SGLT2i-treated heart failure patients with a reduced ejection fraction: A meta-analysis

QIANG YE and KELAN ZHA

Department of Cardiology, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan 646000, P.R. China

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Abstract. The aim of this study was to investigate the effects of SGLT2 inhibitors (SGLT2i) on patients with heart failure (HF) and reduced ejection fraction, with or without diabetes. A systematic review of randomized controlled trials (RCTs) was conducted, comparing SGLT2i to a placebo for HF patients. Relevant studies from PubMed, Web of Science, and EMBASE were searched from inception to July 2021, without any language restrictions. The pooled effect was estimated using the odds ratio (OR) and 95% confidence interval (CI). Depending on the heterogeneity test results, either random effects or fixed effects models were selected to estimate the pooled effects. Sensitivity analysis was conducted by gradually removing each study to evaluate the results' stability. A total of 5 RCT studies were included in the analysis. The fixed-effects model demonstrated that the patients in the SGLT2i group had a lower risk of hospitalization for HF/cardiovascular death (OR=0.72; 95% CI, 0.67-0.78), P<0.0001; I^2=0.0%, P=0.966), cardiovascular death (OR=0.84, 95% CI (0.77, 0.93), P<0.0001; I^2=0.0%, P=0.633), hospitalization for HF (OR=0.69, 95% CI (0.63, 0.75), P<0.0001; I2=0.0%, P=0.933), and all-cause mortality (OR=0.79, 95% CI (0.71, 0.89), P<0.0001; I^2=3.3%, P=0.376) compared to the placebo group. Sensitivity analysis showed that the pooled effect value remained stable within the corresponding range, even after each study was gradually removed. In conclusion, SGLT2i can reduce the risk of HF hospitalization, cardiovascular death, and all-cause mortality in patients with HF and a reduced ejection fraction, regardless of the presence or absence of diabetes.

Introduction

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a type of medication developed to control diabetic hyperglycemia that works by reducing renal glucose reabsorption and inducing glycosuria (1,2). Recent clinical trials have shown that SGLT2i is effective in reducing mortality and hospitalization due to heart failure (HF) in patients with type 2 diabetes, regardless of whether they have HF (3,4). In patients with diabetes, SGLT2i reduced the risk of all-cause death and hospitalization for HF by 23% (5).

Studies have also shown that SGLT2i has a positive effect on renal function, urinary sodium excretion, myocardial metabolism, and vascular function, making it beneficial for patients with heart disease (6,7). Preliminary randomized clinical trials (RCTs) authorized by the US Food and Drug Administration have also demonstrated the cardiovascular safety of SGLT2i. Empagliflozin, a commonly used SGLT2i, has been shown to reduce hospitalization rates, cardiovascular death, and biomarkers in patients with HF (8). RCTs have evaluated the effects of SGLT2i in patients with HF for improving symptoms, mortality, hospitalization, and the levels of relevant biomarkers (9,10). Based on data from mechanistic studies and preliminary clinical trials, larger clinical trials with SGLT2i are currently investigating the potential use of SGLT2i in patients with HF with and without diabetes mellitus type 2 (T2D) (11). In previous large sample trials, empagliflozin also showed different outcomes in combination with cardiovascular endpoints (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke); it was found that the incidence of primary composite cardiovascular outcomes and of death from any cause was lower after empagliflozin treatment (12). Subjects with diabetes and atherosclerosis were at greater risk of hospitalization for HF and vascular disease (13). Therefore, there is a need for more effective and safer drug treatments. According to the existing RCT studies, the present meta-analysis aimed to further elucidate the role of SGLT2i in patients with preexisting HF with a reduced ejection fraction with or without diabetes.

Methods

Search strategy. The present meta-analysis was performed in accordance with the established Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (14). The relevant literature published from conception of a database to July 2021 was comprehensively and systematically searched across multiple databases, including PubMed, Embase, Web of Science, and other databases without language

Correspondence to: Dr Qiang Ye, Department of Cardiology, The Affiliated Hospital of Southwest Medical University, 25 Taiping Street, Luzhou, Sichuan 646000, P.R. China
Email: art006023@yeah.net

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limitations. A range of relevant keywords were used, including 'Sodium-glucose cotransporter-2 inhibitors' or 'SGLT2i' or 'canagliflozin' or 'dapagliflozin' or 'empagliflozin' or 'ertugliflozin' and 'HF' or 'HF with reduced ejection fraction' and 'randomized clinical trials' or 'RCTs'.

Inclusion and exclusion criteria. The following were the criteria for inclusion of studies: i) RCTs; ii) study population consisted of patients with HF and a low ejection fraction with or without diabetes [left ventricular ejection fraction (LVEF) <40%]; iii) treatment measures had to be SGLT2i and placebo-controlled; iv) the primary outcome indicators were hospitalization for HF/cardiovascular death, cardiovascular death, hospitalization for HF and all causes mortality. The exclusion criteria were: i) Duplicate articles; ii) conference abstracts, comments, letters, systematic reviews, and meta-analysis; iii) non-RCTs; and iv) studies where major research indicators were not reported.

Data extraction. The researchers independently searched the studies and extracted the data, including trial design, patient baseline data statistics, and clinical results.

Quality assessment. The literature included underwent a risk bias assessment using the RCT bias risk assessment tool provided by the Cochrane Collaboration (15). The bias assessment included various domains, such as random sequence generation and allocation concealment, blinding of patients and investigators, blinding of outcome assessors, flawed outcome data, and selective reporting.

Statistical analysis. Statistical analyses were undertaken using Stata statistical software (version 15.0; StataCorp, LLC). Review Manager version 5.3 (Cochrane Collaboration) was used to assess the risk of bias. The combined effect was estimated using the odds ratio (OR) and 95% confidence interval (CI). Based on the heterogeneity test, random or fixed effects models were selected to estimate the pooled effects. The Q test and I^2 test were used to estimate inter-study heterogeneity. When P>0.1 and $I^2 \leq 50\%$, the fixed effects model was adopted, whereas when P<0.1 and $I^2 \geq 0\%$, the random effects model was adopted. Each study was gradually removed for sensitivity analysis, which evaluated the stability of the results. Due to the small number of studies included in the present study, funnel plots and Egger's test were not used for publication bias analysis. P<0.05 was considered to indicate a statistically significant difference.

Results

Search results. A total of 181 studies were retrieved and identified, and 11 duplicate studies were eliminated. The titles and abstracts were read, after which 145 irrelevant studies were excluded, and 25 full papers were read. According to the inclusion and exclusion criteria, 20 studies were excluded, and 5 studies were included in the present meta-analysis. The flow chart of the study selection process is shown in Fig. 1. Information on the included studies is presented in Table I. The mean age of patients was >60 years. The types of SGLT2i used in the included studies were empagliflozin and dapagliflozin, with the same intervention dose of 10 mg. The mean LVEF% was <40%. The intervention time was >12 months.

Study characteristics and risk of bias. The results of the risk bias evaluation in studies are shown in Fig. 2. The 5 studies included were all RCTs performed with a clear randomization method. Stratified seclusion, implementation of blinding, data integrity without loss, and other risks were unknown. The included studies were all low-risk and of high quality.

Pooled effect estimation of the risk of hospitalization for HF/cardiovascular death. The pooled effect estimation of the risk of hospitalization for HF/cardiovascular death is shown in Fig. 3A. The fixed-effect model showed that the risk of hospitalization for HF/cardiovascular death in the SGLT2i group was lower than that in the placebo control group and the differences were statistically significant [OR=0.72, 95% CI (0.67-0.78), P<0.0001; I^2=0.0%, P=0.966]. There was no heterogeneity among the studies. A subgroup analysis of the patients with or without diabetes found that the risk of hospitalization for HF/cardiovascular death was lower than that of the placebo control group and the difference was statistically significant [OR=0.73, 95% CI (0.67-0.80), P<0.0001; I^2=0.0%, P=0.937; and OR=0.70, 95% CI (0.61-0.80), P<0.0001; I^2=0.0%, P=0.729]. Analysis of sensitivity results is shown in Fig. 3B. Each study was gradually removed, and the pooled effect value was within the range of the 95% CI (0.67-0.78) and the results of the study were stable.

Pooled effect estimation of the risk of cardiovascular death. The pooled effect estimation of the risk of cardiovascular death is shown in Fig. 4A. The fixed-effect model showed that the risk of cardiovascular death in the SGLT2i group was lower than that in the placebo control group and the difference was statistically significant [OR=0.84, 95% CI (0.77-0.93), P<0.0001; I^2=0.0%, P=0.633]. There was no heterogeneity among the studies. A subgroup analysis of patients with or without diabetes found that the risk of cardiovascular death was lower than that of placebo control and the difference was statistically significant [OR=0.86, 95% CI (0.77-0.97), P=0.013; I^2=0.0%, P=0.804; and OR=0.80, 95% CI (0.67-0.95), P<0.0001; I^2=28.7%, P=0.013]. The results of the sensitivity analysis are shown in Fig. 4B. Each study was gradually removed, and the pooled effect value was within the range of the 95% CI (0.77-0.93), and the results of the study were stable.

Pooled effect estimation of the risk of hospitalization for HF. The pooled effect estimation of the risk of hospitalization for HF is shown in Fig. 5A. The fixed-effect model showed that the risk of hospitalization for HF in the SGLT2i group was lower than that in the placebo control group and the differences were statistically significant [OR=0.69, 95% CI (0.63-0.75), P<0.0001; I^2=0.0%, P=0.933]. There was no heterogeneity among the studies. A subgroup analysis of patients with or without diabetes found that the risk of hospitalization for HF was lower than that of the placebo controls and the differences were statistically significant [OR=0.68, 95% CI (0.61-0.76), P<0.0001; I^2=0.0%, P=0.850; and OR=0.70, 95% CI (0.60-0.82), P<0.0001; I^2=0.0%, P=0.613]. The results of the sensitivity analysis are shown in Fig. 5B. Each study was

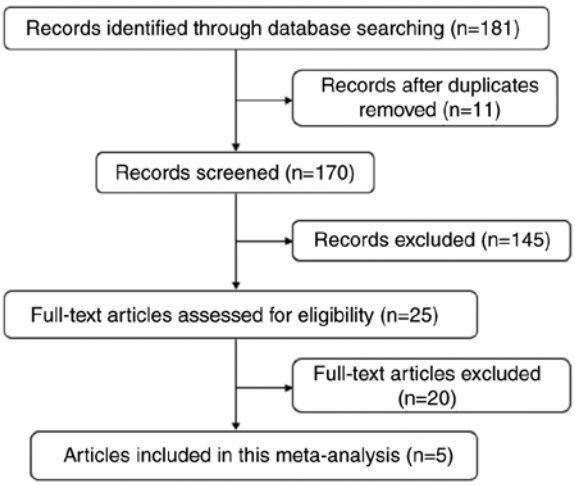

Figure 1. Flowchart of the study selection process.

gradually removed, and the pooled effect value was within the range of the 95% CI (0.63-0.75), and the results of the study were stable.

Pooled effect estimation of all-cause mortality. The pooled effect estimate of all-cause mortality is shown in Fig. 6A. The fixed-effect model showed that the risk of all-cause mortality in the SGLT2i group was lower than that in the placebo control group and the difference was statistically significant [OR=0.79, 95% CI (0.71-0.89), P<0.0001; I^2=3.3%, P=0.376]. There was no heterogeneity among the studies. A subgroup analysis of patients with or without diabetes found that all-cause mortality was lower than that of placebo controls and the difference was statistically significant [OR=0.71, 95% CI (0.58-0.88), P<0.0001; I^2=27.6%, P=0.240; and OR=0.84, 95% CI (0.73-0.96), P=0.012; I^2=0.0%, P=0.659]. The results of the sensitivity analysis are shown in Fig. 6B. Each study was gradually removed, and the pooled effect value was within the range of the 95% CI (0.71-0.89) and the results of the study were stable.

Discussion

Studies have shown that SGLT2 is present in early proximal brush like margin tubules and functions by reabsorbing almost all filtered glucose (16,17). SGLT2i blocks glucose reabsorption of proximal convoluted tubules, further leading to secondary osmosis and then sodium diuretic and diuretic effects (16). The SGLT2i dagliflozin not only lowers blood glucose but has also shown a positive effect on patients with HF in recent studies (18). Blood sugar levels drop due to the increased glucose excretion. In the case of hypoglycemia, a reduction in mortality from HF was observed in cohort studies (19). Given the low levels of SGLT2 in cardiomyocytes, there is evidence that SGLT2-independent effects are likely to be achieved by the off-target effect of SGLT2 in the myocardium (20). It is well established that individuals with diabetes have a higher risk of cardiovascular complications, and appropriate diabetes control helps to minimize these complications. SGLT2i has been shown to be an effective treatment for diabetes with favorable renal side effects and improved cardiovascular

Table I. Baseline characteristics of the included studies.

First author, year	Study type	Diabetes status	HFrEF sample, n I/C	Intervention	Control	Age, years, I/C	Mean LVEF%, I/C	Duration of treatment	(Refs.)
Packer *et al*, 2020	Random double-blind trail	No diabetes	1,863/1,867	Empagliflozin 10 mg daily	Placebo	67.2±10.8/ 66.5±11.2	27.7±6.0/ 27.2±6.1	16 months	(8)
Kato *et al*, 2019	Randomized double-blind multinational, phase IIIb study	Diabetes	318/353	Dapagliflozin 10 mg	Placebo	63(58,68)/-	38(30,40)/-	11.8±7.8 years	(32)
Petrie *et al*, 2020	Double-blind, randomized, parallel-group study	No diabetes Diabetes	1,298/1307 1,075/1064	Dapagliflozin 10 mg	Placebo	66.0±11.8/66.4±11.5 66.3±9.9/66.7±9.8	31.0±6.8/30.8±6.9 31.4±6.6/31.0±6.8	30 months	(33)
Anker *et al*, 2021	Randomized, double blind, parallel-group, placebo-controlled	No diabetes Diabetes	936/938 927/929	Empagliflozin 10 mg	Placebo	67.6±11.6/66.3±10.0 66.8±10.0/66.6±10.3	27.9±6.0/27.2±6.0 27.6±6.0/27.2±6.1	-	(34)
McMurray *et al*, 2019	Phase III, random, placebo-controlled trial	No diabetes	2,373/2,371	Dapagliflozin 10 mg	Placebo	66.2±11.0/ 66.5±10.8	31.2±6.7/ 30.9±6.9	18.2 months	(35)

I, intervention; C, control; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.

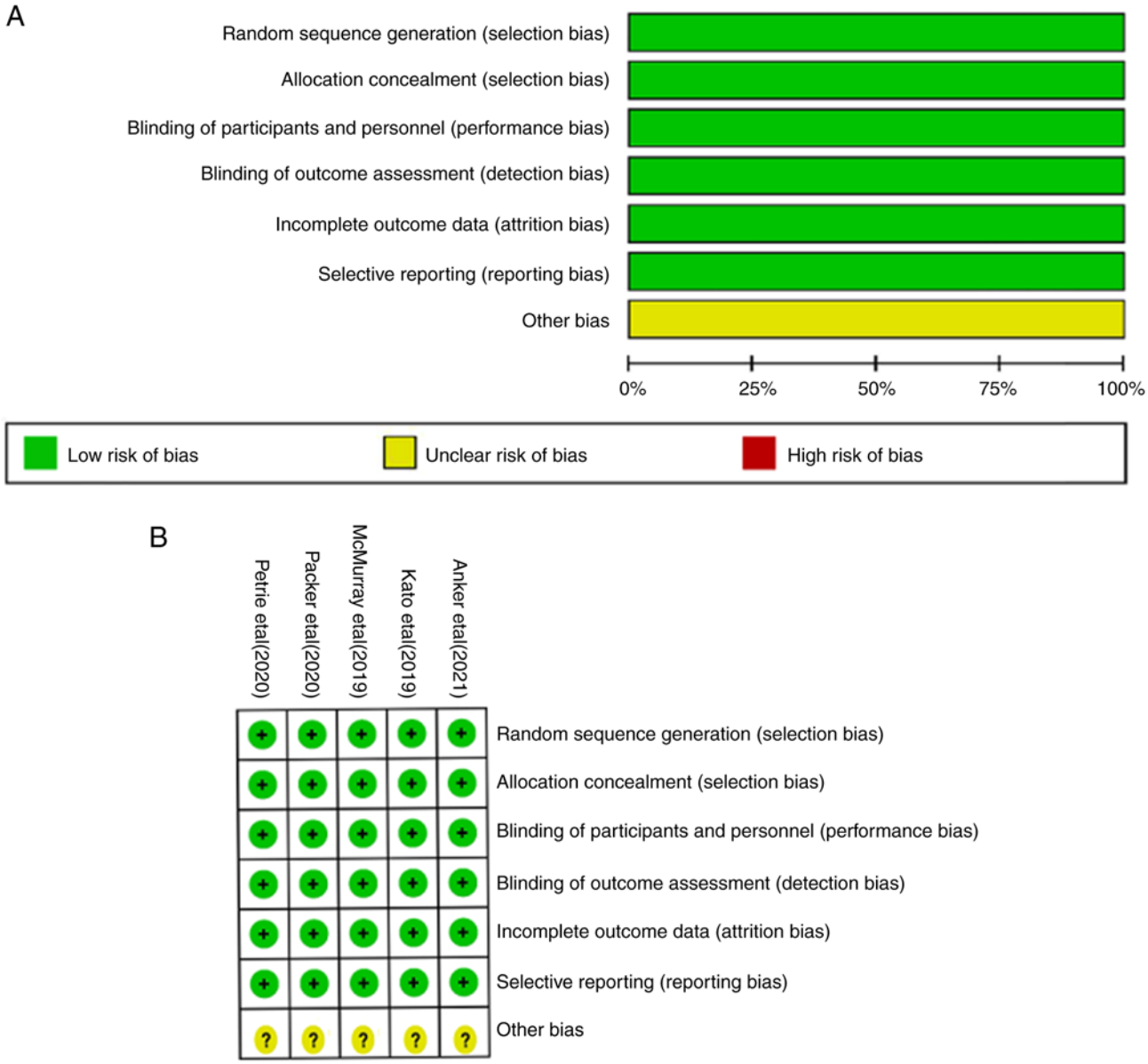

Figure 2. Assessment of the risk of bias of the included studies. (A) Risk of bias graph: The review authors' assessment of the risk of bias items presented as percentages across all included studies. (B) Risk of bias summary: The review authors' judgements regarding the risk of bias items for each included study.

outcomes (5,21,22). The present meta-analysis focused on treating patients with known HF and showed a significant reduction in cardiovascular death or hospitalization for HF compared with placebo groups.

The role of cardiologists and HF specialists in diabetes management is changing with the introduction of SGLT2i and its improvement in cardiovascular outcomes in both diabetic and non-diabetic patients. Studies have shown equivalent efficacy with SGLT2i therapy in patients without diabetes or with glycated hemoglobin levels ≥5.7% and <5.7% (23,24). Consistent with the above research results, the results of the present meta-analysis showed that for patients with a reduced ejection fraction, regardless of whether they had diabetes or not, SGLT2i had a better effect on the treatment of HF. Salah *et al* (25) showed that the use of SGLT2i in AHF patients reduced the risk of HF readmission by 48% and improved Kansas City Cardiomyopathy Questionnaire (KCCQ) scale scores. Spertus *et al* (26) showed that SGLT2i in HF patients could alleviate HF symptoms regardless of whether patients had diabetes as was observed based on the increased KCCQ Total Symptom Score. The present meta-analysis included patients with HF with or without diabetes mellitus and an ejection fraction of <40%, and it was concluded that cardiovascular death or hospitalization for HF was significantly lower in patients treated with SGLT2i. In this systematic review and meta-analysis, 5 RCTs with a total of 34,108 participants were included. The fixed-effect model showed that hospitalization/cardiovascular death, cardiovascular death, hospitalization for HF, and death from all causes in patients treated with SGLT2i were significantly lower than those treated with placebo. That is, the SGLT2i group exhibited significantly better outcomes compared with the placebo group. In addition, dapagliflozin reduced the risk of death and worsening of HF and alleviated the symptoms of the disease in patients of different ages (27).

Treatment with SGLT2i in patients with T2D has been shown to reduce the risk of hospitalization for HF and

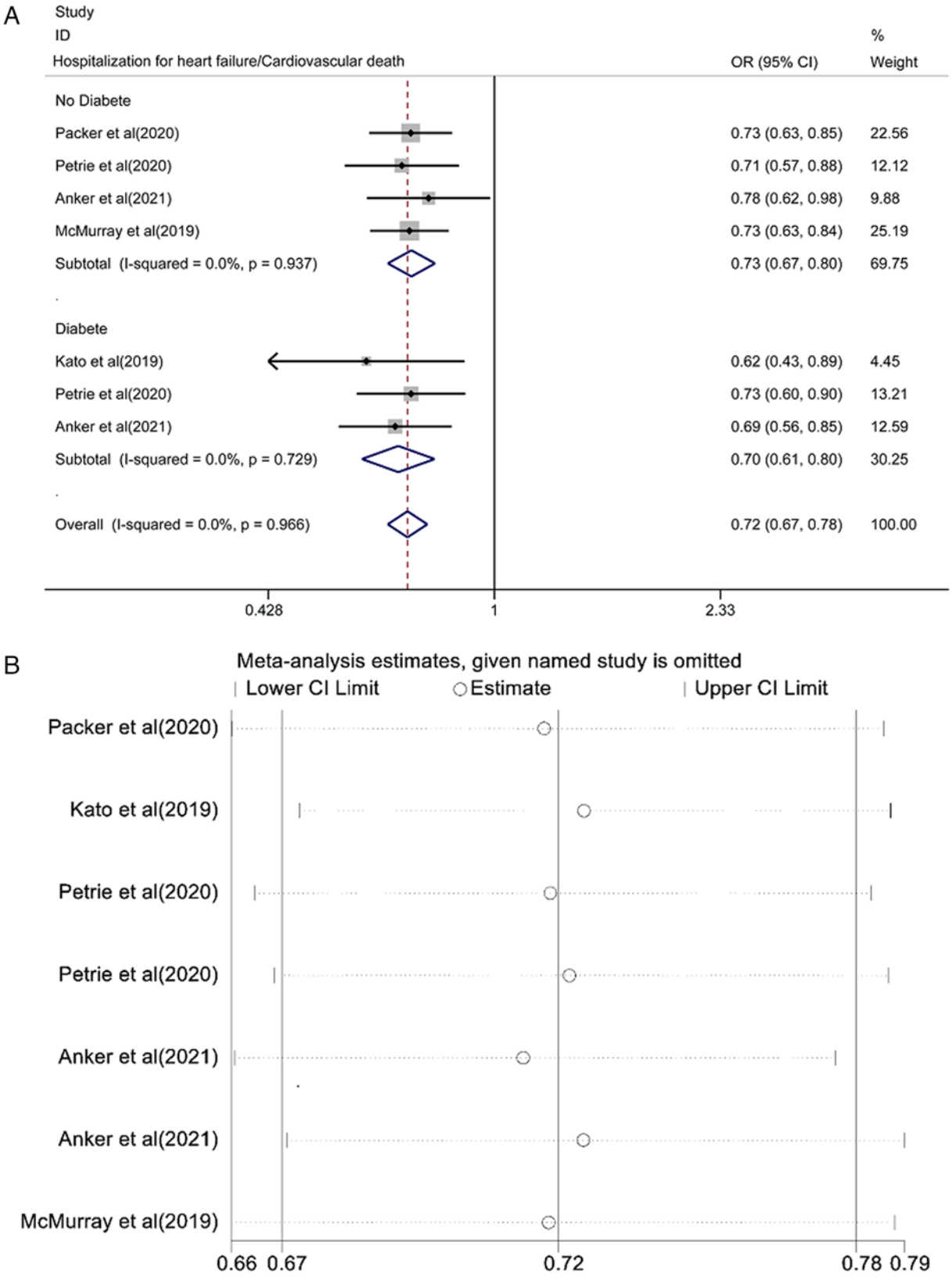

Figure 3. The pooled effects of hospitalization for heart failure/cardiovascular death. (A) Fixed effect model and (B) Sensitivity analysis.

slow the progression of kidney diseases (5). There is a link between diabetes and HF. However, no approved drugs reduce the risk of HF in diabetics. Similar to the findings of the present analysis, a systematic review and meta-analysis in 2021 showed that patients in the empagliflozin group had lower rates of cardiovascular mortality and hospitalization for worsening HF than those in the placebo group (28). The present study more comprehensively included the SGLT2i studies and incorporated the latest research. The present study excluded the effect of diabetes and found that SGLT2i

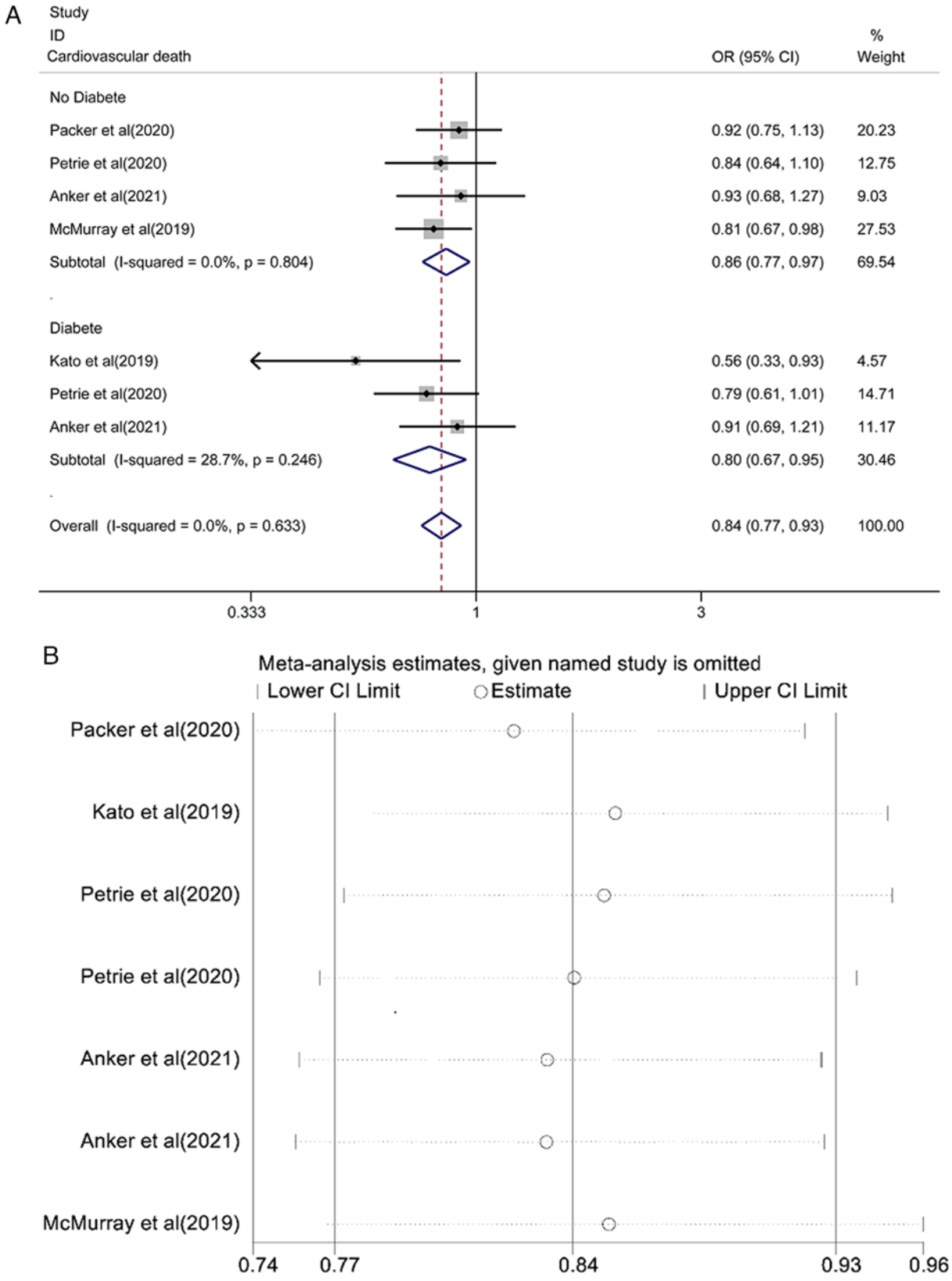

Figure 4. The pooled effects of cardiovascular death. (A) Fixed effect model and (B) Sensitivity analysis.

could improve the risk of HF in terms of HF hospitalization, cardiovascular death, and all-cause mortality. One study found that compared with placebo, SGLT2i primarily improved mortality, HF hospitalization rate, HF emergency department visits, and reduced serious adverse events (29). A recent study found that SGLT2i reduced the risk of cardiovascular death and hospitalization for HF in patients with diabetes (30). Gager *et al* (31) found that empagliflozin did not achieve statistical significance in reducing cardiovascular and all-cause mortality. The studies included in the present

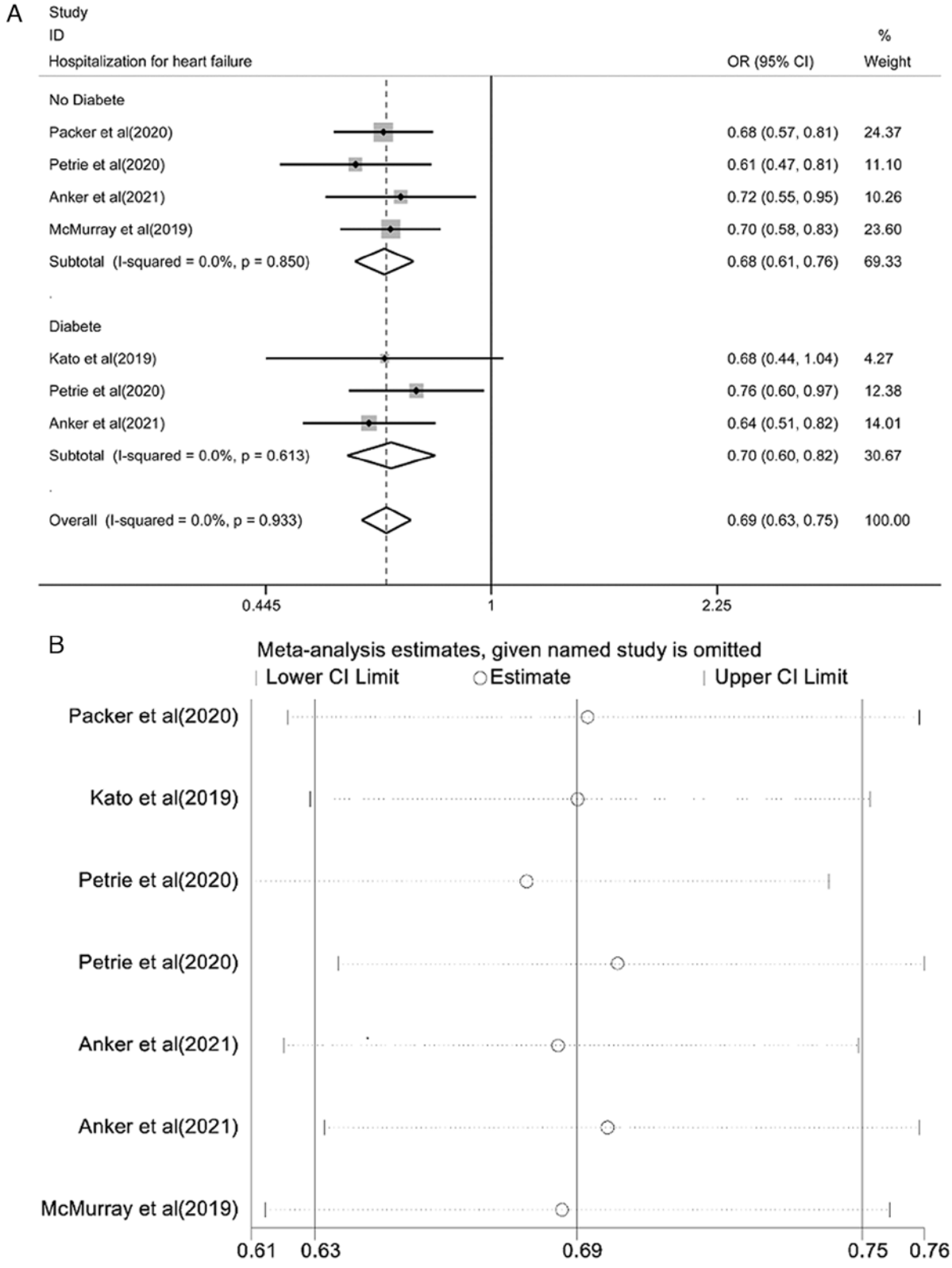

Figure 5. The pooled effects of hospitalization heart failure. (A) Fixed effect model and (B) Sensitivity analysis.

analysis found that empagliflozin significantly reduced all-cause mortality in patients with a reduced ejection fraction and HF. One explanation for the difference may be due to differences in the range of patients included. Studies have shown that SGLT2i significantly reduced the risk of cardiovascular mortality or HF in patients with a lower ejection fraction (32). Therefore, all patients with HF included in the present study had an ejection fraction <40%.

The present analysis has several limitations. Although there are several SGLT2i, studies using only two SGLT2i (dapagliflozin and empagliflozin) were included to compare with placebo. The number of RCTs included in the present

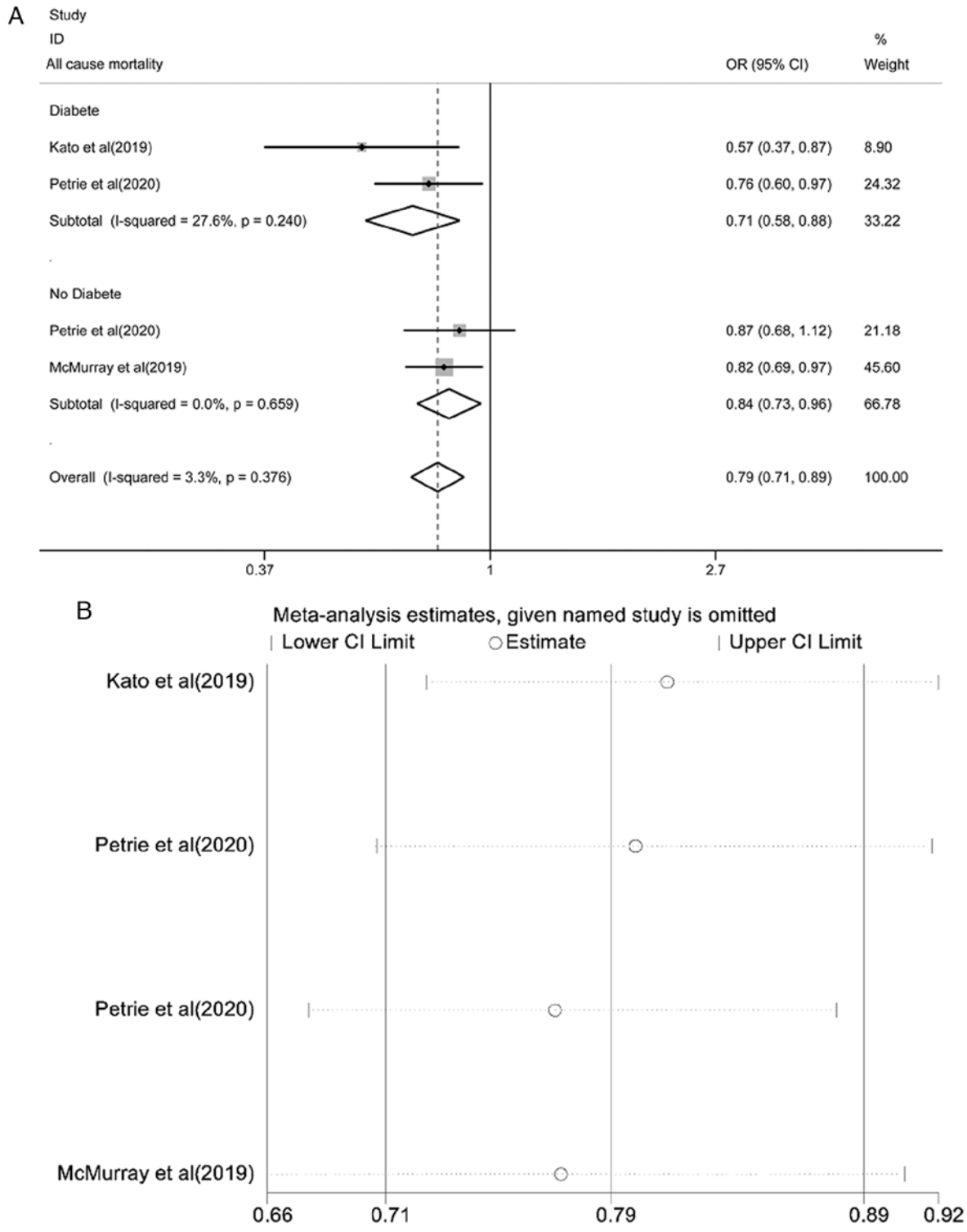

Figure 6. The pooled effects of all-cause mortality. (A) Fixed effect model and (B) Sensitivity analysis.

analysis was too small; thus, subgroup analysis of two different SGLT2icould not be performed. Additional high-quality articles are required to improve our understanding of the benefits of SGLT2i for the management of patients with HF with a reduced ejection fraction.

In conclusion, SGLT2i can reduce the risk of HF hospitalization, cardiovascular death, and all-cause mortality in patients with HF and a reduced ejection fraction, regardless of the presence or absence of diabetes.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

KZ and QY contributed to the conception and design of the study, preparation of the material, collection of the data, and analysis of the data. QY wrote the first draft. KZ and QY both contributed to the revision of the manuscript. KZ and QY have read and approved the final manuscript. KZ and QY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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