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AIMS AND SCOPE

The primary aim of *World Journal of Nephrology* (*WJN*, *World J Nephrol*) is to provide scholars and readers from various fields of nephrology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJN mainly publishes articles reporting research results obtained in the field of nephrology and covering a wide range of topics including acute kidney injury, acute or chronic interstitial nephritis, AIDS-associated nephropathy, anuria, chronic kidney disease and related complications, CKD-MBD, diabetes insipidus, diabetic nephropathies, Fanconi syndrome, glomerular diseases, inborn or acquired errors renal tubular transport, renal hypertension, kidney cortex necrosis, renal artery obstruction, renal nutcracker syndrome, renal tuberculosis, renal tubular acidosis, thrombotic microangiopathy, uremia, and Zellweger syndrome, *etc*.

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SYSTEMATIC REVIEWS

Heterogeneity in cardiorenal protection by Sodium glucose cotransporter 2 inhibitors in heart failure across the ejection fraction strata: Systematic review and meta-analysis

Saeed Taheri

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Abstract

BACKGROUND

Gliflozins or Sodium glucose cotransporter 2 inhibitors (SGLT2i) are relatively novel antidiabetic medications that have recently been shown to represent favorable effects on patients' cardiorenal outcomes. However, there is shortage of data on potential disparities in this therapeutic effect across different patient subpopulations.

AIM

To investigate differential effects of SGLT2i on the cardiorenal outcomes of heart failure patients across left ventricular ejection fraction (LVEF) levels.

METHODS

Literature was searched systematically for the large randomized double-blind controlled trials with long enough follow up periods reporting cardiovascular and renal outcomes in their patients regarding heart failure status and LVEF levels. Data were then meta-analyzed after stratification of the pooled data across the LVEF strata and New York Heart Associations (NYHA) classifications for heart failure using Stata software version 17.0.

RESULTS

The literature search returned 13 Large clinical trials and 13 *post hoc* analysis reports. Meta-analysis of the effects of gliflozins on the primary composite outcome showed no significant difference in efficacy across the heart failure subtypes, but higher efficacy were detected in patient groups at lower NYHA classifications (I^2 = 46%, P = 0.02). Meta-analyses across the LVEF stratums revealed that a baseline LVEF lower than 30% was associated with enhanced improvement in the primary composite outcome compared to patients with higher LVEF levels at the borderline statistical significance (HR: 0.70, 95%CI: 0.60 to 0.79 *vs* 0.81, 95%CI: 0.75 to 0.87; respectively, P = 0.06). Composite renal

outcome was improved significantly higher in patients with no heart failure than in heart failure patients with preserved ejection fraction (HFpEF) (HR: 0.60, 95%CI: 0.49 to 0.72 *vs* 0.94, 95%CI: 0.74 to 1.13; *P* = 0.04). Acute renal injury occurred significantly less frequently in heart failure patients with reduced ejection fraction who received gliflozins than in HFpEF (HR: 0.67, 95%CI: 51 to 0.82 *vs* 0.94, 95%CI: 0.82 to 1.06; *P* = 0.01). Volume depletion was consistently increased in response to SGLT2i in all the subgroups.

CONCLUSION
Heart failure patients with lower LVEF and lower NYHA sub-classifications were found to be generally more likely to benefit from therapy with gliflozins. Further research are required to identify patient subgroups representing the highest benefits or adverse events in response to SGLT2i.

Key Words: Sodium glucose cotransporter 2 inhibitors; Cardiovascular; Renal outcome; efficacy; Heart failure with preserved ejection fraction; Heart failure with reduced ejection fraction

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Core Tip: Compared to placebo, treatment with Sodium glucose cotransporter 2 inhibitors improve cardiorenal outcomes in a broad range of disorders with significant heterogeneity in the subgroup of patients who are likely to benefit most from the treatment across their heart failure subtypes, New York Heart Associations classifications and ejection fraction levels. There are also adverse events associated with these drugs that deserve further research.

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INTRODUCTION

Anti-hyperglycemic medications have been shown to improve cardiovascular outcomes and renal health in a range of disorders; yet in specific patient subpopulations there is a possibility that their side effects outweigh the protection they offer. For the same reason, large and expensive clinical trials have been conducted to investigate their impact on health entities, and protective roles have been reported for a number of these drugs that went beyond their antihyperglycemic effects[1,2].

Gliflozins or Sodium glucose cotransporter 2 inhibitors (SGLT2i) are relatively novel antidiabetic medications that lower blood levels of glucose through increasing its urinary excretion and therefore they also induce weight loss[1]. Recently a number of large clinical trials have shown significant cardiorenal protection by these drugs in a spectrum of diseases including patients with type 2 diabetes mellitus (T2DM), heart failure and chronic kidney diseases. However, the patient populations were inconsistent in these trials in several aspects, and there is a need for further research regarding the potential factors that might contribute in this effect. In fact, a number of systematic reviews have already been published covering a broad spectrum of cardiac, renal and metabolic factors, including meta-analyses showing significant improvements in the composite outcomes of cardiovascular death or hospitalizations in heart failure patients with either preserved (HFpEF) or reduced ejection fraction (HFrEF)[3-6]. The purpose of this systematic review and meta-analysis is to examine potential effects of SGLT2i therapy on the composite or specific cardiac or renal outcomes in heart failure patients across baseline left ventricular ejection fraction (LVEF) levels.

MATERIALS AND METHODS

Search strategy and selection criteria

Supplementary Figure 1 summarizes the search strategy of the current systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist was followed in this study (Supplementary Figure 2). A systematic search of the literature was performed using Cochrane Library, Reference Citation Analysis, nejm.org, and EuropePMC search engines to April 15, 2023. Pubmed/MEDLINE could not be reached due to internet filtering. Further search of the literature was performed using Google Scholar to find the *post hoc* analyses and substudies from the included large randomized controlled trials, regarding the subjects of interest for this systematic review (Figure 1).

In order to minimize potential publication biases, the inclusion criteria assigned eligibility only to the reports of double-blind and placebo-controlled trials if they were large (defined as at least 1000 subjects in the SLGT2i arm and at least half as many patients in the placebo arm) with long enough follow up time (at least 6 mo), assessing SGLT2i, and reported any of the efficacy or safety outcomes of interest in this review, as specified. Finally 27 studies (13 trials and 14

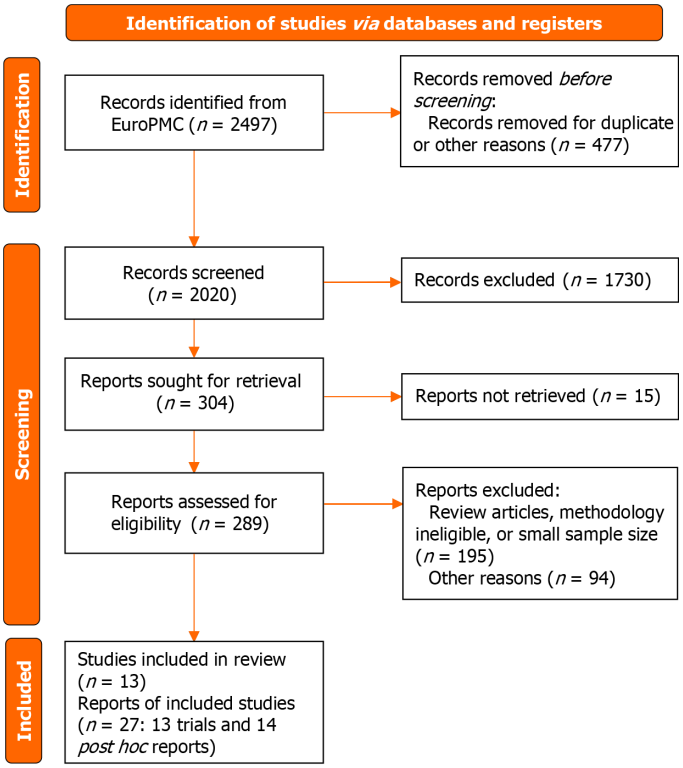

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Figure 1 PRISMA flow diagram.

post hoc analyses) were found and reviewed[7-33].

Outcomes of interest

The evaluated outcomes in this systematic review and meta-analysis included the primary composite outcome as defined by each study and irrespective of the disparities between them, cardiovascular death, the composite outcome of cardiovascular death or hospitalization (or an urgent visit) for heart failure, composite renal outcome (serious renal events defined by different studies and irrespective of potential differences between trials) and death from any cause.

Specific renal outcomes: As mentioned above, the composite renal outcomes were inconsistently defined by different studies and included a heterogeneous combinations of the following indicators: Doubling of serum creatinine measures, substantial decrease in estimated glomerular filtration rate (*i.e.* ≥ 40% decrease; falling below 60 to less than 15 mL/min/1.73 m^2 in different studies), end-stage kidney disease; renal replacement therapy initiation (*i.e.* dialysis or renal transplantation), and renal death. Wherever there were reports from more than one combination of renal outcomes, the one with the larger spectrum was used as the composite renal outcome for inclusion into the meta-analysis. Other renal outcomes that were evaluated in this study included renal disease progression/worsening renal function, acute kidney injury/acute renal failure, volume depletion, and diabetic ketoacidosis.

Stratifications across LVEF stratums

Heart failure subtypes: Data for primary outcomes of interests were extracted and meta-analysis were conducted across specific stratification strategies. The patients' heart failure status and the type of heart failure (*i.e.* HFpEF), HFrEF and mid-range/mildly-reduced ejection fraction (HFmrEF) were also extracted. The definition of HFpEF has varied across different trials, with HFpEF defined as EF > 40% in the EMPEROR-Preserved[16] and DELIVER[18], and as EF ≥ 50% in the SCORED[13], CANVAS[12], EMPA-REG OUTCOME[21], and SOLOIST-WHF[17] trials. Likewise, HFrEF was inconsistently defined as EF < 40% in the SCORED[13] and SOLOIST-WHF[17], as ≤ 40% in the EMPEROR-Reduced[15] and DAPA-HF[14], as EF < 45% in DECLARE-TIMI 58[33], as EF ≤ 45% in the VERTIS-CV[24], and as EF < 50% in the CANVAS[22] and EMPA-REG OUTCOME[21] trials. Heart failure with mildly reduced (mid-range) EF was consistently defined as EF between 40%-49%. Only in Supplementary Figure 3, LVEF rates between 35% and 55% were also considered HFmrEF. Finally, heart failure not-otherwise-specified (nos) as patients diagnosed with heart failure (presence of signs and symptoms of HF, elevated levels of natriuretic peptides in the plasma and evidence of structural heart disease - left ventricular hypertrophy or left atrial remodeling - or the presence of diastolic dysfunction) with no further stratifications. Patients who had baseline LVEF ranged within the definitions but without the documented diagnosis of heart failure were excluded from the respective subgroups.

LVEF stratums: Meta-analyses of the outcomes were repeated after stratification of the LVEF rates by LVEF stratums (*i.e.* documented heart failure patients with LVEF measures above or below the cutoff values of 30%, 40%, 45%, 50%, and

60%). However, since the outcome analyses across all the predefined LVEF cutoff points were not exactly performed by all the reviewed studies, an alternative approach was employed wherever there were reports that fell in ranges totally within the study subgroups defined across the cutoff points of this study; *e.g.* in meta-analysis of outcomes across LVEF of 40%, if a trial had only provided data of LVEF over 50% or below 30%, the data were included as LVEF over 40% or ≤ 40%, respectively (since LVEF values ≥ 50% falls totally within the range of > 40% and LVEF < 30% falls fully within the range of ≤ 40%). But data of patients with LVEF < 50% was not included into meta-analysis of patients with LVEF < 40%, since it doesn't totally fall within the specified range. Moreover, if data was available for two LVEF ranges for any particular study, both falling within the meta-analysis ranges, the one that was closest to the cutoff and therefore encompassed the largest possible patient population was chosen for inclusion (*e.g.* if LVEF > 45% and > 50% were available for a trial, in meta-analysis of outcomes across LVEF 40%, data of LVEF > 45% was included in the reports of LVEF > 40%).

Statistical analysis

Hazard ratio (HR) and 95% confidence interval (CI) were pooled using a random-effects DerSimonian and Laird model. Inverse of the variance was used to assign weights to each study. Heterogeneity among studies was assessed using the Higgins I^2 value. Meta-regression analysis was conducted using mixed-effects modelling to evaluate factors potentially explaining any observed heterogeneity for the study outcomes (*i.e.* composite study outcome, cardiovascular death and/or heart failure hospitalizations and composite or specific renal outcomes). Meta-regression models using demographic or disease-specific baseline data (*i.e.* age, gender, ethnicity, glycated hemoglobin, past medical history, *etc.*) inputs were not possible due the lack of the baseline data discriminately reported across the study groups (*i.e.* heart failure subtypes, LVEF cutoff levels and NYHA). The only factor that could be included into meta-regression without controversy was the type of gliflozins employed. Some other factors were also used for this purpose (including mean study follow-up time, T2DM and chronic kidney disease (CKD) as inclusion criterions to the study) which might sound controversial since the follow up times could be inconsistent in patient subgroups, as were T2DM and CKD status in studies not having them as inclusion criterions. Even though, no observed heterogeneity in any of the meta-analyses could be explained by the gliflozin type, with no significant effect returned by meta-regression analysis. The same observation was made for meta-regression analysis of the more controversial factors mentioned above.

No special dosage preferences were made for trials in which more than one SGLT2i dosage had been sought and the pooled effects were used for analyses wherever applicable and otherwise, data from the higher SGLT2i dosage was considered. Subgroup analysis was conducted to assess for variability of therapeutic effects across the LVEF stratums, heart failure subtypes and NYHA subclass populations. Study quality was assessed using version 2 of the Cochrane risk-of-bias tool. 2-tailed *P* values with statistical significance specified at 0.05 were used in all analyses. Stata version 17 (Stata Corp.) and Microsoft Excel 2013 (Microsoft Corp.) were used for analyses.

RESULTS

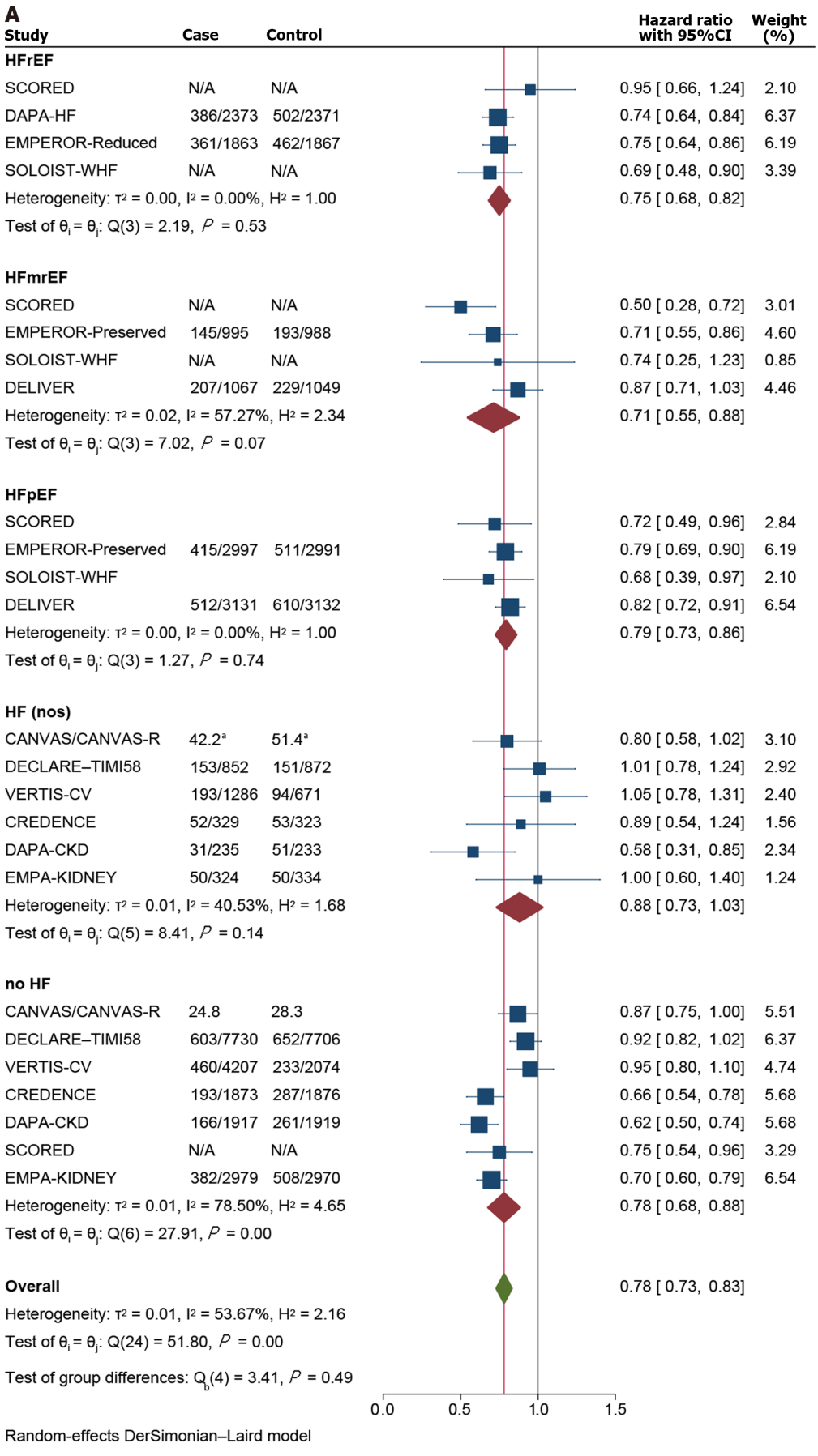
The literature search returned 13 large clinical trials evaluating impact of SGLT2i on the outcome of patients[7-19], and their characteristics are summarized in Table 1. Fourteen more studies reporting *post hoc* analysis of the reviewed trials were also found and reviewed[20-33]. Five trials were on heart failure patients, in seven trials only diabetic patients included and four trials were conducted specifically on patients with chronic kidney diseases. Patients' data and outcome reports were extracted regarding their heart failure status and included in the meta-analyses.

Meta-analyses across heart failure subtypes

Meta-analysis of the effects of gliflozins on the primary composite outcomes (cardiorenal events as defined by each study) showed that compared to placebo, SGLT2i significantly decreased the event rates (HR: 0.78, 95%CI: 0.73 to 0.83, I^2 = 53.7%), with no significant difference in efficacy across the heart failure status or subtypes (P = 0.49, Figure 2A). Likewise, when cardiovascular death and/or urgent visits/hospitalization for heart failure was used as the outcome, gliflozins were superior to placebo with no heterogeneity between the subgroups (HR: 0.76, 95%CI: 0.72 to 0.79, P = 0.68, I^2 = 0%, Figure 2B). Compared to placebo, SGLT2i therapy was again found to be significantly associated with lower cardiovascular death (HR: 0.84, 95%CI: 0.78 to 0.90, I^2 = 19.9%) and all-cause mortality (HR: 0.86, 95%CI: 0.81 to 0.91, I^2 = 32.1%), with no significant difference between the subgroups [P = 0.98 (Supplementary Figure 3) and P = 0.21 (Figure 3), respectively]. However, a trend toward higher effectiveness was observed for patients with HFrEF *vs* HFpEF; though it failed to reach the statistical significance just at the borderline level; P = 0.07 (Supplementary Figure 4).

Although no significant difference was detected in efficacy measures between the heart failure subtypes in any of the above-mentioned meta-analyses, interestingly SGLT2i seem to offer significant benefits in survival outcome (i.e. cardiovascular death or all-cause mortality) only to HFrEF or (to a lesser degree) HFmrEF patients, and the respective outcome effects did not reach significance level for HFpEF (HR: 0.89, 95%CI: 0.75 to 1.02; HR: 0.96, 95%CI: 0.88 to 1.05; respectively, Supplementary Figure 3 and Figure 3).

Meta-analyses of the primary composite outcomes across NYHA classes revealed significant improvement in the outcome rates [HR: 0.74(0.67-0.82)], although as is illustrated in Figure 4, this favorable effect was not consistent across all the NYHA subclasses and those at lower classes significantly better responded to SGLT2i (I^2 = 46%, P = 0.02; Figure 4).


A
Study
Case
Control
Hazard ratio with 95%CI
Weight (%)
HFrEF
SCORED N/A N/A 0.95 [0.66, 1.24] 2.10
DAPA-HF 386/2373 502/2371 0.74 [0.64, 0.84] 6.37
EMPEROR-Reduced 361/1863 462/1867 0.75 [0.64, 0.86] 6.19
SOLOIST-WHF N/A N/A 0.69 [0.48, 0.90] 3.39
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.75 [0.68, 0.82]
Test of θi = θj: Q(3) = 2.19, P = 0.53
HFmrEF
SCORED N/A N/A 0.50 [0.28, 0.72] 3.01
EMPEROR-Preserved 145/995 193/988 0.71 [0.55, 0.86] 4.60
SOLOIST-WHF N/A N/A 0.74 [0.25, 1.23] 0.85
DELIVER 207/1067 229/1049 0.87 [0.71, 1.03] 4.46
Heterogeneity: τ² = 0.02, I² = 57.27%, H² = 2.34 0.71 [0.55, 0.88]
Test of θi = θj: Q(3) = 7.02, P = 0.07
HFpEF
SCORED 0.72 [0.49, 0.96] 2.84
EMPEROR-Preserved 415/2997 511/2991 0.79 [0.69, 0.90] 6.19
SOLOIST-WHF 0.68 [0.39, 0.97] 2.10
DELIVER 512/3131 610/3132 0.82 [0.72, 0.91] 6.54
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.79 [0.73, 0.86]
Test of θi = θj: Q(3) = 1.27, P = 0.74
HF (nos)
CANVAS/CANVAS-R 42.2[a] 51.4[a] 0.80 [0.58, 1.02] 3.10
DECLARE–TIMI58 153/852 151/872 1.01 [0.78, 1.24] 2.92
VERTIS-CV 193/1286 94/671 1.05 [0.78, 1.31] 2.40
CREDENCE 52/329 53/323 0.89 [0.54, 1.24] 1.56
DAPA-CKD 31/235 51/233 0.58 [0.31, 0.85] 2.34
EMPA-KIDNEY 50/324 50/334 1.00 [0.60, 1.40] 1.24
Heterogeneity: τ² = 0.01, I² = 40.53%, H² = 1.68 0.88 [0.73, 1.03]
Test of θi = θj: Q(5) = 8.41, P = 0.14
no HF
CANVAS/CANVAS-R 24.8 28.3 0.87 [0.75, 1.00] 5.51
DECLARE–TIMI58 603/7730 652/7706 0.92 [0.82, 1.02] 6.37
VERTIS-CV 460/4207 233/2074 0.95 [0.80, 1.10] 4.74
CREDENCE 193/1873 287/1876 0.66 [0.54, 0.78] 5.68
DAPA-CKD 166/1917 261/1919 0.62 [0.50, 0.74] 5.68
SCORED N/A N/A 0.75 [0.54, 0.96] 3.29
EMPA-KIDNEY 382/2979 508/2970 0.70 [0.60, 0.79] 6.54
Heterogeneity: τ² = 0.01, I² = 78.50%, H² = 4.65 0.78 [0.68, 0.88]
Test of θi = θj: Q(6) = 27.91, P = 0.00
Overall 0.78 [0.73, 0.83]
Heterogeneity: τ² = 0.01, I² = 53.67%, H² = 2.16
Test of θi = θj: Q(24) = 51.80, P = 0.00
Test of group differences: Qb(4) = 3.41, P = 0.49
0.0
0.5
1.0
1.5
Random-effects DerSimonian–Laird model

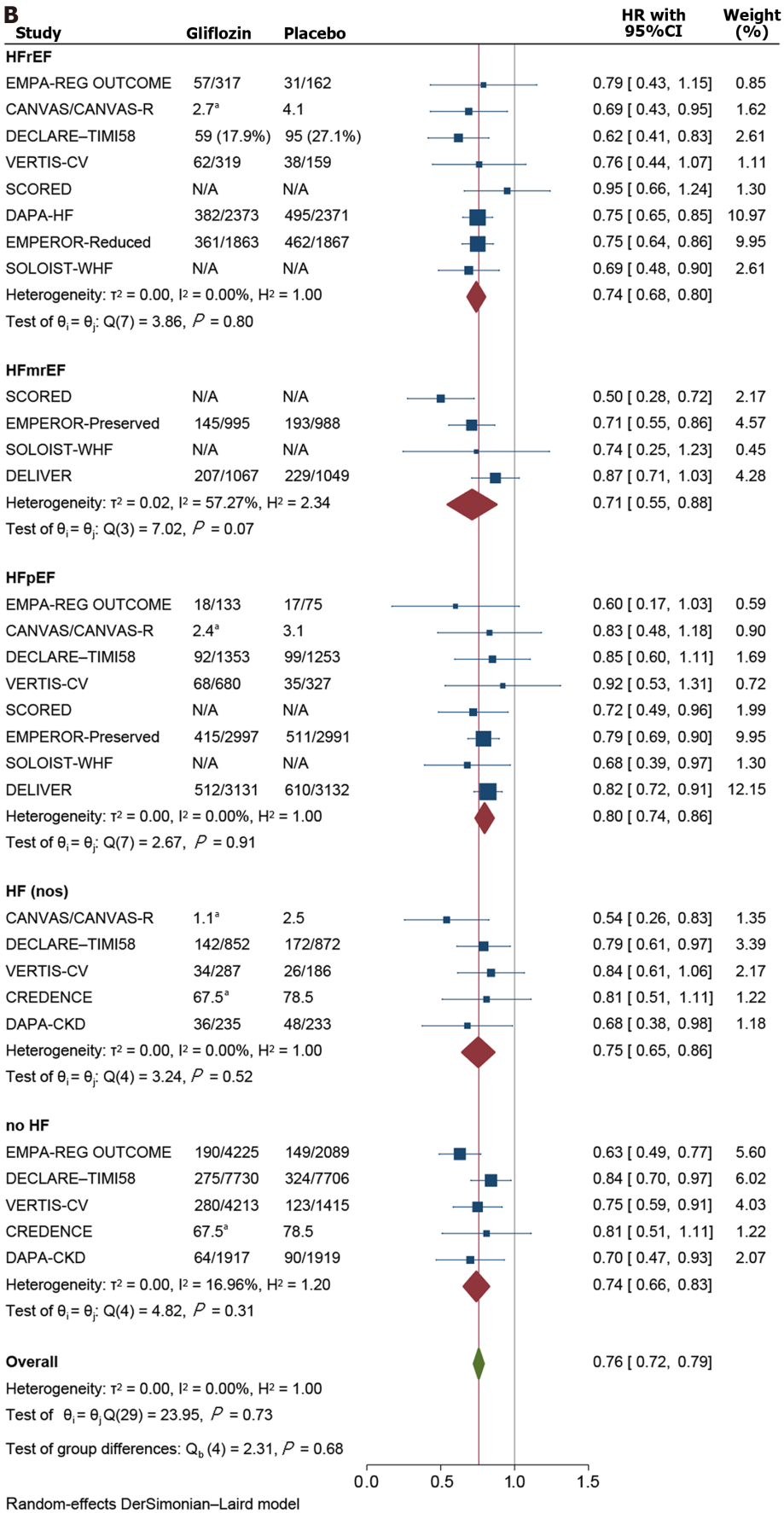


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Figure 2 Meta-analysis of primary composite outcome. A: Gliflozins' effect on the primary composite outcome across heart failure subtypes; B: Gliflozins' effect on the composite outcome of 'cardiovascular deaths or hospitalizations due to heart failure or urgent visits' across heart failure subtypes. HF: Heart failure;

HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; nos: Not otherwise specified; N/A: Not available. [a]per 1000 person-years; [b]per 100 person-years.

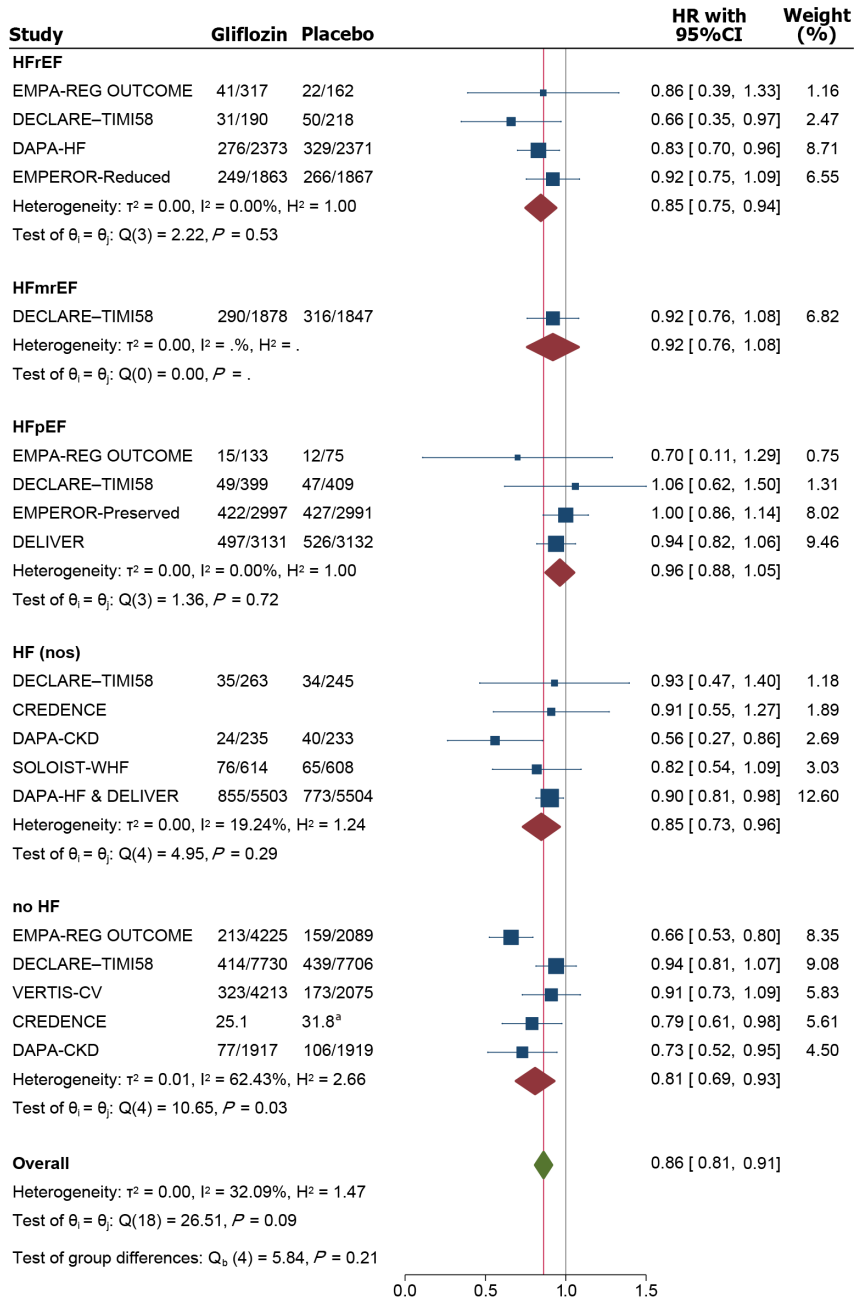

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Figure 3 Meta-analysis of the effects of Sodium glucose cotransporter 2 inhibitors on the all-cause mortality across the heart failure subtypes. HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; nos: Not otherwise specified. [a]per 1000 person-years.

Meta-analysis across LVEF stratums

Meta-analyses were repeated across the LVEF stratums, irrespective of the authors' definitions of the heart failure subtypes. The primary composite outcomes across all the LVEF cutoff levels showed significant efficacy for gliflozins compared to placebo, with no significant difference between the subgroups. Notably, patients with a baseline LVEF of 30% or less represented enhanced improvement in the primary composite outcome compared to patients with LVEF over 30%, but at the borderline statistical significance (HR: 0.70, 95%CI: 0.60 to 0.79 *vs* 0.81, 95%CI: 0.75 to 0.87; respectively, *P* = 0.06; Supplementary Figure 4).

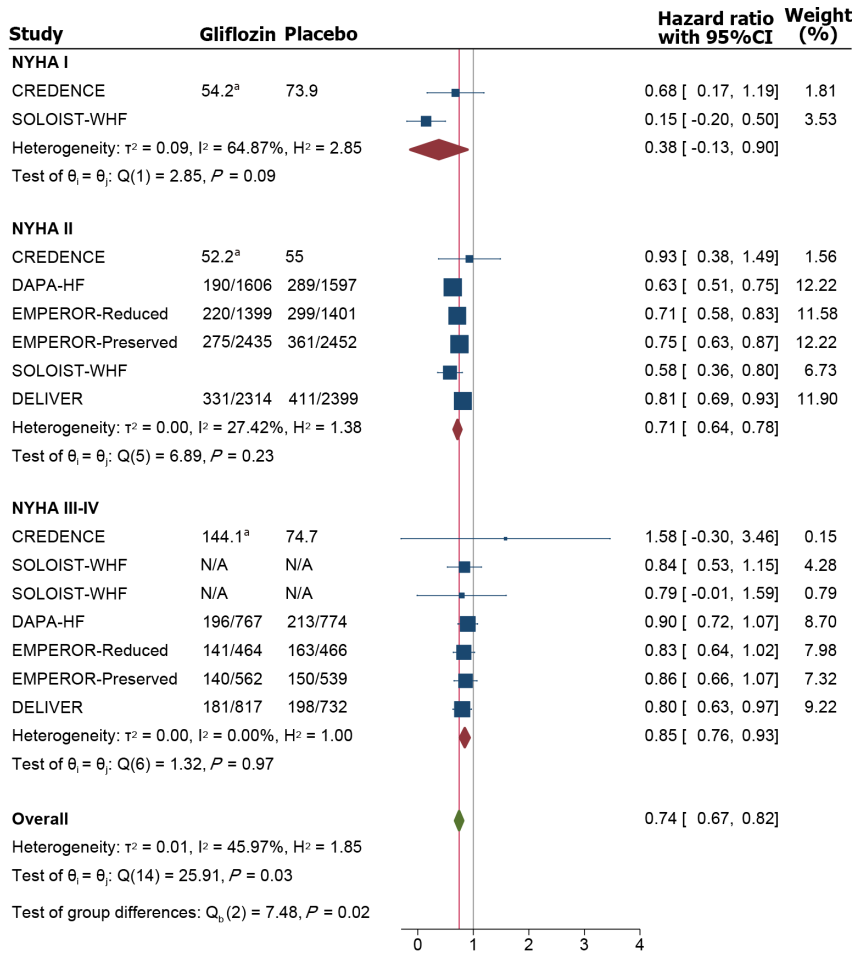

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Figure 4 Meta-analysis of the effects of Sodium glucose cotransporter 2 inhibitors on the primary composite outcome of heart failure patients across different New York Heart Associations classifications. [a]per 1000 person-years.

Similar to the results of primary outcome analyses, meta-analysis of the composite outcome of 'cardiovascular death or hospitalizations (or urgent visits) due to heart failure' exhibited significant improvement in response to treatment with SGLT2i at all the LVEF levels though again, compared to patients with LVEF above 30%, the subgroup of patients with the baseline LVEF of 30% or less showed a stronger response to gliflozins at borderline significance (HR: 0.69, 95%CI: 0.61 to 0.76 *vs* 0.78, 95%CI: 0.71 to 0.85; $P = 0.07$). Further analyzes at higher cutoff values showed no significant difference for the respective outcome ($P > 0.4$ for all; Figure 5). All-cause mortality also showed significant benefit across LVEF stratums with the relatively best effect size in patients with LVEF ≤ 40% (versus LVEF > 40%) but no statistical significance was reached; Figure 6.

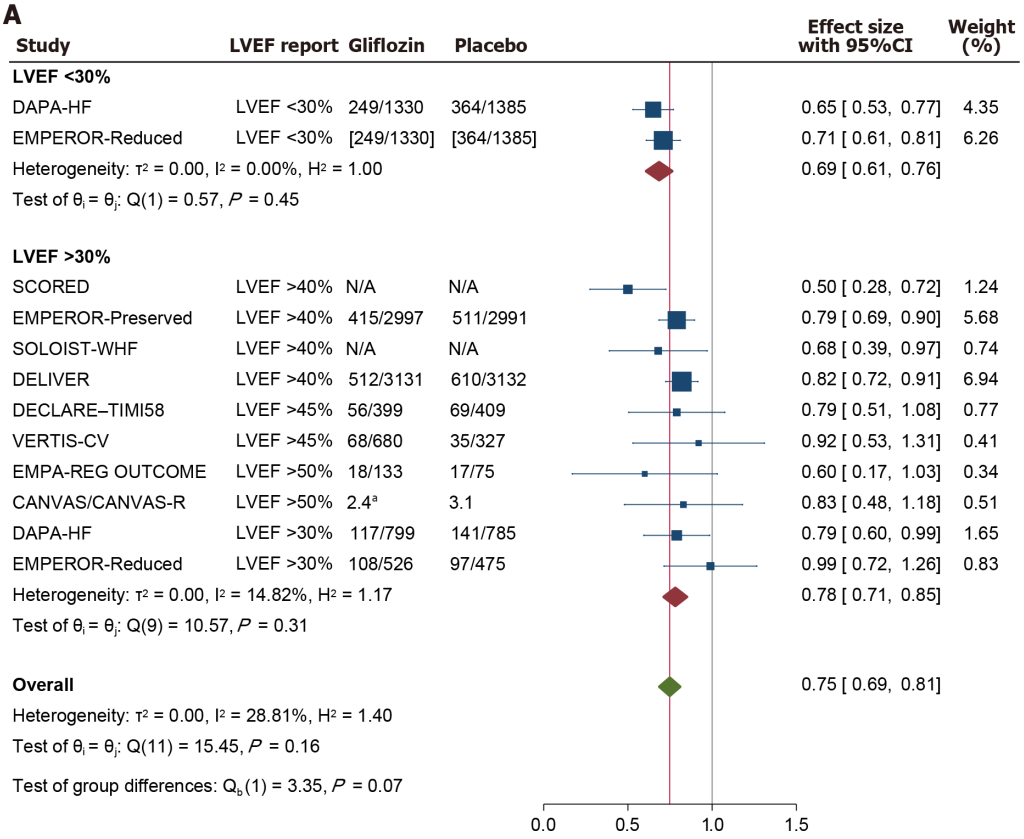
Renal outcome meta-analyses across heart failure subtypes

Composite renal events: Composite renal events was an unspecific terminology that comprised a diverse spectrum of unfavorable renal events (described in methods) As could be perceived from Figure 6A, SGLT2i significantly improved composite renal events as compared to the placebo-treated group (HR: 0.69, 95%CI: 0.59 to 0.79), but significant difference across the meta-analysis patient groups was observed with HFpEF and no-heart failure patients representing the lowest and the highest response rates, respectively (HR: 0.94, 95%CI: 0.74 to 1.13 and 0.60, 95%CI: 0.49 to 0.72, respectively); $P = 0.04$, Figure 7.

Acute kidney injury (or acute renal failure) was also shown to occure significantly less frequently in patients receiving SGLT2i compared to placebo (HR: 0.83, 95%CI: 0.75 to 0.92; Figure 7B); however this effect was not consistent across the heart failure groups and HFrEF and HFpEF patients respectively represented the highest and the lowest response rates with significant difference between, after excluding other subgroups from the meta-analysis (HR: 0.67, 95%CI: 51 to 0.82 *vs* 0.94, 95%CI: 0.82 to 1.06; $P = 0.01$, Supplementary Figure 5).

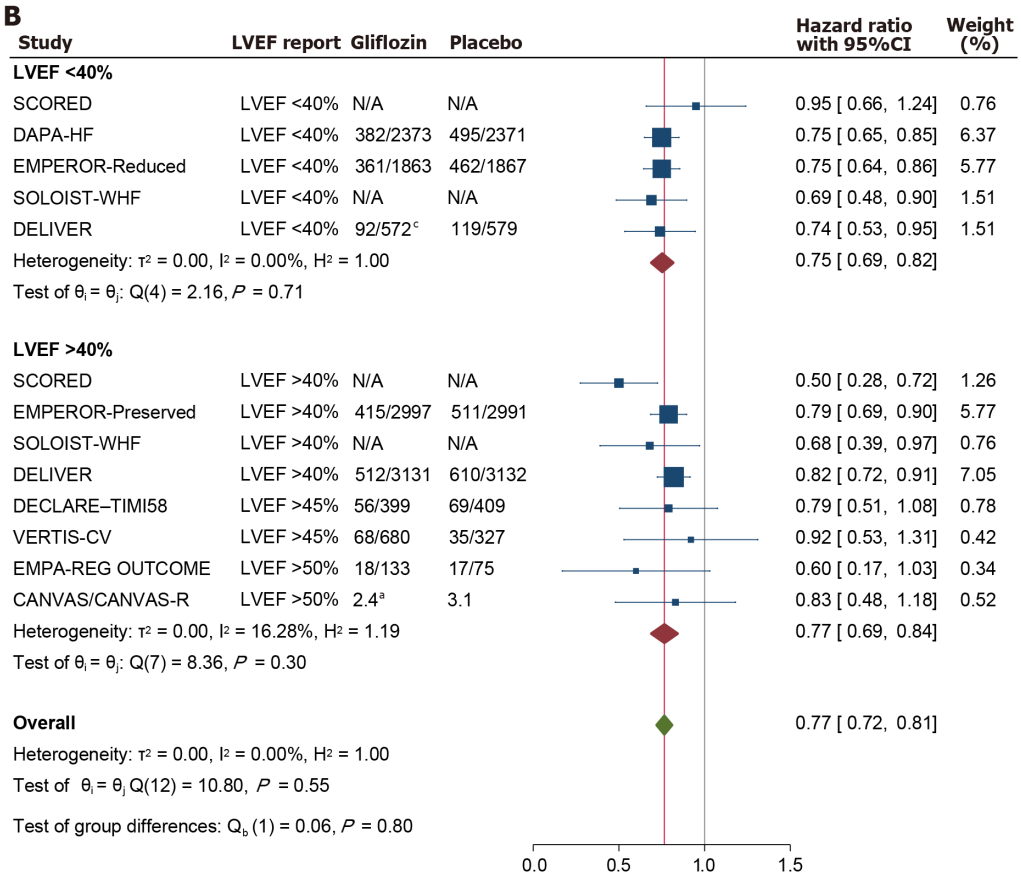
Renal disease progression or worsening renal function: Gliflozins significantly reduced renal disease progression in the meta-analysis (HR: 0.63, 95%CI: 0.55 to 0.71). But unlike the composite renal event, no significant difference was found regarding the heart failure status or across subtypes ($P = 0.52$; Supplementary Figure 6).

A



Random-effects DerSimonian–Laird model

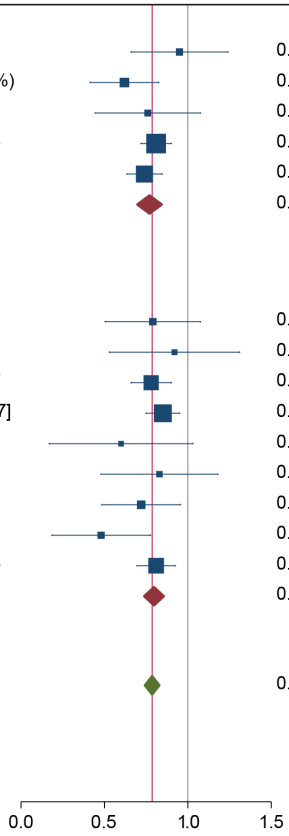
B



Random-effects DerSimonian–Laird model

C

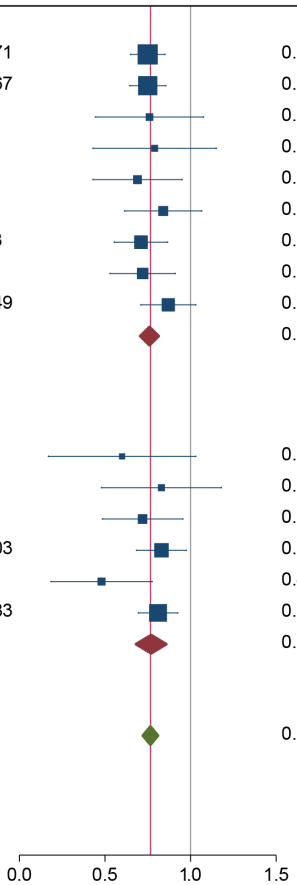
Study	LVEF report	Gliflozin	Placebo	Hazard ratio with 95%CI	Weight (%)
LVEF <45%					
SCORED	LVEF <40%	N/A	N/A	0.95 [0.66, 1.24]	0.76
DECLARE–TIMI58	LVEF <45%	59 (17.9%)	95 (27.1%)	0.62 [0.41, 0.83]	1.51
VERTIS-CV	LVEF <45%	62/319	38/159	0.76 [0.44, 1.07]	0.64
DAPA-HF plus DELIVER	LVEF <45%	473/2824	595/2784	0.81 [0.72, 0.90]	7.86
EMPEROR (both)	LVEF <45%	423/2253	537/2251	0.74 [0.63, 0.85]	5.77
Heterogeneity: τ^2 = 0.00, I^2 = 13.16%, H^2 = 1.15				0.77 [0.70, 0.84]	
Test of $\theta_i = \theta_j$: Q(4) = 4.61, P = 0.33					
LVEF >45%					
DECLARE–TIMI58	LVEF >45%	56/399	69/409	0.79 [0.51, 1.08]	0.78
VERTIS-CV	LVEF >45%	68/680	35/327	0.92 [0.53, 1.31]	0.42
EMPEROR-Preserved	LVEF >45%	353/2610	436/2607	0.78 [0.66, 0.90]	4.42
DELIVER	LVEF >45%	[440/2680]	[533/2687]	0.85 [0.75, 0.95]	6.37
EMPA-REG OUTCOME	LVEF >50%	18/133	17/75	0.60 [0.17, 1.03]	0.34
CANVAS/CANVAS-R	LVEF >50%	2.4[a]	3.1	0.83 [0.48, 1.18]	0.52
SCORED	LVEF >50%	.	.	0.72 [0.49, 0.96]	1.15
SOLOIST-WHF	LVEF >50%	30.6[b]	64	0.48 [0.18, 0.77]	0.73
DELIVER	LVEF >50%	305/2064	381/2083	0.81 [0.69, 0.93]	4.81
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00				0.80 [0.74, 0.85]	
Test of $\theta_i = \theta_j$: Q(8) = 7.28, P = 0.51					
Overall				0.79 [0.74, 0.83]	
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00					
Test of $\theta_i = \theta_j$: Q(13) = 12.20, P = 0.51					
Test of group differences: $Q_b(1)$ = 0.33, P = 0.57					



Random-effects DerSimonian–Laird model

D

Study	LVEF report	Gliflozin	Placebo	Hazard ratio with 95%CI	Weight (%)
LVEF <50%					
DAPA-HF	LVEF <40%	382/2373	495/2371	0.75 [0.65, 0.85]	6.37
EMPEROR-Reduced	LVEF <40%	361/1863	462/1867	0.75 [0.64, 0.86]	5.77
VERTIS-CV	LVEF <45%	62/319	38/159	0.76 [0.44, 1.07]	0.64
EMPA-REG OUTCOME	LVEF <50%	57/317	31/162	0.79 [0.43, 1.15]	0.49
CANVAS/CANVAS-R	LVEF <50%	2.7[a]	4.1	0.69 [0.43, 0.95]	0.94
SCORED	LVEF <50%	N/A	N/A	0.84 [0.61, 1.06]	1.26
EMPEROR-Preserved	LVEF <50%	145/995	193/988	0.71 [0.55, 0.86]	2.65
SOLOIST-WHF	LVEF <50%	56.9[b]	79.9	0.72 [0.53, 0.91]	1.76
DELIVER	LVEF <50%	207/1067	229/1049	0.87 [0.71, 1.03]	2.49
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00				0.76 [0.71, 0.81]	
Test of $\theta_i = \theta_j$: Q(8) = 3.25, P = 0.92					
LVEF >50%					
EMPA-REG OUTCOME	LVEF >50%	18/133	17/75	0.60 [0.17, 1.03]	0.34
CANVAS/CANVAS-R	LVEF >50%	2.4[a]	3.1	0.83 [0.48, 1.18]	0.52
SCORED	LVEF >50%	.	.	0.72 [0.49, 0.96]	1.15
EMPEROR-Preserved	LVEF >50%	270/2002	318/2003	0.83 [0.68, 0.97]	3.03
SOLOIST-WHF	LVEF >50%	30.6[b]	64	0.48 [0.18, 0.77]	0.73
DELIVER	LVEF >50%	305/2064	381/2083	0.81 [0.69, 0.93]	4.81
Heterogeneity: τ^2 = 0.00, I^2 = 12.10%, H^2 = 1.14				0.77 [0.68, 0.86]	
Test of $\theta_i = \theta_j$: Q(5) = 5.69, P = 0.34					
Overall				0.77 [0.72, 0.81]	
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00					
Test of $\theta_i = \theta_j$: Q(14) = 9.07, P = 0.83					
Test of group differences: Q_b (1) = 0.03, P = 0.85					



Random-effects DerSimonian–Laird model

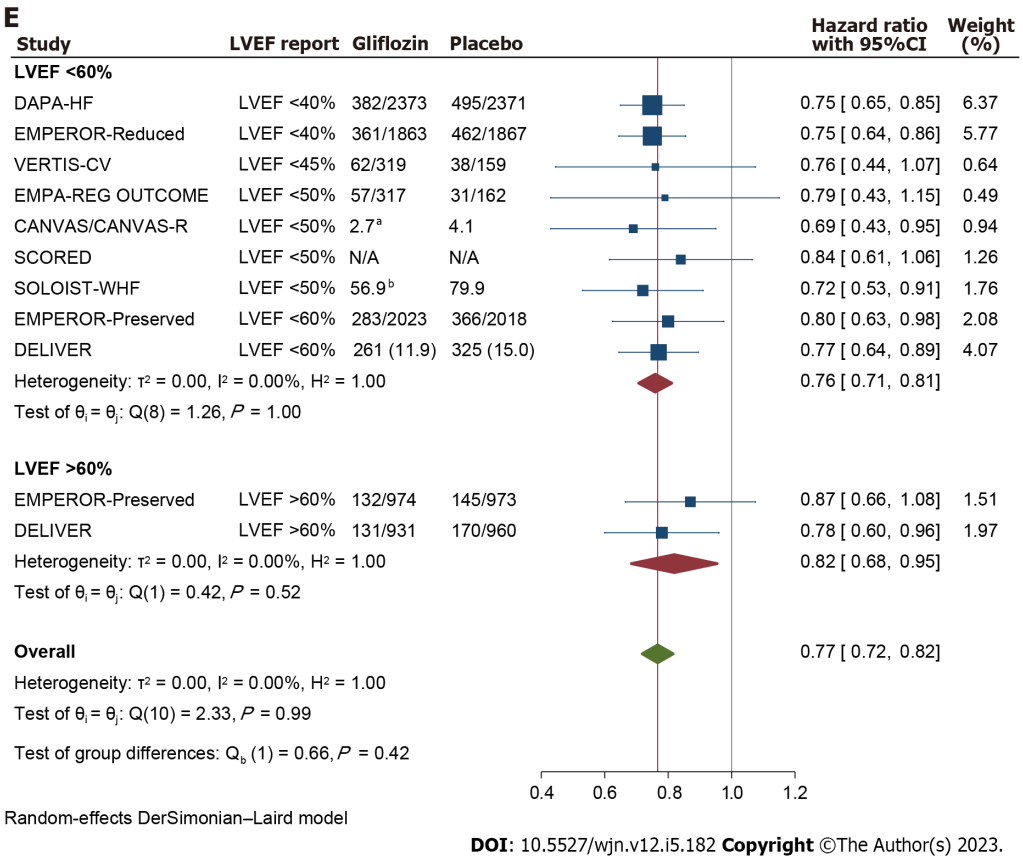


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Figure 5 Meta-analysis of Sodium glucose cotransporter 2 inhibitors' effect on 'cardiovascular death or heart failure hospitalizations or urgent visits' across the patients' baseline left ventricular ejection fraction strata. A: Left ventricular ejection fraction (LVEF) < 30% *vs* ≥ 30%; B: LVEF < 40% *vs* ≥ 40%; C: LVEF < 45% *vs* LVEF ≥ 45%; D: LVEF < 50% *vs* LVEF ≥ 50%; E: LVEF < 60% *vs* LVEF ≥ 60%. [a]per 1000 person-years; [b]per 100 person-years; [c]analysis based on the "history of previous LVEF < 40%" reported by DELIVER trial; LVEF: Left ventricular ejection fraction; N/A: Not available.

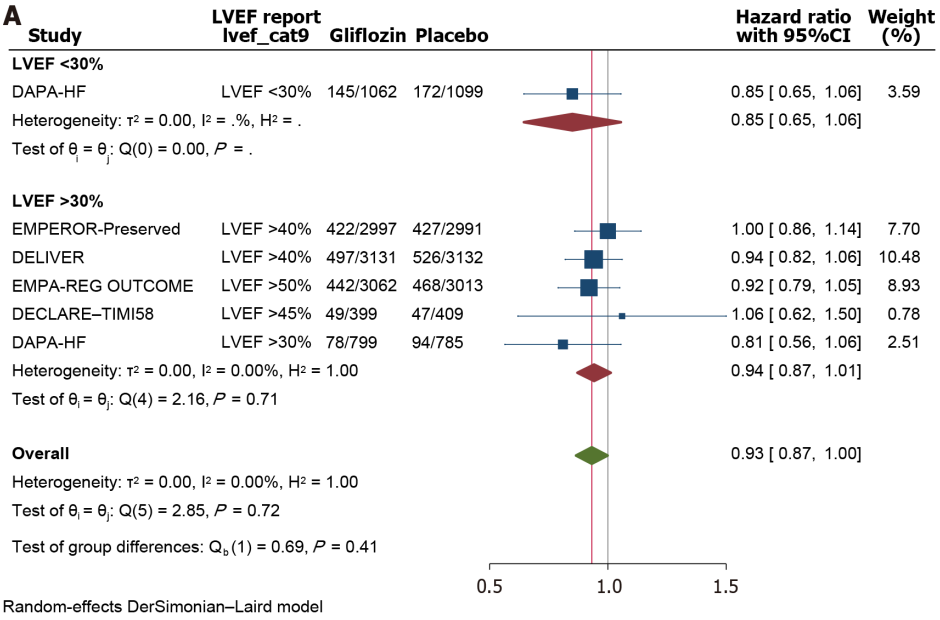
Volume depletion: As is evident from Supplementary Figure 7, SGLT2i therapy was associated with significantly higher rates of volume depletion in the pooled data meta-analysis with no significant difference across the study subgroups (HR: 1.14, 95%CI: 1.02 to 1.26; $P = 0.33$).

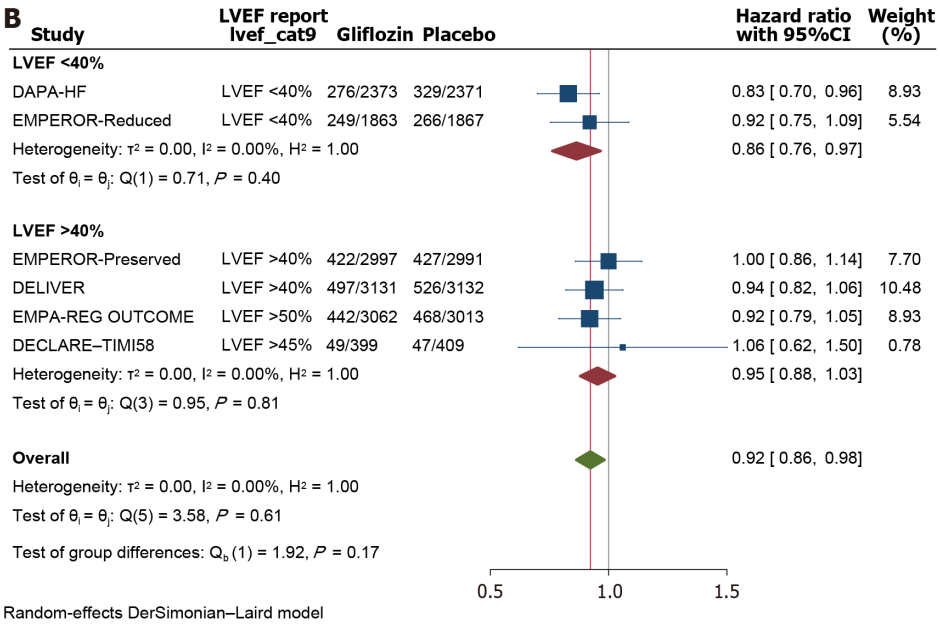
Diabetic ketoacidosis: As is summarized in Supplementary Table 1, diabetic ketoacidosis was a rare observation in both the SGLT2i and placebo groups, and therefore meta-analyses were not possible. The distribution of the outcomes between the two groups reveals no heterogeneity.

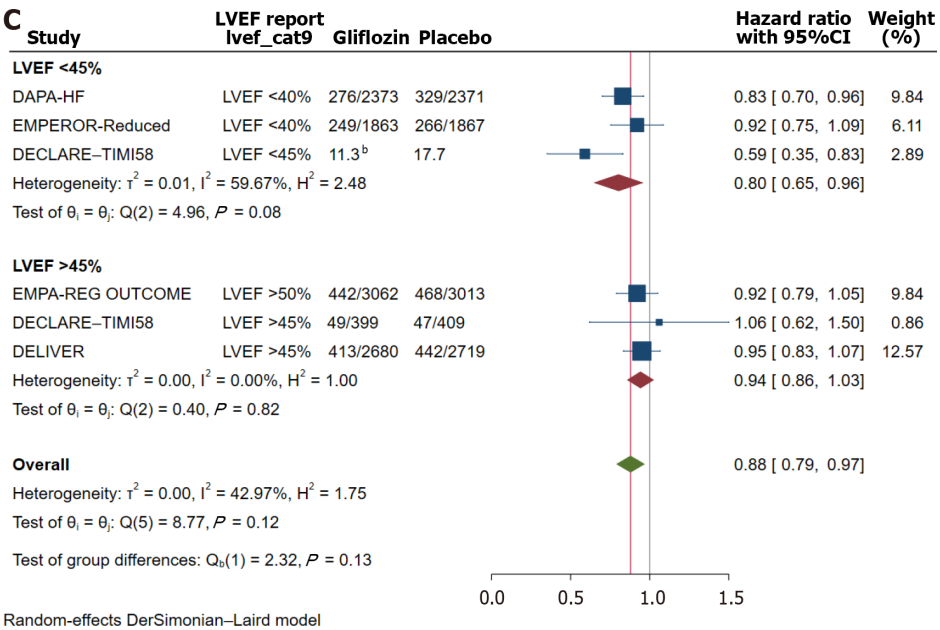
DISCUSSION

In this meta-analysis of 13 large clinical trials, data of 45918 patients were screened and significant but inequivalent protective effects for SGLT2i were found across the patients' LVEF strata, regarding a spectrum of cardiovascular and renal outcomes. Compared to HFpEF patients, HFrEF exhibited more dramatic response to gliflozins in a good number of the predefined outcomes. This finding is in contrast to a previous study in which authors found equivalent efficacy in heart failure patients across a full spectrum of LVEF[30]. One reason for this disparity could be related to the number of studies and patients entered into the analysis, with the current study encompassing substantially larger population (including data from the mentioned study). As well, in the current study the analyses were performed across different cutoff points compared to the analyses across the spectrum of LVEF, which leaves only a limited number of subjects for each subgroup. Moreover the spectrum of specific outcomes investigated in the current study was relatively broader.

Previous review articles have explored several predicting factors on response to SGLT2i. In a comprehensive review, Baigent *et al*[20] analyzed the impact of diabetes mellitus on the cardiorenal protective effects of SGLT2i treatment and found no disparity regarding diabetes status. In another review study, Zelniker *et al*[2] reported that the cardiovascular benefits of gliflozins in diabetic population seem to be largely confined to patients with established atherosclerotic cardiovascular disease. Bhatia *et al*[34] provided evidence for SGLT2i protective effects in a broader range of cardiac, renal and metabolic derangements, and in another very recent *post hoc* analysis from DELIVER trial, Peikert *et al*[35] reported substantial improvements in a large range of symptoms, functionality indices, and quality of life in HFmrEF/HFpEF patients in response to SGLT2i. The current systematic review provides further data on the variability of response


A
Study
LVEF report lvef_cat9
Gliflozin
Placebo
Hazard ratio with 95%CI
Weight (%)
LVEF <30%
DAPA-HF LVEF <30% 145/1062 172/1099 0.85 [0.65, 1.06] 3.59
Heterogeneity: τ² = 0.00, I² = .%, H² = . 0.85 [0.65, 1.06]
Test of θi = θj: Q(0) = 0.00, P = .
LVEF >30%
EMPEROR-Preserved LVEF >40% 422/2997 427/2991 1.00 [0.86, 1.14] 7.70
DELIVER LVEF >40% 497/3131 526/3132 0.94 [0.82, 1.06] 10.48
EMPA-REG OUTCOME LVEF >50% 442/3062 468/3013 0.92 [0.79, 1.05] 8.93
DECLARE–TIMI58 LVEF >45% 49/399 47/409 1.06 [0.62, 1.50] 0.78
DAPA-HF LVEF >30% 78/799 94/785 0.81 [0.56, 1.06] 2.51
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.94 [0.87, 1.01]
Test of θi = θj: Q(4) = 2.16, P = 0.71
Overall 0.93 [0.87, 1.00]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(5) = 2.85, P = 0.72
Test of group differences: Qb(1) = 0.69, P = 0.41
0.5
1.0
1.5
Random-effects DerSimonian–Laird model


B
Study
LVEF report lvef_cat9
Gliflozin
Placebo
Hazard ratio with 95%CI
Weight (%)
LVEF <40%
DAPA-HF LVEF <40% 276/2373 329/2371 0.83 [0.70, 0.96] 8.93
EMPEROR-Reduced LVEF <40% 249/1863 266/1867 0.92 [0.75, 1.09] 5.54
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.86 [0.76, 0.97]
Test of θi = θj: Q(1) = 0.71, P = 0.40
LVEF >40%
EMPEROR-Preserved LVEF >40% 422/2997 427/2991 1.00 [0.86, 1.14] 7.70
DELIVER LVEF >40% 497/3131 526/3132 0.94 [0.82, 1.06] 10.48
EMPA-REG OUTCOME LVEF >50% 442/3062 468/3013 0.92 [0.79, 1.05] 8.93
DECLARE–TIMI58 LVEF >45% 49/399 47/409 1.06 [0.62, 1.50] 0.78
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.95 [0.88, 1.03]
Test of θi = θj: Q(3) = 0.95, P = 0.81
Overall 0.92 [0.86, 0.98]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(5) = 3.58, P = 0.61
Test of group differences: Qb(1) = 1.92, P = 0.17
0.5
1.0
1.5
Random-effects DerSimonian–Laird model


C
Study
LVEF report lvef_cat9
Gliflozin
Placebo
Hazard ratio with 95%CI
Weight (%)
LVEF <45%
DAPA-HF LVEF <40% 276/2373 329/2371 0.83 [0.70, 0.96] 9.84
EMPEROR-Reduced LVEF <40% 249/1863 266/1867 0.92 [0.75, 1.09] 6.11
DECLARE–TIMI58 LVEF <45% 11.3[b] 17.7 0.59 [0.35, 0.83] 2.89
Heterogeneity: τ² = 0.01, I² = 59.67%, H² = 2.48 0.80 [0.65, 0.96]
Test of θi = θj: Q(2) = 4.96, P = 0.08
LVEF >45%
EMPA-REG OUTCOME LVEF >50% 442/3062 468/3013 0.92 [0.79, 1.05] 9.84
DECLARE–TIMI58 LVEF >45% 49/399 47/409 1.06 [0.62, 1.50] 0.86
DELIVER LVEF >45% 413/2680 442/2719 0.95 [0.83, 1.07] 12.57
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.94 [0.86, 1.03]
Test of θi = θj: Q(2) = 0.40, P = 0.82
Overall 0.88 [0.79, 0.97]
Heterogeneity: τ² = 0.00, I² = 42.97%, H² = 1.75
Test of θi = θj: Q(5) = 8.77, P = 0.12
Test of group differences: Qb(1) = 2.32, P = 0.13
0.0
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Random-effects DerSimonian–Laird model

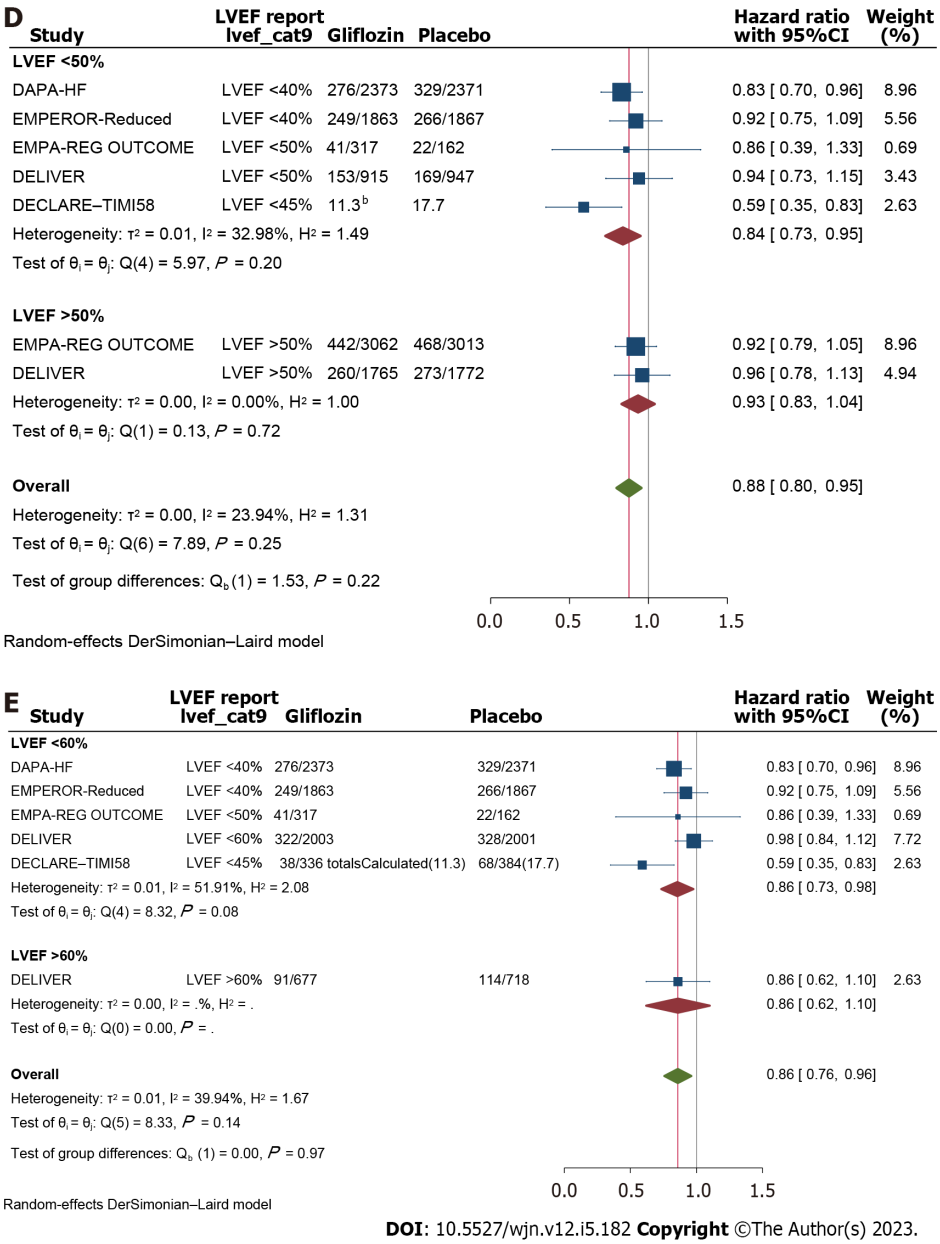

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Figure 6 Meta-analysis of gliflozins' effect on the all-cause mortality across left ventricular ejection fraction strata (versus placebo). A: Left ventricular ejection fraction (LVEF) ≤ 30% *vs* > 30%; B: LVEF ≤ 40% *vs* > 40%; C: LVEF ≤ 45% *vs* LVEF > 45%; D: LVEF ≤ 50% *vs* LVEF > 50%; E: LVEF ≤ 60% *vs* LVEF > 60%. [b]per 100 person-years. LVEF: Left ventricular ejection fraction; N/A: Not available.

to gliflozins in heart failure patients regarding their LVEF levels and NYHA classifications, which could have significant clinical implications for the practitioners.

It is noteworthy that all the clinical trials reviewed in this study have compared the outcome of patients receiving gliflozins *vs* placebo. Although this verifies favorable effects for the drug, it doesn't provide robust evidence that this protective effect outweighs the advantages that are expectable from conventional medications prescribed in this patients; therefore it is still an open question as to whether or not gliflozins' protection outweighs the conventional medications or is there some sort of synergistic relationship between them. But this was out of the scope of the current systematic review, and future studies are required to issue this questions.

Cardiac outcomes: Gliflozins significantly improved the primary composite outcome of cardiovascular death and hospitalizations in patients with or without heart failure and across all the subgroups. However this effect seemed to be skewed in favor of HFrEF compared to HFpEF (the number of patients needed to be treated to save one additional patient from the primary composite outcome in the HFpEF was twice as large as the HFrEF in CANVAS/CANVAS-R trial[22] and 2.9 times for EMPEROR-Reduced *vs* either EMPEROR-Preserved or DELIVER[16,18]; this result was not reproduced in EMPA-REG OUTCOME trial[21]). Reanalyses of the patients' composite outcomes as described above (*i.e.* cardiovascular death or associated hospitalizations) were based on arbitrary definitions of heart failure subgroups by LVEF levels, inconsistently made by the authors in the different trials; therefore in order to have more precise conclusions, definitive cutoff points across LVEF were set and sought for the evaluation of the outcome, and it has been revealed that for a

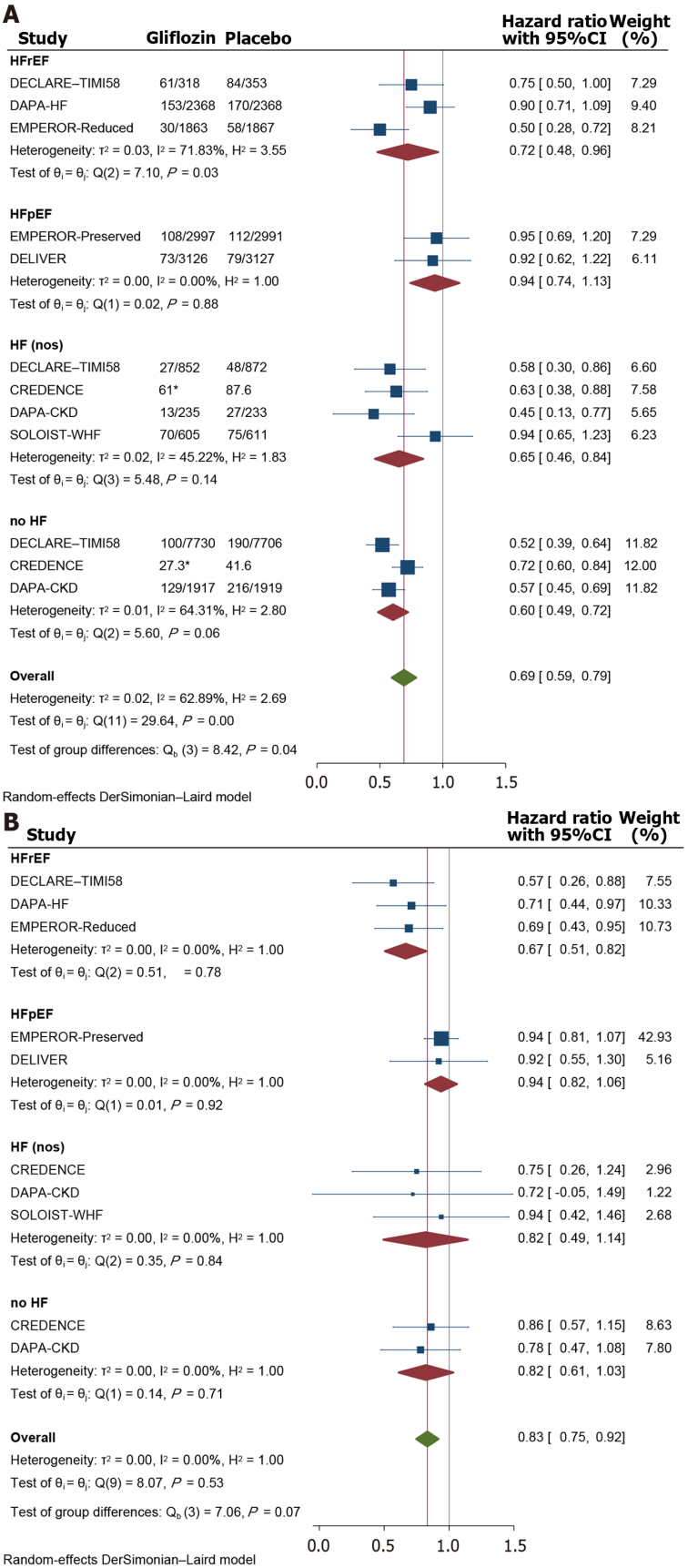

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Figure 7 Meta-analysis of the Sodium glucose cotransporter 2 inhibitors' effect on different renal outcome indices across heart failure subtypes. A: Composite renaloutcome; B: Acute kidney injury. HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; nos: Not otherwise specified.

Table 1 Summary of the reviewed trials

Ref.	Ref-post-hoc	Trial	Year	Follow (yr)	N	Participants	Diabetes proportion %	Heart failure proportion (%)	SGLT2i	Primary outcome
[7]	21	EMPA-REG OUTCOME	2015	3.1	7020	T2DM with established CVD; eGFR ≥ 30 mL/min/1.73 m^2	7020 (100)	706 (10)	Empagliflozin	CV death+non-fatal MI+non-fatal stroke
[8]	22	CANVAS/CANVAS-R	2017	2.4	10142	T2DM with CVD or multiple RFs for CVD; eGFR ≥ 30 mL/min/1.73 m^2	10142 (100)	1461 (14)	Canagliflozin	CV death+non-fatal MI+non-fatal stroke
[9]	23	DECLARE–TIMI58	2019	4.2	17160	T2DM with CVD or multiple RFs for CVD	17160 (100)	1724 (10)	Dapagliflozin	CV death+MI+ischemic stroke
[10]	24	VERTIS-CV	2020	3.5	8246	T2DM with established CVD; eGFR ≥ 30 mL/min/1.73 m^2	8246 (100)	1958 (24)	Ertugliflozin	CV death+non-fatal MI+non-fatal stroke
[11]	25	CREDENCE	2019	2.6	4401	T2DM with CVD+albuminuria (uACR 300–5000); eGFR 30–90 mL/min/1.73 m^2	4401 (100)	652 (15)	Canagliflozin	ESKD, doubling of serum creatinine/death from renal/CV cause
[12]	26, 27	DAPA-CKD	2020	2.4	4304	CVD + albuminuria +/- T2DM (eGFR 25-75 mL/min/1.73 m^2)	2906 (68)	468 (11)	Dapagliflozin	ESKD, sustained ≥ 50% eGFR decline, death from renal or CV cause
[13]	-	SCORED	2020	1.3	10584	T2DM with CVD & RFs for CVD; (GFR) of 30 to 60 mL/min/1.73 m^2	10 584 (100)	3283 (31)	Sotagliflozin	CV death and hospitalizations and urgent visits for HF
[14]	28, 29	DAPA-HF	2019	1.5	4744	HF (EF ≤ 40% & NYHA class II–IV) +/- T2DM; eGFR ≥ 30 mL/min/1.73 m^2	2139 (45)	4744 (100)	Dapagliflozin	Worsening HF and CV death
[15]	31	EMPEROR-Reduced	2020	1.3	3730	HF (EF ≤ 40% & NYHA class II–IV) +/- T2DM	1856 (50)	3730 (100)	Empagliflozin	Composite of HF hospitalization and CV death
[16]		EMPEROR-Preserved	2021	26.2 months	5988	HF (EF > 40% & NYHA class II–IV) +/- T2DM; eGFR ≥ 20 mL/min/1.73 m^2	2938 (49)	5988 (100)	Empagliflozin	Composite of cardiovascular death or hospitalization for HF
[17]	32	SOLOIST-WHF	2020	0.75	1222	T2DM & recent hospitalization for HF; eGFR ≥ 30 mL/min/1.73 m^2	1222 (100)	1222 (100)	Sotagliflozin	CV death and hospitalizations and urgent visits for HF
[18]	30	DELIVER	2022	2.3	6263	HF (EF > 40% & NYHA class II–IV) +/- T2DM	3150 (50)	6263 (100)	Dapagliflozin	Hospitalization for HF or an urgent visit for HF or CV death
[19]		EMPA-KIDNEY	2023	2.0	6609	CKD [eGFR > 20 & < 45 OR 45 < eGFR < 90 mL/min/1.73 m^2 & (proteinuria)]	3040 (46)	658 (10)	Empagliflozin	eGFR to < 10 OR decrease in eGFR of ≥ 40% OR renal death

CKD: Chronic kidney disease; CV: Cardiovascular; CVD: Cardiovascular disease; EF: Ejection fraction; eGFR: Esetimated glomerular filtration rate; HF: Heart failure; MI: myocardial infarction; NYHA: New York Hear Associations classification of heart failure; RF: Risk factor; T2DM: Type 2 diabetes mellitus; SGLT2i: Sodium glucose cotransporter 2 inhibitors; NYHA: New York Heart Associations.

number of major outcomes, the benefit from SGLT2i therapy reaches significant difference in favor of the patients with lower LVEF, at the cutoff point of 30% (Supplementary Figure 4 and Figure 5). Interestingly, repeating the meta-analysis across NYHA classifications showed significantly enhanced therapeutic effects for patients at lower *vs* higher NYHA subclasses. These findings broaden our understanding on the subgroups of the heart failure patients who are likely to benefit most from the SGLT2i.

Death outcomes: Meta-analysis of the impact of SGLT2i on cardiovascular death and all-cause mortality also exhibited benefit with relative but none-significant difference between the subgroups (Figures 3 and 6 and Supplementary Figure 3). No significant survival benefit was detected for patients with HFpEF or in meta-analysis of data from patients with LVEF over 40%. For patients with HFmrEF, gliflozins failed to improve all-cause mortality but improved cardiovascular death just at the borderline significance (Figure 3 and Supplementary Figure 3). This findings rule out SGLT2i as a life-saving medication for HFpEF, and adds it to the list of drugs that have failed to extend life in these tough-to-treat patient population.

Renal specific outcom: Renal outcomes are of special interest in patients with either heart failure or diabetes mellitus and a main focus of attention in most of the reviewed trials. Although previous systematic reviews have shown the benefits of SGLT2i on renal events[20], potential variability in the magnitude of this protection across LVEF rates could have clinical implcations. Interestingly, results of the meta-analysis of composite renal outcomes were consistent with the respective analyses on the cardiovascular outcomes, with the HFrEF patients responding relatively but not significantly better to the treatment than HFpEF, though with an unexpected finding of detecting the most pronounced renal protective effects in patients without heart failure (Figure 7A). This offers that gliflozins' renoprotective effects are unlikely to be associated with their heart failure modifying effects and deserves further investigations.

In the meta-analyses of more specific renal outcomes, acute kidney injury was reduced by 32% in patients with HFrEF compared to only 6% in HFpEF, a difference that was statistically significant (Figure 7B). On the other hand, not every specific renal outcome benefited by SGLT2i, and volume depletion had been shown to be significantly exacerbated by 14% compared to patients receiving placebo. This finding warns of the possible risks to patients receiving gliflozins and emphasisthe need for close monitoring of patients for signs of volume depletion.

Limitations and strengths: There are strengths and limitations associated with this study that warrants further discussion. Different patient populations (exclusive inclusion of patients with diabetes mellitus, chronic kidney disease or heart failure, or variations in the proportions of these patients in different studies), large variations in the follow up times, and inconsistencies in the outcome definitions and reports between the reviewed trials are a number of limitations that could undermine the findings of this study. The principle strength of the current systematic review is providing a stratified outcome analysis across the LVEF stratums of patients with heart failure, and introducing the patient subgroups that are most or least likely to benefit from treatment with gliflozins. Identifying the patient populations that don't benefit the treatment gives a message to the scientific community that further research and developments are needed.

CONCLUSION

In conclusion, compared to placebo, SGLT2i have shown significant therapeutic effects in patients with or without heart failure regarding cardiovascular and renal outcomes. These effects are generally more pronounced in HFrEF patients at the lowest LVEF levels compared to HFpEF, with no survival advantage for the latter group. Patients with lower NYHA classifications were also found to respond more vigorously to the study drugs. Further well-designed studies are needed to determine other potential factors with significant roles in response to gliflozins.

ARTICLE HIGHLIGHTS

Research background

Gliflozins have been shown effective to improve outcomes in patients with heart failure.

Research motivation

Finding the indications for the prescription of gliflozins would help to concentrate research on subgroups that need further research and novel therapeutic approach.

Research objectives

To find the subpopulations of heart failure patients that benefit most from Sodium glucose cotransporter 2 (SGLT2) inhibitors based on their left ventricular ejection fraction levels.

Research methods

A systematic review and meta-analysis of data of patients receiving gliflozin thepay in large and robust randomized double-blind placebo trials was conducted. Meta-analyses were conducted after stratification of the patients based on their left ventricular ejection fraction (LVEF) levels.

Research results
Gliflozins were generally superior to placebo in improving composite outcome of patients with heart failure across LVEF levels. This therapeutic effects were more pronounced in patients with reduced LVEF and low New York Heart Associations classes. No survival benefit was detected for patients with preserved ejection fraction disease.

Research conclusions
Gliflozins are effective in improving the outcome in patients with heart failure.

Research perspectives
Further research would be needed to examine the magnitude of gliflozins' efficacy as well as its cost-effectiveness compared to the other therapeutic options in this patient population.

FOOTNOTES

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