


SGLT2i versus ARNI in heart failure with reduced ejection fraction: a systematic review and meta-analysis

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Abstract

Aims This study aimed to determine the effects of sodium-glucose cotransporter-2 inhibitor (SGLT2i) in heart failure with reduced ejection fraction (HFrEF), compare the effect of SGLT2i with angiotensin receptor neprilysin inhibitor (ARNI), and find whether combination of SGLT2i and ARNI is better than monotherapy.

Methods and results Embase, Medline, and Cochrane Central Registry of Controlled Trials were searched for randomized controlled trials evaluating SGLT2i or ARNI in HFrEF. And a total of six trials were included. SGLT2i was found to significantly reduce the risk of cardiovascular death or hospitalization for heart failure by 27% [hazard ratio (HR) 0.73, 95% confidence interval (CI) 0.67–0.80], hospitalization for heart failure by 31% (HR 0.69, 95% CI 0.62–0.77), cardiovascular death by 16% (HR 0.84, 95% CI 0.74–0.95), and all-cause death by 16% (HR 0.84, 95% CI 0.75–0.94) in HFrEF only with a statistically higher risk of genital infection (risk ratio (RR) 2.78, 95% CI 1.46–5.29). The reduction in cardiovascular death or hospitalization for heart failure was of similar magnitude in patients with or without diabetes mellitus (HR 0.71, 95% CI 0.64–0.80 vs. HR 0.75, 95% CI 0.65–0.87) using SGLT2i. Indirect treatment comparison showed that SGLT2i and ARNI had similar effects on primary outcome (HR 0.93, 95% CI 0.82–1.06). And combination of SGLT2i and ARNI achieved a better prognosis performance (HR 0.68, 95% CI 0.53–0.89) compared with ARNI monotherapy.

Conclusions SGLT2i could safely reduce cardiovascular death or hospitalization for heart failure in HFrEF regardless of diabetes mellitus status. SGLT2i and ARNI demonstrate similar effects, while combination of SGLT2i and ARNI results in a better cardiovascular protective effect.

Keywords Sodium-glucose cotransporter-2 inhibitor; Angiotensin receptor neprilysin inhibitor; Heart failure with reduced ejection fraction; Meta-analysis

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Introduction

Heart failure is defined as cardiac systolic and diastolic dysfunction caused by various factors and characterized by reduced cardiac output and pulmonary and systemic congestion. It has become the most common complication of different heart diseases, such as coronary heart disease, valvular heart disease, and cardiomyopathy. It is also the cause of many disabilities and deaths worldwide. Lots of effort have been devoted to seeking the optimal treatment for heart failure, which could relieve symptoms and improve

prognosis. Diuretics and digitalis, which can reduce the cardiac load and increase contractility of the heart muscle, respectively, are commonly used in patients with heart failure to relieve their congestive symptoms. Beta-blockers, mineralocorticoid receptor antagonists, and angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor inhibitors (ARB) have been used due to their effects on both symptom and prognosis improvement, including enhancing the quality of life, improving ventricular remodelling, and reducing fatality and hospitalization rates.^{1–3} For a time, the combined application of these drugs has been considered to be the best

treatment for patients with heart failure.^{4,5} In recent years, two newly emerged drugs, sodium-glucose cotransporter-2 inhibitor (SGLT2i) and angiotensin receptor neprilysin inhibitor (ARNI), have shown better cardiovascular protective effects in patients with heart failure compared with conventional treatments.^{6,7}

ARNI, which is a combined preparation of valsartan and sacubitril, has been shown to have greater haemodynamic and neurohormonal effects in patients with heart failure. However, ARNI has not demonstrated any significant prevention effects on cardiovascular events in patients with preserved ejection fraction (EF).⁸ In heart failure with reduced ejection fraction (HFrEF), ARNI was superior to ACEI in reducing the risk of cardiovascular death or hospitalization for heart failure.⁹ SGLT2i is a new hypoglycaemic drug that has been found to have a pleiotropic function in addition to lowering serum glucose in patients with diabetes mellitus (DM), including lowering blood pressure, reducing cardiovascular risk, and protecting kidney function.^{10,11} A previous meta-analysis that pooled three large-scale trials, EMPA-REGOUTCOME, DECLARE-TIMI 58, and CANVAS, has found that SGLT2i usage in patients with heart failure history significantly reduced the occurrence of cardiovascular death and hospitalization for heart failure.¹² However, the definition of heart failure history varied among the three trials, and stratified heart failure results were unclear. Whether patients with confirmed HFrEF could also benefit from SGLT2i needed further exploration. However, much evidence for cardiovascular event prevention by SGLT2i came from patients with DM, and it is unclear whether it has the same protective effect in patients with HFrEF without DM. Then whether SGLT2i or ARNI is more effective in reducing cardiovascular event risk has not been investigated yet. Lastly, whether combination usage of these two drugs would achieve better outcomes than a monotherapy is also unclear. The goal of the present systematic review and meta-analysis was to explore these questions in detail, relying upon available evidence.

Methods

Search strategy and selection criteria

Electronic databases, including Embase, PubMed, and Cochrane Central Registry of Controlled Trials (CENTRAL), were searched for randomized controlled trials (RCTs) that evaluated the effects of SGLT2i or ARNI in patients with HFrEF published up to 1 September 2020. The inclusive criteria were as follows: (i) clinical RCTs; (ii) patients with HFrEF with left ventricular EF of <45%; and (iii) trials providing primary outcome data (cardiovascular death or hospitalization for heart failure). The search items included the following: valsartan/sacubitril, angiotensin receptor-neprilysin

inhibitor, LCZ696, sodium-glucose cotransporter-2 inhibitors, empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, tofogliflozin, sotagliflozin, heart failure, reduced ejection fraction, cardiovascular death, and hospitalization for heart failure. A highly sensitive search strategy for identifying RCTs was also used. The detailed search strategies are illustrated in Supporting Information, *Appendix S1*. Three investigators independently reviewed all of the database searches and retrieved the eligible trials by viewing the title and abstract, followed by the full text. Disagreements were resolved by discussion.

Data extraction and quality assessment

Two reviewers independently extracted detailed information from the trials, which included study and patient population characteristics, definition of HFrEF, SGLT2i and ARNI type, comparator type, and clinical outcomes. The extracted data were compared and disagreements were resolved either through discussion or by involving a third party to achieve consensus when necessary. Bias risk evaluation tools from the Cochrane Collaboration for assessment of risk of bias in RCTs were used, which contained the following items: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias.

Statistical analysis

Dichotomous data were computed using hazard ratio (HR) or risk ratio (RR) and 95% confidence interval (CI). The traditional head-to-head meta-analyses were calculated using the inverse variance method with a fixed model. Heterogeneity was assessed using Cochrane Q statistic and Higgins and Thompson I^2 . Heterogeneity was considered to be low if $I^2 = 25%$, moderate if $I^2 = 50%$, or high if $I^2 = 75%$. Comparisons without direct evidence were analysed using the indirect treatment comparison (ITC) with a fixed model. STATA/MP software Version 14.0 (StataCorp, College Station, Texas) was used for both traditional direct head-to-head comparison and indirect comparison result calculation. The use of $P < 0.05$ was considered to indicate statistical significance.

Systematic review registration

We have registered in PROSPERO, and the registered number is CRD 42020205920.

Results

Eligible studies and subject characteristics

The study selection flow chart is presented in *Figure 1*. A total of 566 potential trials were identified from electronic databases. A total of six RCTs (DECLARE-TIMI 58, DAPA-HF, EMPEROR-HF, SOLOIST-WHF, PARADIGM-HF, and PIONEER-HF) were included in the mixed meta-analysis,^{6,7,13–16} of which four trials were directly designed to evaluate the efficacy of SGLT2i in patients with HFrEF and two to investigate the efficacy of ARNI. And the data of DECLARE-TIMI 58 and PIONEER-HF were extracted from the second analyses and SOLOIST-WHF from a post hoc. The definition of HFrEF included an EF of $\leq 40\%$ in four trials, while the remaining trial was defined by $EF < 45\%$. Detailed baseline characteristics information for the included trials is presented in *Table 1*. All trials were in low risk bias. Risk bias assessment summary results were shown in Supporting Information, *Figure S1*.

SGLT2i efficacy evaluation in patients with HFrEF

Meta-analysis was conducted to perform SGLT2i efficacy evaluation in patients with HFrEF using data from four trials, including DECLARE-TIMI 58, DAPA-HF, EMPEROR-HF, and SOLOIST-WHF. The pooled results demonstrated that SGLT2i significantly reduced the risk of composite cardiovascular death or hospitalization for heart failure outcomes by 27% (HR 0.73, 95% CI 0.67–0.80). For individual

outcomes, only the former three trials provided needed information, and the results showed that SGLT2i reduced the occurrence of hospitalization for heart failure by 31% (HR 0.69, 95% CI 0.62–0.77) and cardiovascular death by 16% (HR 0.84, 95% CI 0.74–0.95). The SGLT2i group also demonstrated a lower risk of all-cause death (HR 0.84, 95% CI 0.75–0.94). Because moderate heterogeneity presented in cardiovascular death and all-cause death analyses, a random model was used to compute these data meanwhile. The results also showed a similar SGLT2i prevention effect on cardiovascular death (HR 0.82, 95% CI 0.67–0.99) and all-cause mortality (HR 0.82, 95% CI 0.69–0.98) reduction. Detailed information on clinical outcome evaluation is presented in *Figure 2*.

SGLT2i safety evaluation in patients with HFrEF

Drug safety is a matter of great concern during application. SGLT2i has been considered to be a possible cause of volume depletion, bone fracture, amputation, hypoglycaemia, urinary tract infection, or genital infection. The present meta-analysis found that there were no significant differences between the SGLT2i and control groups in volume depletion (RR 1.11, 95% CI 0.96–1.27), fracture (RR 1.07, 95% CI 0.83–1.37), amputation (RR 1.31, 95% CI 0.81–2.13), major hypoglycaemia (RR 0.92, 95% CI 0.60–1.43), and urinary tract infection (RR 1.03, 95% CI 0.79–1.35). Only the risk of genital infection was significantly higher in the SGLT2i group (RR 2.78, 95% CI 1.46–5.29) (*Figure 3*).

Figure 1 Flow diagram of included trials.

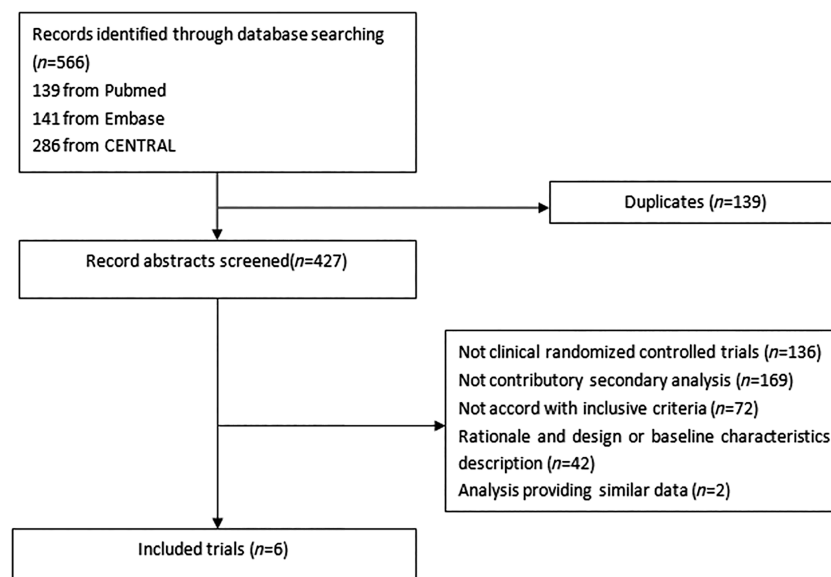
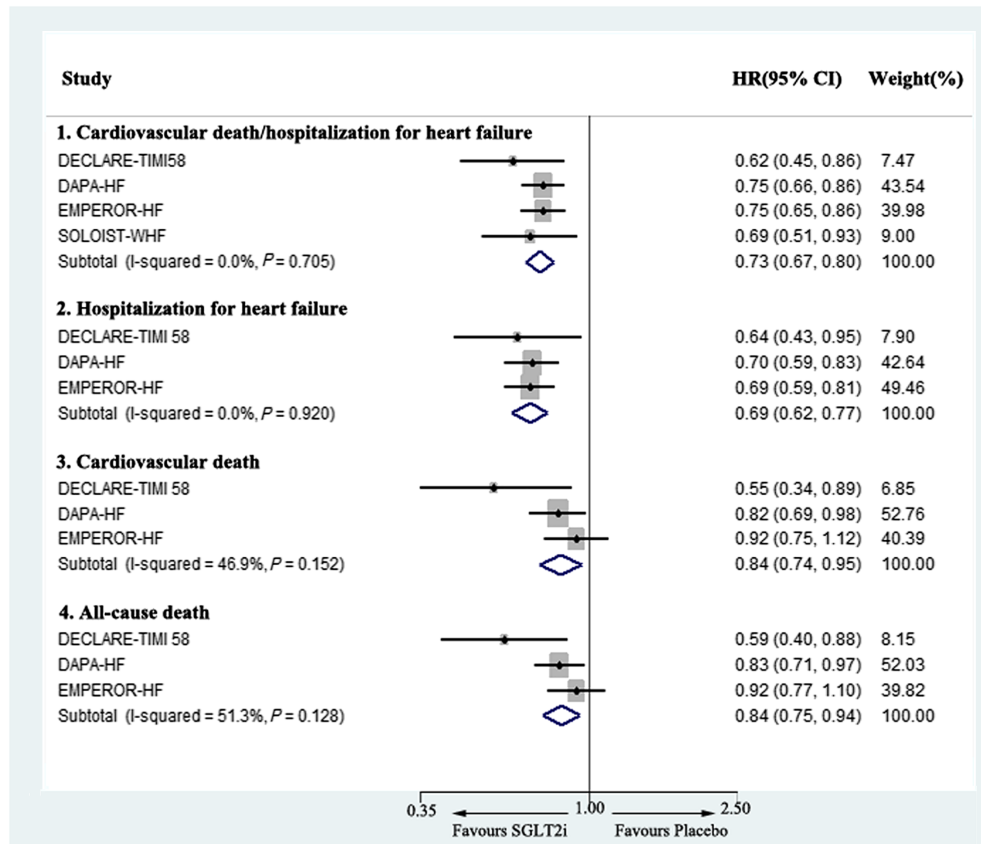


Table 1 Baseline characteristics of included trials

	DECLARE-TIMI 58 ¹⁶	DAPA-HF ⁷	EMPEROR-HF ¹⁴	SOLOIST-WHF ^{a,15}	PARADIGM-HF ⁶	PIONEER-HF ¹³
Comparison	Dapagliflozin 10 mg daily vs. placebo	Dapagliflozin 10 mg daily vs. placebo	Empagliflozin 10 mg daily vs. placebo	Sotagliflozin 200 mg once daily (with a dose increase to 400 mg, depending on side effects) vs. placebo	Sacubitril/valsartan titrated to 200 mg twice daily vs. enalapril titrated to 10 mg twice daily	LCZ696 200 mg twice daily vs. enalapril 10 mg twice daily
Publication year	2019	2019	2020	2020	2014	2018
HFrEF definition	EF < 45%	EF ≤ 40%	EF ≤ 40%	<40%	EF ≤ 40%	EF ≤ 40%
Median left ventricular ejection fraction (%)	38	31.1	27.4	NA	29.5	24.5
Median follow-up	50.4 months	18.2 months	16 months	9 months	27 months	8 weeks
Number of participants	671	4744	3730	725	8399	881
Median age (years)	63	66.3	64.6	NA	63.8	62
Sex, no. (%)						
Men	565 (84.2)	3635 (76.6)	2837 (76.1)	NA	6567 (78.2)	635 (72.1)
Women	106 (15.8)	1109 (23.4)	893 (23.9)	NA	1832 (21.8)	246 (27.9)
NYHA class, no. (%)						
I	217 (32.4)	0	0	NA	389 (4.6)	9 (1)
II	378 (56.4)	3203 (67.5)	2800 (75.1)	NA	5919 (70.5)	222 (25.2)
III	73 (10.8)	1498 (31.6)	910 (24.4)	NA	2018 (24)	552 (62.7)
IV	0	43 (0.9)	20 (0.5)	NA	60 (0.7)	75 (8.5)
Not assessed	3 (0.5)	0	0	NA	13 (0.2)	23 (2.6)
Median NT-proBNP (pg/mL)	NA	1437	1907	NA	1612	2709
Medical history, no. (%)						
Atrial fibrillation	NA	1818 (38.3)	1369 (36.7)	NA	3091 (36.8)	NA
Diabetes mellitus	671 (100)	1983 (41.8)	1856 (49.8)	NA	2907 (34.6)	NA
Main clinical outcomes	Composite of cardiovascular death or hospitalization for heart failure; cardiovascular death; hospitalization for heart failure; all-cause mortality	Composite of worsening heart failure or death from cardiovascular causes; hospitalization for heart failure; cardiovascular death; composite of hospitalization for heart failure or cardiovascular death; death from any cause	Composite of cardiovascular death or hospitalization for heart failure; hospitalization for heart failure; cardiovascular death; death from any cause	Occurrence of either death from cardiovascular causes or hospitalization for heart failure, as described in the trial protocol	Death from cardiovascular causes or a first hospitalization for heart failure; death from cardiovascular causes; first hospitalization for worsening heart failure; death from any cause	Composite of major clinical events; death from any cause; rehospitalization for heart failure; composite of death and rehospitalization for heart failure

EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction; NA, not applicable; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association. ^aPost hoc.

Figure 2 Meta-analysis of the effects of SGLT2i on the composite of cardiovascular death or hospitalization for heart failure, cardiovascular death, hospitalization for heart failure, and all-cause death in heart failure with reduced ejection fraction. CI, confidence interval; HR, hazard ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitor.



SGLT2i in patients with or without DM

SGLT2i was first used as a drug for glucose control. It was unexpectedly found to have cardiovascular protective effects in patients with DM with a risk of cardiovascular disease. Previous research has also demonstrated a lower risk of cardiovascular death or hospitalization for heart failure in patients with HFrEF. However, whether the results in patients with HFrEF with or without DM would be the same needed additional exploration. The present pooled results showed that a reduction in cardiovascular death or hospitalization for heart failure was of similar magnitude in patients with HFrEF with or without DM, with a slightly lower HR in patients with DM (HR 0.71, 95% CI 0.64–0.80) when compared with patients without DM (HR 0.75, 95% CI 0.65–0.87) (Figure 4).

SGLT2i and ARNI comparison in patients with HFrEF

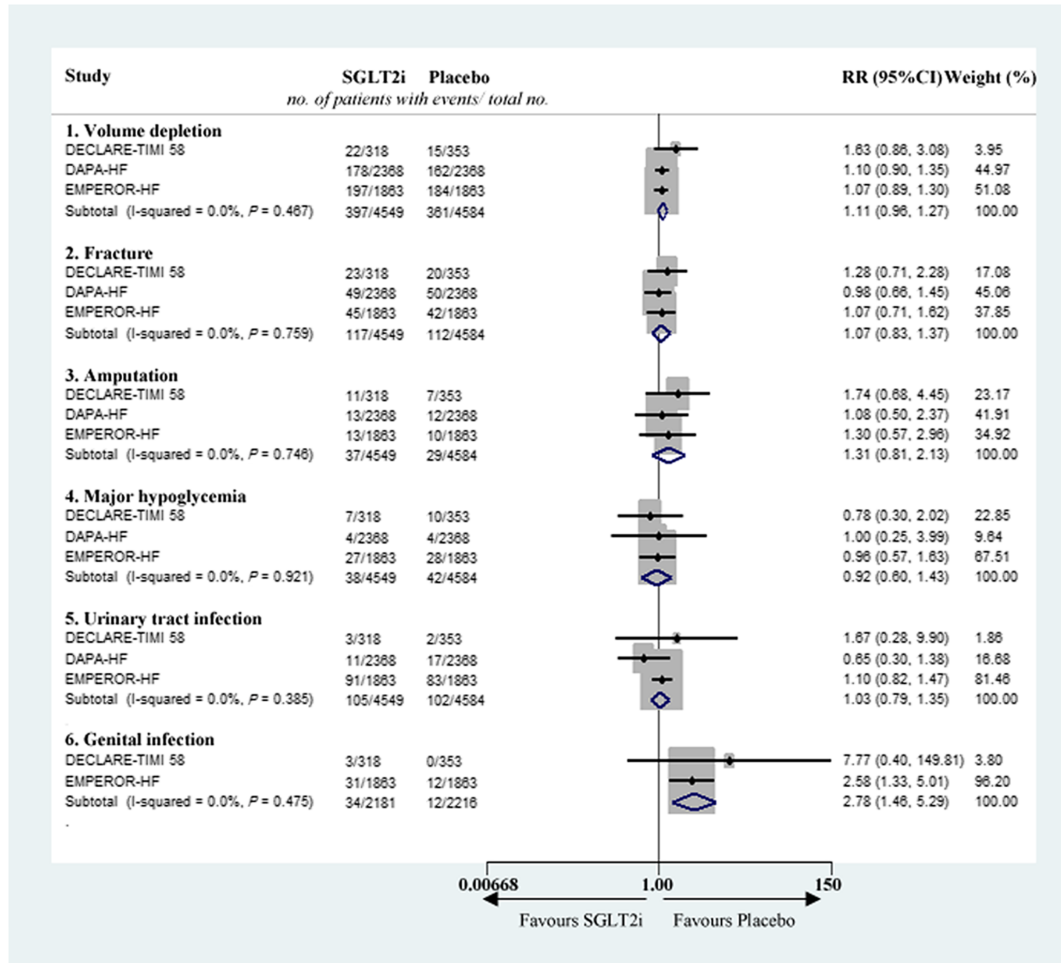
Both SGLT2i and ARNI have been shown to reduce the risk of cardiovascular events in patients with HFrEF. However, it

remains unclear which one possesses a better prevention effect. This section was designed to explore this issue. Because there was no direct comparison evidence existed between these two therapy strategies, data analysis using the ITC method was performed with data from the included six trials (four for SGLT2i and two for ARNI). The comparator treatment for all included trials was recommended therapy for heart failure (containing ACEI/ARB, mineralocorticoid receptor antagonists, beta-blockers, diuretics, digitalis, etc.). In order to ensure the accuracy of the result, patients in DAPA-HF and EMPEROR-HF using SGLT2i in combination with ARNI were excluded. Pooled results showed that SGLT2i and ARNI had similar effects on cardiovascular death or hospitalization for heart failure prevention in patients with HFrEF (HR 0.93, 95% CI 0.82–1.06) without significant heterogeneity ($P = 0.28$) (Figure 5).

Combination application of SGLT2i and ARNI versus ARNI monotherapy

Because the aforementioned results showed similar prevention effects of SGLT2i and ARNI in patients with HFrEF, it

Figure 3 Meta-analysis of safety evaluation of SGLT2i on volume depletion, fracture, amputation, major hypoglycaemia, urinary tract infection, and genital infection. CI, confidence interval; RR, risk ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitor.



was worth investigating whether combination usage of these two drugs would achieve better outcomes than a monotherapy. In the DAPA-HF trial, 508 included patients (250 in the SGLT2i group and 258 in the control group) had taken ARNI instead of ACEI/ARB upon randomization. In the EMPEROR-HF trial, 727 patients (340 vs. 387 in the treatment and control groups, respectively) were initially prescribed ARNI. The DAPA-HF trial showed no significant difference in cardiovascular death or hospitalization for heart failure between SGLT2i + ARNI group and ARNI monotherapy group, while the EMPEROR-HF trial demonstrated a significant reduction in the primary outcome in the SGLT2i + ARNI group. Pooled meta-analysis data also indicated a lower occurrence of cardiovascular death or hospitalization for heart failure in patients with HFrEF taking both SGLT2i and ARNI (HR 0.68, 95% CI 0.53–0.89) (Figure 6).

Discussion

The present meta-analysis identified excellent SGLT2i effects on cardiovascular death or hospitalization for heart failure prevention in patients with HFrEF, regardless of DM status. No significant differences were found in volume depletion, fracture, amputation, major hypoglycaemia, and urinary tract infection, except for genital infection. In addition, SGLT2i and ARNI had similar effects on reduction of cardiovascular death or hospitalization for heart failure risk. Combination use of SGLT2i and ARNI had a lower occurrence of cardiovascular death or hospitalization for heart failure compared with the ARNI-only treatment.

SGLT2i has been found to be able to lower the level of both haemoglobin A1c and fasting blood glucose without relying on insulin secretion and sensitization.¹⁷ It also plays a

Figure 4 Meta-analysis of the effects of SGLT2i on the composite of cardiovascular death or hospitalization for heart failure in heart failure with reduced ejection fraction with or without DM. CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

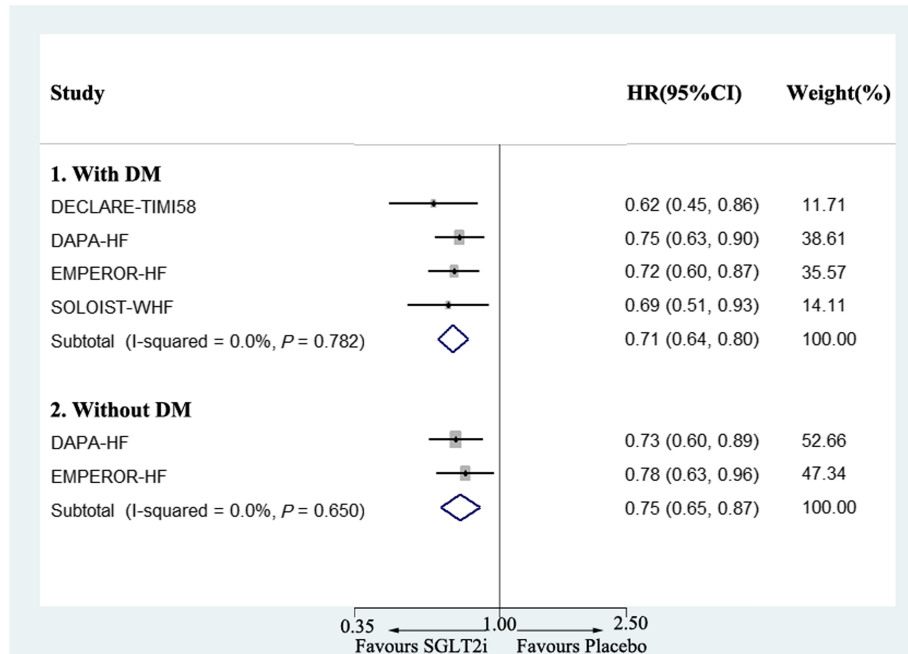
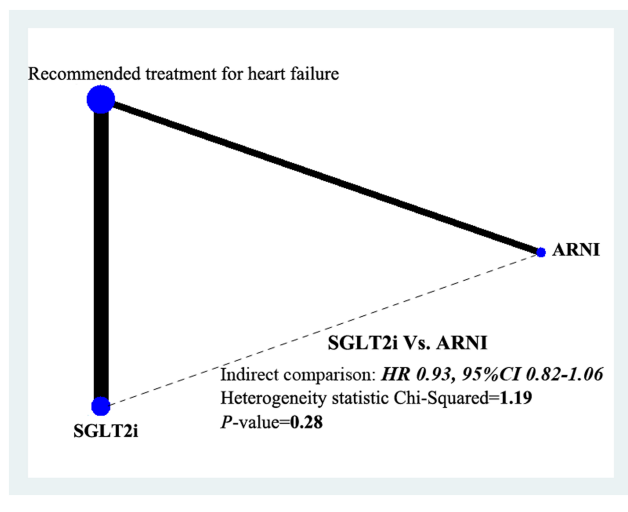


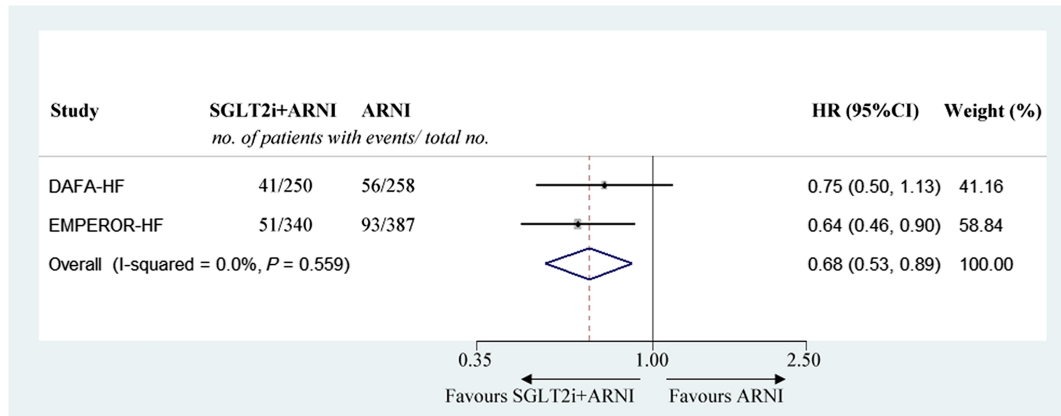
Figure 5 Network plot for the effects comparison between SGLT2i and ARNI on the composite of cardiovascular death or hospitalization for heart failure in heart failure with reduced ejection fraction with indirect comparison evidence from six included trials. CI, confidence interval; HR, hazard ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitor.



role in weight and visceral fat loss in patients with DM.¹⁸ SGLT2i has been safely used in patients with DM without causing hypoglycaemia. EMPA-REGOUTCOME was the first

large-scale RCT evaluating the effects of empagliflozin on cardiovascular morbidity and mortality in patients with type 2 diabetes and high cardiovascular risk. It demonstrated that empagliflozin prominently reduced the risk of death from cardiovascular causes and nonfatal myocardial infarction or nonfatal stroke by 14% (HR 0.86, 95% CI 0.74–0.99).¹⁷ Then more studies were conducted to explore the effects of SGLT2i on cardiovascular protection. The CANVAS study demonstrated similar results, where patients treated with canagliflozin had a lower risk of cardiovascular events (HR 0.86, 95% CI 0.75–0.97).¹⁹ However, the DECLARE-TIMI 58 trial did not show a lower rate of a composite of major adverse cardiovascular events (HR 0.93, 95% CI 0.84–1.03) in dapagliflozin group.¹⁹ All aforementioned three trials presented a significantly lower risk of cardiovascular death or hospitalization for heart failure and individual hospitalization. However, the effects on cardiovascular death remained controversial. Only the EMPA-REG OUTCOME trial showed a significant reduction in cardiovascular death, while the CANVAS and DECLARE-TIMI 58 trials demonstrated no significant differences in cardiovascular death prevention between the treatment and control groups. The three trials included 10–14% of patients with history of heart failure. After pooling these data together, the results demonstrated a lower rate of cardiovascular death or hospitalization for heart failure in the SGLT2i treatment group, indicating that patients with history of heart failure can also benefit from SGLT2i.¹²

Figure 6 Meta-analysis of comparing the effects of combined use of SGLT2i and ARNI versus monotherapy with ARNI on the composite of cardiovascular death or hospitalization for heart failure in heart failure with reduced ejection fraction. CI, confidence interval; HR, hazard ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitor.



Subgroup analysis in the DECLARE-TIMI 58 trial, in which patients were stratified on the basis of EF value, demonstrated a lower risk of cardiovascular events (including cardiovascular death, hospitalization for heart failure, and all-cause death) in patients with HFrEF taking dapagliflozin.²⁰ In order to explore whether SGLT2i had similar effects on patients with HFrEF regardless of DM status, the DAPA-HF and EMPEROR-HF trials were conducted.^{7,14} Their results showed that both dapagliflozin and empagliflozin had a lower rate of composite for cardiovascular death or hospitalization for heart failure and hospitalization for heart failure individually. However, there were differences in death risk (both cardiovascular death and all-cause death) between the two trials. SGLT2i reduced the risk of cardiovascular death by 18% and all-cause mortality by 17% with statistical significance in the DAPA-HF trial compared with only 8% for each in the EMPEROR-HF trial. The present meta-analysis pooled results demonstrated a lower risk of both hospitalization for heart failure and death in the SGLT2i treatment group. However, moderate heterogeneity was present. The mean EF values in the DECLARE-TIMI 58, DAPA-HF, and EMPEROR-HF trials were 38%, 31%, and 27%, respectively. It was difficult to determine whether patients with a higher EF value might benefit more from SGLT2i prescription in preventing cardiovascular and all-cause mortality, because patients with a lower EF might have a poorer prognosis originally. Trials designed to confirm the different effects of SGLT2i on death prevention among patients with stratified EF values are in need.

Both patients with HFrEF with and without DM can benefit from SGLT2i in preventing cardiovascular death or hospitalization for heart failure, indicating that SGLT2i might improve HFrEF patient outcomes via pleiotropic effects, not just by lowering blood glucose levels. SGLT2i administration can lower tissue glucose disposal and

stimulate lipolysis, lipid oxidation, and ketogenesis, and this fuel utilization shift might have a role in improving myocardial metabolism and cardiac function.²¹ Animal experiments have shown that SGLT2i can reduce left ventricular mass, left ventricular end-diastolic volume, and left ventricular end-systolic volume.²² A direct SGLT2i effect on human cardiac myofibroblast phenotype and function by attenuating myofibroblast activity and cell-mediated collagen remodeling has been shown,²³ indicating that SGLT2i might improve ventricular constitution by attenuating fibrosis. In addition, SGLT2i has also been shown to have effects on blood pressure control, weight loss, and osmotic diuresis, which synergistically improve cardiac function.^{11,24,25} Interestingly, SGLT2i has been approved to significantly reduce the cardiovascular events in patients with HFrEF, but it has no prevention effects on patients with heart failure without reduced EF. The second analysis of DECLARE-TIMI 58 showed that SGLT2i reduced the incidence of cardiovascular death, hospitalization for heart failure, and all-cause mortality in HFrEF (EF < 45%) with statistical significance but not in patients with EF \geq 45%.¹⁶ The same result was also noticed in the SOLOIST-WHF trial; sotagliflozin group demonstrated lower risk of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure with statistical significance in patients with EF < 40%. But for patients with heart failure with EF of 40% to <50% or EF \geq 50%, there is no significant difference found between the sotagliflozin group and the control group.¹⁵

As another new pharmacological therapy for heart failure emerged in recent years, ARNI has been proven to be superior to ACEI in reducing the risk of cardiovascular events in patients with HFrEF.^{6,13} Compared with enalapril, ARNI reduces the composite of death from cardiovascular causes or hospitalization for heart failure by 20% (HR 0.8, 95% CI

0.73–0.87) and death from any cause by 16% (HR 0.84, 95% CI 0.76–0.93) in PARADIGM-HF.⁶ These findings are also confirmed by real-world studies.²⁶ There is a research showed that optimal implementation of ARNI therapy was empirically estimated to prevent nearly 28 484 deaths (range 18 230–41 017) each year.²⁷ The side effects that need to pay attention during application of ARNI are hypotension and non-serious angioedema.⁶ Due to the excellent effects on morbidity and mortality prevention, ARNI has been recommended (class I recommendation, moderate-quality evidence) to patients with HFrEF by several guidelines for heart failure management.^{28,29}

Both SGLT2i and ARNI show excellent cardiovascular protective effects in patients with HFrEF, and it is quite intriguing and meaningful to determine which therapy is better. Our trial is the first meta-analysis to evaluate this issue using existing indirect comparison data and ITC method. The result hints that SGLT2i and ARNI may serve as a substitute for each other in reducing cardiovascular death or hospitalization for heart failure in patients with HFrEF. But this conclusion may be more convincing with some direct comparison evidences. Because SGLT2i and ARNI take effect through different mechanisms, whether combined use of SGLT2i and ARNI could reinforce the cardiovascular protective effects with fewer side effects becomes a topic of great interest. Our study obtained the data of 1235 patients from DAPA-HF and EMPEROR-HF, and found that combination therapy was significantly better than ARNI monotherapy in patients with HFrEF. This finding provides us a new therapeutic regimen, which may help to obtain better prognosis in patients with HFrEF in the future.

Several limitations should be acknowledged in the present analysis. Firstly, aggregated study-level data were used other than individual participant data. Secondly, the inclusion criteria for HFrEF patients in PIONEER-HF trial was slightly different from others, and its follow-up period was much shorter, which might result in some internal heterogeneity. Lastly, the exact definition of primary outcomes varied among the included trials, but only slightly.

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Conclusions

SGLT2i can significantly and safely reduce the risk of cardiovascular death or hospitalization for heart failure in patients with HFrEF regardless of DM status. SGLT2i and ARNI have similar effects on cardiovascular death or hospitalization for heart failure prevention. And the combined use of SGLT2i and ARNI results in a better cardiovascular protective effect.

Conflict of interest

Yuling Yan, Bin Liu, Jun Du, Jing Wang, Xiaodong Jing, Yajie Liu, Songbai Deng, Jianlin Du, and Qiang She declare that they have no conflict of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Supporting information.

Data S1. Supporting information.

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