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Protective effect of sacubitril/valsartan in patients with acute myocardial infarction: A meta-analysis

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Abstract. To evaluate the effects and safety of sacubitril/valsartan in patients with acute myocardial infarction (AMI), a total of four databases, including PubMed, Cochrane Library, Embase and Web of Science, and the ClinicalTrials.gov website were searched. Using a combination of medical subject headings and entry terms, the final search was performed in July 2021. A manual search of cross-references from the original articles was also conducted. The meta-analysis was subsequently performed with Revman 5.3 software and a total of four studies comprising 586 patients were included. The results disclosed a significant reduction in major adverse cardiovascular and cerebrovascular events (MACCEs) [odds ratio (OR), 0.47; 95% confidence interval (CI), 0.30-0.73; P=0.0007], readmission (OR, 0.45; 95% CI, 0.29-0.71; P=0.0006), incidence of acute heart failure (AHF) (OR, 0.45; 95% CI, 0.28-0.71; P=0.0007) and N-terminal pro B-type natriuretic peptide [standardized mean difference (SMD), -0.88; 95% CI, -1.55-(-0.21); P=0.01] in the sacubitril/valsartan group compared with that in the control group, and a random effects model was used to pool these data. No significant differences were identified in the incidence of hypotension (OR, 2.91; 95% CI, 0.55-15.51; P=0.21), adverse events (OR, 2.19; 95% CI, 0.42-11.37; P=0.35), left ventricular ejection fraction (mean difference, 1.96; 95% CI, -0.84-4.76; P=0.17) or soluble suppression of tumorigenesis-2 (SMD, -0.45; 95% CI, -1.62-0.71; P=0.45) according to the random effects model. In conclusion, the present meta-analysis revealed that sacubitril/valsartan was able to effectively reduce the incidence of MACCEs, readmission and AHF in patients with AMI after revascularization without any obvious adverse events.

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Key words: sacubitril/valsartan, acute myocardial infarction, meta-analysis, efficacy, safety

Introduction

Acute myocardial infarction (AMI) is a major cause of disability and mortality worldwide (1). Timely revascularization is the most effective approach for reducing cardiomyocyte death, although the incidence of complications following reperfusion therapy remains high (2). Among the postoperative complications, cardiac insufficiency affects the prognosis of patients and their quality of life (3). Following AMI, overactivation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) may cause ventricular remodeling, which is the main pathological event associated with cardiac insufficiency (4).

In recent years, although the application of conventional heart failure treatment following myocardial infarction has reduced the mortality of patients to a certain extent, the incidence of cardiac insufficiency following AMI remains high (5). In 2014, the Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor (ARNI) with Angiotensin-Converting-Enzyme Inhibitor (ACEI) to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial indicated that, compared with enalapril, the cardiovascular mortality, heart failure rehospitalization and all-cause mortality rates of patients with chronic heart failure were all decreased following the administration of sacubitril/valsartan (LCZ 696) (6). Sacubitril/valsartan is a first-in-class ARNI that simultaneously suppresses RAAS activation by blocking angiotensin II type 1 (AT1) receptors and enhances vasoactive peptides, such as natriuretic peptides, by inhibiting neprilysin, the enzyme responsible for their degradation (7). Notably, compared with ACEI or AT1 receptor blockers (ARB), sacubitril/valsartan may modulate the neurohormonal axis by inhibiting angiotensin receptors and neprilysin, and could thus improve the neurohormonal balance more than by blocking the RAAS alone (8). Sacubitril/valsartan is as well tolerated by patients as ACEI or ARB, with the most common side effect being hypotension (9). Furthermore, a series of studies have revealed that treatment with sacubitril/valsartan may lead to enhanced clinical benefits for patients with chronic heart failure (10,11). Considering the mechanism of sacubitril/valsartan, it may also have a protective effect on patients with AMI by inhibiting RAAS activation. However, the clinical benefits of using sacubitril/valsartan in patients with AMI after revascularization remain controversial. Therefore, the aim of the present study was to conduct a systematic review to provide further evidence in support of the clinical application of sacubitril/valsartan in patients with AMI.

Materials and methods

Literature inclusion and exclusion criteria. The inclusion criteria were defined according to the Population, Intervention, Comparison, Outcome and Study design tool (12): i) Population, patients with AMI after coronary revascularization, including percutaneous transluminal coronary intervention (PCI), coronary artery bypass grafting (CABG) or thrombolysis, were included; ii) intervention, the sacubitril/valsartan group was administered sacubitril/valsartan on the basis of conventional treatment strategies; iii) comparison, the control group was treated with ACEI or ARB on the basis of conventional treatment strategies; iv) outcome, the main outcomes were major adverse cardiovascular and cerebrovascular events (MACCEs; including cardiac death, myocardial infarction, severe arrhythmia, stroke, rehospitalization for congestive heart failure and repeated revascularization), readmission rate, adverse events, incidence of acute heart failure (AHF) and incidence of hypotension, whereas the secondary outcomes were N-terminal pro B-type natriuretic peptide (NT-proBNP)/BNP, left ventricular ejection fraction (LVEF) and soluble suppression of tumorigenesis-2 (sST2); and v) study design, randomized controlled trials (RCTs) were included.

The exclusion criteria (in terms of the publications) were as follows: Republished studies, studies with no available data, studies in which the full text was not available, and studies written in a language other than English.

Literature retrieval strategy. PubMed (https://pubmed.ncbi.nlm.nih.gov/), Cochrane Library (https://www.cochranelibrary.com/), Embase (https://www.embase.com/) and Web of Sciences (https://www.webofscience.com/wos/alldb/basic-search) databases, and the ClinicalTrials.gov website (https://www.clinicaltrials.gov/) were searched for AMI and sacubitril/valsartan through the combination of medical subject headings (MeSHs) and entry terms. The literature search start date was not restricted, and the search end date was July 2021. A manual search of cross-references was also conducted based on the original articles. The following search strategy was used for PubMed and modified to suit other databases (the detailed retrieval strategy of other databases is outlined in the Supplementary Data): Search I, myocardial infarction (MeSH terms); search II, (Infarction, Myocardial Title/Abstract) OR [Infarctions, Myocardial (Title/Abstract)] OR [Myocardial Infarctions (Title/Abstract)] OR [Cardiovascular Stroke (Title/Abstract)] OR [Cardiovascular Strokes (Title/Abstract)] OR [Stroke, Cardiovascular (Title/Abstract)] OR [Strokes, Cardiovascular (Title/Abstract)] OR [Myocardial Infarct (Title/Abstract)] OR [Infarct, Myocardial (Title/Abstract)] OR [Infarcts, Myocardial (Title/Abstract)] OR [Myocardial Infarcts (Title/Abstract)] OR [Heart Attack (Title/Abstract)] OR [Heart Attacks (Title/Abstract]; search III, sacubitril and valsartan sodium hydrate drug combination (MeSH terms); search IV [sacubitril valsartan sodium hydrate (Title/Abstract)] OR [sacubitril-valsartan sodium hydrate drug combination (Title/Abstract)] OR [trisodium (3-(1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-3'-methyl-2'-(pentanoyl(2'-(tetrazol-5-ylate)biphenyl-4'-ylmethyl)amino)butyrate hemipentahydrate (Title/Abstract)] OR [sacubitril (Title/Abstract) AND valsartan drug combination (Title/Abstract)] OR [sacubitril valsartan drug combination (Title/Abstract)] OR [sacubitril-valsartan (Title/Abstract)]OR[3-(1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-3'-methyl-2'-(pentanoyl(2'-(tetraz ol-5-ylate)biphenyl-4'-ylmethyl)amino)butyrate (Title/Abstract)] OR [sacubitril (Title/Abstract) AND valsartan sodium anhydrous drug combination (Title/Abstract)] OR [sacubitril valsartan sodium anhydrous (Title/Abstract)] OR [sacubitril-valsartan sodium anhydrous drug combination (Title/Abstract)] OR [LCZ 696 (Title/Abstract)] OR [LCZ696 (Title/Abstract)] OR [LCZ-696 (Title/Abstract)] OR [Entresto (Title/Abstract)] OR [sacubitril/valsartan (Title/Abstract)]; search V, search I OR search II; search VI, search III OR search IV; and search VII, search V AND search VI.

Literature screening and data extraction. Two researchers (SSL and BY) independently searched and screened the literature according to the inclusion and exclusion criteria. Any potential disagreements were resolved by discussion until either a consensus was reached, or a third author (BW or ZXF) was consulted. The extracted information included the basic information of the study in question and the original research data of the outcomes. The data that could not be directly extracted were obtained either by data transformation or by contacting the authors.

Literature quality assessment. The Cochrane collaboration bias risk assessment tool recommended by the Cochrane handbook (13) was used to assess the risk of bias in the included literature. A number of characteristics were evaluated, including random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases.

Statistical methods. Statistical analysis of the data was performed using Review Manager 5.3 (https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman) and STATA 14 software (https://www.stata.com/stata14/). Odds ratio (OR) was used as the effect measure for dichotomous data. The effect measure used for continuous data was the mean differences; either the mean difference (MD) or the standardized mean difference (SMD) when the data were measured based on the different measurement methods. All effect indicators were calculated with 95% confidence intervals (CIs). Statistical heterogeneity was assessed using the χ^2 test according to the I^2 and P-values. Notably, $I^2>50\%$ or $P<0.05$ was taken to indicate a significant level of

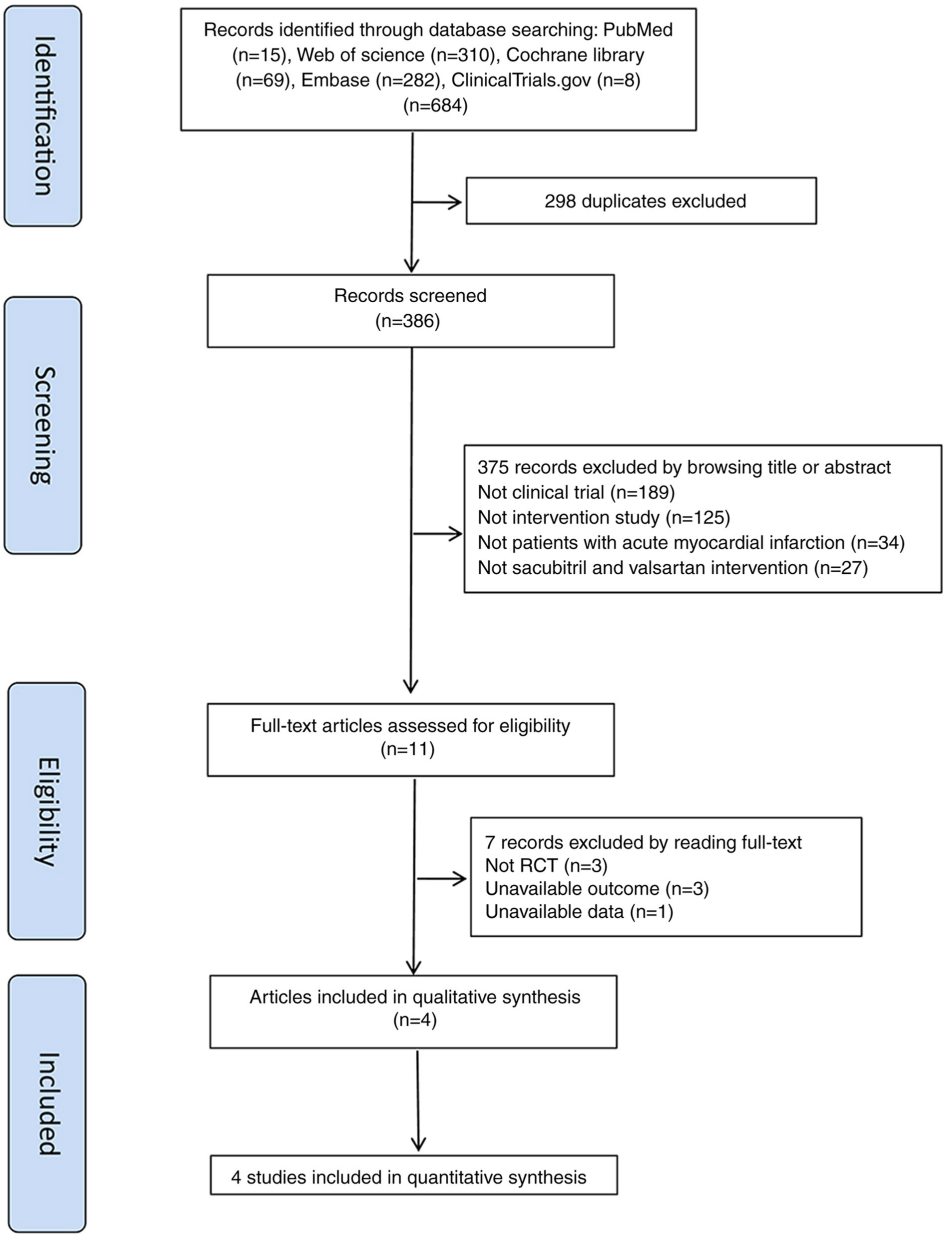

Figure 1. Flow diagram showing the study selection protocol. RCT, randomized controlled trial.

heterogeneity among the studies, so, in this case, the effect indicators were combined using the randomized effects model (REM). If included studies were completely independent of each other, REM was used. Sensitivity analysis was conducted to verify the stability of the model by single study elimination method in STATA 14 software, exploring the possible source of heterogeneity. Publication bias was assessed using funnel plots for meta-analysis and quantified using the Egger method, although it must be mentioned that the test power of this method is limited when only a few studies are included. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Literature search results. A total of 684 articles were obtained by searching the databases, and a total of 386 articles were retrieved after removing duplicates. By reading the titles and abstracts, 375 articles were initially excluded according to the inclusion and exclusion criteria (189 were found not to be clinical trials, 125 were not intervention studies, 34 were not dealing with patients with AMI, and 27 articles were not concerned with sacubitril and valsartan interventions). A total of 11 articles were subsequently investigated, and seven of them were excluded upon reading their full text. For the seven excluded articles, three were not RCTs, three articles had unavailable outcomes and one was without available data. Ultimately, four studies were included in the meta-analysis (14-17) (Fig. 1).

Basic characteristics of the included literature. A total of four studies were included. The basic information of the included studies is shown in Table I. The total sample size of 586 patients was included, involving cases from

Table I. Characteristics of the included studies.

First author, year	Country	Research	Characteristics	Sample size, T/C	Sex, M/F		Mean age ± SD, years		Type of AMI	AMI treatment	Intervention		Dosage of Sal/Val	Time between AMI and intervention	Follow-up, months	(Refs.)
					T	C	T	C			T	C				
Zhang, *et al* 2021	China	Prospective single-center RCT	Not double-blinded	79/77	59/20	55/22	60.30±11.70	60.00±10.90	All STEMI	All PCI	Sal/Val + RBT	Perindopril + RBT	According to patient condition	Early administration of Sal/Val within 24 h after PCI	6	(14)
Wang, *et al* 2021	China	Prospective single-center RCT	Blinded	68/69	52/16	54/15	59.13±7.15	60.56±7.62	All STEMI	All PCI	Sal/Val + RBT	Enalapril + RBT	24/26 or 49/51 mg bid and then up titration	When hemodynamic stabilization reached after PCI	6	(15)
Rezq, *et al* 2021	Egypt	Prospective multicenter RCT	Double-blinded	100/100	86/14	88/12	52.00±9.20	57.00±11.60	All STEMI	All PCI	Sal/Val + RBT	Ramipril + RBT	50 or 100 mg bid	After PCI	6	(16)
Docherty, *et al* 2021	UK	Prospective multicenter RCT	Double-blinded	47/46	42/5	43/3	61.80±10.60	57.00±11.60	90 STEMI and 30 NSTEMI	86 PCI, one thrombolysis and three CABG	Sal/Val + RBT	Valsartan + RBT	24/26, 49/51 and 97/103 mg bid	>3 months after PCI	12	(17)

RCT, randomized controlled trial; T, experimental group; C, control group; AMI, acute myocardial infarction; STEMI, ST segment elevation myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous transluminal coronary intervention; CABG, coronary artery bypass grafting; Sal, sacubitril; Val, valsartan; RBT, routine basic treatment; bid, two times per day; M, male; F, female.

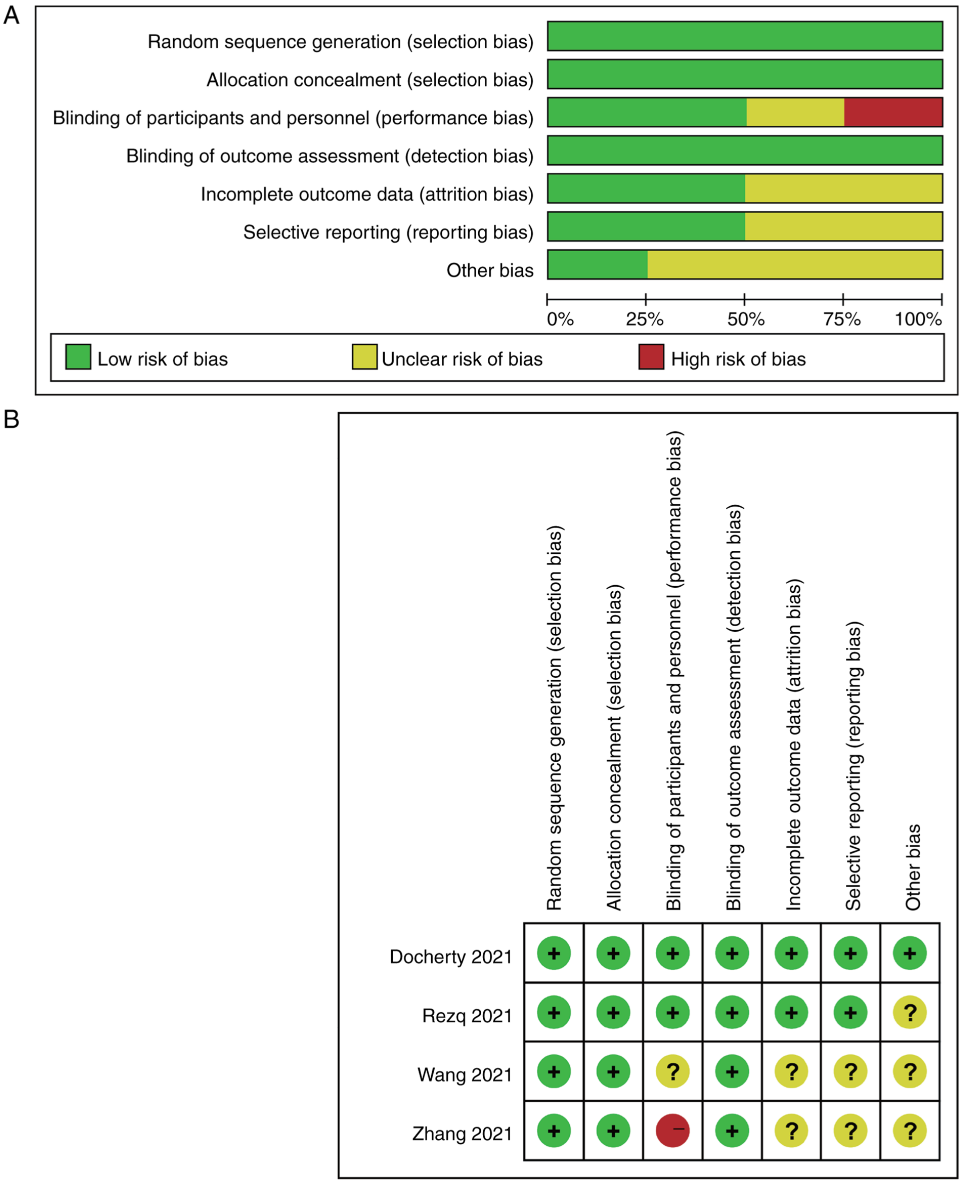

Figure 2. Quality evaluation of the included studies. (A) Risk of bias graph and (B) risk of bias summary.

China, Egypt and the UK. The four studies comprised two prospective single-center RCTs and two prospective multicenter RCTs. Regarding the type of AMI involved, three studies assessed ST-elevation myocardial infarction (STEMI) that was treated with PCI, whereas the remaining study assessed STEMI and non-STEMI (NSTEMI) that was treated with PCI, thrombolysis or CABG. The intervention used for all experimental groups was sacubitril and valsartan, although the time between the onset of AMI and the intervention varied, including early administration of sacubitril/valsartan and treatment with sacubitril/valsartan over several months following PCI. Regarding the dose of sacubitril/valsartan, Zhang *et al* (14) decided on dose titration and medication changes according to patient condition. Wang *et al* (15) decided on a starting dose of 24/26 or 49/51 mg sacubitril/valsartan (two times per day for 2 weeks). At the end of the run-in period (2 weeks), uptitration of sacubitril/valsartan, if tolerated by the patient, was allowed. Rezq *et al* (16) administered sacubitril/valsartan orally twice daily at a dose of 50 mg and increased to 100 mg twice daily after 2 weeks if tolerated. Docherty *et al* (17) administered sacubitril/valsartan twice daily at a dose of 24/26, 49/51 or 97/103 mg depending on renal function, blood pressure and ACEI or ARB dose at randomization. The treatments used in the control groups included perindopril, enalapril, ramipril and valsartan, and the follow-up period was 6 or 12 months.

Quality assessment of the included studies is shown in Fig. 2. All of the studies had a low risk of bias for random sequence generation, allocation concealment and blinding of outcome assessment. With regard to blinding of participants and personnel, in the study by Zhang *et al* (14), the staff knew the patient grouping and medication changes were performed according to the patients' condition; therefore, the study was 'not double-blinded' and was considered to have high risk of bias. In addition, Wang *et al* (15) described the study as 'blinded'; however, it was not possible to determine whether the study was double-blinded or not. By contrast, the other two

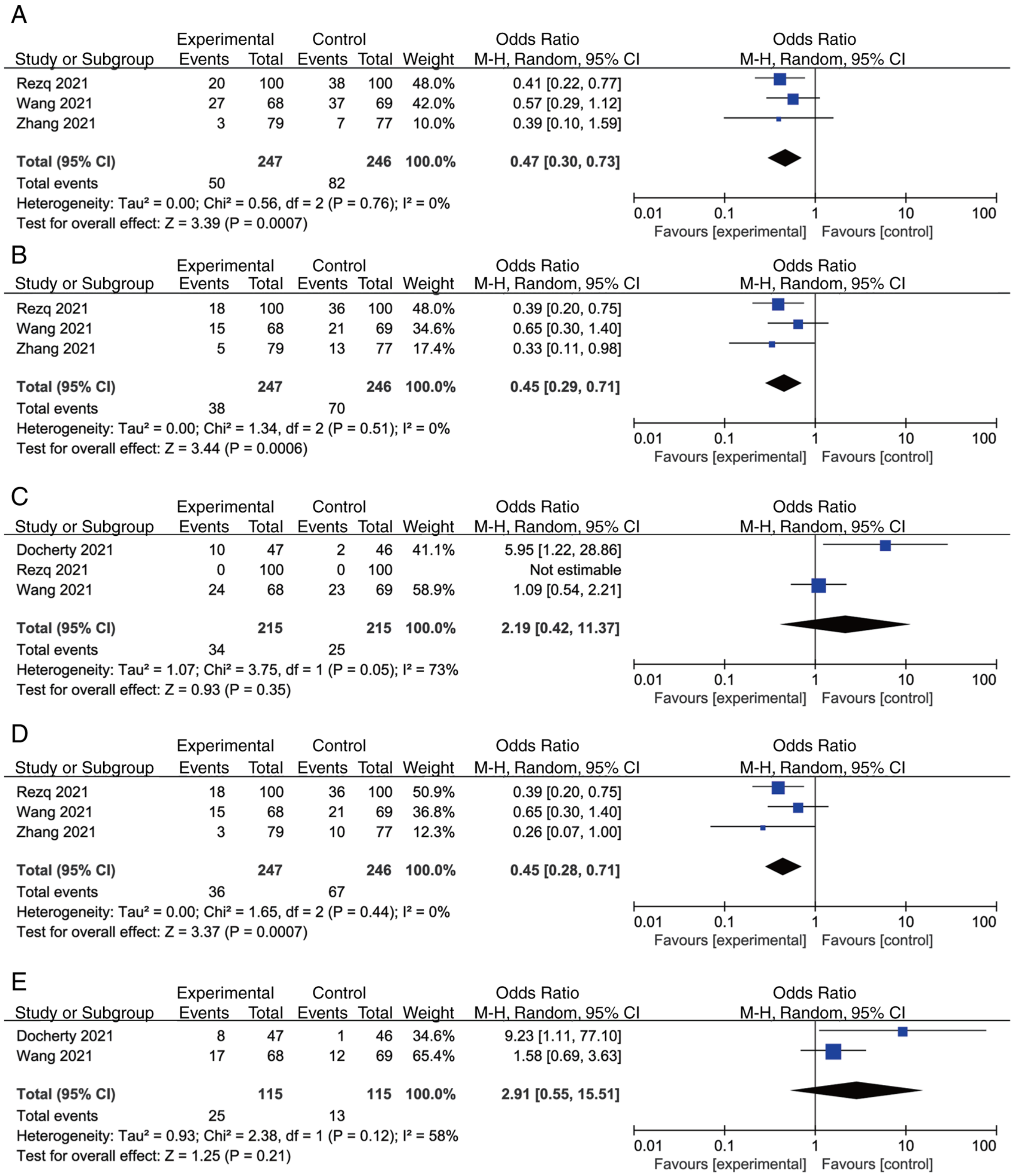

Figure 3. Forest plots of (A) MACCEs, (B) readmission, (C) adverse events, (D) incidence of AHFs and (E) hypotension. MACCEs, major adverse cardiovascular and cerebrovascular events; AHF, acute heart failure; 95% CI, 95% confidence interval.

studies were double-blinded with low risk. In addition, there was unclear risk of bias for incomplete outcome data, selective reporting and other bias in Zhang *et al* and Wang *et al* (14,15)

Overall analysis. An overall analysis for the primary outcomes is presented in Fig. 3, whereas that for the secondary outcomes is provided in Fig. 4. The results of the meta-analysis revealed a significant reduction in MACCEs (OR, 0.47; 95% CI, 0.30-0.73; P=0.0007, Fig. 3A), readmission (OR, 0.45; 95% CI, 0.29-0.71; P=0.0006, Fig. 3B), incidence of AHF (OR, 0.45; 95% CI, 0.28-0.71; P=0.0007, Fig. 3D) and NT-proBNP [SMD, -0.88; 95% CI, -(1.55-0.21); P=0.01, Fig. 4A] in the sacubitril/valsartan group compared with that in the control group, and a REM was used to pool these data. No significant differences were identified in hypotension (OR, 2.91; 95% CI, 0.55-15.51; P=0.21, Fig. 3E), adverse events (OR, 2.19; 95% CI, 0.42-11.37; P=0.35, Fig. 3C), LVEF (MD, 1.96; 95% CI, -0.84-4.76; P=0.17, Fig. 4B) and sST2 (SMD, -0.45; 95% CI, -1.62-0.71; P=0.45, Fig. 4C) with the REM. There was a significant statistical heterogeneity when the effect sizes of adverse events were combined (I^2, 73%; individual I^2 values: NT-proBNP, 86%; LVEF, 74% and sST2, 95%, Fig. 4). Sensitivity analysis of LVEF was performed and indicated a significant elevation in LVEF (OR, 3.11; 95% CI, 1.67-4.55; P<0.0001,

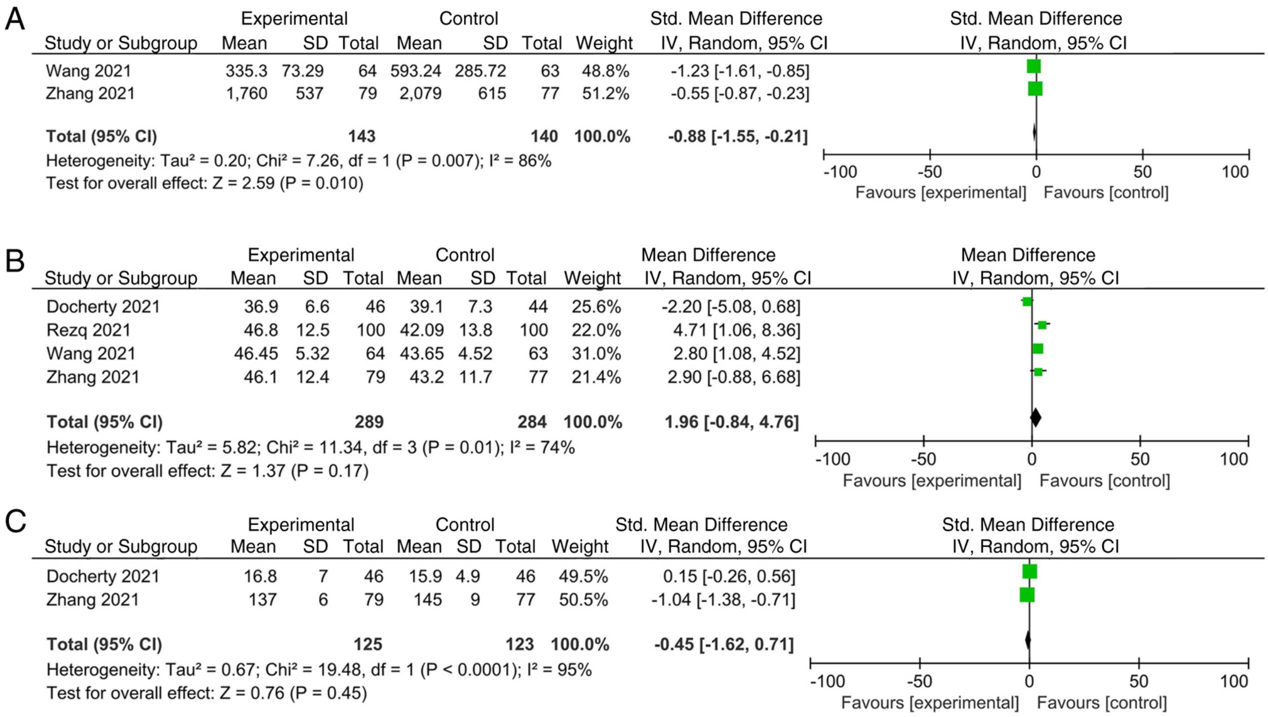

Figure 4. Forest plots of (A) NT-proBNP, (B) LVEF and (C) sST2. NT-proBNP, N-terminal pro B-type natriuretic peptide; LVEF, left ventricular ejection fraction; sST2, soluble suppression of tumorigenesis-2; 95% CI, 95% confidence interval.

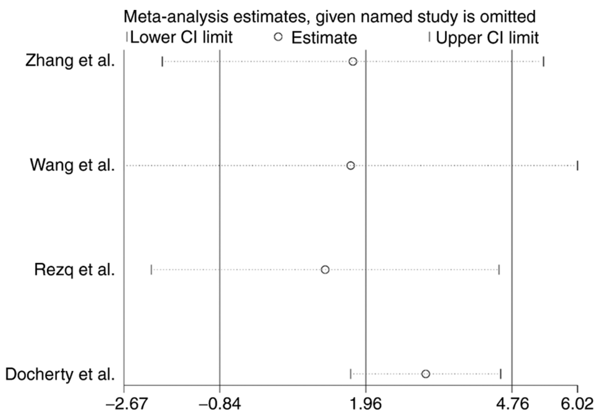

Figure 5. Sensitivity analysis of LVEF. The S-axis presents the odds ratio with the respective study omitted. LVEF, left ventricular ejection fraction; CI, confidence interval.

Fig. 5) in the sacubitril/valsartan group compared with that in the control group after exclusion of Docherty *et al* (17). This result indicated that Docherty *et al* (17) may be the source of heterogeneity (Fig. 5).

Discussion

Following AMI, disordered ventricular muscle contraction, activation of the RAAS and ventricular remodeling may lead to cardiac insufficiency, or even pump failure (18). At present, the drugs that are recommended by guidelines have a low effect on inhibiting excessive activation of the nonendocrine system in the mechanism of heart failure following AMI and are unable to bring about the rapid rectification of hemodynamic disorders (19,20). Notably, the overall therapeutic effects of treatments often do not meet clinical expectations. Therefore, choosing an effective drug treatment after reperfusion therapy is essential in terms of improving functional recovery and prognosis. Sacubitril/valsartan has fulfilled an important role in the treatment of chronic heart failure in the clinic (21). It has been recommended by the 2016 European Chronic Heart Failure Guidelines, the US Heart Failure Management Guidelines and the 2018 Chinese Heart Failure Guidelines for the treatment of chronic heart failure (22,23). However, at present there is no consensus on the application of sacubitril/valsartan in heart failure following AMI. The application of sacubitril/valsartan has been trialed in animal experiments and in clinical trials of AMI, and this has achieved impressive results that are continually expanding the clinically applicable scope of sacubitril/valsartan.

As the first dual-effect compound preparation of an enkephalinase inhibitor and ARB, sacubitril and valsartan have been reported to exert a dual role in neuroendocrine system activity (24). Valsartan not only exerts its effects by blocking angiotensin receptors to relax blood vessels, but also acts as an antagonist of aldosterone, producing diuresis and sodium excretion, resulting in a net reduction of water and sodium retention (25). As an enkephalinase inhibitor, sacubitril can block enkephalinase activity and reduce the degradation of BNP (26). Sacubitril not only can strengthen the activity of BNP, expand blood vessels, discharge natriuretic and diuresis, but it may also reduce the role of pro-fibrotic signal transduction markers in heart failure.

Recently published clinical studies have revealed that early application of sacubitril/valsartan following emergency PCI in patients with AMI can effectively improve left ventricular remodeling, reduce the occurrence of cardiac insufficiency and adverse cardiovascular events, and reduce the rehospitalization rate (14-17). In addition, a meta-analysis performed by Zhao *et al* (27) also indicated that early initiation of Sacubitril/Valsartan in patients after AMI was reasonable, but more data are required to support this. Of note, the results of the present study revealed a significant reduction in MACCEs, readmission and incidence of AHF, without there being any statistically significant differences in adverse events noted between the sacubitril/valsartan group and the control group. In addition, no significant differences in LVEF were identified between the two groups of this meta-analysis, a finding that is inconsistent with previous research results on chronic heart failure (28). This difference may be associated with the length of follow-up time. Considering the influence of follow-up time and the number of included studies, further big-data RCTs are required to verify these findings. The Prospective ARNI vs. ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI study (29) aimed to evaluate the efficacy of sacubitril/valsartan in patients with left ventricular systolic dysfunction after AMI compared with ramipril, and the impact that this therapy may have on the composite end-points of cardiovascular death and heart failure hospitalization. The results of this study should provide new evidence for the treatment of heart failure following AMI.

The present study has a number of limitations. First, the number of included studies was only four and the study sample size was small. Hence, although there were no significant differences in hypotension between the two groups, it must be emphasized that attention should be paid to changes in blood pressure considering that this is the most common side effect of sacubitril/valsartan. Furthermore, certain studies did not provide blinding of participants. In addition, certain articles did not specify what the specific medications for the conventional/control treatment were. The heterogeneity in the meta-analysis of the primary outcome, adverse events, was significant. The differences in study design, including differences in patient age, severity of MI, comorbidities, the dose of sacubitril/valsartan and the specific medications for conventional treatment, may have resulted in heterogeneity in the meta-analysis of adverse events. However, the type of adverse event may be slightly different, which may cause the heterogeneity. Rezq *et al* (16) defined adverse events as symptomatic hypotension, significant hyperkalemia, worsening renal function or angioedema. Docherty *et al* (17) regarded adverse events as serum creatinine ≥2.5 mg/dl, serum potassium >5.5 mmol/l, symptomatic hypotension with systolic blood pressure <90 mmHg, angioedema and cough, whereas Wang *et al* (15) considered hypotension, cough, renal impairment and hyperkalemia as adverse events. Sensitive analysis revealed that Docherty *et al* (17) may be the source of heterogeneity, which may be due to disparities compared with the other three studies with regard to the types of AMI and AMI treatment. Docherty *et al* (17) included STEMI and NSTEMI, and conducted thrombolysis, PCI and CABG to treat AMI, whereas the others only assessed STEMI and implemented PCI.

In conclusion, the present meta-analysis revealed that sacubitril/valsartan may effectively reduce the incidence of MACCEs, readmission and AHF in patients with AMI following revascularization without any obvious adverse events. However, given the limitations in the quality and quantity of the included articles and the risk of bias, these findings need to be further confirmed by big-data and high-quality prospective randomized controlled studies in order to provide corroborating evidence.

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Availability of data and materials

The present meta-analysis was performed, and has been reported, according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (CRD42021269433, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=269433). The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

BY and ZXF conceived and designed the current study, defined the content of the research, conducted literature search, performed statistical analysis and prepared and edited the manuscript. SSL is the guarantor of study integrity, designed the current study, defined the content of the research and reviewed the manuscript. BW conducted the literature search, acquired data and performed statistical analysis. BY and ZXF confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

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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