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REVIEW

The effect of SGLT2 inhibitors on health status in patients with heart failure: a systematic review and meta-analysis

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Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been shown to improve health status in patients with heart failure (HF). We aimed to evaluate the effect of SGLT2i on health status [by Kansas City Cardiomyopathy Questionnaire (KCCQ)] and if effect varied by ejection fraction (EF). Randomized clinical trials of SGLT2i in patients with HF until November 2022 were assessed. Change in KCCQ total symptom score (TSS), clinical summary score (CSS), and overall summary score (OSS) from baseline to 12-16 weeks, 32 weeks, and 52 weeks follow-up were assessed. Weighted mean differences (MD) in scores and odds ratios (OR) were pooled using a random-effects model. Twelve trials (n=23,679) were included. SGLT2i significantly improved KCCQ-TSS at 12-16 weeks [MD 2.16 (1.67, 2.65); p<0.001], 32 weeks [MD 1.98 (1.43, 2.54); p<0.001] and 52 weeks [MD 1.94 (1.19, 2.69); p<0.001] follow-up. At 12-16 weeks, patients treated with SGLT2i had significantly higher odds of KCCQ-TSS improvement by ≥5 points [OR 1.27 (1.16, 1.39); p<0.001], ≥10 points [OR 1.21 (1.11, 1.32); p<0.001] and ≥15 points [OR 1.23 (1.14, 1.33); p<0.001]. Similar results were observed at mid- and long-term follow-up, and for CSS and OSS. For all analyses, findings were consistent in patients with HF with reduced or preserved EF, acute/worsening or chronic HF, and type of SGLT2i used (p-interaction >0.20 for all). SGLT2i improve health status in patients with HF, with consistent and sustained benefits across all summary scores and HF subtypes. Treatment benefits were apparent within months of initiation and sustained to at least 1 year.

Key words: sodium-glucose cotransporter-2 inhibitors, HFrEF, HFpEF, quality of life, KCCQ.

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Introduction

Patients with heart failure (HF) have a high risk of hospitalizations and death. As importantly, these patients experience high burden of symptoms and physical limitations, and a poor quality of life.[1] Patient reported outcomes such as the impact of HF symptoms on daily activities, psychological health, social function, and functional limitations have great utility to monitor therapy effectiveness, change in status, and predict prognosis.[2]

Improvement in health status is an important therapeutic target in HF, recognized as such by clinicians, guideline developers, clinical trialists and regulators.[3] The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a validated patient reported outcome instrument approved by the FDA to assess health status.[1,2,4] Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have demonstrated clinical outcome improvements in both HF with reduced ejection fraction (HFrEF) and with preserved EF (HFpEF).[5-14] These agents have also shown improvements in health status; however, the numerical extent

of benefit has varied across trials, in part due to differences in study design and patient characteristics. While prior meta-analyses of SGLT2i have demonstrated improvements in health status in patients with HF, those studies were conducted specific to a subtype of HF (HFrEF or HFpEF), did not include recent landmark trials, or did not study health status as the primary outcome of the meta-analysis.[15-19]

The aim of this study level meta-analysis was to assess the effect of SGLT2i as a class on all KCCQ summary scores across multiple time points and assess if the effect is consistent across EF spectrum in the clinical setting of HF.

Materials and Methods

Data sources and search strategy

This study level meta-analysis was conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic review and Meta-Analyses) guidelines.[20] An electronic search of the MEDLINE and Cochrane CENTRAL databases was conducted from inception until November 2023. The following keywords and their MeSH terms were employed for the search (sodium glucose cotransporter-2 inhibitors OR SGLT2 inhibitors OR SGLT2 inhibitor OR SGLT2i OR flozins OR empagliflozin OR dapagliflozin) AND (heart failure OR HF OR heart failure with reduced ejection fraction OR HFrEF OR heart failure with preserved ejection fraction OR HFpEF) AND (quality of life OR QoL OR health status OR standard of life OR functional status OR symptoms in heart failure patients OR improvement in daily life OR KCCQ OR Kansas City Cardiomyopathy Questionnaire) (Supplementary Table 1).

Study selection, outcomes of interest, and data extraction

The selected articles were exported to EndNote Reference Library software (Version X9; Clarivate Analytics, Philadelphia, Pennsylvania), and duplicates were removed. Initial screening was done based on title and abstract, following which full texts were reviewed. Articles were screened by two reviewers (MSU and SQ) independently and discrepancies were sorted with consensus. The following prespecified eligibility criteria was used to select studies: i) randomized control trials (RCT) or post-hoc analyses of RCTs comparing SGLT2i with placebo; ii) included adult HF patients; iii) assessed health status using the KCCQ questionnaire; and iv) reported at least one of the predefined outcomes of interest.

The primary outcome of interest was health status as measured by the KCCQ score. Amongst all patient reported outcome instruments, the KCCQ has consistently been identified as one of the most reliable, responsive, and valid instruments.[2] KCCQ-23 was used in majority of trials. This includes 23 items that map to seven components: symptom frequency, symptom burden and stability, physical limitations, social limitations, quality of life, and self-efficacy. The questionnaire has three summary scores: total symptom score (TSS) that consists of symptom frequency and symptom burden components; clinical summary score (CSS), that consists of TSS and physical limitation domain; and overall summary score, that consists of CSS, quality of life, and social limitation components. For each summary, the scores range from 0-100, with 100 being the best possible score. KCCQ-23 has been shown to be a valid and reliable assessment of health status in HF regardless of ejection fraction, with scores associated with hospitalization and mortality risk. The SOLOIST-WHF (Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure) trial was the only RCT that utilized KCCQ-12,[12] which is a short version of the KCCQ-23 and preserves the validity, reliability, prognostic importance, and interpretability of the KCCQ-23.[21]

The mean change in KCCQ-CSS, -TSS and -OSS at short- (12-16 weeks), mid- (32 weeks) and long-term (52 weeks) follow-up in the SGLT2i and the placebo arms were extracted from selected trials. Findings from the responder analyses were also extracted using established thresholds for clinically meaningful changes in KCCQ (≥5, ≥10, and ≥15 points for improvement and ≥5 point for deterioration).

Statistical analysis

Baseline characteristics of participants in each study are reported as frequencies and percentages for categorical and means with standard deviations (SD) for continuous variables. At a study level, mean differences (MD) in KCCQ scores and corresponding SD were pooled using the random-effects model to derive weighted mean differences (WMD) or standard mean differences (SMD), along with corresponding 95% confidence intervals (CI). WMD was used as the measure of treatment effect when all studies within a forest plot used the KCCQ-23. SMD was used as the measure of treatment effect in cases where certain studies used KCCQ-23 while others used KCCQ-12. As SOLOIST-WHF used KCCQ-12, SMD from TSS scores was used for trials utilizing KCCQ-23 in the acute versus chronic HF analysis. For the responder analysis, odds ratios with 95% CI were pooled using a random-effects model. Statistical heterogeneity was evaluated using the Higgins I^2 statistic. I^2 >75% was considered significant heterogeneity. The inverse variance method was used to allocate study weights. Publication bias was assessed via visual inspection of Begg's funnel plot. Visual inspection of the funnel plot revealed significant asymmetry suggesting potential small study bias in our study (Supplementary Figure 2). Quality of evidence was assessed with the GRADE scale (Supplementary Tables 2-4). All statistical analysis was performed on Review Manager (Version 5.4.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A p-value ≤0.05 was considered statistically significant in all cases.

Results

Search results and baseline characteristics

The PRISMA flow chart summarizes the search and study selection (Supplementary Figure 1). From 1830 records, data from 12 RCT were included. Five trials included patients with HFrEF: DEFINE-HF (Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in Patients with HFrEF),[5] DAPA-HF (Dapagliflozin and Prevention of Adverse-Outcomes in HF),[6] EMPIRE HF (Empagliflozin in HFrEF),[22] EMPERIAL (Effect Of Empagliflozin On Exercise Ability And HF Symptoms In Patients With Chronic HF) Reduced,[23] EMPEROR-Reduced (Empagliflozin Outcomes Trial in Patients With Chronic HFrEF).[7] Four trials included patients with HFpEF: PRESERVED HF,[8] EMPERIAL Preserved,[23] EMPEROR-Preserved,[9] and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved EF HF).[10,13] Three trials included patients with both HFrEF and HFpEF: CHIEF-HF (Canagliflozin: Impact on Health Status, Quality of Life and Functional Status in HF),[11] EMPULSE (Empagliflozin for acute heart failure who have been stabilized),[13,24] SOLOIST-WHF (Sotagliflozin in Patients with Diabetes and Recent Worsening HF).[12]

The overall study population comprised of 23,679 patients (11,849 in the SGLT2i arm; 11,830 in the placebo arm) with mean age ranging from 62 to 71 years and 45% women. The HFrEF, HFpEF, and mixed subpopulations included 9361, 12,566, and 1752 patients, respectively (Supplementary Tables 5-7). SOLOIST-WHF was the only trial where all participants had diabetes. Prevalence of diabetes was ~50% for majority of trials; EMPIRE-HF had the lowest prevalence (17.4%). (Supplementary Table 5). Baseline KCCQ-TSS, -CSS, and -OSS data were available for EMPERIAL-Reduced, DEFINE-HF, EMPIRE-HF, PRESERVED-HF, and EMPERIAL-HF. Baseline KCCQ scores for HFrEF trials were higher than HFpEF trials, and amongst all trials EMPIRE-HF had the highest KCCQ scores at baseline.

Health status

SGLT2i significantly improved KCCQ-TSS at short-term [MD 2.16 (1.67, 2.65); I^2=0%]. These findings were consistent in patients with HFrEF [MD 2.38 (1.73, 3.04) I^2=0%], HFpEF [MD 1.78 (1.02, 2.54) I^2=0%], and *mixed* [MD 4.45 (0.31, 8.59)] subgroups (p-interaction=0.28). Similar findings were observed with KCCQ-CSS and KCCQ-OSS (Figure 1). SGLT2i improved KCCQ-TSS at mid-term [MD 1.98 (1.43, 2.54) I^2=18%]. These findings were consistent in patients with HFrEF [MD 2.13 (1.05, 3.21) I^2=32%] and HFpEF [MD 1.93 (1.08, 2.79) I^2=51%] (p-interaction 0.78). Similar effects were observed with KCCQ-CSS and KCCQ-OSS (Figure 2).

Only the EMPEROR-Reduced and Preserved trials published KCCQ results at 52 weeks. SGLT2i significantly improved KCCQ-TSS [MD 1.94 (1.19, 2.69) I^2=0%], with no difference between HFrEF and HFpEF (p-interaction=0.64). Similar effects were observed with KCCQ-CSS and KCCQ-OSS (Figure 3). SGLT2is significantly improved KCCQ in both acute/worsening HF [SMD 2.76 (1.59, 3.93) I^2=13] and chronic HF [SMD 2.18 (1.74, 2.61) I^2=0%] (p-interaction=0.36; Figure 4).

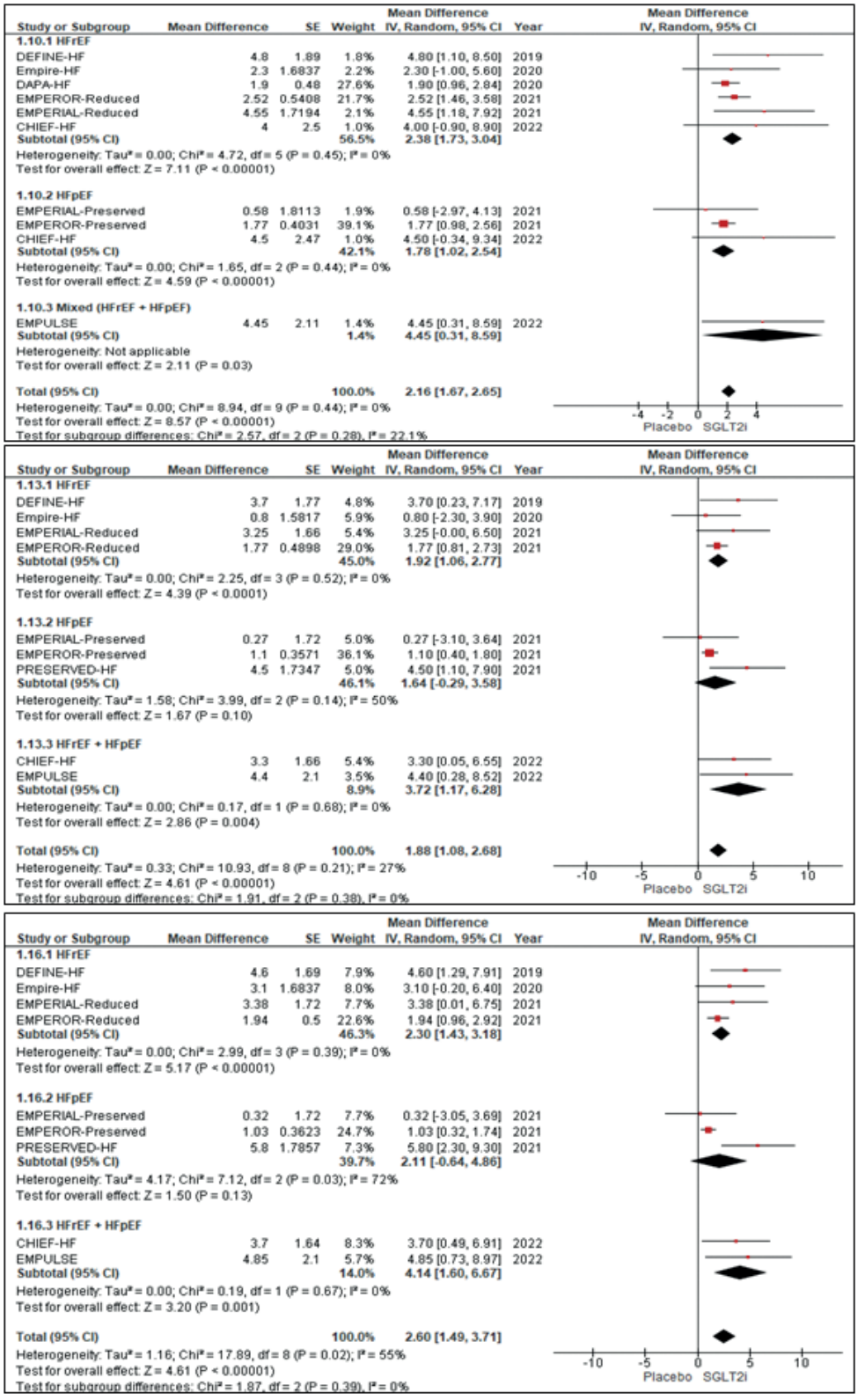
Responder analysis

Results of responder analysis are summarized in Figure 5. Patients randomized to SGLT2i had greater odds of improvement in KCCQ-TSS by ≥5, ≥10, and ≥15 points at short, mid, and long-term follow-up (p<0.05 for all) (Supplementary Figures 3-5). There was no significant interaction between the HFrEF and HFpEF (p-interaction>0.1 for all outcomes at all time points). Similar findings were observed for KCCQ-OSS and KCCQ-CSS (Supplementary Figure 6-11). Patients on SGLT2is were less likely to have a ≥5 point deterioration in KCCQ-TSS at short, mid, and long-term follow-up (p<0.05 for all) (Supplementary Figure 12). These findings were consistent in patients with HFrEF and HFpEF (p-interaction>0.1 for all outcomes at all time points). Similar findings were observed when KCCQ-CSS and -OSS were evaluated (Supplementary Figures 13 and 14).

Discussion and Conclusions

This meta-analysis of 23,679 patients with HF demonstrates that SGLT2i use produces significant improvements in health status. These improvements were consistent across all three KCCQ summary scores (TSS, CSS and OSS), appeared as early as 12-16 weeks, and were sustained up till 52 weeks (Figure 6). The benefits were also consistent across the range of ejection fraction, and regardless of the clinical setting (acute/worsening HF and chronic HF). Patients on SGLT2i were significantly more likely to experience at least small, moderate, and large improvements. They were also less likely to experience deterioration in any of the KCCQ summary scores, at all the time points studied.

The observed improvements were a mean difference of 1.5-2.6 points in KCCQ-OSS scores at 3-12 months from SGLT2i initiation. These estimates are modestly higher than those of other efficacious HF drug and device therapies. In patients with HFrEF, sacubitril/valsartan demonstrated a 1.3-point improvement in KCCQ-OSS at 8 months and in patients with HFpEF, spironolactone demonstrated a 1.4-point improvement in KCCQ-OSS at 4 months.[25,26] Similarly, cardiac resynchronization therapy demonstrated a 1.29 points improvement in KCCQ-TSS.[27] Although a 5 point improvement is often considered a clinically meaningful improvement in KCCQ scores from baseline, this threshold does not translate well when quantifying mean differences on a population level. Furthermore, previous studies suggest that the minimal clinically significant difference may be below 5 points.[1,28] Clinically, the best analytic method to examine whether the effects are clinically meaningful is the responder analysis which calculates the odds to achieve various thresholds of improvement.[1] The current study demonstrated that



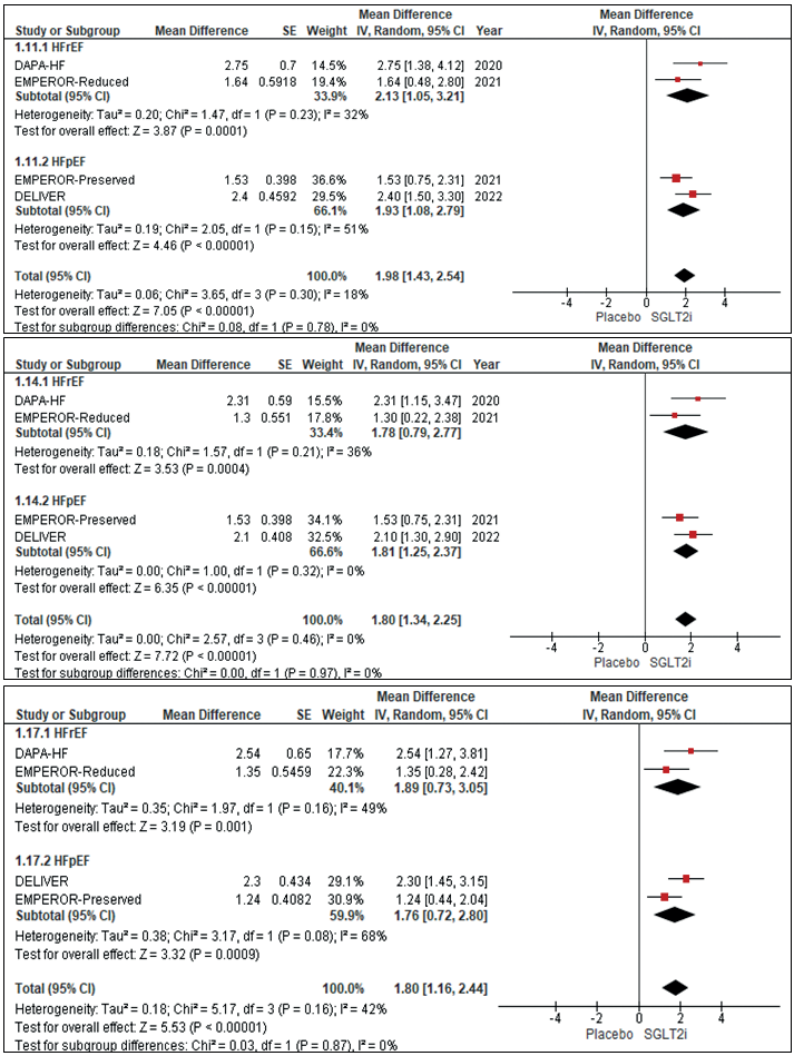
CSS, clinical summary score; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; OSS, overall summary score; SGLT2i, Sodium glucose cotransporter 2 inhibitors; TSS, total symptom score.

Figure 1. Effect of SGLT2i on health status at short-term (12-16 weeks) follow-up. A) total symptom score, B) overall summary score, C) clinical summary score.

patients on SGLT2i were 27% more likely to experience improvement in KCCQ-TSS ≥5 points, and even larger improvements of ≥10 and ≥15 points, as early as 3 months which supports significant early improvements in health status with SGLT2i use.

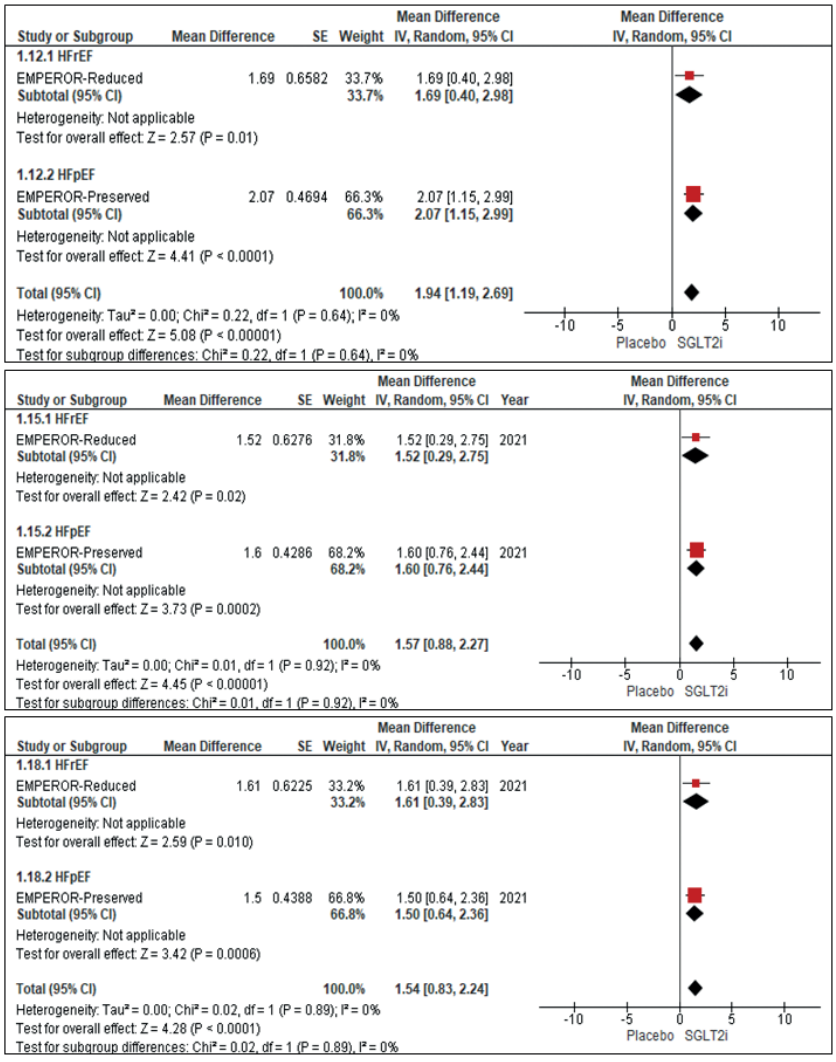
Amongst the 11 included trials, the EMPIRE-HF and EMPERIAL-Preserved trials did not demonstrate a statistically significant improvement in KCCQ scores. While the point estimate for mean difference in EMPIRE-HF was similar to that of other trials (2.3), the mean difference for EMPERIAL-Preserved was lower than that of other trials (0.58). A possible explanation why EMPIRE-HF did not meet statistical significance was that the trial enrolled a greater proportion of less symptomatic patients. EMPIRE-HF had a greater proportion of patients with NYHA functional class I-II symptoms and higher KCCQ scores at baseline compared with other trials. Whereas, the EMPERIAL-Preserved trial may have not met statistical significance due to enrolment of the eldest population amongst all trials, and age is associated with a greater risk of worsening health status.[22,23,29] These factors may have contributed to minimal improvement in KCCQ scores on follow-up.

It is difficult to assess and compare health status across trials. Assessment and reporting of health status in HF trials should be standardized. Trials frequently do not report baseline KCCQ scores across all three summary scores. In addition,



CSS, clinical summary score; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; OSS, overall summary score; SGLT2i, Sodium glucose cotransporter 2 inhibitors; TSS, total symptom score.

Figure 2. Effect of SGLT2i on health status at mid-term (32 weeks) follow-up. A) total symptom score, B) overall summary score, C) clinical summary score.



CSS, clinical summary score; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; OSS, overall summary score; SGLT2i, Sodium glucose cotransporter 2 inhibitors; TSS, total symptom score.

Figure 3. Effect of SGLT2i on health status at long-term (52 weeks) follow-up. A) total symptom score, B) overall summary score, C) clinical summary score.

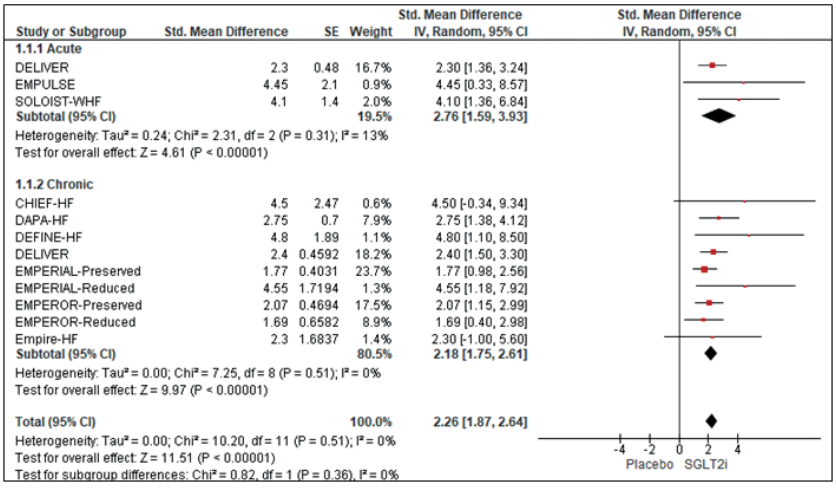
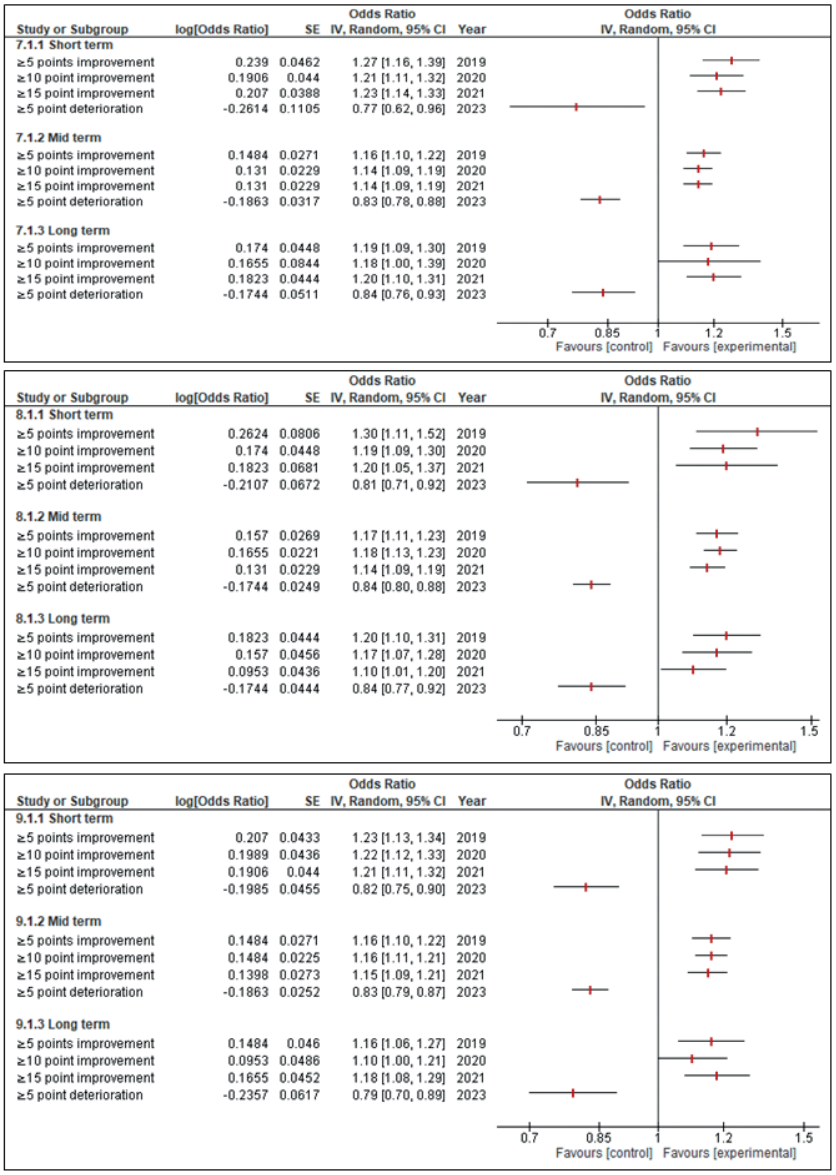


Figure 4. Effect of SGLT2i on health status in patients with acute/worsening *versus* chronic heart failure.

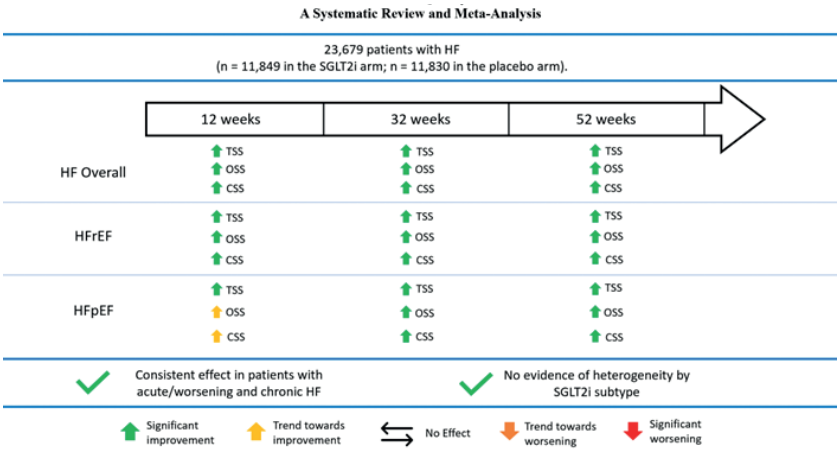
findings should be reported as per standardized categorical scales, e.g., 0-24: very poor to poor; 25-49: poor to fair; 50-74: fair to good; and 75-100: good to excellent.[1] Moreover, health status should be assessed at multiple time points, which also ideally can be standardized, to assess whether the treatment effect is acute and/or sustained. Many trials of SGLT2i have reported change in health status at 3 to 4 months, and four trials reported data at 32 weeks. Data at time points beyond 52 weeks is lacking. Two trials, the CHIEF-HF and EMPULSE trial, captured change in KCCQ at 2 weeks and demonstrated a significant early improvement. Similarly, only two trials, EMPEROR-Reduced and EMPEROR-Preserved, reported data at 52 weeks. Standardization of KCCQ assessment timelines will limit variability between trials to permit qualitative comparisons.

In addition to standardizing timelines of KCCQ assessment, the stability of KCCQ summary scores between follow-up assessments needs to be reported. Trials report KCCQ scores



CSS, clinical summary score; OSS, overall summary score; SGLT2i, Sodium glucose cotransporter 2 inhibitors; TSS, total symptom score.

Figure 5. Summary of responder analysis for the effect of SGLT2i *versus* placebo on health status at short, mid and long-term follow-up. A) total symptom score, B) overall summary score, C) clinical summary score.



CSS, clinical summary score; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; OSS, overall summary score; SGLT2i, Sodium glucose cotransporter 2 inhibitors; TSS, total symptom score.

Figure 6. Effect of SGLT2 inhibitors on health-related quality of life in patients with heart failure.

at different time points (as early as 2 weeks and as late as 52 weeks) and change of KCCQ score from baseline (≥5, ≥10, ≥15-point change). However, changes observed at one time point may be due to chance, day-to-day variability, or a transient effect of the intervention. This raises concerns of the stability of observed treatment effect. By collecting and analyzing data from serial health status assessments on a patient level (*i.e*. from 12 week to 52 week change or stability), investigators gain insight into the stability of benefit over time on a patient level. In addition to sustained improvement this also allows investigators to phenotype which patients revert to a neutral or worsened category after initial benefit. Furthermore, this approach offers the benefit of eliminating interference due to chance factors, disease state variability, or instrument variability.[30]

The current study has limitations. KCCQ data was missing for some participants. Not all trials reported data for all KCCQ summary scores at all time points; treatment effects at 52 weeks were only reported by the two trials. Furthermore, there is heterogeneity in how trials handle death of a participant before follow-up, which cannot be accounted or adjusted for.

In conclusion, treatment with SGLT2i improves health status and prevents decline in health status in patients with HF. These effects are consistent across all KCCQ summary scores, across the range of ejection fraction, regardless of the clinical setting (acute or chronic HF), are evident early and sustained for at least 1 year.

Contributions

MSU and AH contributed to the conception of the study, interpretation of data, and drafting the manuscript. SUQ contributed to the analysis of data, interpretation of data, and drafting the manuscript. MNK, DLB, MSK, and MV contributed to the study by making substantial revisions to the manuscript. JB contributed to the study by conception of the study and making substantial revisions to the manuscript.

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Online supplementary material:

Supplementary Table 1. Search Strategy used in each database.

Supplementary Table 2. GRADE Scale for Quality Assessment of Evidence for mean change in KCCQ scores.

Supplementary Table 3. GRADE Scale for Quality Assessment of Evidence for deterioration of greater than five points in participants.

Supplementary Table 4. GRADE Scale for Quality Assessment of Evidence for responder analysis of improvement.

Supplementary Table 5. Baseline characteristics in HFrEF trials.

Supplementary Table 6. Baseline characteristics in HFpEF trials.

Supplementary Table 7. Baseline characteristics in mixed HFrEF and HFpEF trials.

Supplementary Figure 1. PRISMA flowchart showing results of literature search.

Supplementary Figure 2. Funnel plot for publication bias.

Supplementary Figure 3. Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-TSS at 12 weeks.

Supplementary Figure 4. Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-TSS at 32 weeks.

Supplementary Figure 5. Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-TSS at 52 weeks.

Supplementary Figure 6. Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-OSS at 12 weeks.

Supplementary Figure 7. Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-OSS at 32 weeks.

Supplementary Figure 8. Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-OSS at 52 weeks.

Supplementary Figure 9. Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-CSS at 12 weeks.

Supplementary Figure 10. Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-CSS at 32 weeks.

Supplementary Figure 11. Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-CSS at 52 weeks.

Supplementary Figure 12. Responder analysis; KCCQ-TSS deterioration by ≥5 points at (A) 12, (B) 32 and (C) 52 weeks.

Supplementary Figure 13. Responder analysis; KCCQ-OSS deterioration by ≥5 points at (A) 12, (B) 32 and (C) 52 weeks.

Supplementary Figure 14. Responder analysis; KCCQ-CSS deterioration by ≥5 points at (A) 12, (B) 32 and (C) 52 weeks.