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REVIEW
Heart failure/cardiomyopathy

Sodium glucose co-transporter 2 inhibitors and quality of life in patients with heart failure: a comprehensive systematic review and meta-analysis of randomized controlled trials

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Background Sodium glucose co-transporter 2 inhibitors (SGLT2i) are one of the cornerstones of heart failure (HF) therapy. While benefits in terms of HF hospitalizations and death are well established, their impact on quality-of-life (QoL) has not been systematically investigated.

Objective This systematic review and meta-analysis aims to evaluate the impact of SGLT2i treatment on QoL in patients with HF, by analysing data from randomized clinical trials (RCTs).

Methods We identified a total of 23 RCTs that investigated the role of SGLT2i on quality of life in patients with HF, irrespective of their left ventricular ejection fraction (LVEF). RCTs that used Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OSS) to assess QoL and had a minimum follow-up of 3 months were included. The difference in mean change of the KCCQ-OSS between the SGLT2i group and the standard of care (SOC) group at 3 and 6 months from baseline was considered as the outcome measure.

Findings Fourteen RCTs (21 737 patients) were included in the analysis. A significant improvement in KCCQ-OSS over time ($p < 0.001$) was observed in both patients receiving SOC and those receiving SGLT2i in addition. The pooled estimate showed a significant improvement of 1.94 points [95% confidence interval (CI), 1.41–2.46] in KCCQ-OSS mean change at 3 months and of 2.18 points (95% CI, 1.13–3.24) at 6 months from baseline, with SGLT2i compared to SOC alone, irrespective of LVEF. A greater improvement in KCCQ-OSS was observed among patients with a recent episode of worsening HF compared to those with chronic stable HF.

Conclusions Among patients with HF, irrespective of their LVEF and clinical status, the addition of SGLT2i to SOC demonstrated a significant improvement in quality of life as early as at 3-month follow-up.

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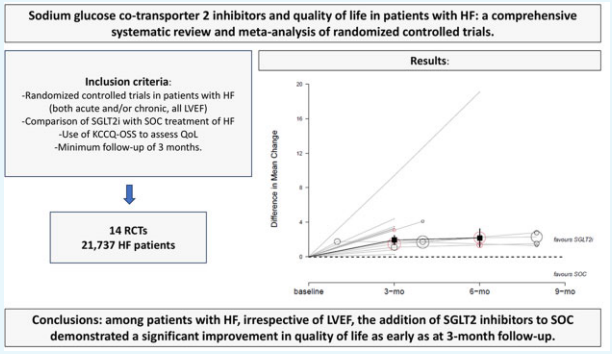
Graphical Abstract



Keywords SGLT2 inhibitors • dapagliflozin • empagliflozin • heart failure • quality of life • health status • KCCQ

Introduction

Sodium glucose co-transporter 2 inhibitors (SGLT2i), also referred as gliflozins, inhibit glucose and sodium reabsorption by binding to the relative carrier protein in the proximal renal tubule. Initially developed as anti-diabetic drugs, SGLT2i have consistently shown benefits on cardiovascular outcomes in patients with heart failure (HF) regardless of comorbid type 2 diabetes.[1]

SGLT2i are currently recommended for HF treatment, with rising evidence supporting their use across the entire left ventricular ejection fraction (LVEF) spectrum.[2–6] While benefits in reducing HF hospitalization, as well as cardiovascular and all-cause death, are well established,[7] their impact on short-term and long-term quality-of-life (QoL) has been less systematically evaluated through meta-analysis. Nonetheless, it's noteworthy that randomized clinical trials (RCTs) with varying designs, primary endpoints, and patient populations have consistently reported positive effects of SGLT2i on QoL, an aspect that a meta-analysis can further solidify and make more homogeneous. Indeed, the assessments of patient-reported outcomes (PROs) with standardized and validated scores are increasingly recognized as a clinically meaningful endpoint.[8,9] Furthermore, improving health status, particularly from the patient's perspective, is a key goal in HF management.[10]

The aim of the present study was to evaluate the impact of SGLT2i initiation on QoL in patients with HF, regardless of LVEF and clinical setting, by an updated meta-analysis of randomized controlled trials (RCTs).

Methods

Search strategy and selection criteria

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[11] guidelines and the recommendations of the Setting International Standards in Analyzing Patients-Reported Outcomes and Quality of Life Endpoints Data Consortium.[12] We systematically searched Pubmed and ClinicalTrials.gov, from database inception to 15 March 2023. Two investigators (C.O. and D.T.) independently searched the databases. Our search criteria included terms related to HF (e.g. 'heart failure,' 'cardiac insufficiency,' and 'cardiomyopathy'), SGLT2i (e.g. 'Sodium glucose co-transporter 2', 'SGLT2 inhibitor', 'SGLT2i','gliflozins', 'dapagliflozin', 'empagliflozin', 'canagliflozin', and 'sotagliflozin'), PROs, and QoL endpoints (e.g. 'quality of life,' 'QoL', 'patient reported outcome,' 'PRO', and 'Kansas City Cardiomyopathy Questionnaire', 'KCCQ'). Additionally, we applied filters to select randomized controlled trials or clinical trials. We ensured comprehensiveness by employing a multidisciplinary approach, thoroughly reviewing references from included papers, and examining other systematic reviews in the literature.

Studies were considered eligible for inclusion if they were RCTs meeting the following criteria: (i) inclusion of patients affected by HF (both stable chronic and acute or worsening HF); (ii) comparison of SGLT2i with a matching placebo added to standard of care (SOC) treatment of HF; (iii) use of Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OSS) to assess QoL; and (iv) a minimum follow-up of 3 months.

The Kansas city cardiomyopathy questionnaire

Most RCTs use the KCCQ score to assess QoL and the related impact of treatment in patients with HF. KCCQ is a 23-item self-administered questionnaire developed to independently measure the patient's perception of their health status. It encompasses various domains such as HF symptoms (frequency, burden, and stability), impact on physical and social functioning, QoL, and self-efficacy. Symptoms frequency and burden can be combined to create the total symptom score (KCCQ-TSS), which, together with physical impairment forms the clinical summary score (KCCQ-CSS). The symptoms, physical limitations, social limitations, and QoL domains can also be combined to generate an overall summary score (KCCQ-OSS).[13,14] To enhance the feasibility of implementing the KCCQ in routine clinical care, a shorter version of 12-items was developed. The KCCQ-12 as well includes the symptom frequency, physical limitations, social limitations, and QoL domains, and it can also generate the CSS and OSS with excellent concordance to the respective scores of the full 23-item instrument.[15] All KCCQ scores are represented on a 0-to-100-point scale, where lower scores indicate more severe symptoms and/or limitations, while scores of 100 indicate no symptoms, no limitations, and an excellent QoL. Studies[13,16] have demonstrated that the KCCQ, including both the KCCQ-23 and KCCQ-12, is a reliable tool for assessing clinical changes in patients with HF, surpassing the New York Heart Association (NYHA) classification and the 6-minute walking test (6-MWT) in terms of accuracy.

Selection of KCCQ-OSS as primary endpoint

KCCQ-OSS was selected as primary endpoint because, unlike other domains (i.e. KCCQ-TSS, KCCQ-CSS), which only assess symptom aspects, it incorporates the KCCQ-QoL subdomain, which independently evaluate

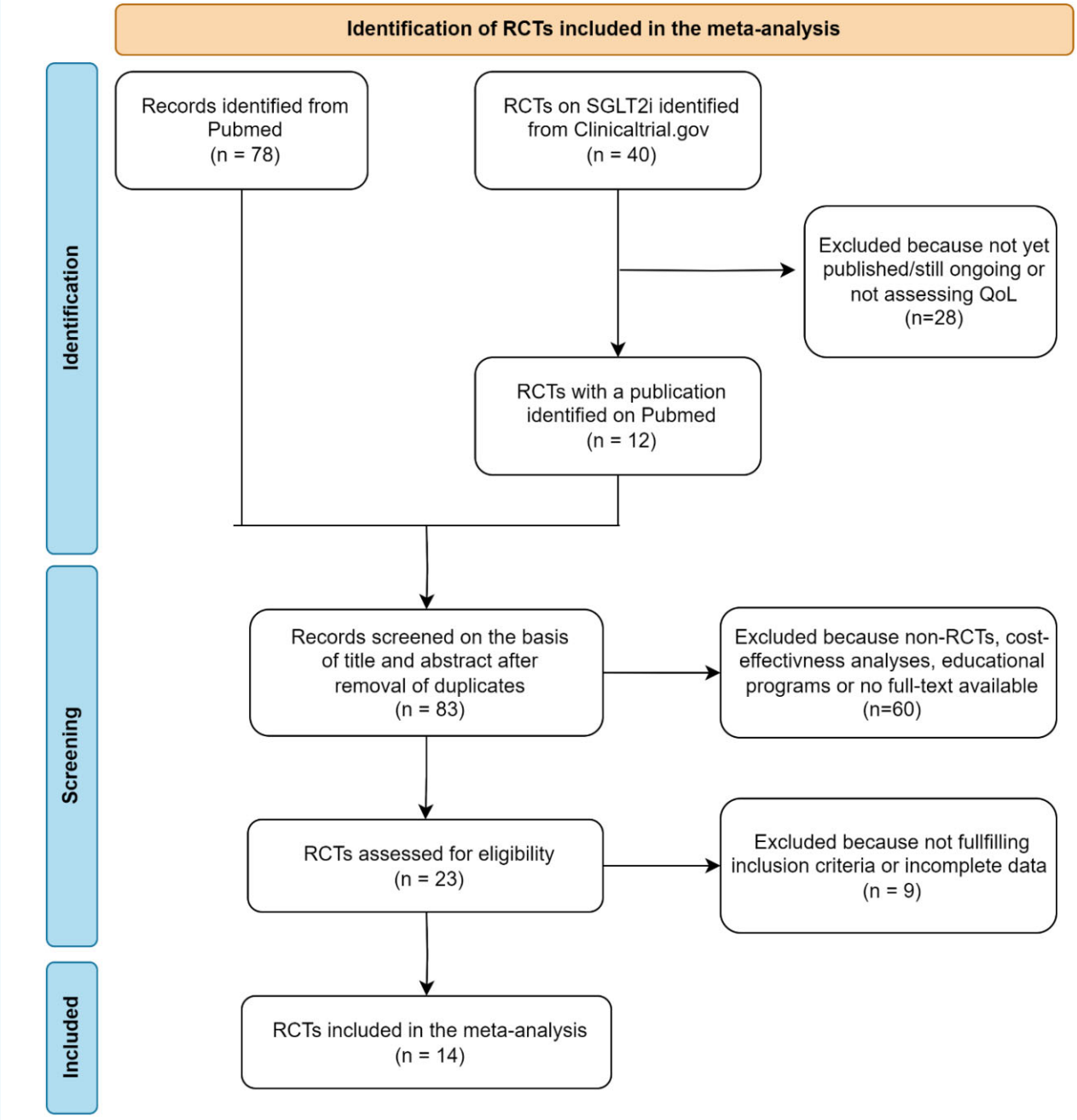


Figure 1 PRISMA flow chart.
Abbreviations: QoL, quality of life; RCT, randomized controlled trial; SGLT2i, sodium glucose co-transporter 2 inhibitors.

QoL, a crucial aspect of our investigation. KCCQ-QoL could not serve as the primary endpoint due to its limited availability in the included studies. Therefore, we chose KCCQ-OSS as a comprehensive measure of QoL consistently reported across a wide range of studies.

Data extraction and quality assessment

Full-text articles were independently reviewed by two authors (C.O. and D.T.) with any discrepancies resolved through discussion and consensus among all authors. When duplicate publications were identified, only the most recent and complete report was included. To ascertain risk of bias, the methodologic quality of each trial was assessed using the Cochrane Risk of Bias 2 tool (Supplementary material online, Table S1).[17] Overall, the trials demonstrated a high quality, with low risk of bias in selection, deviations from intended interventions, outcome measurement, and result reporting. The only potential bias that might have affected some of these RCTs was related to missing outcome data, although it is worth noting that all these trials ensured that the percentage of missing data was balanced between patients receiving SGLT2i plus SOC and patients receiving only SOC.

We extracted data on the following variables: study name, first author and year of publication, study design, number of patients, follow-up time,

Table 1 Characteristics of the RCTs included in the meta-analysis

Study	Trial name	Chronic/acute or WHF	LVEF categories	Experimental arm [a] (*N* pts[b])	Control arm (*N* pts[b])	Age (years)[c]	Sex (% female)
Spertus et al. (2022)[20]	CHIEF-HF	chronic	All	Canagliflozin (222)	SOC (226)	63.4 ± 13.3	45
Kosiborod et al. (2020)[21]	DAPA-HF	chronic	HFrEF	Dapagliflozin (2222)	SOC (2221)	66.0 ± 11.0	23
Nassif et al. (2019)[25]	DEFINE-HF	chronic	HFrEF	Dapagliflozin (131)	SOC (132)	62.0 ± 11.1	25
Kosiborod et al. (2023)[26]	DELIVER	chronic[d]	HFpEF (or HFmrEF)	Dapagliflozin (2903)	SOC (2892)	71.0 ± 9.5	44
Nassif et al. (2021)[27]	EMBRACE-HF	chronic	All	Empagliflozin (33)	SOC (32)	66.0 ± 12.6	37
Santos-Gallego et al. (2021)[28]	EMPA-TROPISM	chronic	HFrEF (or HFmrEF)	Empagliflozin (40)	SOC (40)	62.0 ± 12.1	36
Abraham et al. (2021)[29]	EMPERIAL-Preserved	chronic	HFpEF (or HFmrEF)	Empagliflozin (157)	SOC (158)	73.5 ± 8.8	43
Abraham et al. (2021)[29]	EMPERIAL-Reduced	chronic	HFrEF	Empagliflozin (156)	SOC (156)	69.0 ± 10.2	26
Butler et al. (2022)[30]	EMPEROR-Preserved	chronic	HFpEF (or HFmrEF)	Empagliflozin (2884)	SOC (2867)	71.9 ± 9.4	45
Butler et al. (2021)[31]	EMPEROR-Reduced	chronic	HFrEF	Empagliflozin (1776)	SOC (1753)	66.9 ± 11.0	24
Jensen et al. (2020)[32]	Empire HF	chronic	HFrEF	Empagliflozin (94)	SOC (92)	64.0 ± 11.0	15
Kosiborod et al. (2022)[22]	EMPULSE	acute	All	Empagliflozin (245)	SOC (250)	68.5 ± 13.3	34
Nassif et al. (2021)[23]	PRESERVED-HF	chronic	HFpEF (or HFmrEF)	Dapagliflozin (162)	SOC (162)	70.0 (63.0–77.0)	57
Bhatt et al. (2021)[24]	SOLOIST-WHF	WHF	All	Sotagliflozin (608)	SOC (614)	70.0 (64.0–76.0)	34

[a]In addition to standard of care (SOC).
[b] Number of patients with KCCQ-OSS evaluation at baseline.
[c] Mean ± SD if available (when only subgroup-specific data was available, we calculated a weighted mean or SD using the subgroup data), median (IQR) otherwise.
[d]A total of 654 patients had acute HF, but stratified estimates of KCCQ-OSS were not available.
Abbreviations: 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-OSS, Kansas City Cardiomiopathy Questionnaire overall summary score; SOC, standard of care; and WHF, worsening heart failure.

treatment groups, type of HF (including LVEF), age, sex, KCCQ domains used, and KCCQ-OSS results.

Statistical analysis

We conducted a meta-analysis considering as effect size of interest the difference in mean change of the KCCQ-OSS between the SGLT2i group and the SOC group at 3 and 6 months from baseline. Data were retrieved from original papers. Graphically reported arm-specific mean changes or absolute values were extracted using WebPlotDigitizer.[18] If KCCQ-OSS scores were provided at different timepoints from those selected for pooled synthesis (i.e. 3- and 6-month follow-up), we estimated the required scores using linear interpolation between the adjacent timepoints, if available (Supplementary material online, Table S2). Additional information regarding the data imputation procedures can be found in the Supplementary material.

Random-effect models were used to calculate the pooled estimates. Heterogeneity among studies was described using the I^2 index. An I^2 value of 50% or more was considered indicative of a considerable level of heterogeneity. To evaluate the influence of individual studies on the overall pooled estimates, we conducted a leave-one-out sensitivity analysis.

In an exploratory analysis, we investigated the effects of SGLT2i on QoL across the LVEF spectrum (HF with reduced ejection fraction [HFrEF] or at most HF with mildly reduced ejection fraction [HFmrEF] vs. HF with preserved ejection fraction [HFpEF] or at most HFmrEF). We also explored the effects of SGLT2i on QoL according to clinical status (stable and chronic HF vs. acute or worsening HF).

A one-stage meta-analytical approach based on pseudo individual patient data (IPD) was used to investigate the interaction between time and treatment effect.[19]

A two-tailed *P*-value of <0.05 was considered statistically significant. All analyses were performed using SAS v9.4 and R v4.2.1.

Results

Out of the 23 identified RCTs assessed for eligibility, 8 did not meet the inclusion criteria (4 RCTs used a different type of questionnaire to assess QoL, 3 reported different domains of KCCQ but not the KCCQ-OSS, and 1 had a maximum follow-up time of only 1 month) and 1 did not report complete data (*Figure 1*). In the analysis, we therefore included 14 trials,[20–32] involving a total of 21 737 patients, 10 935 receiving SGLT2i plus SOC and 10 802 receiving SOC. Key studies and patients' characteristics are summarized in *Table 1*. Among the included trials, 6 (43%) trials enrolled patients with HF and reduced (or at most mildly reduced) LVEF, 4 (29%) trials enrolled patients with preserved (or at most mildly reduced) LVEF, and 4 (29%) trials enrolled patients with HF regardless their LVEF. In terms of SGLT2i agents, empagliflozin was administered in 8 studies, dapagliflozin in 4 studies, and canagliflozin and sotagliflozin (an SGLT1 and 2 inhibitor) in 1 study each. Regarding the patients included in the assessment of QoL, 4 studies involved a substantial number of patients (over 3000), 3 studies included fewer than 200 patients, while the remaining studies had varying numbers of patients in between. The shorter version of the questionnaire, KCCQ-12, was employed in 3 trials (i.e. EMPA-TROPISM, PRESERVED-HF, and SOLOIST-WHF), while the standard version with 23 items was used in the remaining studies. The median follow-up time across the included trials was 3 months, with a maximum follow-up of 12 months.

At 3 months, there was a significant between-group difference in mean change of KCCQ-OSS from baseline, favouring the SGLT2i-treated group, with a pooled estimate of 1.94 (95% CI, 1.41–2.46) (*Figures 2* and *3*). Moderate heterogeneity was observed among single study estimates ($I^2 = 40.1\%$, p-heterogeneity $= 0.06$).

At 6 months, data on KCCQ-OSS were available for 17 132 patients. The analysis showed a mean change between 6 month and baseline 2.18 (95% CI, 1.13–3.24) points higher for patients treated with SGLT2i compared to those treated with SOC. (*Figures 2* and *3*). A significant heterogeneity was observed among single study estimates ($I^2 = 84.7\%$, p-heterogeneity < 0.001).

The analysis on pseudo-IPD (i.e. one stage meta-analytical approach) provided further confirmation of what was previously reported and a more detailed understanding of treatments effect. Consistent with the aggregate data analysis, the treatment benefit of SGLT2i compared to SOC at both 3- and 6-month remained

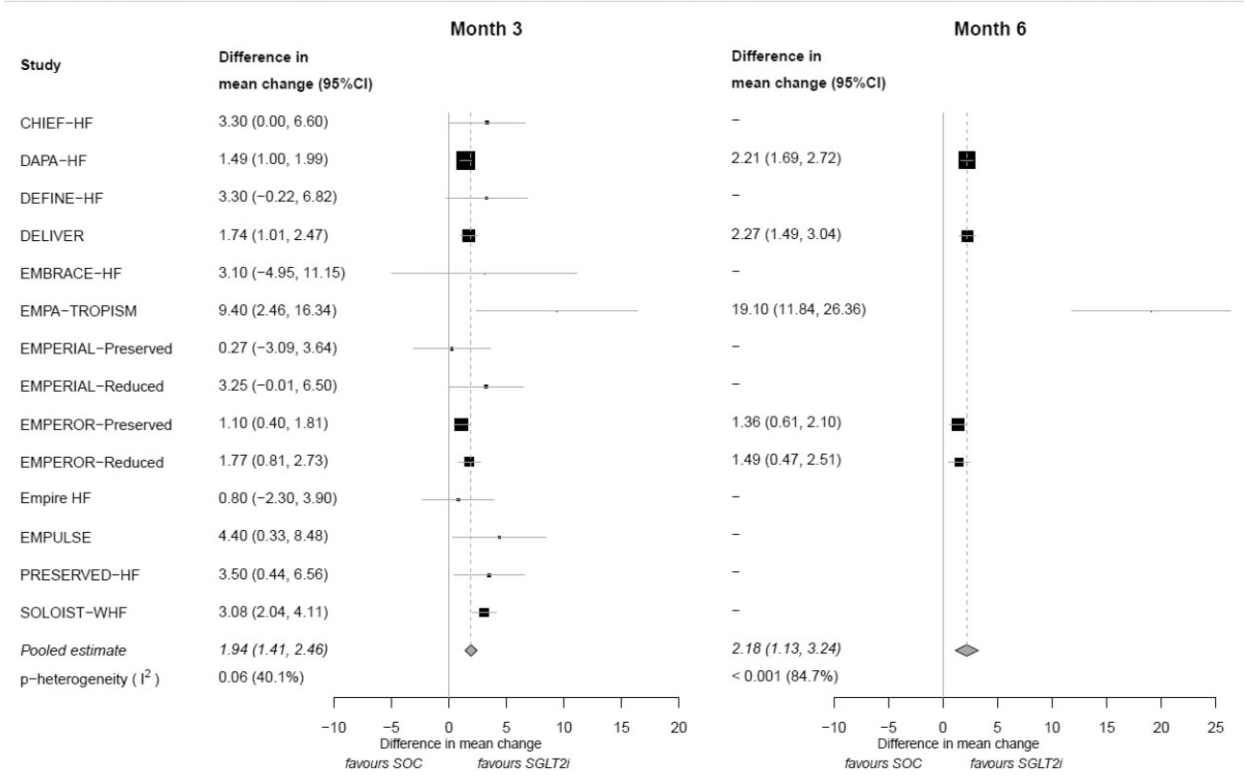


Figure 2 Forest plot of between-arms difference in mean change of KCCQ-OSS from baseline to 3 months and to 6 months according to experimental treatment groups. The figure shows the between-arms difference in mean change of KCCQ-OSS assessed from baseline to 3 months (left panel) or 6 months of follow-up (right panel), for patients assigned to SGLT2i-containing arms compared with those assigned to SOC arms. Each square represents the study-specific mean change difference, with values above 0 indicating superiority of the SGLT2i-containing arm over SOC arm. The size of the square is proportional to the precision of the estimate (i.e. the inverse of the variance). Horizontal lines represent the 95% confidence interval (95% CI). Diamonds represent the pooled mean change differences of KCCQ-OSS between treatment arms, calculated at 3 and 6 months of follow-up, with their corresponding 95% CI. The dashed vertical lines indicate the pooled differences in mean change, while the solid vertical line represents a mean change difference of 0, which is the null-hypothesis value (i.e. no difference between treatment arms).

statistically significant. A significant improvement in the QoL over time ($P < 0.001$) was observed in both patients receiving SOC and those receiving SGLT2i in addition. The time-dependent impact of SGLT2i did not substantially differ from that of SOC (interaction $P = 0.6$) even though patients in the SGLT2i group showed a tendency towards a faster rate of improvement over time. In a leave-one-out sensitivity analysis, we observed that pooled estimates remained consistent and statistically significant after the exclusion of each individual study (Supplementary material online, Table S3).

Role of LVEF

The positive effects of SGLT2i on QoL were consistent across the entire spectrum of LVEF, with similar results when considering trials enrolling patients with reduced (or at most mildly reduced) LVEF and patients with preserved (or at most mildly reduced) LVEF. Differences in mean change were 1.83 (95% CI, 1.03–2.63) and 1.46 (95% CI, 0.83–2.09), respectively, with no significant heterogeneity between the pooled estimates (p-heterogeneity = 0.58) (*Figure 4*). Supplementary material online, Figure S1 reports the pooled estimates at 6 months stratified by LVEF, showing no significant differences between groups (p-heterogeneity = 0.44).

Stable vs. worsening HF

This subgroup analysis was feasible only at 3 months since the two trials including patients with acute or worsening HF (i.e. EMPULSE and SOLOIST-WHF) did not extend beyond this timeframe. In both groups, patients treated with SGLT2i in addition to SOC experienced a positive impact on their QoL. Specifically, the difference in mean change was 3.16 (95% CI, 2.15–4.16) for patients with an ongoing or a recent hospitalization due to acute HF and 1.61 (95% CI, 1.21–2.00) for those with chronic stable HF (*Figure 5*). A significant heterogeneity was found between the pooled estimates (p-heterogeneity = 0.006).

SGLT2i type

The stratified analysis based on the type of SGLT2i administered included canagliflozin, dapagliflozin, empagliflozin, and sotagliflozin at 3 months, whereas only dapagliflozin and empagliflozin at 6 months as some studies did not extend beyond the 3-month follow-up. Across all SGLT2i types, when added to the SOC, we consistently observed a positive impact on patients' QoL. Pooled estimates at 3 and 6 months, stratified by SGLT2i type, are reported in Supplementary material online, Figure S2. No statistically significant heterogeneity was found among different drugs.

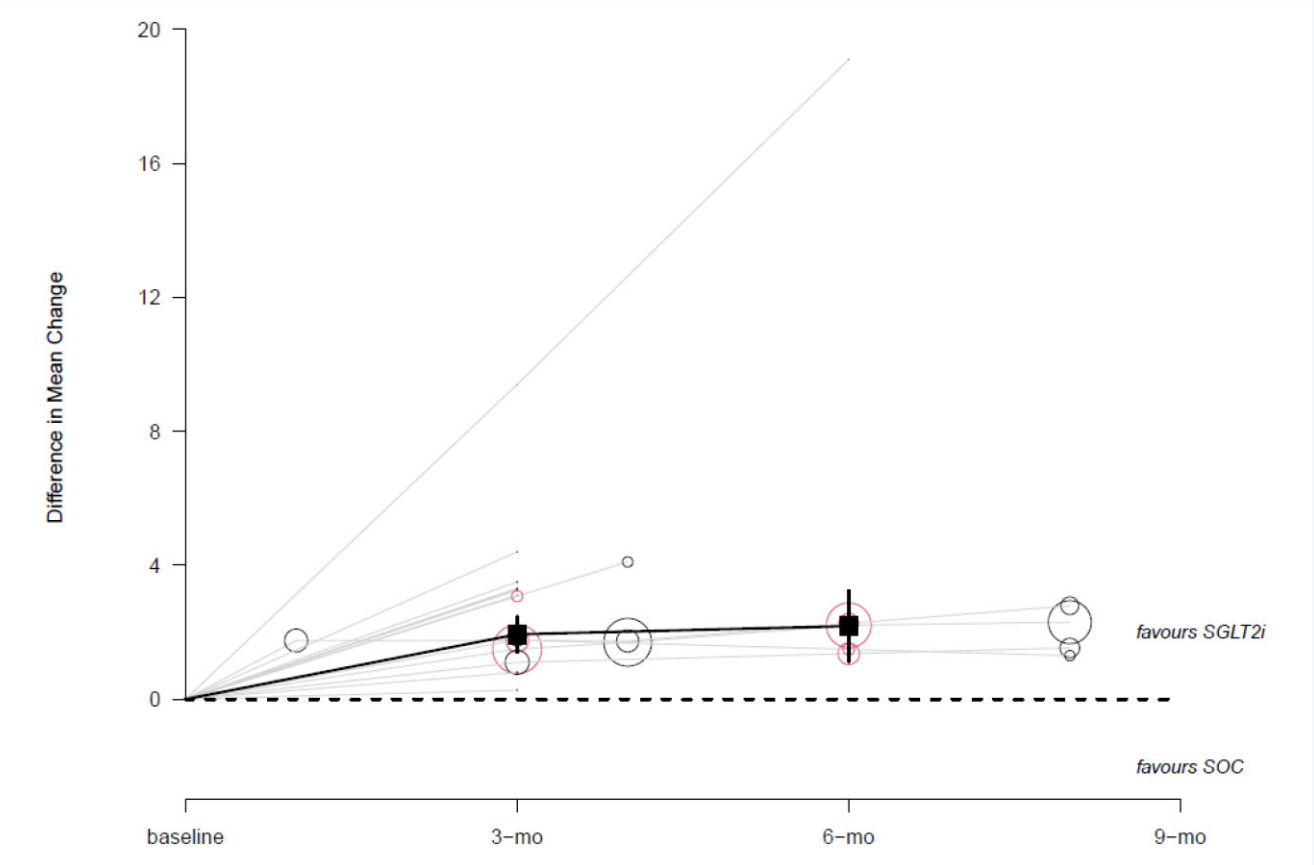


Figure 3 Trajectories over time of between-arms difference in KCCQ-OSS mean change assessed in each trial and pooled estimates according to experimental treatment groups. The figure shows difference in mean change of KCCQ-OSS over time, for each treatment comparison (grey lines) along with the meta-analytic pooled estimates according to experimental treatment groups with their corresponding 95% CI. Each grey line represents a single treatment comparison, with the size of each circle indicating the precision of the corresponding effect. For trials where the comparisons at 3 and 6 months of follow-up were not reported or derivable (red circles), these were estimated using available information from the previous and subsequent time points.

Discussion

In this meta-analysis, including more than 20 000 patients treated in 14 RCTs, we provided evidence of the positive impact of SGLT2i therapy on QoL in patients with HF (**Graphical Abstract**). The assessment of QoL was based on the inclusion of trials that reported the KCCQ-OSS as an endpoint and had a minimum follow-up of 3 months. Although a relatively modest (<5 points) albeit significant KCCQ-OSS improvement was observed at 3 and 6 months, these benefits were observed across the entire spectrum of LVEF and in various clinical settings encompassing both stable chronic HF and acute or worsening HF.

In a recent meta-analysis of the 5 major RCTs investigating SGLT2i in patients with HF (DAPA-HF, DELIVER, EMPEROR-Reduced, EMPEROR-Preserved, and SOLOIST-WHF), Vaduganathan *et al.* demonstrated that SGLT2i significantly reduced the risk of all-cause mortality, cardiovascular mortality, and worsening HF.[33] Furthermore, SGLT2i trials showed a significant improvement in QoL measured by different domains of KCCQ in patient with stable HF.[21,26,30,31] In individual patient-level pooled analyses of DAPA-HF and DELIVER, dapagliflozin improved multiple domains of health status as measured by KCCQ, regardless of LVEF.[34] Similar results were found with empagliflozin in a pooled analysis of the EMPEROR-Reduced and EMPEROR-Preserved trials. In the recent EMPULSE trial, initiation of empagliflozin in patients hospitalized for acute HF ameliorated symptoms compared to placebo as early as 15 days and through 3 months follow-up.[22,35]

Our large meta-analysis, including all studies that investigated SGLT2i in patients with HF irrespective of LVEF and clinical setting, confirms and extends the previous results. We observed an early significant improvement in KCCQ-OSS, namely as early as 3 months after SGLT2i initiation. Furthermore, when SGLT2i were initiated during a hospitalization due to acute HF or early after an episode of worsening HF, we observed a significant greater improvement in KCCQ-OSS, compared to patients who initiated SGLT2i during the chronic phase of HF. This could also be related to the steep decline in KCCQ preceding a HF hospitalization.[36] SGLT2i could further enhance the improvement in QoL among patients with a recent severe worsening of health status.

Thus, the present study supports the early initiation of SGLT2i during the clinical course of the disease, as well as the urgent need for pre-discharge optimization of HF medical therapy in patients with a recent hospitalization due to acute HF in order to improve clinical outcomes and health status.[37,38] Furthermore, results were consistent over time, showing a tendence to progressive improvement of QoL at 6 months.

It is questionable whether the benefit could be clinically meaningful, since we observed an improvement in KCCQ-OSS that

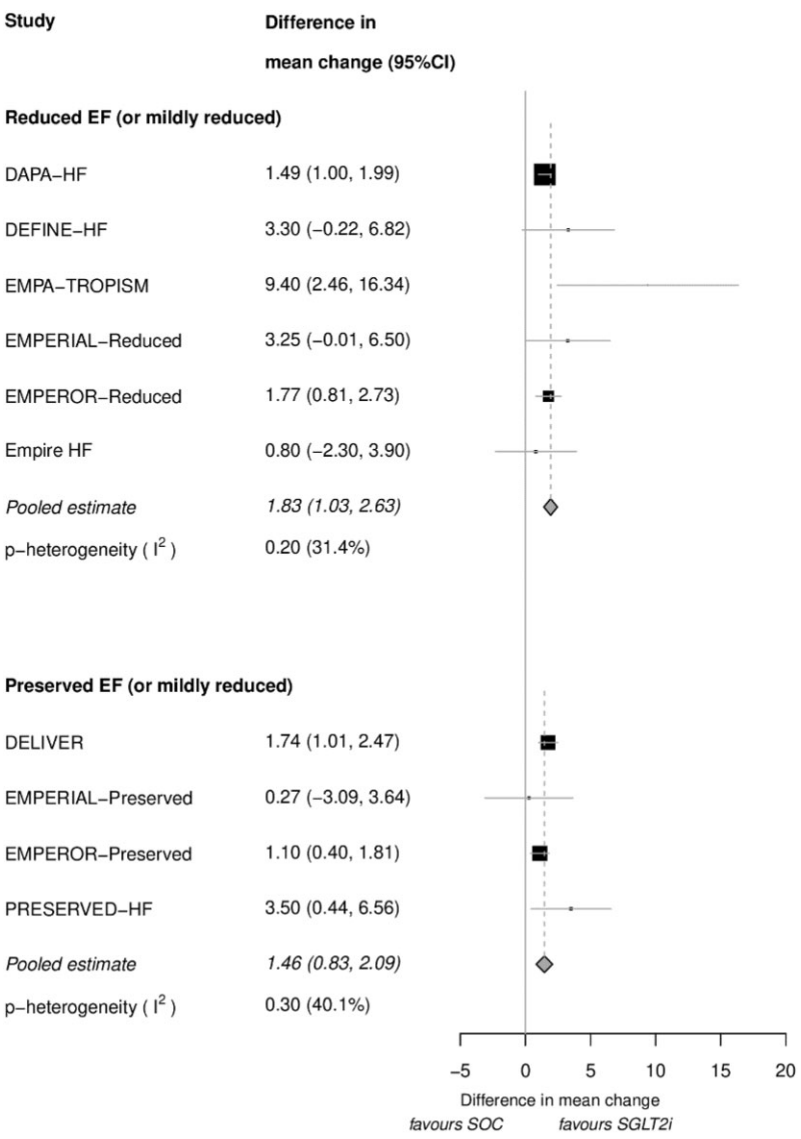


Figure 4 Forest plot of between-arms difference in mean change of KCCQ-OSS from baseline to 3 months according to experimental treatment groups stratified by LVEF. The figure shows the between-arms difference in mean change of KCCQ-OSS assessed from baseline to 3 months, for patients assigned to SGLT2i-containing arms compared with those assigned to SOC arms. Studies are grouped according to LVEF (i.e. reduced or at most mildly reduced, preserved or at most mildly reduced). Each square represents the study-specific mean change difference, with values above 0 indicating superiority of the SGLT2i-containing arm over SOC arm. The size of the square is proportional to the precision of the estimate (i.e. the inverse of the variance). Horizontal lines represent the 95% CI. Diamonds represent the pooled mean change differences of KCCQ-OSS between treatment arms, calculated at 3 months of follow-up, with their corresponding 95% CI. The dashed vertical lines indicate the pooled differences in mean change, while the solid vertical line represents a mean change difference of 0, which is the null-hypothesis value (i.e. no difference between treatment arms).

is under the standard threshold of 5 points that is considered as relevant in most recent studies.[39,40] However, while differences in mean changes in KCCQ-OSS were relatively modest, in participant-level pooled analyses of DAPA-HF and DELIVER, the proportion of patients achieving moderate (≥10 point increases) or large (≥15 point increases) improvement in health status was significantly greater in those randomized to dapagliflozin vs. placebo.[34]

Dapagliflozin and empagliflozin have been established as a foundational treatment for HF with reduced LVEF in both European and American guidelines for the management of HF.[2,3,41,42] American guidelines have also included SGLT2i for the treatment of HF with mildly reduced and preserved LVEF (class IIa) as they were published after the EMPEROR-Preserved trial.[3] Given the results of EMPEROR-Preserved and DELIVER, the 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF has also recommended dapagliflozin and empagliflozin for the treatment of patients with HFmrEF and HFpEF (Class of recommendation I, level of evidence A).[6] We confirmed the benefits of SGLT2i on QoL across the entire LVEF spectrum.

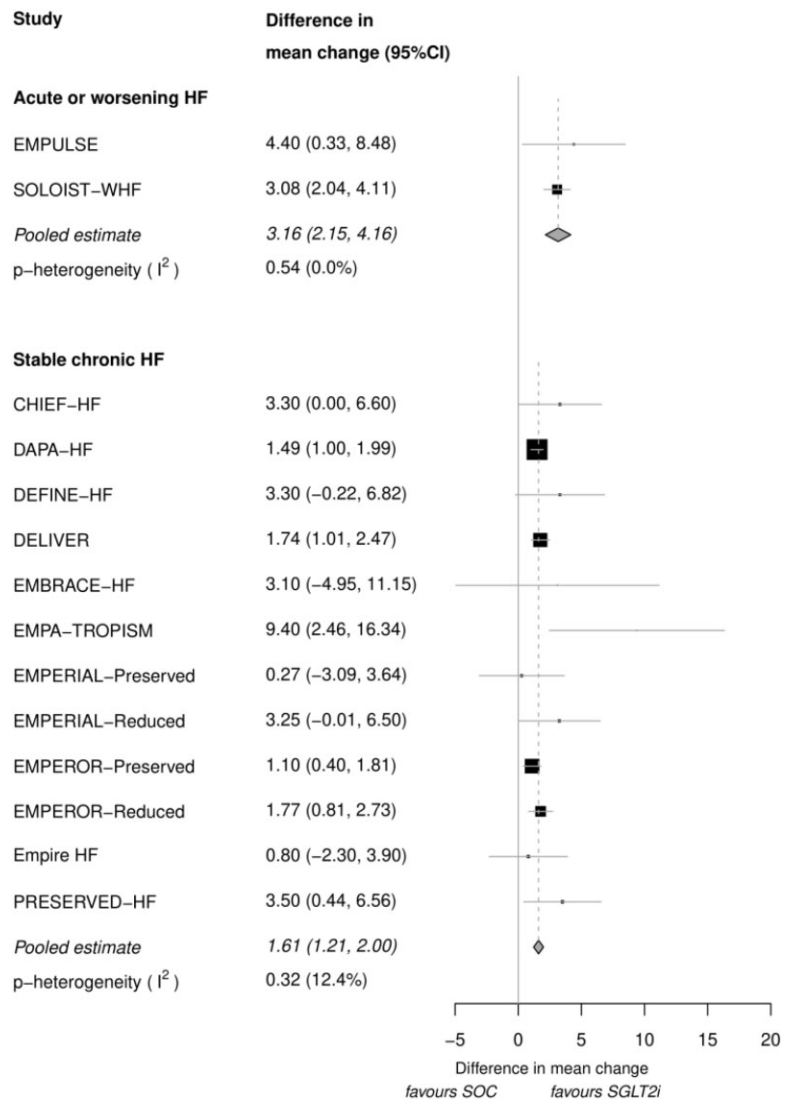


Figure 5 Forest plot of between-arms difference in mean change of KCCQ-OSS from baseline to 3 months according to experimental treatment groups stratified by stable chronic HF vs. acute or worsening HF. The figure shows the between-arms difference in mean change of KCCQ-OSS assessed from baseline to 3 months, for patients assigned to SGLT2i-containing arms compared with those assigned to SOC arms. Studies are grouped according to stable chronic HF vs. acute or worsening HF. Each square represents the study-specific mean change difference, with values above 0 indicating superiority of the SGLT2i-containing arm over SOC arm. The size of the square is proportional to the precision of the estimate (i.e. the inverse of the variance). Horizontal lines represent the 95% CI. Diamonds represent the pooled mean change differences of KCCQ-OSS between treatment arms, calculated at 3 months of follow-up, with their corresponding 95% CI. The dashed vertical lines indicate the pooled differences in mean change, while the solid vertical line represents a mean change difference of 0, which is the null-hypothesis value (i.e. no difference between treatment arms).

In the current meta-analysis, we included also trials investigating canagliflozin and sotagliflozin (an SGLT1 and 2 inhibitor). The stratified analysis based on the type of SGLT2i administered showed a consistent benefit on QoL irrespective of different drugs. Thus, our results further support the consensus of a class effect of SGLT2i in terms of their positive impact on patients' symptoms.

SGLT2i are nowadays recommended in patients with HFrEF as an addition to optimal medical therapy with renin–angiotensin–aldosterone system inhibitors, beta-blockers, and mineralcorticoid receptor antagonists. In patients with HFpEF, the treatment of comorbidities is also recommended. Importantly, the benefits of gliflozins were shown to be independent and additive from other treatments.[33,37] In our meta-analysis, we observed that also patients in the SOC group (without SGLT2i) experienced an improvement in QoL from baseline to 3 and 6 months. This might be explained by their involvement in clinical trials, which often imply a closer follow-up and higher-intensity care, or by the optimization of guideline-recommended medical therapy before the enrollment. Additionally, an improvement in QoL during mid-term follow-up could be expected after discharge for patients experiencing a hospitalization for worsening HF, also due to the optimization of evidence-based therapies during hospitalization.[43,44] However, it is important to note

that mean changes in KCCQ-OSS at follow-up were significantly higher in patients receiving SGLT2i, highlighting the additional benefits provided by these medications on top of SOC.

We acknowledge the limitation related to the lack of information on functional capacity, such as cardiopulmonary exercise testing, 6-MWT or NYHA class, and important parameters for a comprehensive assessment of the health status of HF patients. However, PROs demonstrated precision in the evaluation of disease status and have a good association with prognosis in several RCTs.[9] Also, the use of PROs in clinical practice might help to switch traditional care to a more patient-centered approach and should be implemented.

Limitations

This study has limitations that should be acknowledged. First, our analysis was based on published aggregate data rather than IPD. However, this limitation was partially mitigated by our use of reconstructed IPD,[18] which allowed for a more comprehensive analysis.

We focused on studies that assessed QoL using the KCCQ-OSS. Different domains of the KCCQ or alternative questionnaires, such as the Minnesota Living with Heart Failure Questionnaire (MLWHF), may yield different results. While we do not anticipate significant differences, it is worth considering this potential variability in QoL assessments. Also, we included studies that assessed QoL as either primary or secondary endpoint. We have confidence in the absence of publication bias in our analysis, given that no statistically significant difference was detected between studies that assessed QoL as the primary endpoint (i.e. CHIEF-HF, PRESERVED-HF) vs, those that assessed it as a secondary endpoint (data not shown).

Additionally, we used linear interpolation to estimate the KCCQ-OSS at 3 or 6 months where the data was missing. While this method is an acceptable approach in these situations, we acknowledge that it introduces a potential source of error. This should be considered when interpreting our results.

Furthermore, at the 6-month follow-up, we observed heterogeneity among the estimates from individual studies. This heterogeneity may be attributed to several factors, such as differences in study populations, treatment protocols, and baseline characteristics. We employed random-effects models to account for such variations, providing a more robust analysis.

Notwithstanding these limitations, we believe our study provided useful evidence regarding the effect of SGLT2i on QoL in individuals with HF. Further research preferably using IPD and comprehensive outcome measures would be beneficial to validate and expand upon our findings.

Conclusion

Our meta-analysis provided evidence of a beneficial effect of SGLT2i on QoL in patients with HF, irrespective of their LVEF and clinical status (stable vs. worsening HF). These finding suggest the importance of incorporating SGLT2i in the treatment of HF, not only for reducing mortality and worsening HF as demonstrated in other studies, but also to improve QoL.

Disclosures

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Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

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