3,730	HFrEF	Empagliflozin 10 mg once daily	Placebo	16 months	1)Hospitalization 2)CV mortality 3)KCCQ symptoms 4)Decline in eGFR
EMPULSE 2022 ¹³	RCT	530	HFrEF HFmrEF HFpEF in AHF	Empagliflozin 10 mg once daily	Placebo	3 months	1)CV death 2)KCCQ symptoms 3)Time to death

HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; CV, cardiovascular; eGFR, estimated glomerular filtration rate

similar studies in the relevant search, but all of the published and ongoing studies focused on a specific spectrum of HF.

Study Characteristics

The five RCTs included in the study were DAPA-HF, DELIVER, EMPEROR PRESERVED, EMPEROR REDUCED and EMPULSE. There were a total of 21,255 participants included, with 10,629 in the SGLT-2 inhibitor group and 10,626 from the control group. Several comorbidities were accounted for, and most patients had hypertension, diabetes and chronic kidney disease.⁹⁻¹³ All study populations were started on a standard dosage, whether they were in the acute decompensated HF or chronic HF (Table 1).

Risk of bias in included studies

All trials performed a randomized, double-blind, placebo-controlled trial. Most employed an interactive voice- or web-response system that used a permuted-block design. The only bias that was encountered during the review was selection bias, wherein one trial did not specify how the allocation was concealed. All of the trials had regular follow-up as early as 3 months up to 26 months.

Outcomes of the meta-analysis

The KCCQ-TSS quantifies symptom frequency and severity, while the scoring system ranges from 0 to 100. Higher scores

indicated fewer symptoms and physical limitations associated with HF. The treatment effect was shown as a win ratio, in which a value greater than one indicated superiority. Data were extracted and analyzed using random effects model on both dichotomous and generic inverse variance data types via Review Manager V5.4. Analysis in improvement in quality of life using the KCCQ-TSS showed improvement in HF symptoms in the treatment arm. There is statistical significance in using SGLT-2 inhibitor compared to placebo in the initiation phase, wherein the treatment arm showed more than three times improvement in quality of life (HR 3.39 [95%CI: 2.95-3.89] $I^2 = 68\%$, $p < 0.00001$). There are both clinical and statistical substantial heterogeneity identified in this analysis with $I^2 = 68\%$. The clinical heterogeneity identified was that patients enrolled in the EMPULSE trial were patients in acute HF that generally have higher risk features and with relatively poorer prognosis that can lead to lesser response to treatment. Also, the interval when the KCCQ-TSS was performed could be a source of heterogeneity (Figure 3). Therefore, a subgroup analysis that specifically monitored patients during the eighth month and excluding patients in acute HF were done. There was more than three times improvement in using SGLT-2 inhibitors with no significant heterogeneity (HR 3.16 [95%CI: 2.98-3.36] $I^2 = 8\%$, $p < 0.00001$) (Figure 4).

	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)	Other bias
DAPA-HF 2019	+	+	+	+	+	+	+
DELIVER 2022	+	+	+	+	+	+	+
EMPEROR-PRESERVED 2021	+	+	+	+	+	+	+
EMPEROR-REDUCED 2020	+	+	+	+	+	+	+
EMPULSE 2022	+	?	+	+	+	+	+

LEGEND: Low Risk - , Moderate Risk - , High Risk - 

Figure 2. Cochrane Risk of Bias Assessment

Note: The figure shows the review authors' judgments about each risk-of-bias item in the column for each included study in the rows. A green dot with a plus symbol indicates presence of a bias item in a corresponding study. A red dot with a minus symbol indicates absence of a bias item in a corresponding study.

On the other hand, the secondary outcome showed lower risk of cardiovascular death in the SGLT-2 inhibitor group (RR 0.87 [95%CI: 0.80-0.95] $I^2 = 0$, $p = 0.002$). There was a 13% decrease in risk of cardiovascular death in using SGLT-2 inhibitors compared to placebo in patients with HF on GDMT. It was statistically significant with a p-value of 0.002 and no heterogeneity was documented (Figure 5).

Reporting Bias

Based on visual inspection, there was symmetry in the funnel plot on both KCCQ-TSS and cardiovascular death. This suggests that there was no significant publication bias (Figure 6 and 7).

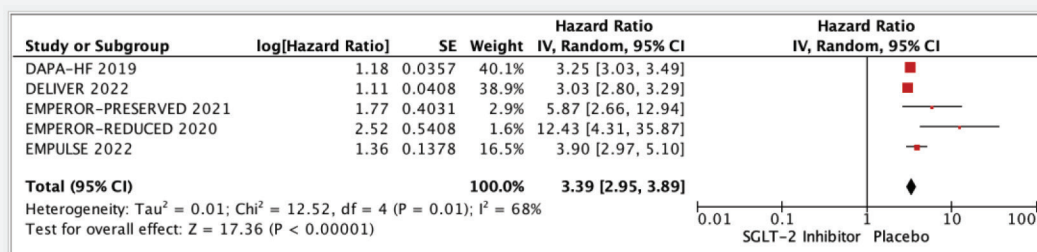


Figure 3. KCCQ-TSS Forest Plot Comparison of SGLT-2 Inhibitor Versus Placebo.

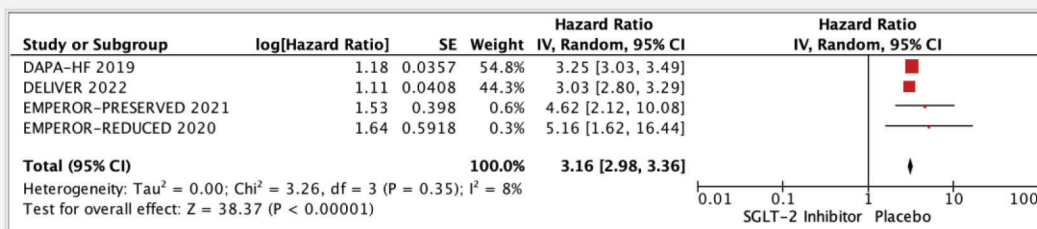


Figure 4. KCCQ-TSS Forest Plot Comparison of SGLT-2 Inhibitor Versus Placebo in the 8th Month.

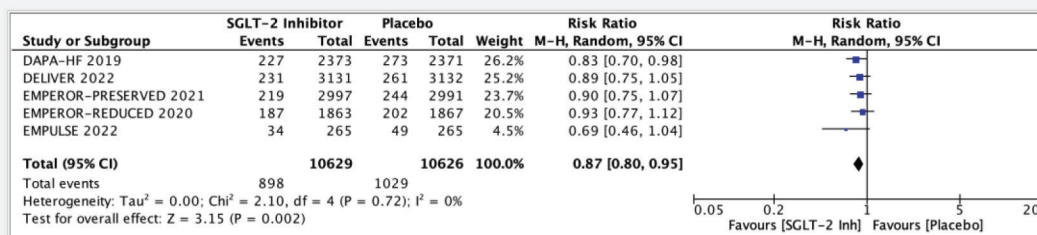


Figure 5. Cardiovascular Death Forest Plot Comparison of SGLT-2 Inhibitor Versus Placebo

DISCUSSION

Summary of Key Findings and Comparison with Literature

This systematic review evaluated evidence from five RCT studies involving 21,255 patients with history of HF from 2017 to 2022. This meta-analysis determined that SGLT-2 inhibitors substantially improved quality of life in terms of HF-related symptoms. The subgroup analysis showed marked improvement in terms of quality of life in the treatment arm (HR 3.16 [95%CI: 2.98-3.36] $I^2 = 8\%$, $p < 0.00001$) and decreased risk of cardiovascular death (RR 0.87 [95%CI: 0.80-0.95] $I^2 = 0$, $p = 0.002$).

Several previous studies have demonstrated improvement using SGLT-2 inhibitors in improving quality of life,¹³⁻¹⁴ which was attributed by the natriuresis and osmotic diuresis effect that resulted in improvement of the left ventricular loading condition and reducing preload. However, there are conflicting studies stating that even if there is improvement in LV ventricular loading condition, there seems to be recurrent hospitalization and persistent HF-related symptoms despite maximizing available medical treatment. In this meta-analysis, the results showed 3.16 times improvement in quality of life based on the KCCQ-TSS after the eighth month of treatment with SGLT-2 inhibitors.

In regard to cardiovascular mortality, those who took SGLT-2 inhibitors had 0.87 times the risk of having cardiovascular mortality than those in the placebo group (RR 0.87 [95%CI: 0.80-0.95] $I^2 = 0$, $p = 0.002$). Overall, there are lower events of cardiovascular death. A meta-analysis was done by Razuk, et al. in 2022, wherein 22,653 patients were included. SGLT-2 inhibitors in patients with history of HF had lower events of cardiovascular death (HR 0.87 [95%CI: 0.80-0.95] $I^2 = 0$) when compared to placebo. Thus, it may support the efficacy of initiating SGLT-2 inhibitors.¹⁵

Strengths and Limitations

This manuscript presented a comprehensive systematic review and meta-analyses of using SGLT-2 inhibitors in adult patients ≥ 18 years old with history of HF and decompensated HF (de novo or acute on top of chronic HF). A systematic critical appraisal of included studies was done using the review manager risk of bias tool. The studies consisted of large multi-centered RCTs resulting in a minimum level of discriminative power providing more precise treatment effect. However, there was documented substantial clinical and statistical heterogeneity among them with observed variability in clinical characteristics and interval when KCCQ-TSS was performed.

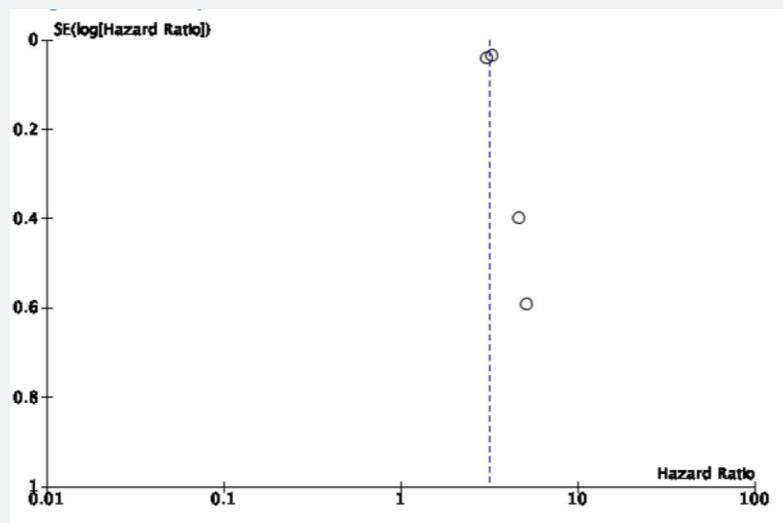


Figure 6. Funnel Plot Comparison of SGLT-2 Inhibitor Versus Placebo on KCCQ-TSS

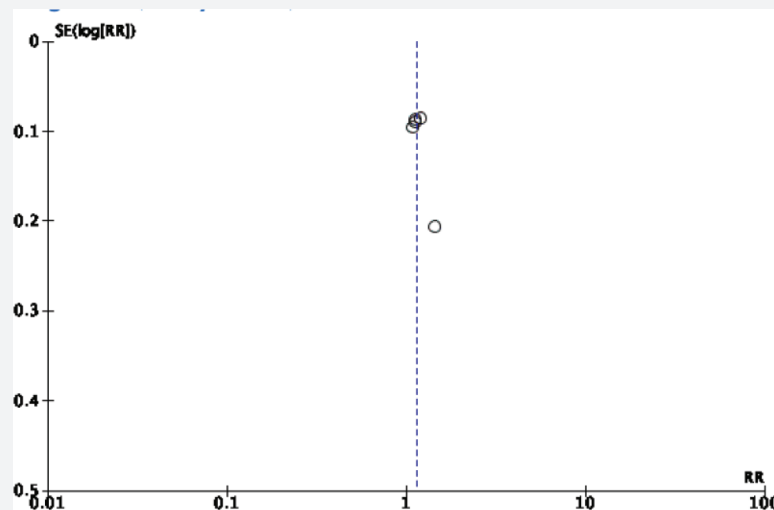


Figure 7. Funnel Plot Comparison of SGLT-2 Inhibitor Versus Placebo on Cardiovascular Death

The present meta-analysis has important limitations. First, despite the large sample size ($n = 21,255$), there are variations in follow-up, enrollment criteria and different SGLT-2 inhibitor subtypes that may have contributed to heterogeneity across studies. Second, allocation concealment in one study was not clearly elucidated that might have led to some degree of selection bias.

Implications for practice and research

The overall effect estimate must be considered in assisting physicians in the clinical decision-making process in patient treatment. The cost-effectiveness of the medication must also be taken into account.

Further research may need studies with similar follow-up and more pre-specified criteria for enrollment of patients and bias correction.

CONCLUSION

The meta-analysis showed that initiation of SGLT-2 inhibitors resulted in marked improvement of HF symptoms, which may potentially lead to improvement of patients' quality of life. Furthermore, the study showed a decreased rate of cardiovascular death after initiation of SGLT-2 inhibitors. Therefore, SGLT-2 inhibitors in all types of HF are effective in promoting better quality of life and lowering incidence of cardiovascular death.

FUNDING, DISCLOSURE AND CONFLICT OF INTEREST

The authors state no conflict of interest. The manuscript has not been supported by any sources of support, including sponsorship and any financial sources. The authors declare no relationship to any industries.

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