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Review Article

Efficacy of Sarcupyrine/valsartan in the treatment of acute myocardial infarction: a meta-analysis

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Abstract: Objective: To assess the efficacy of sacubitril-valsartan in the treatment of acute myocardial infarction (AMI) using meta-analysis methods. Methods: Relevant papers on sacubitril/valsartan for treating AMI were searched on PubMed, Embase, Medical Literature Analysis, and Retrieval System On-Line (MEDLINE), Science Direct, The Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journal Database, and Chinese Biomedical Literature Database (CBM). The time range was from their inception to February 1, 2023. Results: A total of 10 articles involving 13,135 patients were included for this meta-analysis according to the inclusion and exclusion criteria. Among these patients, 6,581 were treated with sacubitril/valsartan, as the experimental group, and the other 6,554 patients were classified into the control group. After treatment, the risk of hospitalization for heart failure (HF) in the experimental group was lower than that of the control group (OR=0.77, 95% CI: 0.67-0.88, *P*=0.0002); the average left ventricular end diastolic diameter (LVEDD) (MD=-5.56, 95% CI: -7.92-3.20, *P*<0.0001) was significantly higher and 6-minute-walk distance (6MWD) (MD=95.86, 95% CI: 30.57-161.16, *P*=0.004) was significantly longer in the treatment group than in the control group. Besides, the left ventricular ejection fraction (LVEF) (MD=2.99, 95% CI: 0.47-5.51, *P*=0.02) was significantly lower than that of the control group. Conclusion: Sacubitril/Valsartan improves cardiac function in patients with AMI, reduces the risk of postoperative myocardial reinfarction, and reduces the risk of hospitalization for HF.

Keywords: Sacubitril/valsartan, acute myocardial infarction, effectiveness analysis, meta-analysis

Introduction

Myocardial infarction (MI) is a severe cardiovascular disease that can lead to heart failure (HF) [1]. Acute MI (AMI) is a prevalent form of heart attack, and early treatment is essential to improve patient outcome. Thrombolytic therapy and early revascularization techniques have successfully reduced the mortality rate of AMI in clinical practice [2]. Despite significant advancements in reperfusion therapy, managing the disease course following AMI remains a formidable challenge. Consequently, early detection and effective control of myocardial infarction (MI) size are imperative to mitigate adverse outcomes and enhance the prognosis of AMI patients [3, 4].

Sarcupyrine/valsartan is a compound drug that is a co-crystallization of e Neprilysin Inhibitor (NEPI) Sarcupyrine and Angiotensin Receptor Blocker (ARB) valsartan in equal ratio. This combination effectively regulates both the Neprilysin (NEP) and renin-angiotensin systems, achieving the effect of regulating water/sodium balance, expanding capillaries, and thus inhibiting atrial reconstruction [5]. Studies noted that combining sacubitril with valsartan not only counteracts the potential toxic effects of NEPI but also exerts the positive effects of natriuretic peptides, thus bringing more medical benefit to HF patients. Such combined application can not only inhibit the negative effects of Angiotensin (Ang) but also effectively improve the symptoms of patients with cardiac exhaustion, thus obtaining better clinical outcomes [6-8]. A literature review reveals a paucity of studies investigating the prevention and treatment of HF following AMI using angiotensin

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receptor neprilysin inhibitors (ARNIs), with a notable absence of meta-analyses on sacubitril/valsartan [9]. Therefore, the purpose of this work was to further explore the early clinical efficacy of ARNI, Sarcupyrine/valsartan, in HF after AMI to better understand the application field of ARNI and their early clinical efficacy. In addition, the advantages of ARNI and their mechanism of action are summarized so that HF patients can gain more prevention and treatment benefits after AMI.

Data and methods

Methods for screening the literature

PubMed, Embase, Medical Literature Analysis and Retrieval System On-Line (MEDLINE), Web of Science, Google Scholar, Science Direct, The Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Science and Technology Journal Database, and Chinese Biomedical Literature Database (CBM) were searched to screen the literature focusing on sacubitril/valsartan treatment of HF after AMI from the establishment of the database to February 1, 2023. Chinese database searching terms included AMI, HF, enkephalin inhibitors, sacubitril/valsartan, nohindal, and HF. The English database searching terms included heart failure, HF, sacubitril/valsartan, AMI, enkephalase inhibitors, sacubitril/valsartan, and nohintal. The search strategies were refined after multiple iterations, and professional journals were searched manually to avoid omissions. We focused on studies involving human subjects only. The literature search was conducted using a combination of subject words and free words to ensure comprehensive coverage. To ensure thoroughness, the search process included tracking citations of each relevant document. The literature quality was assessed using RevMan5.3 software provided by the Cochrane Collaboration Network.

Inclusion and exclusion criteria for literature screening

The study employed the PICOS framework (Patient, Intervention, Comparison, Outcome, and Study design) to select randomized controlled trials (RCTs).

The inclusion criteria: 1. RCTs. 2. All patients diagnosed with AMI. 3. Patients received treatment with sacubitril/valsartan. 4. Studies with available relevant clinical outcome measures.

Exclusion criteria: 1. Studies with a sample size of less than 10 cases; a small sample size may lead to bias and inadequate power. 2. Literature types such as duplicate reports, conference proceedings, and abstracts. 3. Non-RCTs. 4. In vitro experiments, animal experiments, experiments involving healthy populations, or pre-experiments.

Two experienced researchers (Jianfei Ye and Weifen Zheng) independently conducted the literature selection process. Initially, articles were selected based on their titles and content of the references. Subsequently, potentially relevant studies underwent a comprehensive review to assess their eligibility according to predetermined inclusion and exclusion criteria. Data extraction encompassed details such as the first author, publication year, subject characteristics, control agents, duration of follow-up, and clinical outcome measures related to the study (including changes in mortality, risk of hospitalization, and cardiac function indicators). In cases of disagreement, a third reviewer was consulted to adjudicate the inclusion of relevant literature.

Methods for data extraction

The data were input into a unified Microsoft Excel (Microsoft, USA) platform for data extraction by the above two researchers independently, followed by a crosscheck. Disagreements were resolved through discussion. The data included basic information (title, first author, year, country, publication journal, literature source); basic characteristics of the subjects: sex ratio, age, sample size in different groups; key elements of bias risk assessment: random method, application of blinded method, allocation hiding; and concerned outcome indicators and outcome measurement data, such as odds ratio (OR), complete response (CR), partial response (PR), safety results, and adverse events (AEs).

Methods for evaluating the literature quality

RevMan5.3 was utilized to evaluate the included literature with reference to the RCT bias risk assessment method under the Cochrane Manual of Systematic Review 5.3 [10]. The specific assessment content is shown in **Table 1**. Based

Table 1. Criteria for literature quality assessment

No.	Aspects	Requirements
1	Random allocation method	Whether the method for generating randomly assigned sequences was described in detail
2	Allocation hiding	Whether the method of hiding the random assignment sequence was described in detail to determine whether the allocation of interventions was predictable before the outcome of the experiment
3	Blind method	Whether subjects, researchers, and outcome assessors were blinded to the assigned interventions
4	Incomplete data	Whether each of the primary outcome data was completely described and whether incomplete outcome data was properly processed
5	Selective reporting	Whether all outcomes of predetermined primary outcome measures were fully reported
6	Other sources	Whether there were other factors that could cause a high risk of bias in the experiment

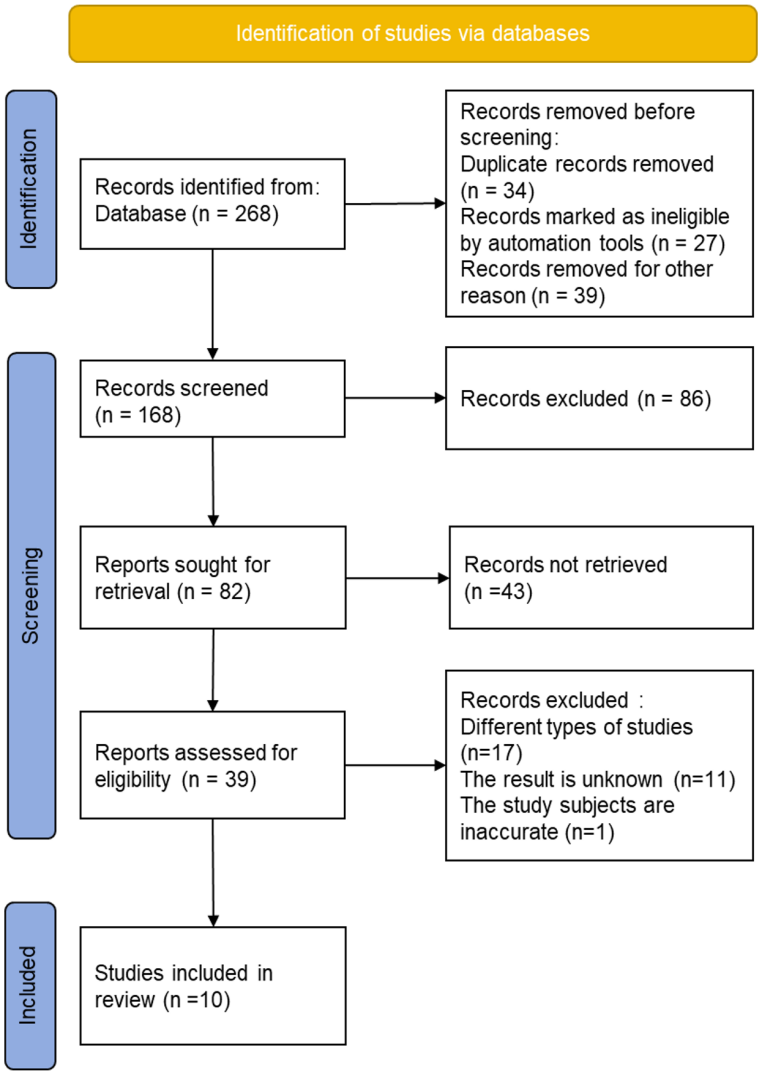

Figure 1. The process for screening eligible studies.

on the potential for bias, assessments were categorized into low, moderate, high, or unknown risk. In instances of discordance, the two researchers engaged in joint discussion, or a third researcher was consulted for intervention.

Statistical analysis

The statistical analysis was conducted using *RevMan5.3*, with baseline patient characteristics and clinical outcomes reported in the form of mean ± standard deviation or counts (percentages).

R language was employed to select effect sizes that accurately reflected the entire dataset based on the characteristics of the data types. The inverse variance method and Mantel-Haenszel method were utilized for dichotomous and continuous outcomes, respectively. Heterogeneity was assessed using the chi-square test for statistical significance and the I^2 statistic to evaluate the degree of heterogeneity among the results included in the meta-analysis.

Table 2. Data extraction for included literature

Author	Year	Type of MI	Sample size		Male/female		Age (Year old)		Intervention measures		Length of treatment (months)
			Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	
Chen [11]	2021	AMI	39	42	24/15	27/15	51.3 ± 6.21	51.28 ± 6.27	Bisoprolol 5 mg, qd	Sacubitril/valsartan 50-200 mg, bid	4 weeks
Docherty [12]	2021	AMI	46	47	43/3	42/5	59.7 ± 10.1	61.8 ± 10.6	Valsartan 160 mg, bid	Sacubitril/valsartan 97/103 mg, bid	13 months
Dong [13]	2022	AMI	66	65	53/13	51/14	60.4 ± 10.0	60.2 ± 9.8	Enalapril 10 mg, bid	Sacubitril/valsartan 97/103 mg, bid	6 months
Fan [14]	2023	AMI	39	39	31/8	28/11	68.0 ± 11.5	71.3 ± 10.5	Irbesartan 150 mg, qd	Sacubitril/valsartan 200 mg, bid	3 months
Halle [15]	2021	AMI	98	103	77/21	86/17	67.6 ± 10.0	66.1 ± 10.8	Enalapril 10 mg, bid	Sacubitril/valsartan 97/103 mg, bid	8 months
Jering [16]	2021	AMI	2,831	2,830	64	64	55.7 ± 9.7	55.7 ± 9.8	Ramipril 5 mg, bid	Sacubitril/valsartan 100 mg, bid	23 months
Rezq [17]	2021	STEMI	100	100	88/12	86/14	57.0 ± 11.6	52.0 ± 9.2	Ramipril 5 mg, bid	Sacubitril/valsartan 100 mg, bid	6 months
Velazquez [18]	2018	TIMI	441	440	63	61	55.7 ± 9.7	55.7 ± 9.8	Enalapril 10 mg, bid	Sacubitril/valsartan 97/103 mg, bid	8 weeks
Pfeffer MA [19]	2021	AMI	2,831	2,830	2,131/700	2,167/663	63.5 ± 11.4	64.0 ± 11.6	Ramipril (5 mg per day)	Sacubitril/valsartan 97/103 mg, bid	4 months
Yang [20]	2023	AMI	63	85	57/6	75/10	59.92 ± 12.02	59.07 ± 11.53	Valsartan 80 mg once daily	Sacubitril/valsartan 100 mg twice daily	6 months

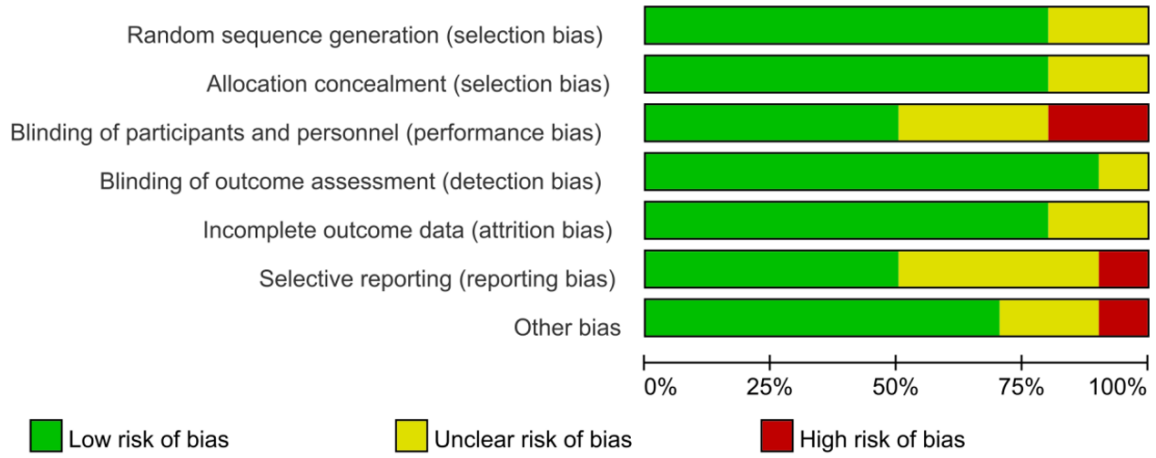

Figure 2. Bias risk of the included literature.

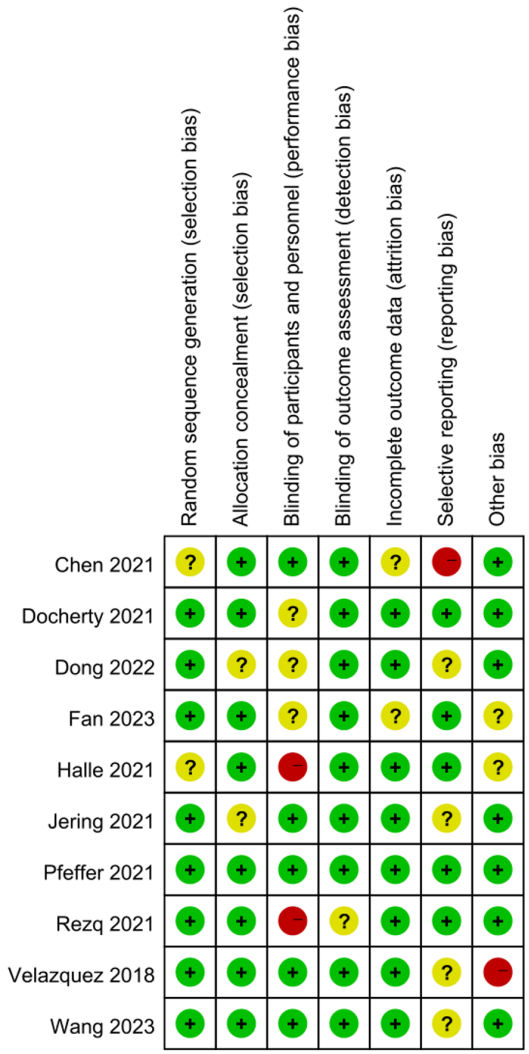

Figure 3. Summary of bias risk. Note: +, -, and ? refer to low, high, and unclear risk, respectively.

The primary measure of heterogeneity used for assessment was the I^2 value, ranging from 0% to 100%. *P*-value <0.05 or I^2>50% indicated heterogeneity exists among the studies included, thus a random effect model was applied; otherwise a fixed effect model was used.

Results

The screened literature and a brief introduction

A total of 268 studies were obtained by searching the databases. The initial screening process excluded 34 duplicates, 27 unqualified studies, and 39 for other reasons. By reading abstracts and titles, an additional 86 studies were excluded. After excluding 43 research reports and review articles, 39 studies remained for further review. After thoroughly reading the full texts, 17 studies with incorrect research types, 11 studies with incomplete or unavailable treatment outcomes, and 1 paper focusing on animals were excluded. 10 studies were included in the final analysis. The detailed screening process is depicted in **Figure 1**.

By reviewing the literature, basic information from 10 included studies [11-20] was extracted, as listed in **Table 2**. These studies collectively included 13,135 patients: 12,504 with AMI, 200 with STEMI, and 881 with TIMI. Among these patients, 6,581 were treated with sacubitril/valsartan, as the experimental group, and the other 6,554 patients were classified as the control group. Seven RCTs reported

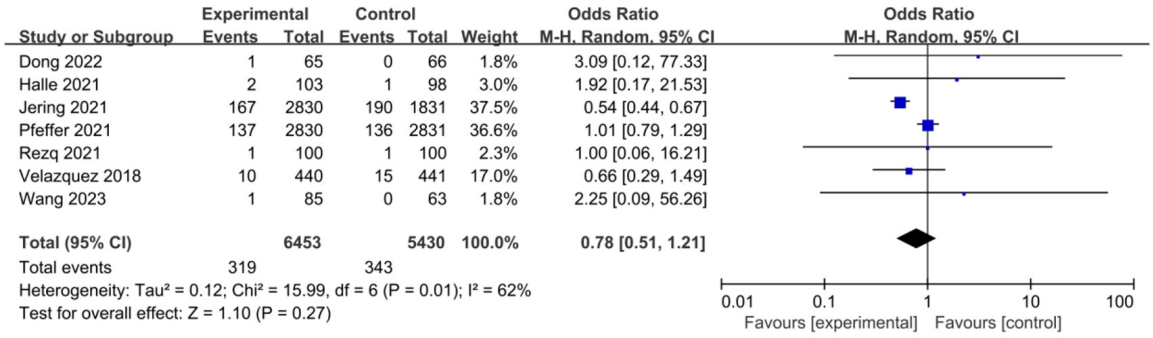

Figure 4. Forest plot of posttreatment mortality of patients.

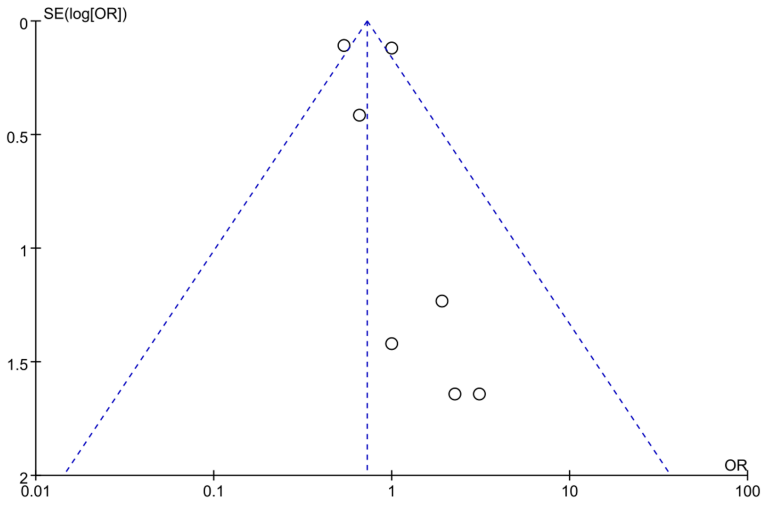

Figure 5. Funnel plot of studies reporting post-treatment mortality.

mortality, and six reported HF-induced hospitalization risk after treatment.

Bias risk

Figure 2 illustrates the bias risk of the 10 studies, which suggested that 8 studies were rated as grade A (75.00%), and 2 were rated as grade B (12.5%). **Figure 3** summarizes the bias risk.

Mortality of patients

Using OR as an indicator of clinical outcome, the OR for posttreatment mortality was 0.87 across 7 studies. There was heterogeneity in mortality rates among different studies (I^2=62%, *P*=0.01) (**Figure 4**), thus a random effects model was used, and the results showed that there was no significant difference in posttreatment mortality rate between the control group and the experimental group (*P*=0.27). The OR was 0.78, with a 95% CI of 0.51 to 1.21. The lowest and highest OR values were 0.54 and 3.09, respectively, with 95% CIs of (0.44, 0.67) and (0.12, 77.33). The funnel plot of posttreatment mortality (**Figure 5**) revealed low risk of publication bias across the 7 studies. According to these results, it was concluded that sacubitril/valsartan can lower the posttreatment mortality of patients with AMI.

Myocardial re-infarction

OR was used as an indicator of clinical outcome in this work. As demonstrated in **Figure 6**, there was no heterogeneity (I^2=0%, *P*=0.77) among studies reporting the myocardial re-infarction count, thus a fixed effects model was used for analysis. The results showed that there was no significant difference (*P*=0.30) in the myocardial reinfarction count between the control group and the experimental group after treatment. The OR was 0.62, with a 95% CI of 0.25 to 1.53. The lowest and highest OR values were 0.21 and 2.88, respectively, with corresponding 95% CIs of (0.02, 2.00) and (0.12, 71.62). The funnel plot of myocardial re-infarction (**Figure 7**) displays a slight risk of publication bias. Based on these findings, sacubitril/valsartan treatment has the ability to decrease the incidence of myocardial re-infarction following treatment.

Risk of HF hospitalization

In **Figure 8**, the risk of HF hospitalization in 8 studies showed an I^2 value of 50% and a *P* value of 0.05. There was no significant hetero-

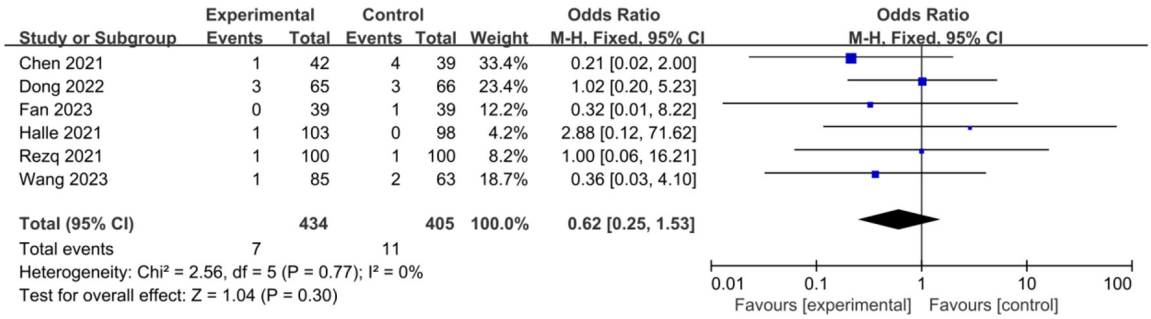

Figure 6. Forest plot of myocardial re-infarction counts after treatment.

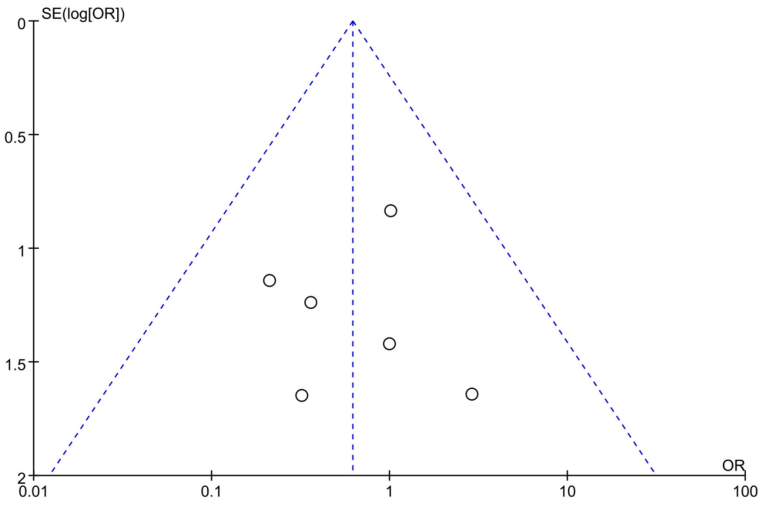

Figure 7. Funnel plot of studies reporting myocardial reinfarction counts.

geneity in the incidence of hospitalization for HF among different studies. Thus, a fixed effects model was used for analysis, and the results showed that the risk of hospitalization for HF in the experimental group was significantly lower than that of the control group after treatment (*P*=0.0002). The overall OR was 0.77, with a 95% CI of 0.67 to 0.88. The highest and lowest OR values were 0.86 and 0.29, with corresponding 95% CIs of (0.70, 1.07) and (0.11, 0.80), respectively. The funnel plot (**Figure 9**) for the HF hospitalization shows low risk for publication bias among the included literature. According to the above results, sacubitril/valsartan can lower the risk of HF hospitalization when applied to treat AMI.

Patients' six-minute walking distance (6MWD)

The mean difference (MD) was used to evaluate the 6MWD of patients in this work. As shown in **Figure 10**, the 6MWD of patients across the 3 studies exhibited an I^2 value of 96% and a *P* value less than 0.00001, indicating significant heterogeneity among different studies. Hence, a random effects model was used for analysis. The results showed that the average 6MWD of patients in the experimental group after treatment was significantly longer than that of the control group (*P*=0.004, MD=95.86, 95% CI: 30.57-161.16). The minimal and maximal MD values were 28.10 and 141.96, respectively, with corresponding 95% CIs of (5.43, 50.77) and (114.78, 169.14), respectively.

Figure 11 is the Galbraith chart for the heterogeneity test of 6MWD of each study. The results show that none of the three included studies showed significant deviation from other points (or were distributed at the edge of the graph), indicating small heterogeneity among the studies. **Figure 12** shows the funnel plot of publication bias analysis of 6MWD related studies. The three included studies were all distributed outside the funnel plot, indicating that there was certain publication bias among the studies.

Patients' left ventricular ejection fraction (LVEF)

In **Figure 13**, the LVEF of patients across 5 studies exhibited an I^2 of 86% and a *P* value less than 0.0001, indicating significant heterogeneity among different studies. Hence, a ran-

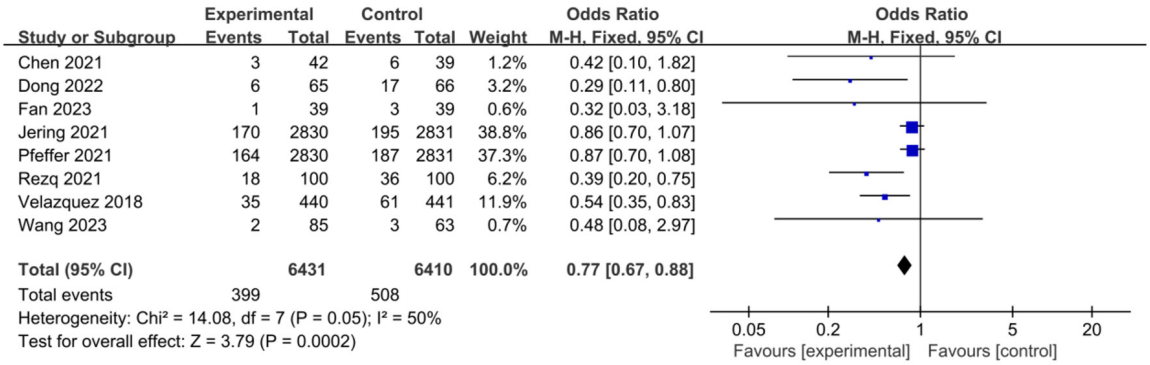

Figure 8. Forest plot of risk of heart failure (HF) hospitalization.

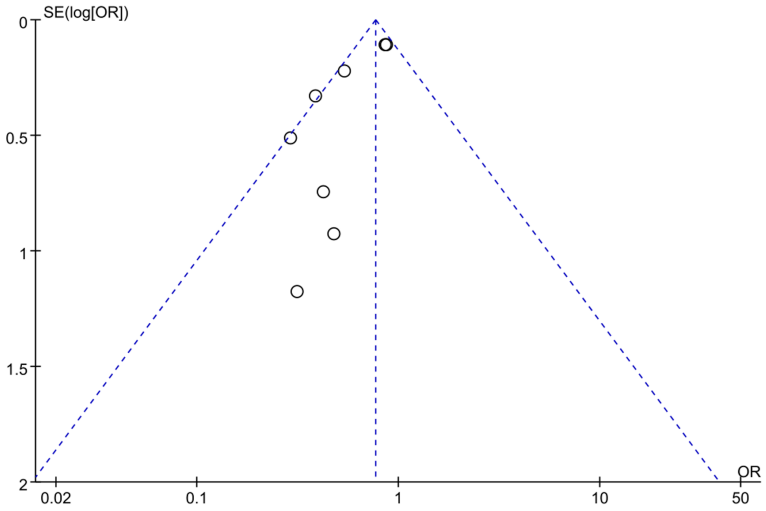

Figure 9. Funnel plot of studies reporting heart failure (HF) hospitalization.

dom effects model was used for analysis, and the results showed that the average LVEF of patients in the experimental group was significantly higher than that of the control group after treatment (P=0.02, MD=2.99, 95% CI: 0.47-5.51). The lowest and highest MD values were -0.30 and 5.46, respectively, with 95% CIs of (-1.75, 1.15) and (1.68, 9.24), respectively.

Figure 14 shows the Galbraith chart for the heterogeneity test of LVEF in each study. The results showed that among the five studies included, two studies significantly deviated from other points (or were distributed at the edge of the chart), indicating significant heterogeneity. **Figure 15** shows the funnel plot of publication bias analysis of LVEF-related studies. Among the five included studies, two studies were distributed outside the funnel plot, indicating that there was certain publication bias among the studies. Based on these findings, it is speculated that sacubitril/valsartan may enhance LVEF in the treatment of acute myocardial infarction. However, further research is needed for verification.

Patients' left ventricular end-diastolic diameter (LVEDD)

In **Figure 16**, the LVEDD across 5 studies showed an I^2 of 84% and a P value less than 0.0001, indicating significant heterogeneity among different studies. Therefore, a random effects model was used for analysis, and the results showed that the average LVEDD of patients in the experimental group was significantly lower than that of the control group after treatment (P<0.00001, MD=-5.56, 95% CI: -7.92-3.20). The lowest and largest MD values were -11.30 and -2.00, respectively, with corresponding 95% CIs of (-14.50, -8.10) and (-4.88, 0.88), respectively.

Figure 17 is the Galbraith chart for the heterogeneity test of LVEDD of each study. The results show that among the five studies included, one study significantly deviates from other points (or is distributed at the edge of the figure). These results indicate that there is some heterogeneity among LVEDD studies. **Figure 18** shows the funnel plot of publication bias analysis of LVEDD related studies. Among the five included studies, one study was distributed outside the funnel plot, indicating that there was certain publication bias among the studies. Based on

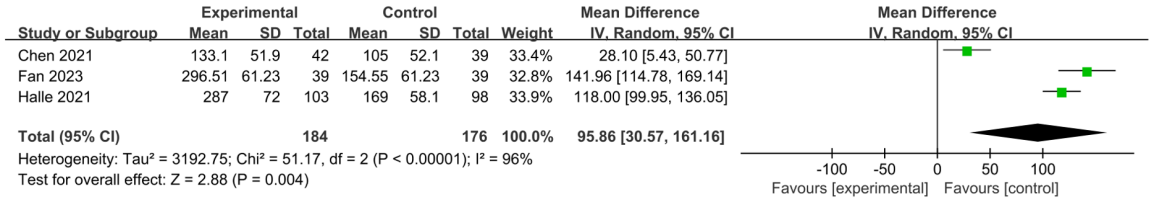

Figure 10. Forest plot of 6-minute walking distance (6MWD).

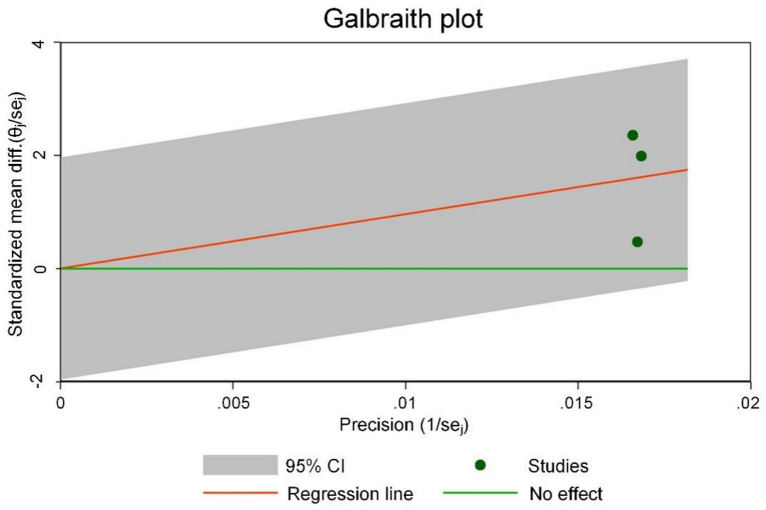

Figure 11. Galbraith heterogeneity test results for the 6-minute walking distance (6MWD).

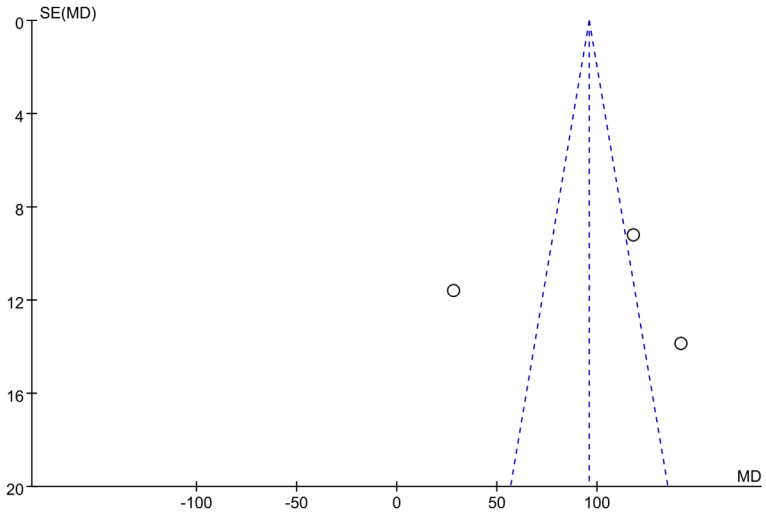

Figure 12. Funnel plot of studies reporting 6-minute walking distance (6MWD).

these findings, sacubitril/valsartan is speculated to improve LVEDD in patients with acute myocardial infarction, but further studies are needed to confirm this.

Discussion

Sacubitril/valsartan is becoming increasingly widespread for AMI in clinical practice. Studies have shown that compared to traditional treatments, sacubitril/valsartan significantly improves myocardial function and therapeutic outcome, thus providing greater clinical treatment value [21]. Furthermore, research indicates that sacubitril/valsartan not only improves cardiac function but also reduces cardiovascular mortality [22]. Based on this, the present study included 10 studies on the efficacy and safety of sacubitril/valsartan in the treatment of AMI.

The preliminary results of the meta-analysis indicated that the OR for myocardial reinfarction from six studies was 0.62, OR for HF hospitalization from eight studies was 0.77, and OR for post-treatment mortality from seven studies was 0.78. These findings suggest that the use of sacubitril/valsartan significantly reduced the risk of post-AMI myocardial reinfarction, HF hospitalization, and post-treatment mortality. These results are consistent with the findings of Desai et al. [23] and Fröhlic et al. [24], who had demonstrated that sacubitril/valsartan effectively improves the prognosis of HF patients. Additionally, Kido et al. [25] showed that higher doses of sacubi-

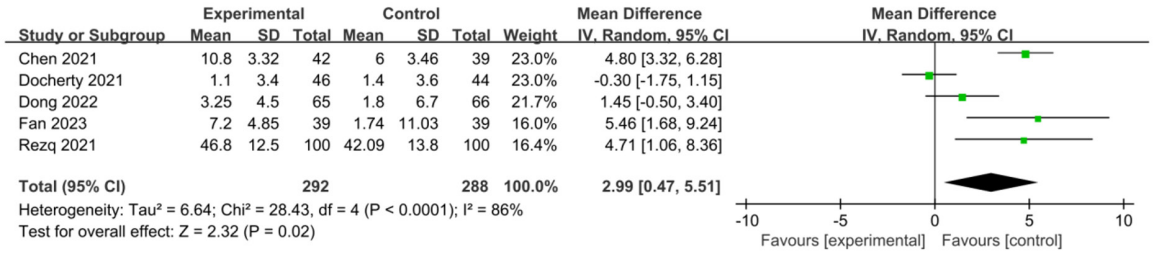

Figure 13. Forest plot of left ventricular ejection fraction (LVEF).

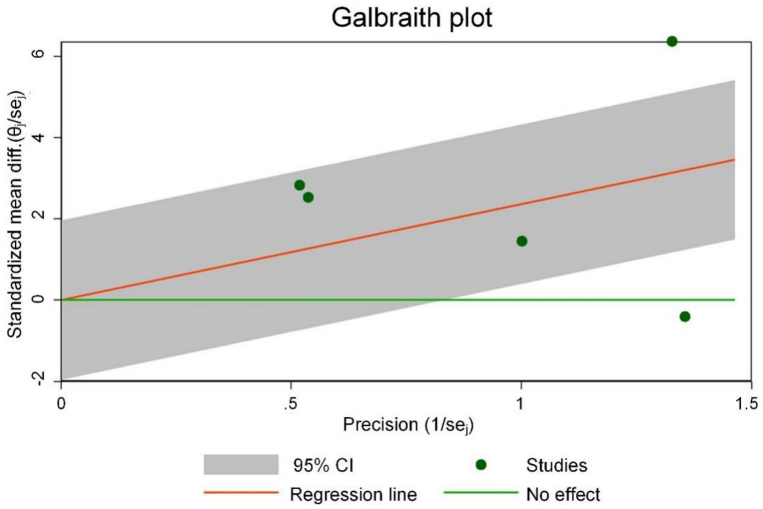

Figure 14. Galbraith heterogeneity for left ventricular ejection fraction (LVEF).

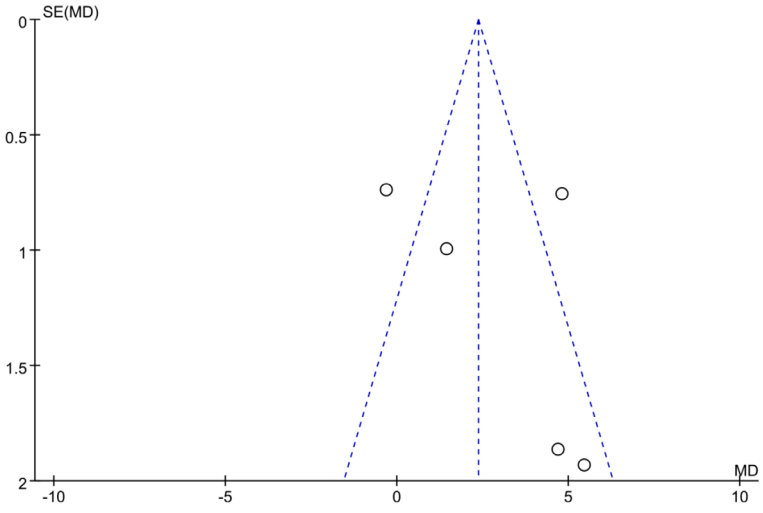

Figure 15. Funnel plot of studies reporting left ventricular ejection fraction (LVEF).

tril/valsartan effectively reduced HF hospitalization rates (16.10% vs. 29.14%, 19.51%) and all-cause mortality (9.27% vs. 29.63%, 17.58%). Acanfora et al. [26] and Correale et al. [27] also confirmed that sacubitril/valsartan significantly reduced mortality in HF patients, substantially improving prognosis and providing clinicians with more effective clinical treatment guidance. The global PARADISE-MI study also indicated the significant efficacy of ARNI in post-MI HF patients, and further evidence was expected to support sacubitril/valsartan as the preferred treatment option for these patients [28, 29].

The meta-analysis further found that the MD of 6MWD in three studies was 95.86, and the MD of LVEDD was -5.56, suggesting that sacubitril/valsartan significantly improved patients' cardiac function, increased 6MWD, and reduced LVEDD. These results are consistent with the findings of McMurray et al. [30], whose study demonstrated that sacubitril/valsartan improved LVEF and cardiac remodeling (reduced LVEDD). Researchers have also confirmed that sacubitril/valsartan treatment reduced LVEF and left atrial volume index (LAVIs) in patients with chronic HF [31, 32]. Additionally, it has been confirmed that the reduction of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTNT) are closely associated with the improvement of LVEF and LAVIs. Rossignol et

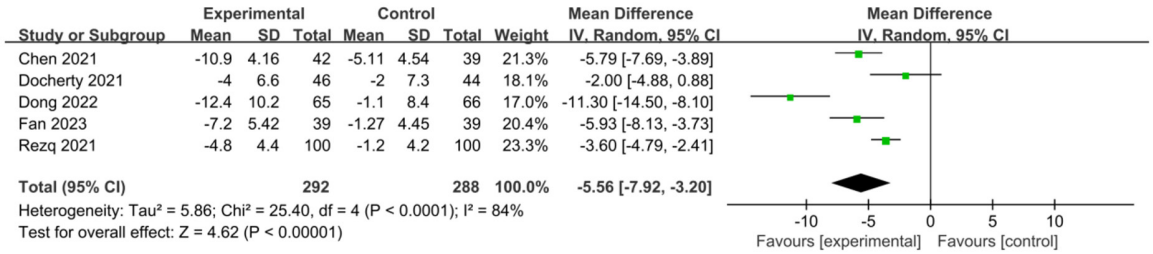

Figure 16. Forest plot of left ventricular end-diastolic diameter (LVEDD).

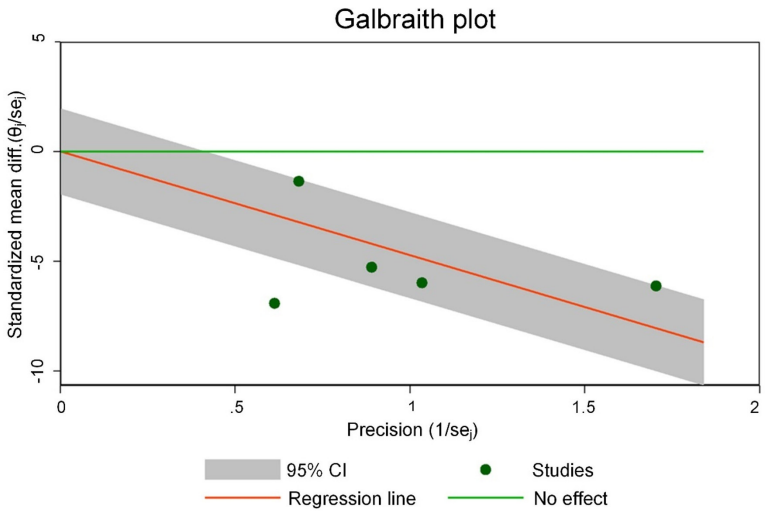

Figure 17. Galbraith heterogeneity test results in left ventricular end-diastolic diameter (LVEDD).

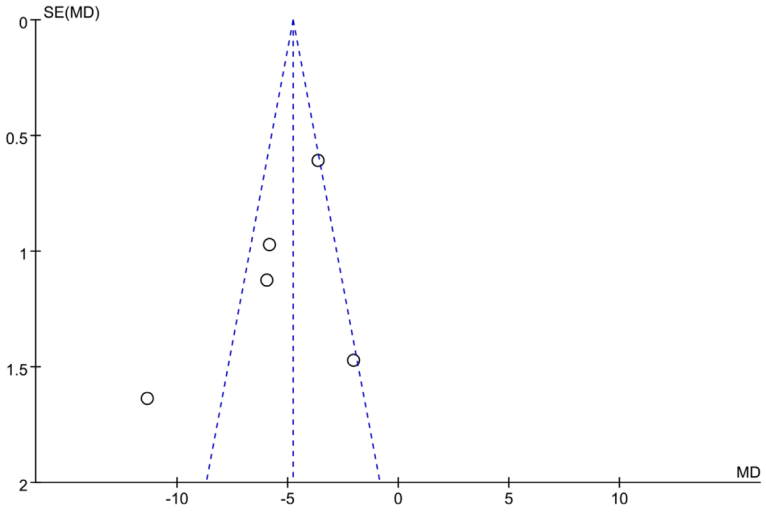

Figure 18. Funnel plot of studies reporting left ventricular end-diastolic diameter (LVEDD).

al. [33] discovered that sacubitril/valsartan had a significant impact on preventing and treating refractory HF, proposing that it can effectively reduce concentrations of NT-proBNP, aldosterone (ALD), and intercellular adhesion molecule 1 (ICAM-1), prevent changes in cardiac function, prolong the 6MWD, and have fewer side effects. Another study indicated that regardless of whether patients underwent vascular reconstruction surgery, sacubitril/valsartan significantly improved their 6MWD [34]. Although some studies suggested limited improvement in LVEF after AMI with sacubitril/valsartan [35], others, including those with larger sample sizes, demonstrated significant improvements in LVEF in HF patients after AMI [36, 37]. This suggests that future research is needed to validate the efficacy and safety of sacubitril/valsartan in different patient populations to better guide clinical practice.

Sacubitril is a neprilysin inhibitor that inhibits the activity of NEP, leading to an increase in levels of brain natriuretic peptide (BNP). BNP is an endogenous diuretic, natriuretic, vasodilator, and antifibrotic substance. By increasing BNP levels, sacubitril promotes diuresis, reduces salt and water retention, vasodilates, and inhibits fibrosis. Valsartan is an angiotensin II receptor antagonist that blocks the binding of angiotensin II to its receptors,

thereby inhibiting the renin-angiotensin system (RAS). Angiotensin II is a potent vasoconstrictor that also promotes salt and water retention and cardiac remodelling. By blocking angiotensin II receptors, valsartan reduces vasoconstriction, decreases salt and water retention, and reduces the workload on the heart. Combining the effects of these two drugs, sacubitril/valsartan acts synergistically in HF patients through two pathways. Sacubitril/valsartan, as a combination therapy, exerts synergistic effects on the treatment of HF through multiple mechanisms, making it one of the important therapeutic options in cardiovascular disease management. However, this meta-analysis did not specifically analyze the mechanism of action of sacubitril/valsartan, hence further exploration is needed.

Conclusion

Sacubitril/valsartan has demonstrated significant efficacy in patients after acute myocardial infarction (AMI). First, sacubitril/valsartan can effectively improve cardiac function and reduce the incidence of myocardial reinfarction after treatment. Second, it can reduce the risk of hospitalization for HR in patients, thereby improving quality of life. In addition, sacubitril/valsartan treatment can reduce mortality and enhance survival after treatment. Functionally, sacubitril/valsartan treatment significantly increased the six-minute walk distance and improved LVEF and LVEDD in patients with AMI, further confirming its role in cardiac function recovery and improvement in quality of life. However, more studies and long-term follow-up data are still needed to validate this conclusion and provide more evidence for clinical practice.

Disclosure of conflict of interest

None.

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