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REVIEW ARTICLE

The role of SGLT-2 inhibitors on health-related quality of life, exercise capacity, and volume depletion in patients with chronic heart failure: a meta-analysis of randomized controlled trials

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Abstract

Background Improving health-related quality of life (HRQoL) is essential in treating heart failure (HF). Evidence of sodium-glucose cotransporter-2 (SGLT-2) inhibitors on HRQoL and exercise capacity needs to be systematically analyzed.

Aim This meta-analysis aimed to summarize the effects of SGLT-2 inhibitors on HRQoL, exercise capacity, and volume depletion in patients with HF.

Method Randomized controlled trials were searched from PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. The intervention arm was the SGLT-2 inhibitor group, and the control group was the placebo group. HRQoL outcomes were the Kansas City Cardiomyopathy Questionnaires (KCCQ)-OSS (Overall Summary Score), KCCQ-CSS (Clinical Summary Score), and KCCQ-TSS (Total Symptom Score). Exercise capacity was a 6-min walk test distance (6MWTD). The last search was conducted in May 2022. Two researchers independently screened articles, extracted data, and evaluated the quality of included trials. The Cochrane risk-of-bias tool was used to assess the quality of each study. Random or fixed-effect models were used in statistical methods. I^2 statistics were used to assess heterogeneity.

Results Eight studies (6,213 patients) were included. Compared to the placebo group, SGLT-2 inhibitors significantly improved HRQoL parameters of the KCCQ-CSS score [mean difference (MD) 5.17, 95% confidence interval (95% CI) 4.61–5.73, $P<0.01$] and the KCCQ-OSS score (MD 4.00, 95% CI 3.44–4.56, $P<0.01$). SGLT-2 inhibitors also significantly improved exercise capacity 6MWTD (MD 21.90, 95% CI 6.54–37.25, $P=0.005$). There were no significant differences in KCCQ-TSS (MD 1.95, 95% CI −1.10 to 5.01, $P=0.21$) and volume depletion [odds ratio (OR) 1.15, 95% CI 0.94–1.42, $P=0.18$] between the treatment and placebo groups.

Conclusion SGLT-2 inhibitors could improve HRQoL and exercise capacity in patients with chronic HF. SGLT-2 inhibitors did not have an impact on volume depletion.

Keywords Heart failure · Meta-analysis · Quality of life · SGLT-2 inhibitors · Volume depletion

Impact statements

- Improving health-related quality of life (HRQoL) is an important outcome for treating heart failure.
- This meta-analysis of randomized controlled trials indicates that SGLT-2 inhibitors have benefits in improving HRQoL in patients with heart failure.
- The meta-analysis also shows that SGLT-2 inhibitors can improve exercise capacity, as measured by the 6-min walk test distance in patients with heart failure.

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Introduction

Heart failure (HF) is a clinical syndrome with signs or symptoms caused by a cardiac abnormality with elevated levels of natriuretic peptides or objective evidence of cardiogenic congestion. HF is associated with other cardiovascular diseases [1, 2]. More than 33.7 million people suffer from heart failure worldwide. HF has become a global public health problem characterized by high morbidity, mortality, and hospitalization rates [3, 4]. HF patients have markedly altered quality of life (QoL) compared to other chronic diseases and healthy populations [1, 4]. Poor health-related quality of life (HRQoL) is associated with adverse long-term prognoses, such as hospitalization and mortality, in patients with HF [5–8]. Maintaining a good QoL is as important as survival for most patients living with HF. Therefore, it is critical to improving the QoL in patients with HF.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are novel hypoglycemic agents that block renal reabsorption of glucose. Studies have shown that SGLT-2 inhibitors improve the outcome of HF. The protective effect of SGLT-2 inhibitors on HF is independent of the reduction in blood glucose [9–13]. Early use of SGLT-2 inhibitors reduces hospitalization and mortality, and improves QoL and health status [14–17]. A systematic review and meta-analysis evaluated the effects of SGL-2 inhibitors on health-related QoL (HRQoL) in patients with HF and reduced ejection fraction (HFrEF) [18]. The meta-analysis included nine studies (n = 9,428) up to March 20, 2021. HRQoL was evaluated using Kansas City Cardiomyopathy Questionnaires (KCCQ), the rate of improvement of KCCQ ≥ 5 points, the rate of deterioration of KCCQ ≥ 5 points, and the exercise capacity of the 6-min walk test distance (6MWTD) [18]. SGLT-2 inhibitors significantly improved HRQoL as measured by KCCQ scores [mean difference (MD) 2.13, 95% confidence interval (95% CI) 1.11–3.14, $P < 0.001$]. The rate of KCCQ-overall summary score ≥ 5 points [relative risk (RR) 1.15, 95% CI 1.08–1.21, $P < 0.001$]. No significant differences in 6MWTD (MD 24.45, 95% CI − 22.82 to 71.72, $P = 0.31$) between the SGLT-2 and placebo groups [18].

SGLT-2 inhibitors can affect hemodynamics and significantly reduce blood pressure [13, 19]. Few studies have reported the effects of SGLT-2 inhibitors on volume depletion in patients with HF [20–22]. In patients with HFrEF, dapagliflozin caused volume depletion of 10.1% in patients with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 and 5.8% in patients with eGFR > 60 mL/min/1.73m^2 [21]. The adverse effect of volume depletion occurred in 6.8% of patients with HF with preserved ejection fraction (HFpEF) treated with dapagliflozin [20]. Volume depletion events occurred in 12.1% of patients in the empagliflozin group compared to 6.3% in the placebo group [22]. In one study [18], HFrEF was the main study population, and volume depletion was not discussed. However, no systematic review or meta-analysis has evaluated the effects of SGLT-2 inhibitors on HRQoL and volume depletion in patients with chronic HF regardless of ejection fraction. Therefore, it is necessary to further investigate the impact of SGLT-2 inhibitors on HF with an updated meta-analysis.

Aim

This meta-analysis aimed to summarize the effects of SGLT-2 inhibitors on HRQoL, exercise capacity, and volume depletion in patients with HF.

Method

Protocol and registration

This meta-analysis was performed according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [23]. The protocol for this meta-analysis was registered with PROSPERO (the International Prospective Register of Systematic Reviews), registration number CRD42022335503.

Search strategy

Data were reviewed from PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. Detailed search terms are shown in Supplemental Table 1. Reference lists of included studies were manually checked for potentially eligible studies. Google Scholar search engines were used to identify additional references. All included studies were published in English. The last search was performed on May 12, 2022.

Inclusion and exclusion criteria

Studies that met the following criteria were included: (1) patients ≥ 18 years of age with chronic HF (HFrEF or HFpEF), (2) randomized, double-blind, placebo-controlled trials, (3) compared SGLT-2 inhibitors with placebo, and (4) reported any of the following outcomes: KCCQ-OSS (overall summary score), KCCQ-CSS (clinical summary score), KCCQ-TSS (total symptom score), 6MWTD, and volume depletion. Review articles and animal experiments were excluded.

Assessment of risk of bias

The Cochrane risk-of-bias quality assessment tool was used to assess the quality of the included randomized controlled

trials. The following seven categories were evaluated: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of the outcome assessment, incomplete outcome data, selective outcome reporting, and other biases [24]. The quality of each study was assessed as "low risk of bias," "high risk of bias," or "unclear risk of bias." The quality assessment was completed independently by two researchers (YW and ZG). A third investigator (JY) was invited to resolve any inconsistencies.

Data extraction

Two researchers (LW and ZG) independently screened the literature against the inclusion criteria. A third researcher (CZ) was invited if there was any dispute. Data extracted from each study included author, year, registry number, group, dose, sample size, population, length of follow-up, sex, and age. The HRQoL outcomes (KCCQ-OSS, KCCQ-CSS, KCCQ-TSS, 6MWTD) and volume depletion were also extracted.

Statistical analyses

Mean differences (MD) with 95%CIs were used to measure the effect size for continuous variable outcomes. Odds ratios (OR) with 95%CIs were used to measure the effect size for the outcomes of dichotomous variables. The Higgins I^2 test was used for statistical heterogeneity. $I^2 < 50\%$ indicates low heterogeneity, $50 \le I^2 \le 75\%$ indicates moderate heterogeneity, and $I^2 \ge 75\%$ indicates high heterogeneity [25]. A fixed-effect model was used if $I^2 < 50\%$ otherwise a random-effect model was used. The source of heterogeneity was explored by subgroup or sensitivity analysis when $I^2 \ge 50\%$. Funnel plots were used to assess publication bias [26]. The meta-analysis was performed using RevMan (version 5.3). $P < 0.05$ was considered statistically significant.

Results

Search results and basic information on the included studies

A total of 1,952 articles were obtained in the initial review. After reading the titles, abstract, and full texts according to the inclusion and exclusion criteria, eight studies were included in the analysis. The literature selection process is shown in Fig. 1.

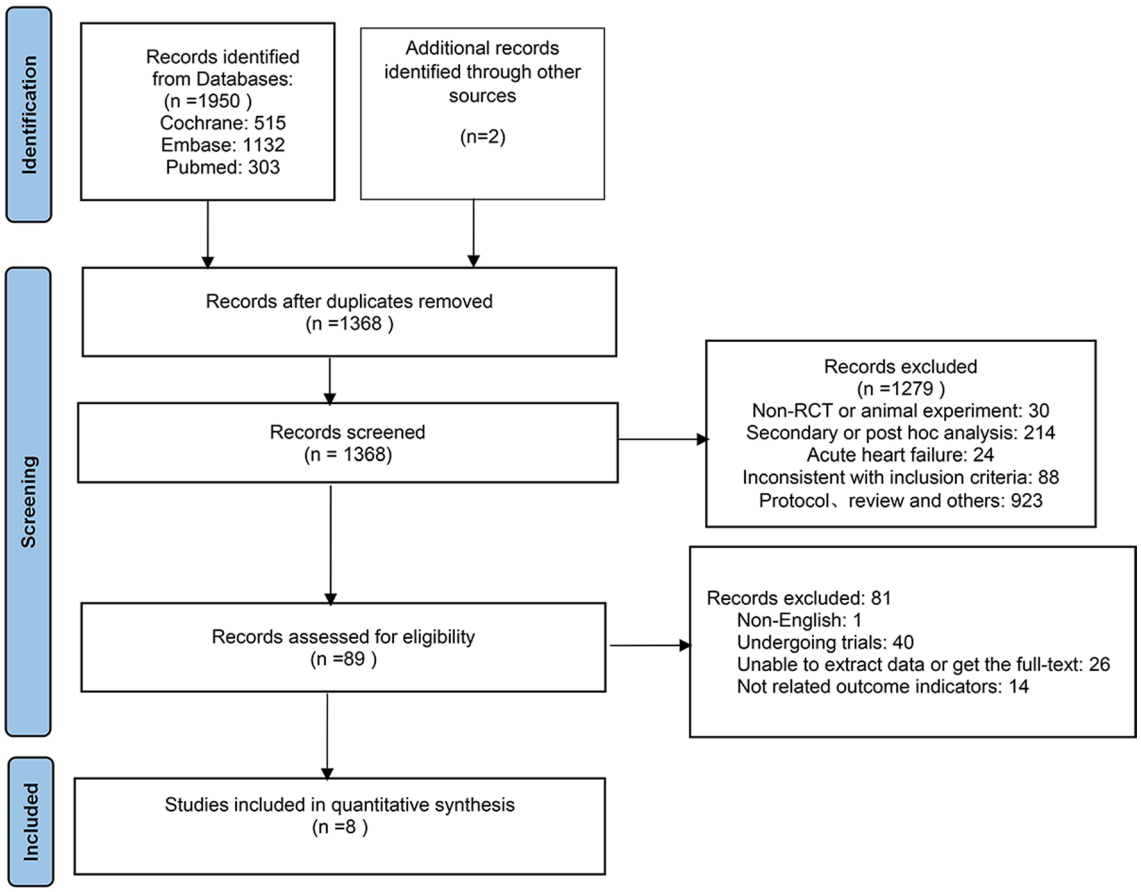

Fig. 1 Study flowchart

These studies included 6,213 patients. There were three dapagliflozin trials enrolling 5,321 patients [20, 21, 27], four empagliflozin trials enrolling 444 patients [22, 28–30], and one canagliflozin trial with 448 patients [31]. The follow-up times ranged from 12 weeks to 27.8 months. The mean age ranged from 59.9 to 71 years. Regarding the patient population, one study was HFpEF patients [20], one was HFrEF (EF 40% or HFpEF) [22], and one was HF (irrespective of EF) [31]. The baseline characteristics of the included studies are shown in Table 1.

Assessment of risk of bias

The risk of bias assessment is shown in Fig. 2. The risk of bias was low to moderate without high risk. Seven RCTs were unclear about allocation concealment (selection bias) and blinding participants and personnel (performance bias). Eight RCTs were unclear in terms of selective reporting (reporting bias).

Health-related quality of life analysis

Five studies reported KCCQ-CSS [20, 22, 27, 28, 31]. There was no statistical heterogeneity between the studies ($P=0.14$, $I^2=42\%$). A fixed-effects model was used for meta-analysis. Compared to the placebo group, the SGLT-2 inhibitor treatment group had a significantly higher KCCQ-CSS score (MD 5.17, 95% CI 4.61–5.73, $P<0.01$) (Fig. 3A). Five studies reported KCCQ-OSS [20, 22, 27, 28, 31]. The studies had no statistical heterogeneity ($P=0.42$, $I^2=0\%$). A fixed-effects model was used for meta-analysis. Compared to the placebo group, the SGLT-2 inhibitor treatment group had a significantly higher KCCQ-OSS score (MD 4.00, 95% CI 3.44–4.56, $P<0.01$) (Fig. 3B). Three studies reported KCCQ-TSS [28, 30, 31]. The studies had no statistical heterogeneity ($P=0.22$, $I^2=33\%$). A fixed-effects model was used for meta-analysis. There were no significant differences in the KCCQ-TSS scores between the SGLT-2 inhibitor treatment and placebo groups (MD 1.95, 95% CI 1.10–5.01, $P=0.21$) (Fig. 3C).

Exercise capacity outcome and impact on volume depletion

Five studies reported 6MWTD [20, 22, 27, 29, 30]. There was statistical heterogeneity among the studies ($P<0.01$, $I^2=93\%$). A random-effects model was used for meta-analysis. Compared to the placebo group, the SGLT-2 inhibitor treatment group significantly improved 6MWTD (MD 21.90, 95% CI 6.54–37.25, $P=0.005$) (Fig. 4A).

Three studies examined volume depletion [20, 21, 28]. The studies had no statistical heterogeneity ($P=0.49$, $I^2=0\%$). A fixed-effects model was used for meta-analysis. Compared to the placebo group, there were no significant differences in volume depletion between the SGLT-2 inhibitor treatment and the placebo groups (OR 1.15, 95% CI 0.94–1.42, $P=0.18$) (Fig. 4B).

Publication bias

The funnel plots of KCCQ-OSS and 6MWTD showed an asymmetric distribution of the studies (Supplemental Figs. 1A, B). A slight asymmetry was observed in the KCCQ-CSS funnel plot (Supplemental Fig. 1C). The funnel plot analysis was not performed for KCCQ-TSS and volume depletion as there were too few studies.

Additional analysis

There was a high degree of heterogeneity in the 6MWTD analysis, $I^2=93\%$. Subgroup analysis was performed based on diabetes and ejection fraction. In the subgroup analysis of patients with diabetes, heterogeneity was not substantially reduced (Supplemental Fig. 2A). However, in the subgroup analysis for the ejection fraction, no heterogeneity was observed when EF ≤ 40% (Supplemental Fig. 2B). After excluding one study [27], the result demonstrated that there was no difference compared to the control group (303.7 vs. 301.3, $P=0.79$), and the heterogeneity in the sensitivity analysis decreased from 93 to 74% (Supplemental Fig. 2C). Although there still exists high heterogeneity after excluding each study one by one, the results tended to be consistent. The influence of heterogeneity on the reliability of the results was small (Supplemental Table 2). Therefore, the primary source of heterogeneity was due to inconsistency in the category of chronic HF.

Discussion

Several large randomized trials have demonstrated cardiovascular protective effects of SGLT-2 inhibitors, such as reduced hospitalization and mortality in heart failure, which go beyond hypoglycemic effects [32–34]. The cardiovascular protective mechanism of SGLT-2 inhibitors involves many aspects, such as inhibiting cardiac Na+/H+exchange activity, reducing preload and afterload, and improving myocardial metabolism [10]. HRQoL is closely related to the prognosis of heart failure. Most meta-analyses analyze the effects of SGLT-2 inhibitors on cardiovascular protection, hospitalization, or mortality in patients with HF [35, 36]. Few trials have evaluated the impact of SGLT-2 inhibitors on QoL in heart failure, which calls for a rethink of endpoints

Table 1 The baseline characteristics of the included studies

Study	Year	Registration	Group	N	Population	Duration	Female (n)	Baseline age (years)	Results
Nassif [27]	2019	NCT02653482	Dapagliflozin	131	HF patients with left ventricular ejection fraction ≤ 40% New York Heart Association (NYHA) class II-III	12 weeks	36	62.2 ± 11.0	KCCQ-CSS:OR[95% CI] 2.35[1.31–4.22]
			Placebo	132			34	60.4 ± 12.0	KCCQ-OSS:OR[95% CI] 1.73[0.98–3.05]
Qintar [22]	2021	NCT03030222	Empagliflozin	33	HFrEF or HFpEF who had a previously implanted CardioMEMS device	12 weeks	12	69.5 ± 12	KCCQ-CSS:OR[95% CI] 3.41[0.72–16.14]
			Placebo	32			12	62.9 ± 13.3	KCCQ-OSS:OR[95% CI] 0.78[0.19–3.12]
Nassif [20]	2021	NCT03030235	Dapagliflozin	162	HFpEF	12 weeks	92	69 (64, 77)	KCCQ-CSS:OR[95% CI] 1.64[0.98–2.75] KCCQ-OSS:OR[95% CI] 1.73[1.05–2.85]
			Placebo	162			92	71 (63, 78)	6MWTD:MD[95% CI] 20.1[5.6–34.7]
Jhund [21]	2021	NCT03036124	Dapagliflozin	2367	HFrEF with or without type 2 diabetes and an estimated eGFR) ≥ 30 mL/min/1.73m^2	27.8 months	564	66.2 ± 11.0	NR
			Placebo	2367			545	66.5 ± 10.8	
Lee [30]	2021	NCT03485092	Empagliflozin	52	New York Heart Association functional class II to IV with a left ventricular (LV) ejection fraction ≤ 40% and type 2 diabetes or prediabetes	36 weeks	18	68.2 ± 11.7	KCCQ-TSS:MD[95% CI] −4.0[−10.2–2.1]
			Placebo	53			10	69.2 ± 10.6	6MWTD:MD[95% CI] −9.9[−34.4–14.7]
Santos-Gallego [29]	2020	NCT03485222	Empagliflozin	42	Non-diabetic HFrEF patients	6 months	15	64.2 ± 10.9	NR
			Placebo	42			15	59.9 ± 13.1	
Jensen [28]	2020	NCT03198585	Empagliflozin	95	New York Heart Association (NYHA) functional class I-III symptoms and a left ventricular ejection fraction (LVEF) of 40% or lower	12 weeks	16	64 (57–73)	KCCQ-CSS:MD[95% CI] 3.1[−0.2–6.4] KCCQ-OSS:MD[95% CI] 0.8[−2.3–3.9]
			Placebo	95			12	63 (55–72)	KCCQ-TSS:MD[95% CI] 2.3[−1.0–5.6]
Spertus [31]	2022	NCT04252287	Canaglifozin	222	Participants with HF, regardless of EF or diabetes status	12 weeks	104	62.9 ± 13.19	KCCQ-CSS:MD[95% CI] 3.3[0.0–6.6] KCCQ-OSS:MD[95% CI] 1.73[1.05–2.85]
			Placebo	226			97	64.0 ± 13.45	KCCQ-TSS:MD[95% CI] 4.3[0.8–7.8]

KCCQ-CSS Kansas City Cardiomyopathy Questionnaires Clinical Summary Score, *MD* mean difference, 95% CI, 95%

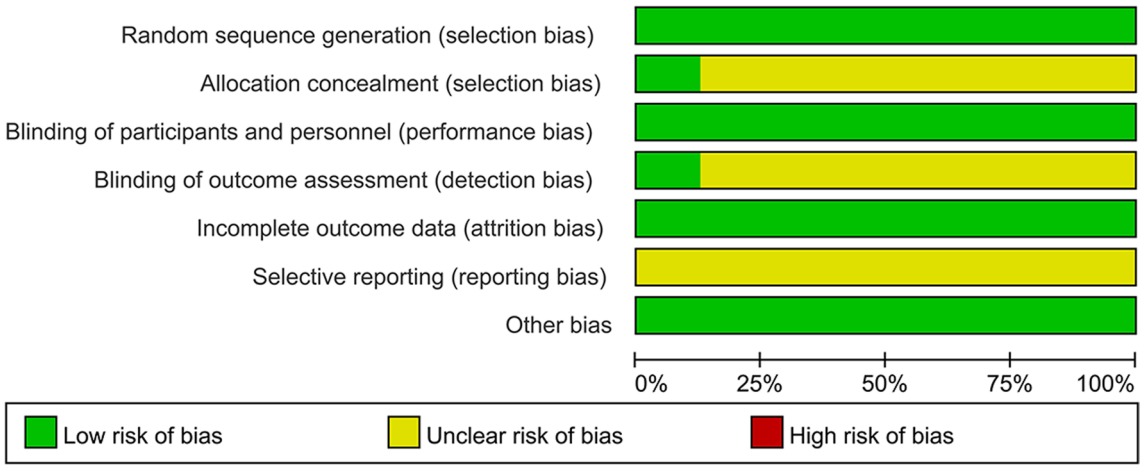

Fig. 2 Risk of bias assessment

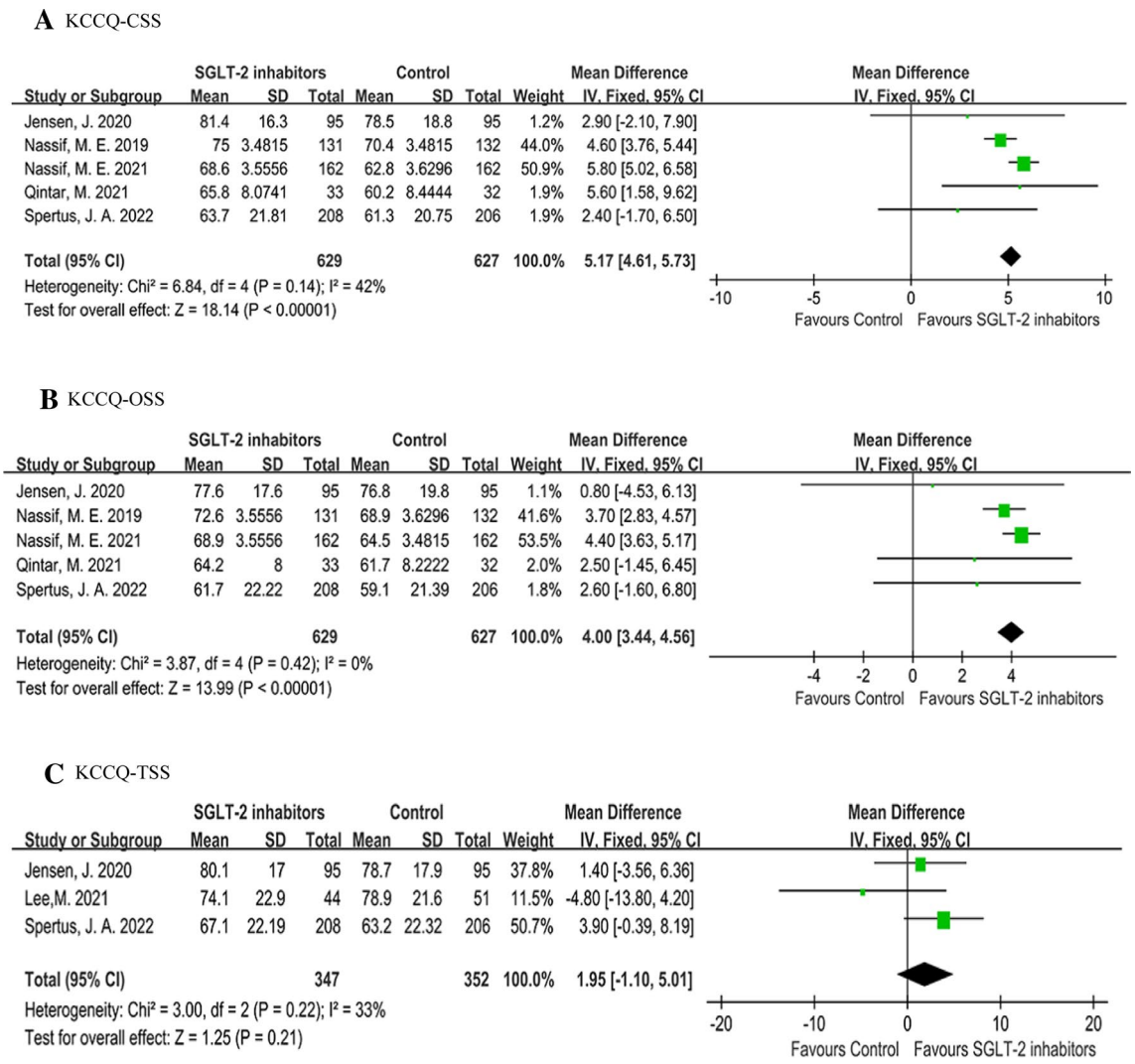

Fig. 3 The health-related quality of life outcome analysis. **A** The Kansas City Cardiomyopathy Questionnaires-Clinical Summary Score (KCCQ-CSS). **B** The Kansas City Cardiomyopathy Questionnaires-Overall Summary Score (KCCQ-OSS). **C** The Kansas City Cardiomyopathy Questionnaires-Total Symptom Score (KCCQ-TSS)

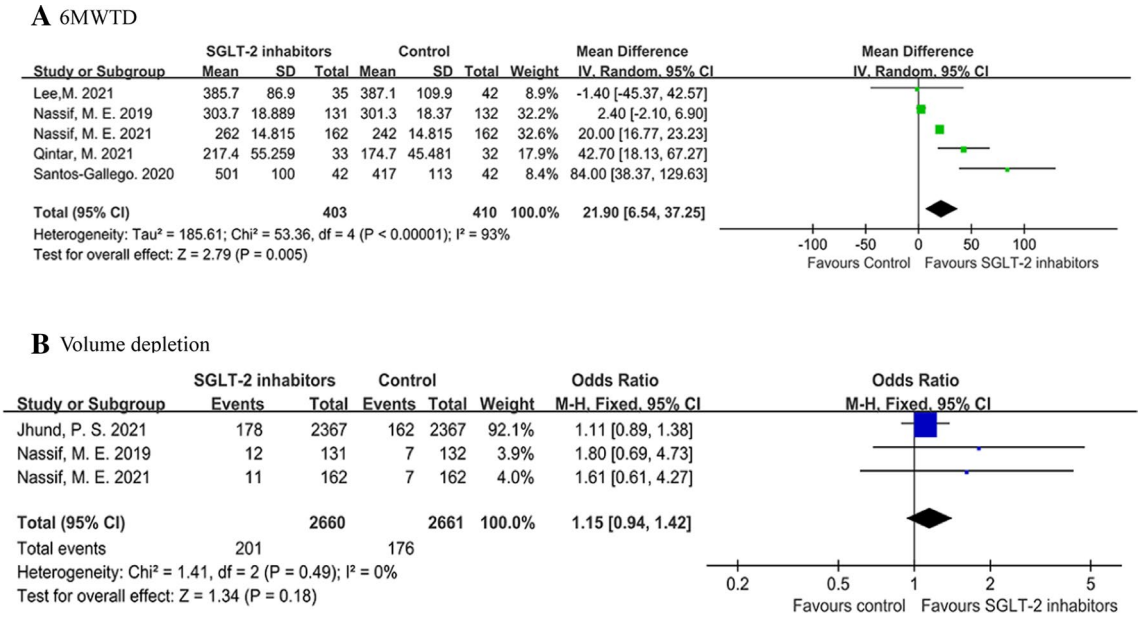

Fig. 4 The exercise capacity outcomes (6 min walk test distance, 6MWTD) and impact on volume depletion analysis. **A** 6 min walk test distance, 6MWTD. **B** impact on volume depletion

for HF studies [14, 37]. Furthermore, the evidence for the effects of SGLT-2 inhibitors on the improvement of HRQoL and exercise capacity seems to be conflicting [18]. In this meta-analysis, SGLT-2 inhibitors improved HRQoL indicators of KCCQ-OSS and KCCQ-CSS in patients with chronic HF regardless of the ejection fraction. The results are similar to the previous meta-analysis in patients with HF failure with reduced EF [18].

Possible adverse effects should be considered when using SGLT-2 inhibitors for cardioprotection. SGLT-2 inhibitors can reduce volume and blood pressure when therapy starts. Volume depletion is significant in type 1 diabetes. The risk of infection, amputation, volume depletion, and diabetic ketoacidosis is higher in patients with cardiovascular disease [38–40]. The present meta-analysis is the first to analyze the impact of SGLT-2 inhibitors on volume depletion in patients with HF. Analysis showed that SGLT-2 inhibitors did not significantly increase the risk of volume depletion in patients with HFrEF or HFpEF. Although volume overload is one of the symptoms of HF, volume reduction is not an important therapeutic goal in chronic HF. Therefore, the adverse effects of volume depletion caused by SGLT-2 inhibitors should be further explored [41].

Unlike the previous meta-analysis [18], this meta-analysis found that SGLT2 inhibitors significantly improved exercise capacity, as measured by 6MWTD, in patients with chronic HF. Inconsistent results could be due to (1) the current analysis included both HFrEF and HFpEF patients instead of just HFrEF patients, and (2) the included trials had longer follow-up periods (up to 6 months) instead of 12 weeks, and the time was updated compared to the previous analysis. The improvement of exercise capacity became evident in HF patients with milder symptoms and over longer periods [18].

To our knowledge, this meta-analysis is the first quantitative analysis of QoL and volume depletion in patients with heart failure. This meta-analysis has the following limitations: (1) there were limited trials for each outcome, the overall quality of the included studies was low to moderate, contributing to publication bias, and (2) three included studies came from the same research group. Therefore, more prospective trials must be conducted to assess the effects of SGLT-2 inhibitors on quality of life, exercise capacity, and volume depletion.

Conclusion

SGLT-2 inhibitors improve the quality of life and exercise capacity in patients with chronic heart failure. SGLT-2 inhibitors have no significant impact on volume depletion in this population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11096-022-01504-6.

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Conflicts of interest The authors declare that they have no conflicts of interest.

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