Systematic Review and Meta-Analysis

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Meta-analyzing the factors affecting the efficacy of gliflozins in patients with heart failure based on heart failure trials

Daogen Yin, MS[a], Mei Qiu, MS[a], Xubin Wei, MS[b], Xueyan Duan, BS[a,*]

Abstract

Background: The factors affecting the efficacy of gliflozins in patients with heart failure (HF) are not clear. We aimed to evaluate the effects of 11 important factors on the efficacy of gliflozins in HF patients.

Methods: Randomized trials assessing gliflozins in HF patients were included. The outcome of interest was composite HF outcome, a composite of cardiovascular death, or hospitalization for HF. Meta-analysis was done according to 11 factors: status of type 2 diabetes, sex, use of angiotensin receptor-neprilysin inhibitor, age, history of hospitalization for HF, estimated glomerular filtration rate, body mass index, New York Heart Association (NYHA) class, race, region, and left ventricular ejection fraction.

Results: Compared with placebo, gliflozins reduced the risk of composite HF outcome by 14% in the subgroup of patients with NYHA class III or IV (hazard ratios [HR] 0.86, 95% confidence intervals [CI] 0.75–0.99), by 34% in the subgroup of patients with NYHA class II (HR 0.66, 95% CI 0.59–0.74), and by 85% in the subgroup of patients with NYHA class I (HR 0.15, 95% CI 0.03–0.73). This between-group difference was approximate to statistical significance ($P_{subgroup} = .06$). The benefit of gliflozins in HF patients was not affected by the other 10 factors ($P_{subgroup} \geq .123$).

Conclusions: Gliflozins are applicable for a broad population of HF patients as for preventing HF events, while gliflozins may lead to greater benefits in patients with mild HF than in those with moderate to severe HF.

Abbreviations: ARNI = angiotensin receptor-neprilysin inhibitor, BMI = body mass index, CIs = confidence intervals, CV = cardiovascular, eGFR = estimated glomerular filtration rate, HF = heart failure, HHF = hospitalization for heart failure, HRs = hazard ratios, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, RCTs = randomized controlled trials, SGLT2is = sodium-glucose transporter 2 inhibitors.

Keywords: gliflozins, heart failure, SGLT2is

1. Introduction

Heart failure (HF) is an increasing and major public health concern worldwide.[1–3] Despite current advances in the treatment of HF, HF remains a highly prevalent disease with substantial morbidity and mortality.[4,5] Recently, a novel drug class of sodium-glucose transporter 2 inhibitors (SGLT2is) has garnered considerable attention in terms of treating HF.[5,6] Large randomized trials[7–9] of patients with HF have revealed the evident efficacy of SGLT2is in lowering HF-associated events among HF patients. However, individual trials do not have sufficient statistical power to evaluate HF-associated endpoints with SGLT2is in various subgroups of HF patients with different baseline characteristics.

A prior meta-analysis[10] which included 2 HF trials[7,8] identified that 7 factors related to baseline characteristics of patients, namely, status of type 2 diabetes, sex, use of angiotensin receptor-neprilysin inhibitor (ARNI), age, history of hospitalization for HF (HHF), estimated glomerular filtration rate (eGFR), and body mass index (BMI), did not significantly affect the efficacy of SGLT2is in HF patients; whereas 3 factors, namely, New York Heart Association (NYHA) class, race, and region, had significant effects on that of SGLT2is. However, that meta-analysis[10] failed to include the latest HF trial, namely the SOLOIST-WHF trial[9]; and also failed to evaluate the impact of left ventricular ejection fraction (LVEF) on the effects of gliflozins in HF patients. Thus, we aimed to carry out an updated meta-analysis including all available HF trials of gliflozins, to evaluate whether 11 factors including 10 factors evaluated in Zannad meta-analysis[10] and

Editor: Jose L. Flores-Guerrero.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Yin D, Qiu M, Wei X, Duan X. Meta-analyzing the factors affecting the efficacy of gliflozins in patients with heart failure based on heart failure trials. Medicine 2021;100:28(e26561).

Received: 5 December 2020 / Received in final form: 11 May 2021 / Accepted: 12 June 2021

http://dx.doi.org/10.1097/MD.0000000000026561

LVEF significantly influence the efficacy of gliflozins in HF patients.

2. Methods

We conducted this study of meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[11]

2.1. Search strategy and inclusion criteria

Embase and PubMed were searched using the pre-planned retrieval strategy (see Table S1, Supplemental Digital Content, http://links.lww.com/MD/G265, which illustrates the whole search strategy respectively used in Embase and PubMed). We searched the databases from the creation date of databases to May 1, 2021. The included studies in this meta-analysis were randomized controlled trials (RCTs) which only enrolled HF patients and compared any SGLT2i with placebo in terms of preventing composite HF outcome. The composite HF outcome was defined as a composite of cardiovascular (CV) death or HHF (preferred), or a composite of CV death or hospitalization or an urgent visit for HF (second choice). The conference articles and grey articles were not considered in this meta-analysis.

2.2. Study selection, data extraction, and quality assessment

After literature retrieval, 2 authors independently implemented study selection, followed by data extraction. The pre-planned data to be extracted from included studies contained study type, type of active treatments, type of comparators, and study outcomes from pre-defined subgroups. Subgroups of interest were respectively defined by the following 11 factors: status of type 2 diabetes (with or without type 2 diabetes), sex (men or women), use of ARNI (yes or no), age (≤65 years or >65 years), history of HHF (yes or no), eGFR (<60 mL/min per 1.73 m^2 or ≥60 mL/min per 1.73 m^2), NYHA class (Class III or IV, Class II, or Class I), race (White, Black, or Asian), region (North America, Latin America, Europe, or Asia), BMI (<30 kg/m^2 or ≥30 kg/m^2), and LVEF (<40% or ≥40%). Included RCTs were evaluated for risk of bias independently by 2 authors, according to the Cochrane risk of bias assessment tool.[12] Any disagreements between the 2 authors mentioned above would be discussed with a third author until an agreement was reached.

2.3. Statistical analysis

We extracted hazard ratios (HRs) and 95% confidence intervals (CIs) from included articles, to conduct a meta-analysis using the random-effects inverse-variance model. Statistical heterogeneity was evaluated by I^2 statistic, and this value greater than 50% represents substantial heterogeneity. Subgroup analysis was performed, respectively stratified by the 11 factors of interest. Random-effects meta-regression analysis was done to examine subgroup effects. $P_{subgroup} < .05$ is considered as statistical significance. All data analyses regarding this meta-analysis were conducted in the Stata/MP software (version 16.0).

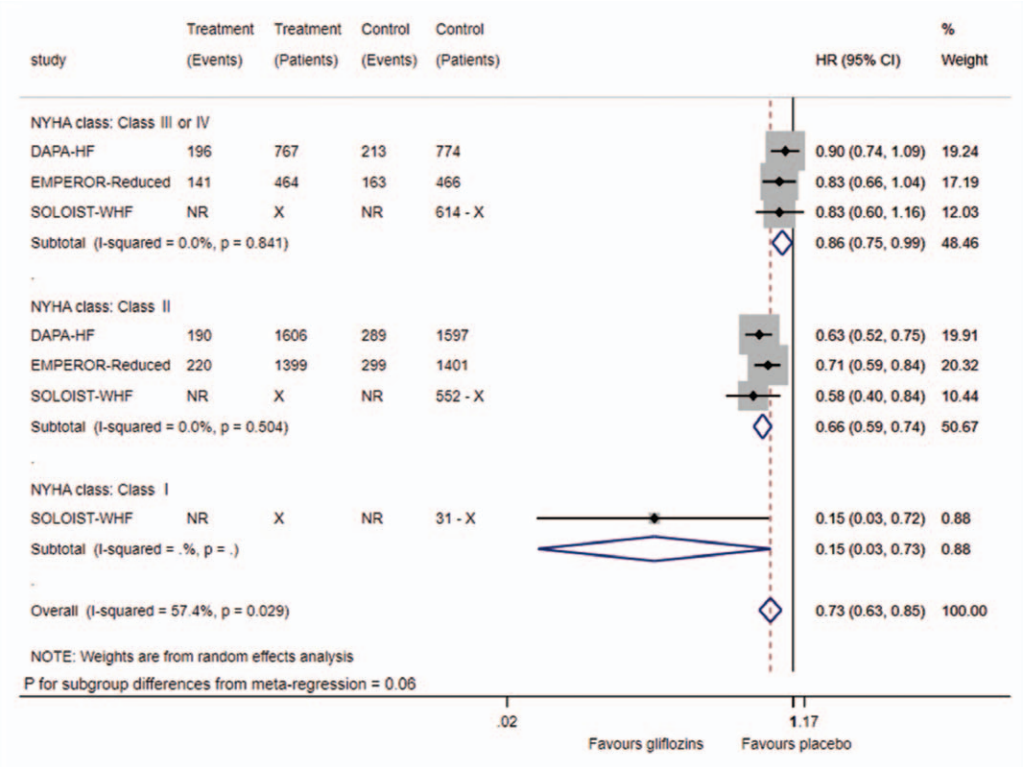

Figure 1. Impact of gliflozins on composite heart failure outcome in heart failure patients, stratified by NYHA class. CI = confidence interval, HR = hazard ratio, NR = not reported in included articles, NYHA = New York Heart Association. "*X*" and "−*X*," indicate that the number of patients in each subgroup was not reported in included articles, but the total number of patients in 2 subgroups was available. For instance, "*X*" and "810 − *X*" means that the total number of patients in 2 subgroups was 810.

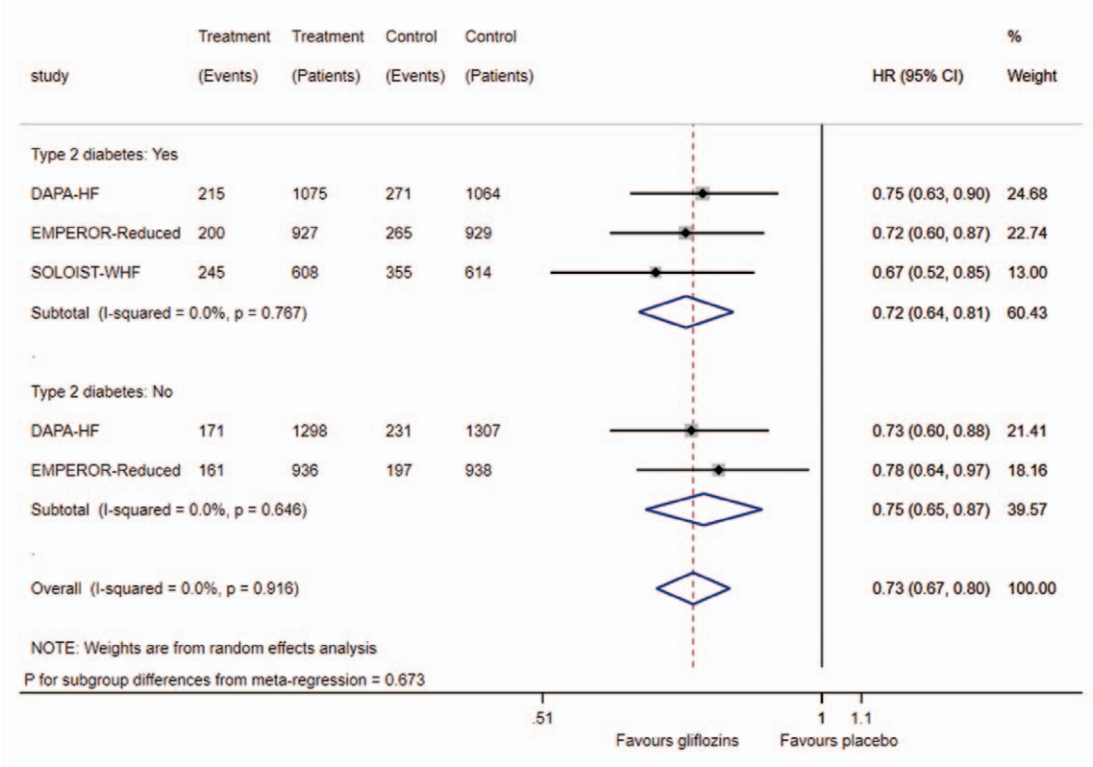

Figure 2. Impact of gliflozins on composite heart failure outcome in heart failure patients, stratified by status of type 2 diabetes. CI = confidence interval, HR = hazard ratio.

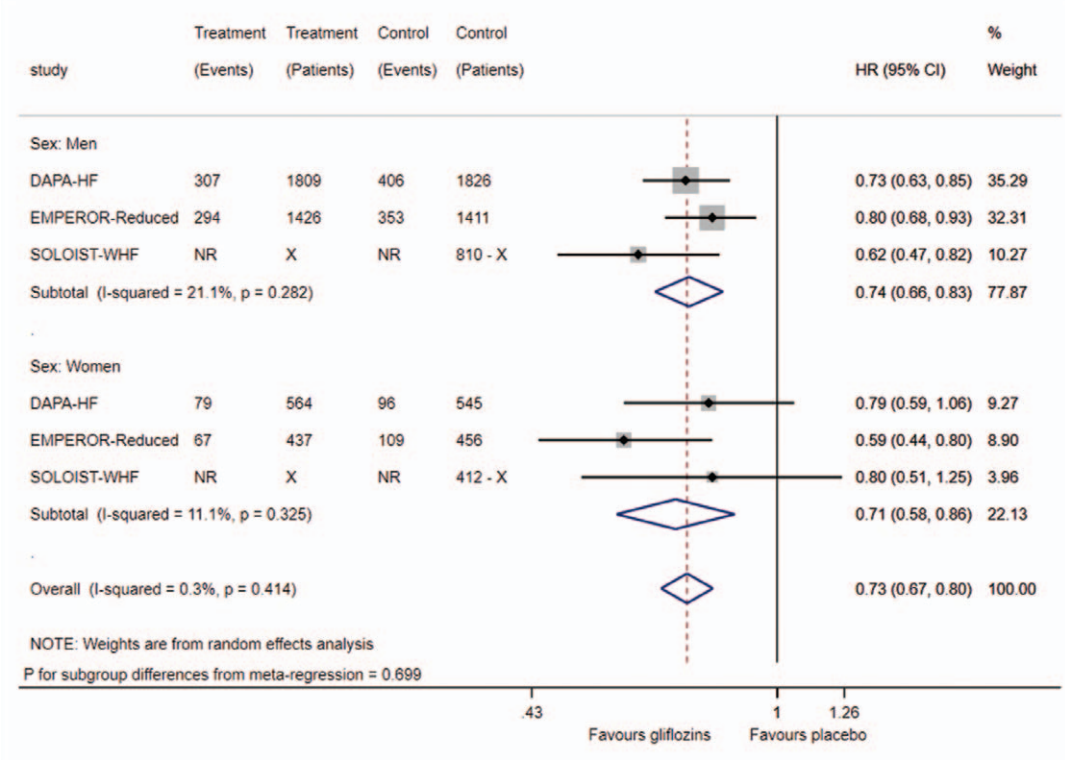

Figure 3. Impact of gliflozins on composite heart failure outcome in heart failure patients, stratified by sex. CI = confidence interval, HR = hazard ratio, NR = not reported in included articles. "*X*" and "−*X*," indicate that the number of patients in each subgroup was not reported in included articles, but the total number of patients in 2 subgroups was available. For instance, "*X*" and "810 − *X*" means that the total number of patients in 2 subgroups was 810.

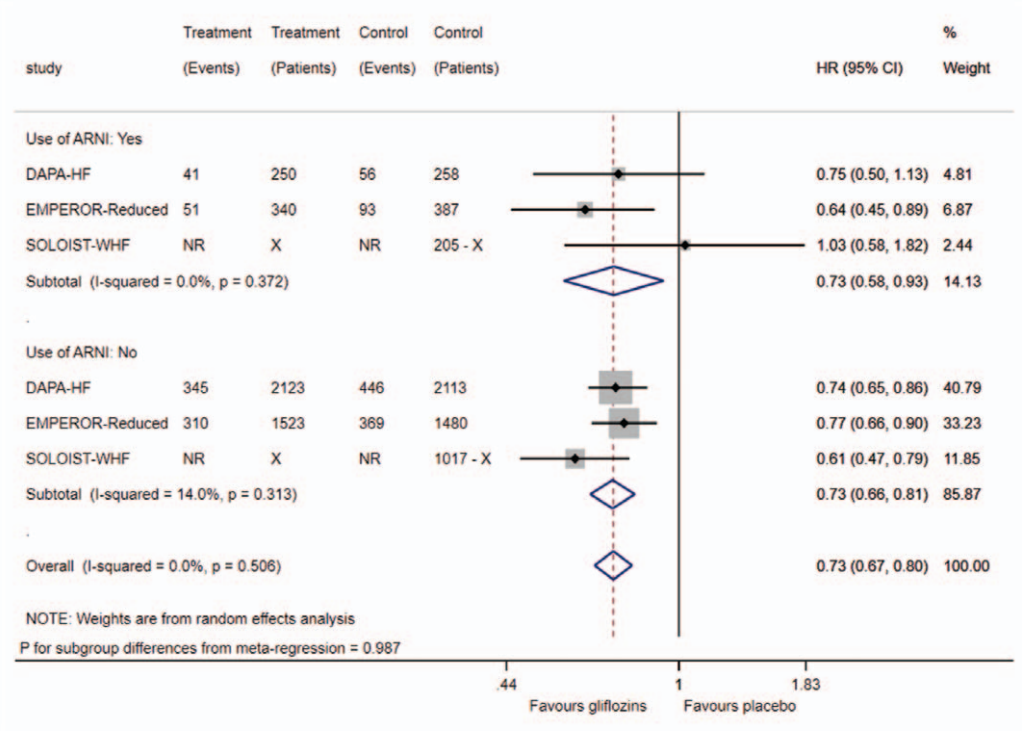

Figure 4. Impact of gliflozins on composite heart failure outcome in heart failure patients, stratified by use of ARNI. ARNI = angiotensin receptor-neprilysin inhibitor, CI = confidence interval, HR = hazard ratio, NR = not reported in included articles. "*X*" and "−*X*," indicate that the number of patients in each subgroup was not reported in included articles, but the total number of patients in 2 subgroups was available. For instance, "*X*" and "810 − *X*" means that the total number of patients in 2 subgroups was 810.

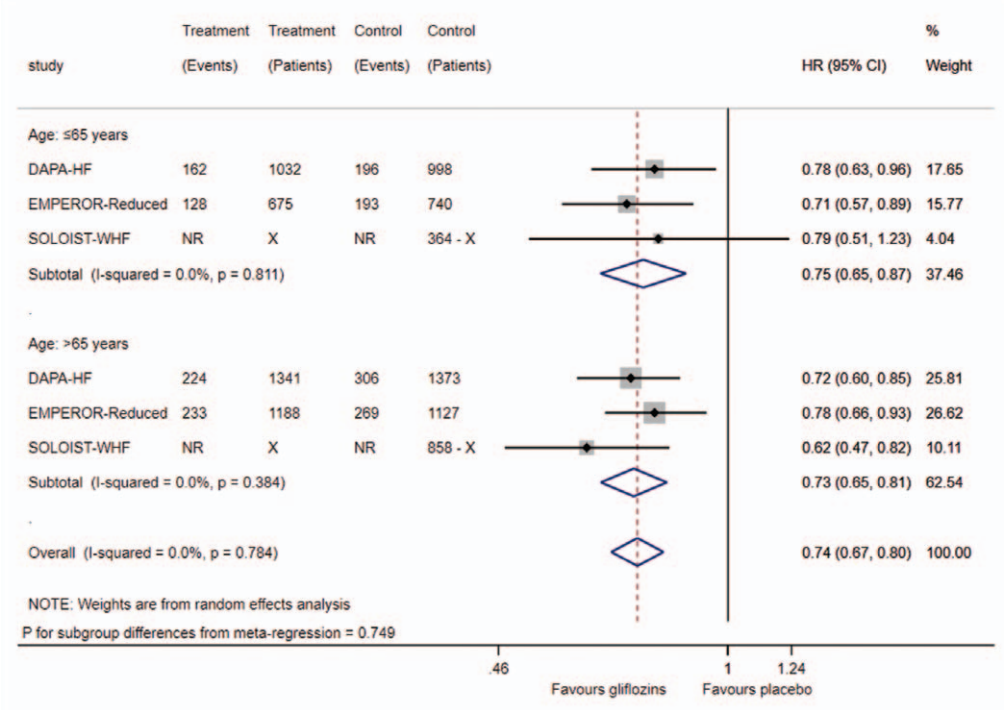

Figure 5. Impact of gliflozins on composite heart failure outcome in heart failure patients, stratified by age. CI = confidence interval, HR = hazard ratio, NR = not reported in included articles. "*X*" and "−*X*," indicate that the number of patients in each subgroup was not reported in included articles, but the total number of patients in 2 subgroups was available. For instance, "*X*" and "810 − *X*" means that the total number of patients in 2 subgroups was 810.

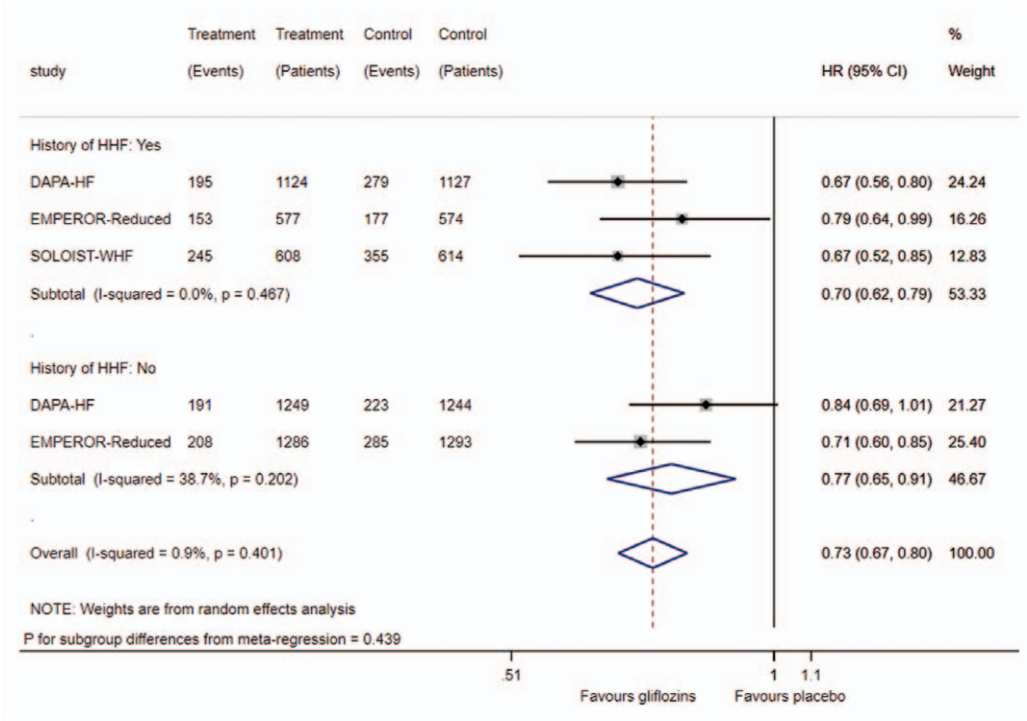

Figure 6. Impact of gliflozins on composite heart failure outcome in heart failure patients, stratified by history of HHF. CI = confidence interval, HHF = hospitalization for heart failure, HR = hazard ratio.

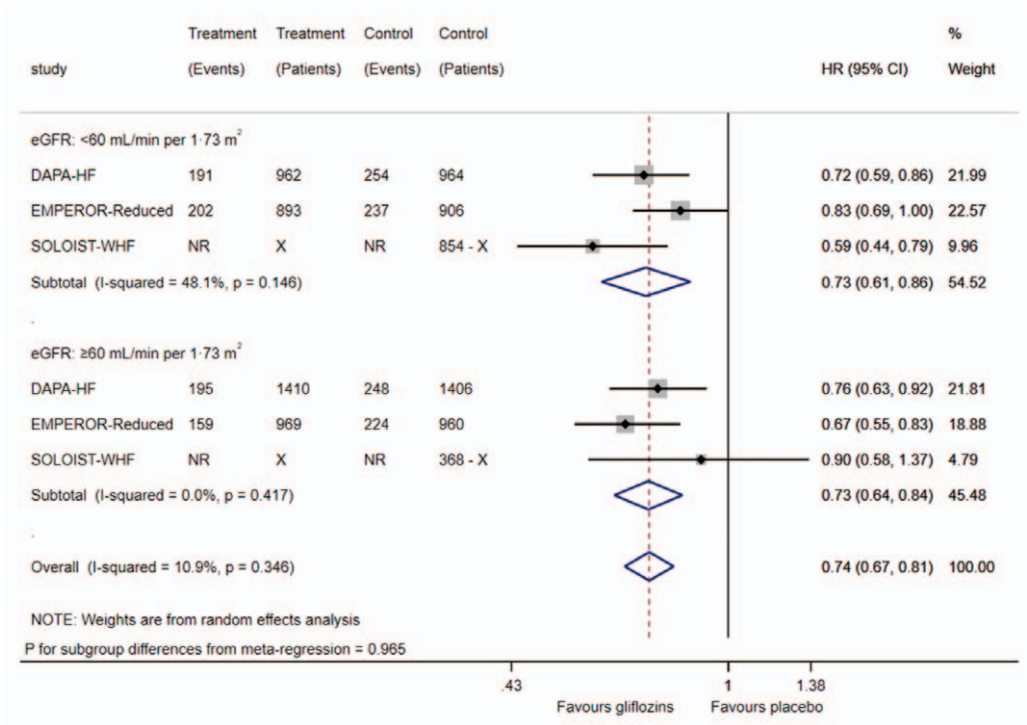

Figure 7. Impact of gliflozins on composite heart failure outcome in heart failure patients, stratified by eGFR. CI = confidence interval, eGFR = estimated glomerular filtration rate, HR = hazard ratio, NR = not reported in included articles. "*X*" and "−*X*," indicate that the number of patients in each subgroup was not reported in included articles, but the total number of patients in 2 subgroups was available. For instance, "*X*" and "810 − *X*" means that the total number of patients in 2 subgroups was 810.

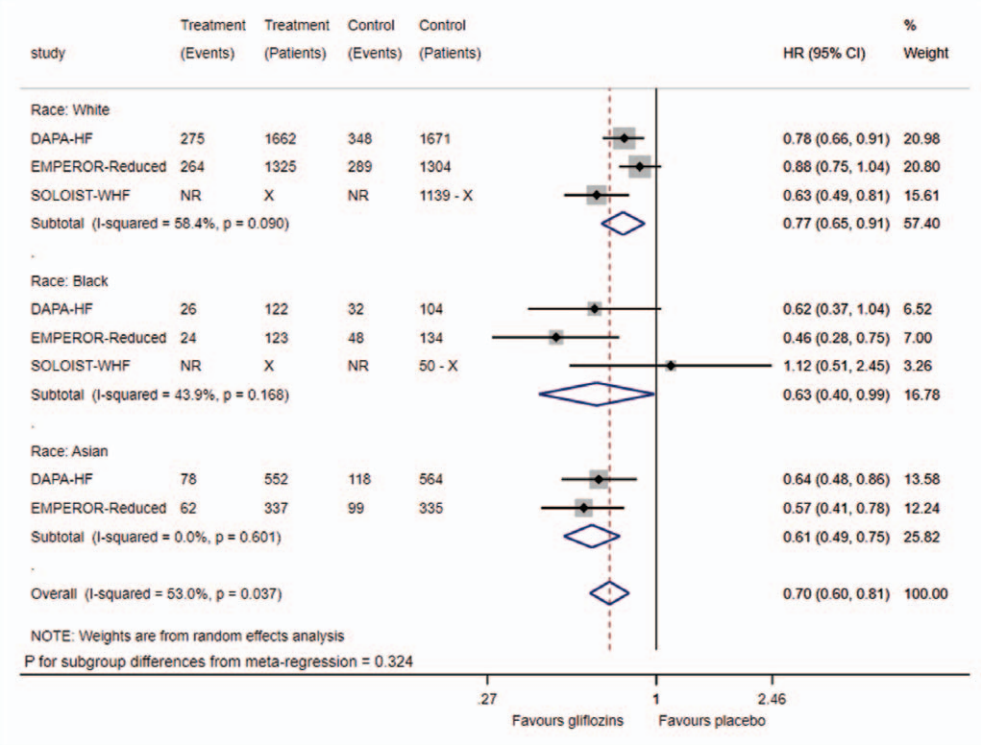

Figure 8. Impact of gliflozins on composite heart failure outcome in heart failure patients, stratified by race. CI = confidence interval, HR = hazard ratio, NR = not reported in included articles. "*X*" and "−*X*," indicate that the number of patients in each subgroup was not reported in included articles, but the total number of patients in 2 subgroups was available. For instance, "*X*" and "810 − *X*" means that the total number of patients in 2 subgroups was 810.

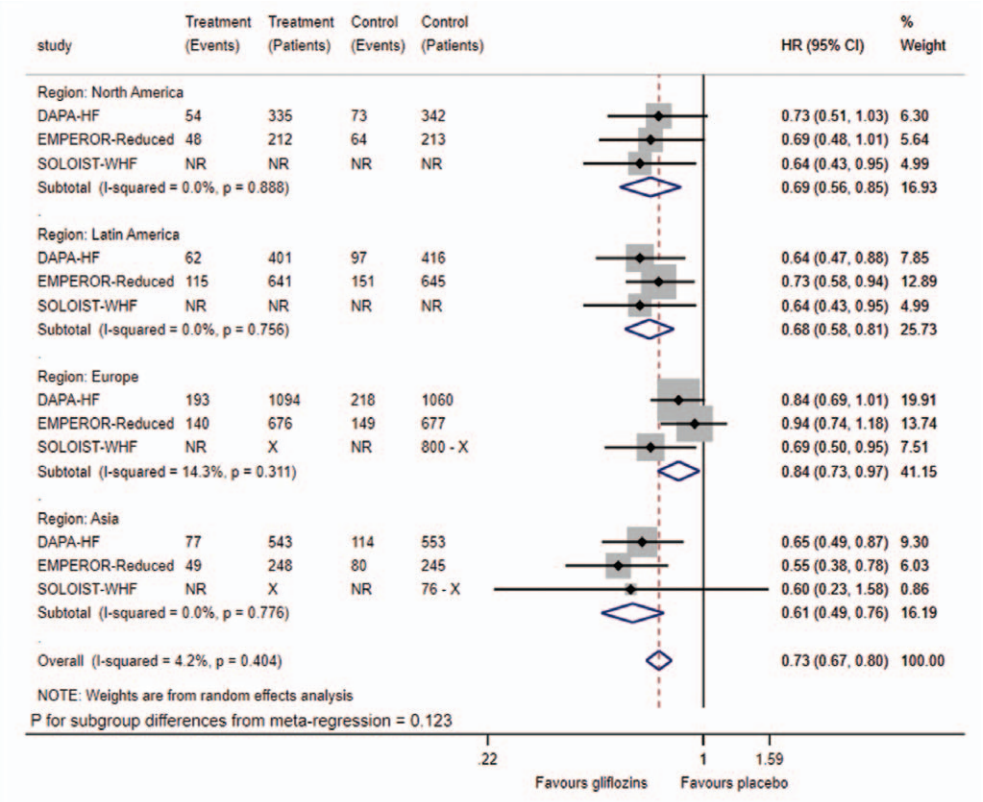

Figure 9. Impact of gliflozins on composite heart failure outcome in heart failure patients, stratified by region. CI = confidence interval, HR = hazard ratio, NR = not reported in included articles. "*X*" and "−*X*," indicate that the number of patients in each subgroup was not reported in included articles, but the total number of patients in 2 subgroups was available. For instance, "*X*" and "810 − *X*" means that the total number of patients in 2 subgroups was 810.

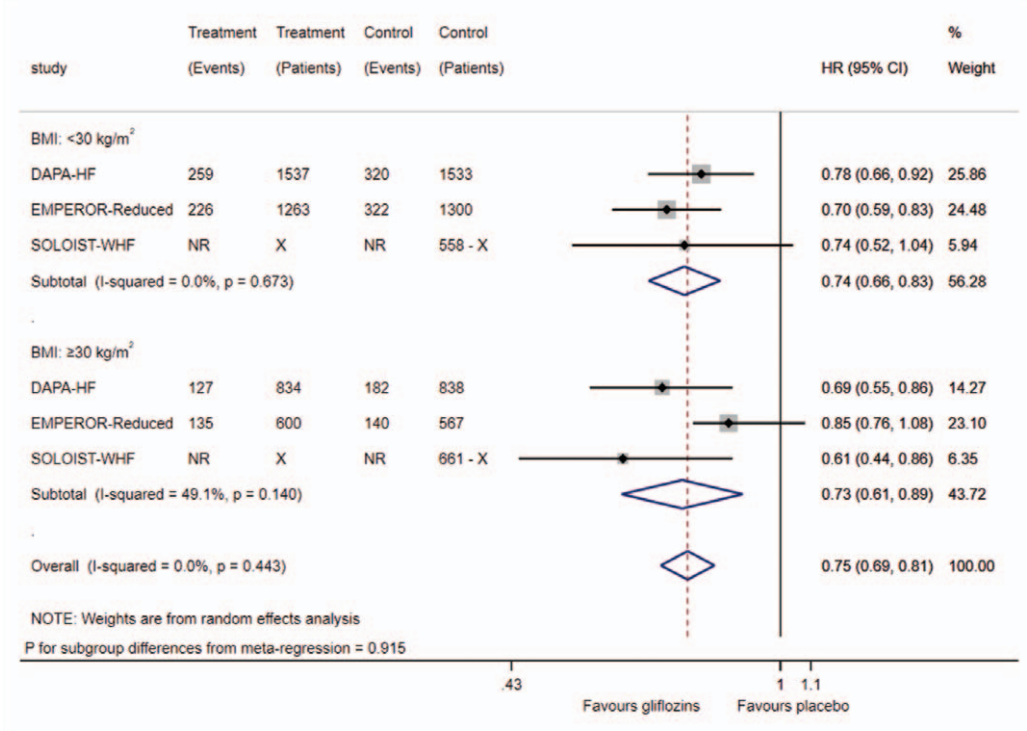

Figure 10. Impact of gliflozins on composite heart failure outcome in heart failure patients, stratified by BMI. BMI = body mass index, CI = confidence interval, HR = hazard ratio, NR = not reported in included articles. "*X*" and "−*X*," indicate that the number of patients in each subgroup was not reported in included articles, but the total number of patients in 2 subgroups was available. For instance, "*X*" and "810 − *X*" means that the total number of patients in 2 subgroups was 810.

2.4. Ethical statement

The data analyzed in this study were extracted from previously published studies, and thus ethical approval was not necessary.

3. Results

3.1. Characteristics of included trials

The process of study selection is detailed in Figure S1, Supplemental Digital Content, http://links.lww.com/MD/G263, which illustrates the whole study selection process. Finally, we included 3 RCTs[7–9] only enrolling HF patients: DAPA-HF[7] (assessing dapagliflozin) and EMPEROR-Reduced[8] (assessing empagliflozin) trials enrolling HF patients regardless of with/without type 2 diabetes and SOLOIST-WHF[9] (assessing sotagliflozin) trial enrolling patients with HF and concomitant type 2 diabetes. The included 3 trials[7–9] involved 9696 HF patients in total. The mean age across included trials ranged from 66.3 to 70.0 years, and the median duration of follow-up ranged from 0.8 to 1.5 years. The risk of bias of included trials was low, as is presented in Figure S2, Supplemental Digital Content, http://links.lww.com/MD/G264, which summarizes the risk of bias of included trials. The original data extracted from included studies are provided in Table S2, Supplemental Digital Content, http://links.lww.com/MD/G266, which illustrates the whole data extracted from included articles.

3.2. Meta-analyses

Figure 1 presents the results of the meta-analysis of the impact of gliflozins on composite HF outcome in 3 subgroups with different NYHA classes. Compared with placebo, gliflozins significantly reduced the risk of composite HF outcome in the subgroup of patients with NYHA class III or IV (HR 0.86, 95% CI 0.75–0.99; P for effect size = .032; $I^2 = 0$), in the subgroup of patients with NYHA class II (HR 0.66, 95% CI 0.59–0.74; P for effect size < .001; $I^2 = 0$), and in the subgroup of patients with NYHA class I (HR 0.15, 95% CI 0.03–0.73; P for effect size = .019; $I^2 = 0$). Gliflozins vs placebo reduced composite HF outcome by 14% in the NYHA class III or IV subgroup, by 34% in the NYHA class II subgroup, and by 85% in the NYHA class I subgroup; and this between-group difference was approximate to statistical significance ($P_{subgroup} = .06$). Compared with placebo, gliflozins significantly reduced composite HF outcome (HR 0.73, 95% CI 0.67–0.80; P for effect size <.001), independent of the following 10 factors: status of type 2 diabetes ($P_{subgroup} = .673$, Fig. 2), sex ($P_{subgroup} = .699$, Fig. 3), use of ARNI ($P_{subgroup} = .987$, Fig. 4), age ($P_{subgroup} = .749$, Fig. 5), history of HHF ($P_{subgroup} = .439$, Fig. 6), eGFR ($P_{subgroup} = .965$, Fig. 7), race ($P_{subgroup} = .324$, Fig. 8), region ($P_{subgroup} = .123$, Fig. 9), BMI ($P_{subgroup} = .915$, Fig. 10), and LVEF ($P_{subgroup} = .737$, Fig. 11).

4. Discussion

This meta-analysis evaluated the impact of 11 important factors (ie, NYHA class, status of type 2 diabetes, sex, use of ARNI, age, history of HHF, eGFR, race, region, BMI, and LVEF) on the efficacy of gliflozins in HF patients. Therefore, it identified that 10 factors (ie, status of type 2 diabetes, sex, use of ARNI, age, history of HHF, eGFR, race, region, BMI, and LVEF) did not significantly affect the efficacy of gliflozins in HF patients ($P_{subgroup} \geq .123$), whereas NYHA class affected the efficacy of

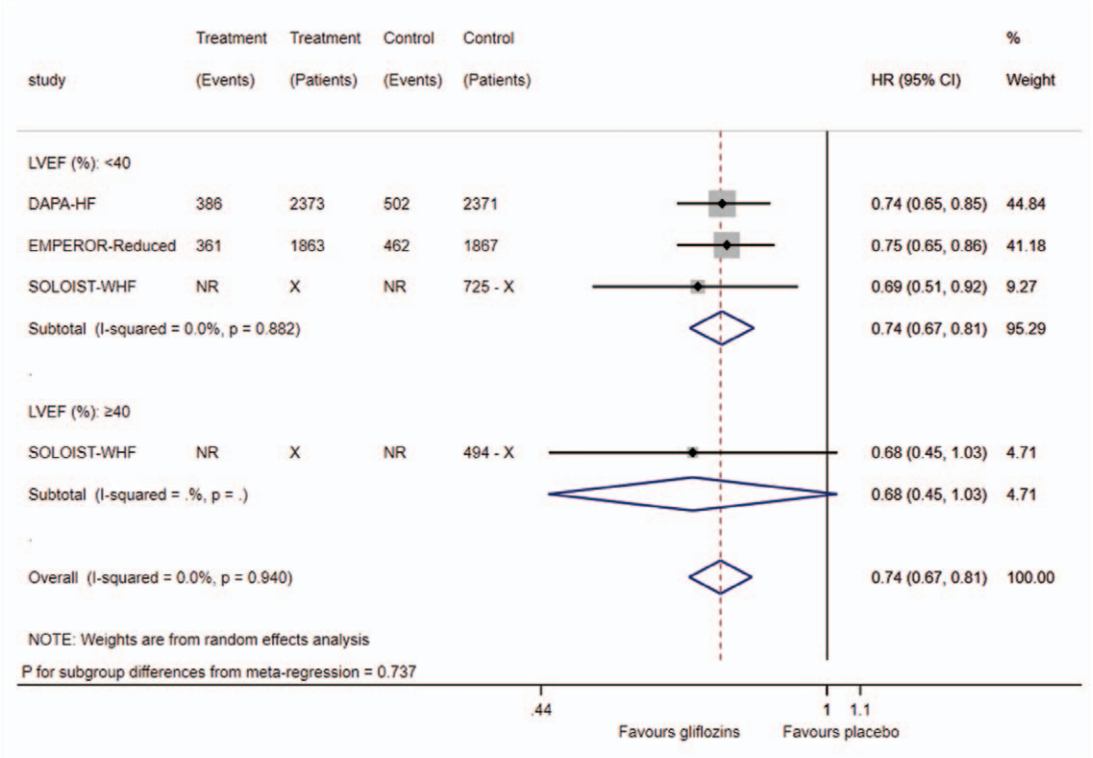

Figure 11. Impact of gliflozins on composite heart failure outcome in heart failure patients, stratified by LVEF. CI = confidence interval, HR = hazard ratio, LVEF = left ventricular ejection fraction, NR = not reported in included articles. "*X*" and "−*X*," indicate that the number of patients in each subgroup was not reported in included articles, but the total number of patients in 2 subgroups was available. For instance, "*X*" and "810 − *X*" means that the total number of patients in 2 subgroups was 810.

gliflozins in HF patients with approximate statistical significance ($P_{subgroup} = .06$). To be more specific, gliflozins led to a greater reduction in composite HF outcome among patients with NYHA class I (vs placebo: an 85% reduction) and among patients with NYHA class II (vs placebo: a 34% reduction) than among patients with NYHA class III or IV (vs placebo: a 14% reduction).

An initial meta-analysis[10] based on 2 HF trials[7,8] of gliflozins suggested the consistent benefits of this drug class for the subgroups based on baseline eGFR, use of ARNI, diabetes, sex, and age, but suggested the treatment-by-subgroup interactions for the subgroups based on race and NYHA class. The present meta-analysis additionally included the latest HF trial of gliflozins, the SOLOIST-WHF trial assessing sotagliflozin, and accordingly provided the up-to-date evidence regarding the factors affecting the efficacy of gliflozins in HF patients.

Several meta-analyses[13–19] confirmed the benefits of gliflozins on CV and/or renal outcomes in HF patients, and moreover, some of them also revealed that these benefits of gliflozins in HF patients were independent of diabetes status,[13–15,19] LVEF,[14] and use of ARNI.[18] However, the previous meta-analyses[13–19] failed to evaluate the impact of most of the factors assessed in the present meta-analysis on the efficacy of gliflozins. Thus, the findings of this meta-analysis will further inform cardiologists and HF patients that gliflozins are applicable for a broad population of HF patients as for preventing HF events, while gliflozins may lead to greater benefits in patients with mild HF than in those with moderate to severe HF.

Two strengths of this study were that the risk of bias of included trials in this meta-analysis was low and that no heterogeneity or only mild heterogeneity was found in most subgroups based on the factors of interest. Oppositely, this study has the following limitations. First, moderate to severe heterogeneity was found in a few subgroups of interest, which needs to be clarified by future meta-analyses of individual patient data. Second, we did not perform the detection of publication bias due to the limited number of included trials. Therefore, we failed to grade the quality of evidence with the Grading of Recommendations Assessment, Development, and Evaluation statement[20] because in this statement[20] several points including the result of publication bias should be considered. Last, the mechanism by which gliflozins lead to greater benefits in patients with mild HF than in those with moderate to severe HF requires to be further investigated.

In conclusion, gliflozins are applicable for a broad population of HF patients as for preventing HF events, while gliflozins may lead to greater benefits in patients with mild HF than in those with moderate to severe HF.

Author contributions

Conceptualization: Xueyan Duan.
Data curation: Daogen Yin, Mei Qiu, Xubin Wei.
Formal analysis: Daogen Yin.
Writing – original draft: Daogen Yin, Mei Qiu.
Writing – review & editing: Xubin Wei, Xueyan Duan.

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