

# The Effects of Sacubitril / Valsartan on Major Adverse Cardiac Events to the Patients of Acute Myocardial Infarction: A Meta-analysis

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**Abstract:** Sacubitril / valsartan is widely used in the patients of heart failure (HF) as an angiotensin receptor-neprilysin inhibitor (ARNI). However, the effects in patients of acute myocardial infarction (AMI) remain unclear. Therefore, in the patients of AMI, we performed this meta-analysis to explore the effects of ARNI on major adverse cardiac events (MACEs). We searched Cochrane Library, PubMed, Web of Science, Embase, China National Knowledge Infrastructure, WanFang, and VIP for randomized controlled trials (RCTs) published up to January 2021, with no language restrictions, compared angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) with ARNI to analyze their effects on MACEs in patients with AMI. All studies met the inclusion and exclusion criteria. PROSPERO registration: CRD42021256018. Our primary outcomes were MACEs, including all-cause mortality, nonfatal myocardial infarction, hospitalization for HF, malignant cardiac event or cardiac death, stroke, re-admission for cardiovascular disease, angina pectoris, malignant arrhythmia, and coronary artery reconstruction. Secondary outcomes included acute or subacute thrombosis, bleeding again, and nonfatal cardiogenic shock. Eleven RCTs (1,125 patients) were recruited. Compared with ACEI / ARBs, sacubitril / valsartan decreased the hospitalization rates for HF (odds ratio (OR), 0.44; 95% confidence interval (CI): 0.33-0.59) and re-admission for cardiovascular diseases (OR, 0.41; 95% CI: 0.18-0.94) in patients with AMI. However, no obvious benefits were found on other MACEs. In the patients of AMI, sacubitril / valsartan decreased the hospitalization rate for HF and re-admission for cardiovascular disease compared with ACEI/ARBs, with no obvious effects on other MACEs.

**Keywords:** Sacubitril / Valsartan. Major Adverse Cardiac Events (MACEs). Acute Myocardial Infarction (AMI). Meta-analysis

## 1. Introduction

AMI is caused by acute and persistent coronary artery ischemia and hypoxia. In patients with AMI, major adverse cardiac events (MACEs) have become the major cause of incidence and fatality [1], which includes all-cause mortality, stroke, nonfatal myocardial infarction, and admission for HF [2]. Fortunately, with the development of cardiac interventional therapy and improvement of traditional secondary prevention drugs (such as ACEI/ARBs), the high incidence and fatality rates of AMI have declined [3]. Among them, the application of ARNI in patients with AMI has been a hot topic in recent years [4, 5]. Sacubitril / valsartan (clinical trial name: LCZ696; trade name: entreso) is the first type of ARNI, the effects on HF have been confirmed in clinical practice [6, 7], although some results are not published [8]. However, the effects on AMI is in the experimental stage. Therefore, we performed this meta-analysis in the patients of AMI to assess the efficacy of ARNI compared with ACEI/ARBs on MACEs.

## 2. Methods

### 2.1. Search Strategy and Studies Included

We have reported this meta-analysis based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [9] statement. Records of RCTs published until January 2021 from

Cochrane Library, PubMed, Embase, China National Knowledge Infrastructure, Web of Science, Wanfang, and VIP were searched using the following keywords: sacubitril / valsartan, acute myocardial infarction (AMI), and randomized controlled trials (RCTs). In patients with AMI, the inclusion criteria were RCTs on sacubitril / valsartan. Two authors (Mei Liu and Yanan He) independently reviewed the titles and abstracts to exclude studies according to the following exclusion criteria: duplicate studies, animal experimental studies, review articles, RCTs that did not report the outcomes of MACEs, and RCTs that were ongoing or not published yet. Controversial studies were included or excluded by discussion among the authors.

## 2.2. Data Extraction and Quality Assessment

The data was extracted by four authors and reached an agreement through discussion together. According to the included studies, we extracted the data following: baseline characteristics of studies (region, sample size, age, male / female) and interventions and controls (dosage, with HF or not, after PCI or not, follow-up duration). The primary outcomes were MACEs, including all-cause mortality, stroke, hospitalization for HF, nonfatal MI, malignant cardiac event or cardiac death, re-admission for cardiovascular disease, angina pectoris, malignant arrhythmia, and coronary artery reconstruction. Acute or subacute thrombosis, bleeding again, and nonfatal cardiogenic shock were analyzed as secondary outcomes.

## 2.3. Risk of Bias Assessment

We used the Cochrane Collaboration Risk of Bias Tool (Review Manager 5.4) to assess the risk of bias.

## 2.4. Statistical Analysis

We used the Review Manager 5.4 to perform Statistical analysis. In the sacubitril/valsartan and control groups, we considered the primary outcomes as dichotomous variables. Chi-square test and  $I^2$  test were used to evaluate the heterogeneity with  $p \leq 0.10$  or  $I^2 \geq 50\%$  indicating significant heterogeneity. The rate of primary outcomes were calculated with ORs and 95% CIs. We used the fixed-effect model. There was statistically significant differences when  $p\text{-value} < 0.05$ , and all  $p\text{-values}$  were two tailed. We reused one study [10] to analyze some of the primary outcomes (nonfatal MI, stroke, malignant cardiac event, hospitalization for HF) because the study used two follow-up durations (1 and 6 months) for comparisons.

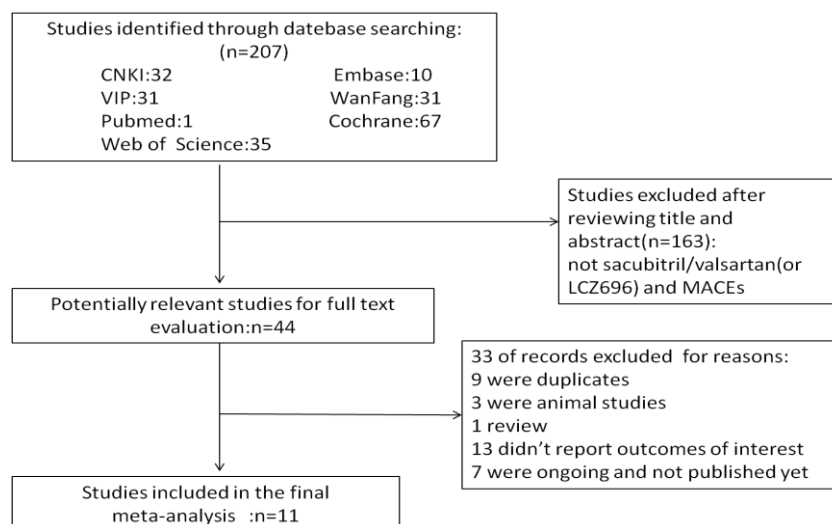


Figure 1: Flow diagram of records selection

## 3. Results

We presented the flow diagram of study selection in Figure 1. 207 studies were identified initially; from these, 163 studies were excluded. We reviewed the full texts of the remaining 44 studies, and 33

studies were excluded according to the exclusion criteria: nine were duplicate studies, three were animal studies, one was a review study, 13 did not report the outcomes of MACEs, and seven were ongoing and not published yet. The remaining 11 RCTs<sup>9-20</sup>, we enrolled 1,125 patients in this meta-analysis. In the included studies, We presented the baseline characteristics. The year of publication was between 2019 and 2021, [10] studies published in Chinese and one in English. In the control group, ACEI/ARBs were used in all included studies. The dosage of interventions and controls was decided according to the patient's tolerance. The majority of records were enrolled to trials after PCI or had been diagnosed with different degrees of HF. The follow-up durations were from 1 to 12 months, but one study [10] used two follow-up durations of 1 and 6 months to compare the effects of ARNI. Of all the studies, only in one study [10], it was clearly stated explicit allocation, concealment, blinding, and randomization strategies were used. In two studies, it was only stated that randomization strategies were used but did not clarify the randomization method used. Therefore, based on the Cochrane Risk of Bias tool, the relatively high risk of bias was found in these studies. Figure 2,3.

Study (first author, year)	Region	Intervention and Controls (dosage)		Sample Size		Age (yr, mean ± SD)		Male/Female		With HF or not	After PCI or not	Follow-up duration Months
		ARNI	ACEI/ARBs	ARNI	ACEI/ARBs	ARNI	ACEI/ARBs	ARNI	ACEI/ARBs			
Chen, C. W. 2019	Chinese	Sacubitril-valsartan 50-200mg bid	Enalapril 5mg qd	26	26	56.30±10.1	55.7±9.7	15/11	14/12	Yes	Yes	6
DanDan Jiang 2020	Chinese	Sacubitril-valsartan 25-100mg bid	Benzapril 10mg qd	22	22	58.10±8.15	56.9±7.67	16/6	14/8	Yes	No	1
JinLun Cai 2020	Chinese	Sacubitril-valsartan 50-200mg bid	Enalapril 5-10mg bid	38	38	67.6±11.51	68.35±7.98	23/15	25/13	Yes	Yes	6
LI Juan* 2020	Chinese	Sacubitril-valsartan 200mg tid	Enalapril 10mg tid	50	50	54.44±5.98	54.87±6.12	28/22	27/23	Yes	Yes	6
LIYing Zhang 2020	Chinese	Sacubitril-valsartan 25-200mg bid	Valsartan 80mg qd	55	55	67.29±3.96	67.92±4.17	32/23	34/21	unclearly	unclearly	12
Rezaq, Ahmed 2021	English	Sacubitril-valsartan 50-100mg bid Sacubitril-valsartan 25-200mg bid	Valsartan 5mg qd-5mg bid Valsartan 20-80mg qd	100	100	52.0±9.2	57.0±11.6	86/14	89/12	unclearly	Yes	1 and 6
WANG Haiyan 2020	Chinese	unclearly dosages		80	80	59.0±10.3	58.0±10.4	69/11	67/13	Yes	Yes	6
Wang, H. 2020	Chinese	Sacubitril-valsartan 25-200mg bid	Enalapril 25mg qd	68	69	59.13±7.15	60.56±7.62	52/16	54/15	Yes	Yes	6
Yang Dong 2020	Chinese	Sacubitril-valsartan 50-200mg bid	Valsartan 40-80mg qd	40	40	63.9±8.2	62.0±7.6	23/17	29/14	Yes	Yes	6
ZHANG Rui-ying 2021	Chinese	Sacubitril-valsartan 50-200mg bid	Enalapril 10-20mg qd	56	67	51.87±3.35	52.84±3.27	36/20	39/28	No	Yes	12
Zhao Yuehua 2020	Chinese	Sacubitril-valsartan 50-200mg bid	Benzapril 20mg qd	22	21	64.6±9.8	62.1±8.7	14/8	14/7	Yes	Yes	3

Abbreviations: ARNI, angiotensin receptor-neprilysin inhibitor; ACEI/ARBs, angiotensin converting enzyme inhibitor/angiotensin receptor blockers; HF, heart failure; PCI, percutaneous coronary intervention

Figure 2: Baseline characteristics of included records

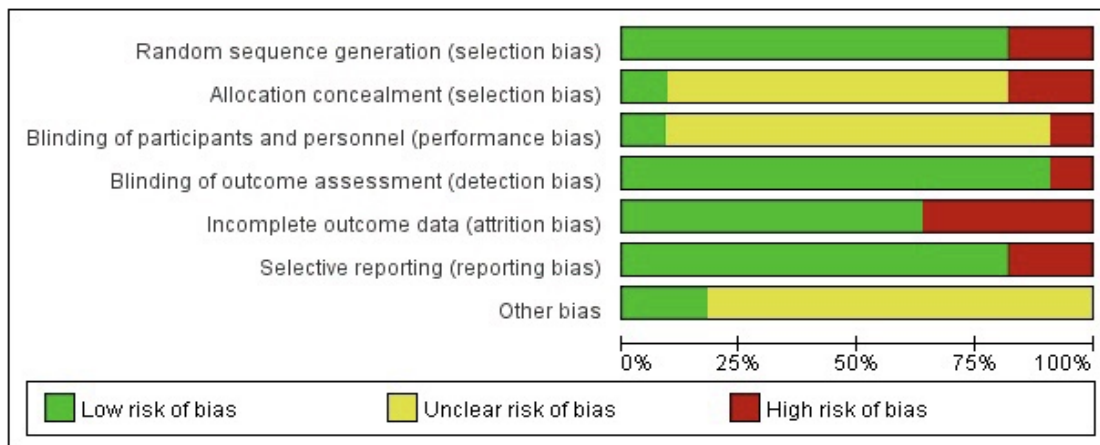


Figure 3: Risk of bias

Regarding the outcomes of all studies included, five studies reported all-cause mortality, eight studies reported hospitalization for HF, eight studies reported nonfatal MI, four studies reported stroke, six studies reported malignant cardiac event or cardiac death, three studies reported re-admission for cardiovascular disease, four studies reported angina pectoris, four studies reported malignant arrhythmia, three studies reported coronary artery reconstruction, two studies reported acute or subacute thrombosis, one study reported bleeding again, and one study reported nonfatal cardiogenic shock.

3.1. Primary Outcomes

Five studies 11-14, 18 with a total of 431 patients reported all-cause mortality. Comparing ARNI with ACEI/ARBs, no significant effects were noted in the reduction of all-cause mortality (pooled OR: 0.33; 95% CI, 0.01-8.21; Figure 4).

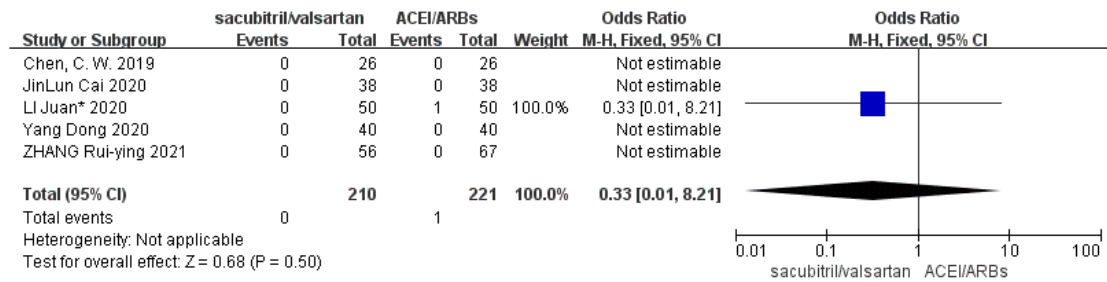


Figure 4: Forest plot of participants compared sacubitril / valsartan with ACEI / ARBs after AMI on all-cause mortality

Eight studies [10-12], 15-19 reported on hospitalization for HF. The hospitalization rate for HF decreased in a total of 908 patients (OR: 0.44; 95% CI: 0.33-0.59, P < 0.00001; P = 0.95 for heterogeneity; I<sup>2</sup> = 0%; Figure 4). To further explore the correlation between hospitalization for HF and the dosages of ARNI and follow-up duration, we performed a subgroup analysis and found that the dosage of 50-100 mg bid (OR: 0.37; 95% CI: 0.20-0.69, P = 0.002; P = 0.90 for heterogeneity; I<sup>2</sup> = 0%) and a longer follow-up duration (OR: 0.45; 95% CI: 0.30-0.69, P = 0.0002; P = 0.63 for heterogeneity; I<sup>2</sup> = 0%) were significantly better for reducing the hospitalization rate for HF (Figure 5).

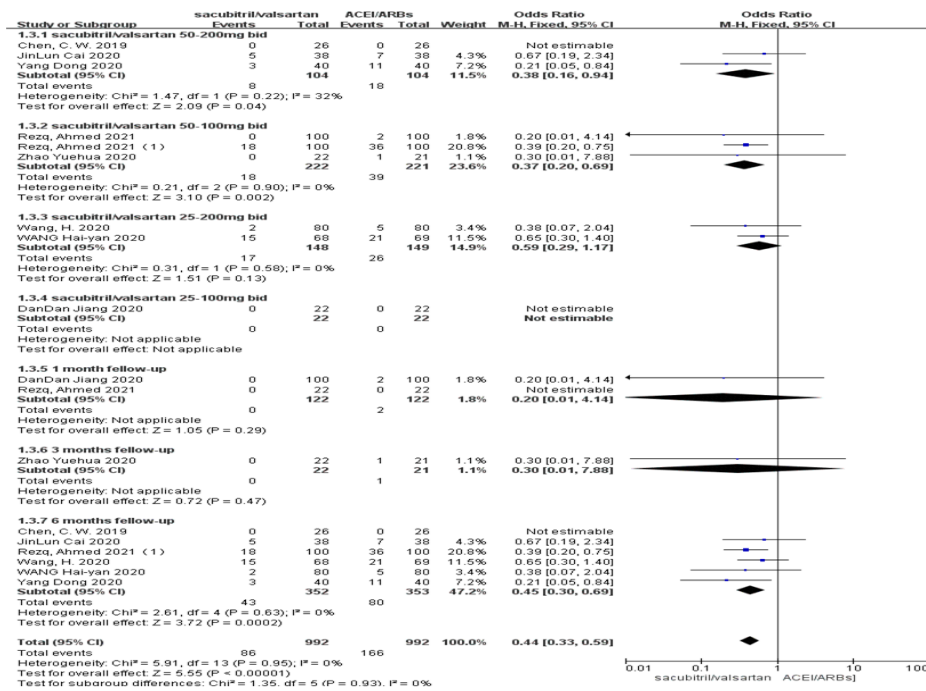


Figure 5: Forest plot of participants compared sacubitril / valsartan with ACEI / ARBs after AMI on hospitalization for heart failure

Compared with ACEI/ARBs, the risk of re-admission for cardiovascular disease was decreased with sacubitril / valsartan based on the records of three studies [12-15] (pooled OR: 0.41; 95% CI: 0.18-0.94; Figure 6).

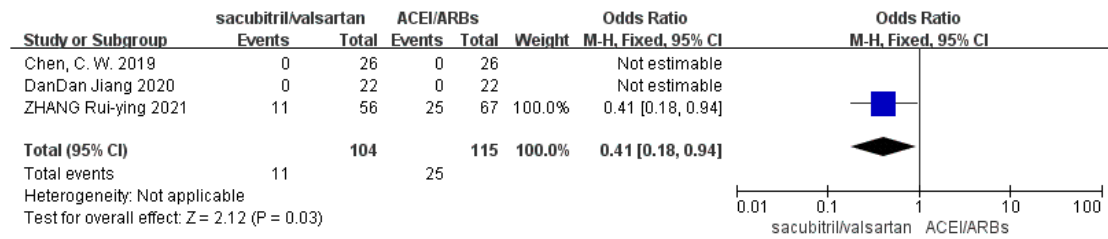


Figure 6: Forest plot of participants compared sacubitril / valsartan with ACEI / ARBs after AMI on re-admission for cardiovascular disease.

Even when no significant differences were noted in nonfatal myocardial infarction in eight studies [10-19] (OR: 0.69; 95% CI: 0.42-1.16, P = 0.16; P = 0.99 for heterogeneity; I<sup>2</sup> = 0%; Figure 6), We performed the subgroup to find the relationship between the dosages and follow-up durations of sacubitril / valsartan and ACEI/ARBs and found no significant differences (Figure 7).

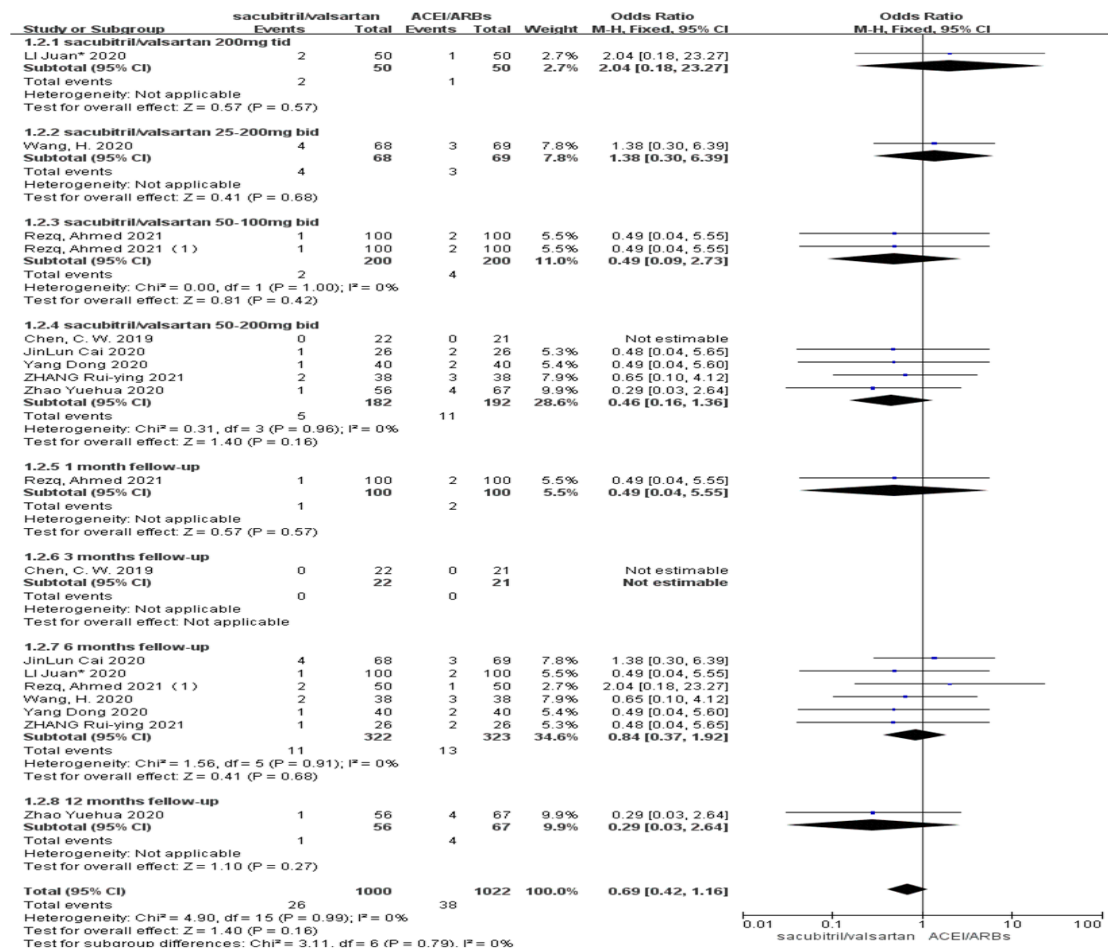


Figure 7: Forest plot of participants compared sacubitril / valsartan with ACEI / ARBs after AMI on nonfatal MI.

Regarding the malignant cardiac events or cardiac death in six studies 10, 14-16, 19, 20, no significant difference were noted in the ARNI and ACEI/ARBs groups (OR: 0.45; 95% CI: 0.17-1.20, P = 0.11; P = 0.62 for heterogeneity; I<sup>2</sup> = 0%; Figure 8), as was noted for malignant arrhythmia in four studies [16-20] (OR: 0.53; 95% CI: 0.24-1.19, P = 0.13; P = 0.55 for heterogeneity; I<sup>2</sup> = 0%; Figure 9), angina pectoris in four studies [13], [17-19] (OR: 0.47; 95% CI: 0.18-1.21, P = 0.12; P = 0.84 for heterogeneity; I<sup>2</sup> = 0%; Figure 10), stroke in four studies [10-12], [14] (OR: 0.59; 95% CI: 0.05-6.69; Figure 11), and coronary artery reconstruction in three studies [12-19] (OR: 0.62; 95% CI: 0.23-1.64, P = 0.33; P = 0.23 for heterogeneity; I<sup>2</sup> = 29%; Figure 12).

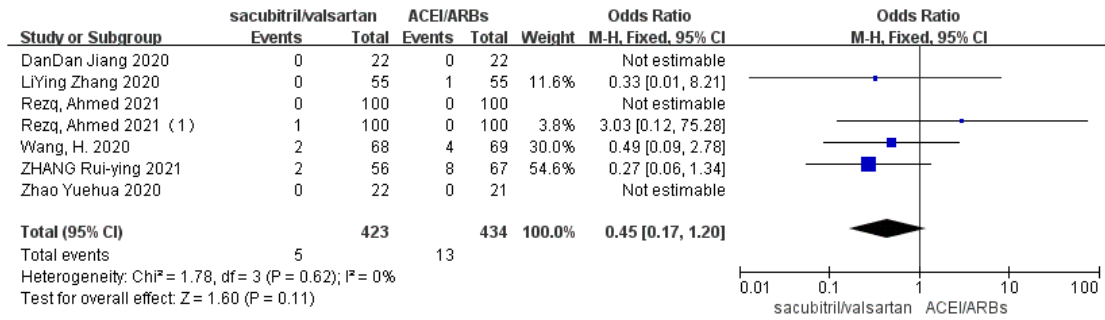


Figure 8: Forest plot of participants compared sacubitril / valsartan with ACEI / ARBs after AMI on malignant cardiac event (or cardiac death)

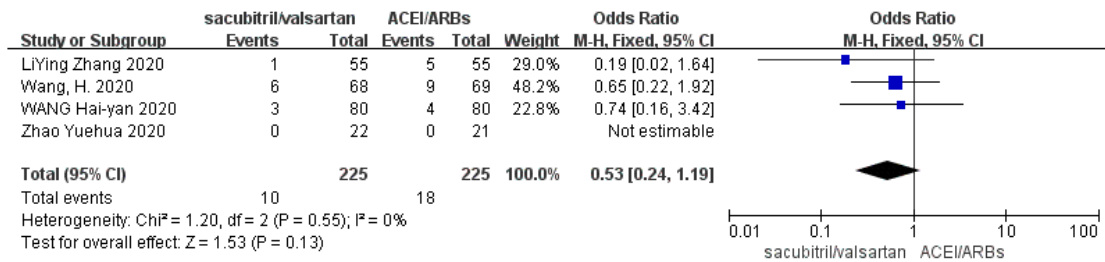


Figure 9: Forest plot of participants compared sacubitril / valsartan with ACEI / ARBs after AMI on malignant arrhythmia

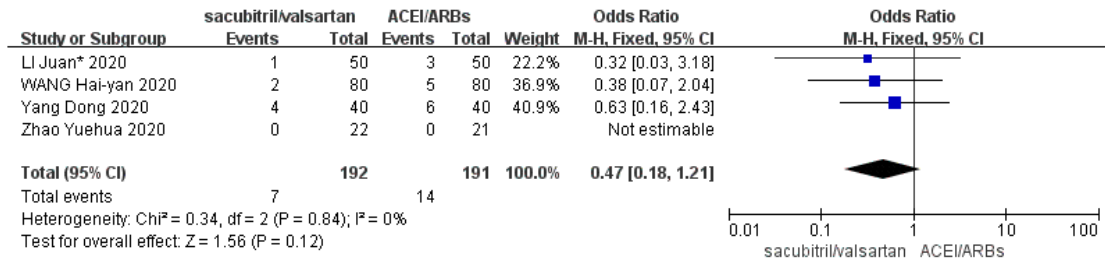


Figure 10: Forest plot of participants compared sacubitril / valsartan with ACEI / ARBs after AMI on angina pectoris

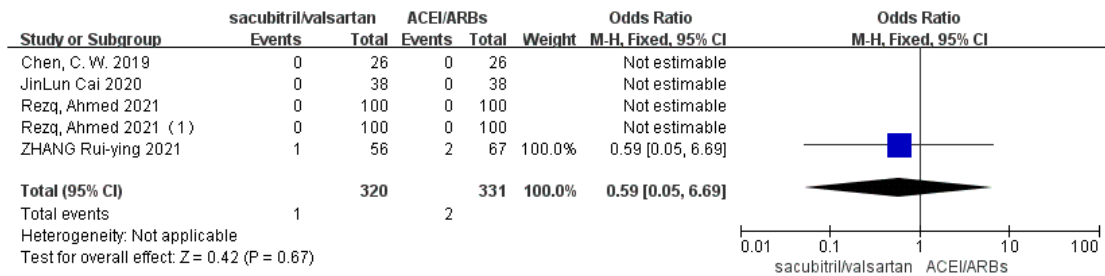


Figure 11: Forest plot of participants compared sacubitril / valsartan with ACEI / ARBs after AMI on stroke

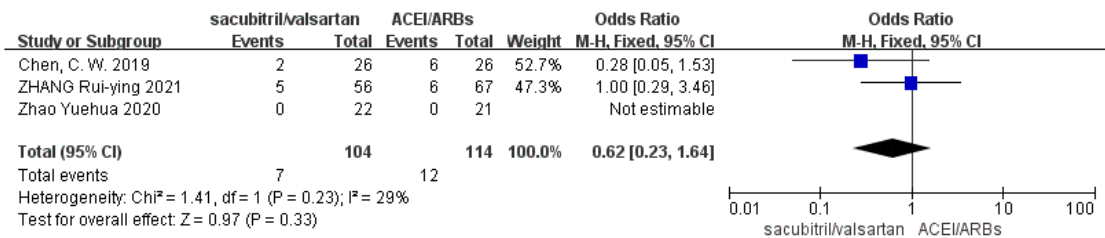


Figure 12: Forest plot of participants compared sacubitril / valsartan with ACEI / ARBs after AMI on coronary artery reconstruction

### 3.2. Secondary Outcomes

Two studies<sup>13</sup>, 19 reported acute or subacute thrombosis, one<sup>20</sup> reported bleeding again, and one<sup>12</sup> reported nonfatal cardiogenic shock as the secondary outcomes; as these studies and their data were small, we chose not to perform the meta-analysis for these outcomes and regarded them as secondary outcomes.

## 4. Discussion

This meta-analysis was performed based on [11] studies, enrolled 1, 125 patients. According to the data analysis, only two positive results were noted: lower hospitalization rates for HF and re-admission for cardiovascular disease. Sacubitril / valsartan exerts its effects in the treatment of HF not only by decreasing the degradation of natriuretic peptide family by inhibiting the activity of neprilysin but also by blocking angiotensin II receptor, subsequently inhibiting the renin-angiotensin-aldosterone system (RAS) and the sympathetic nervous system (SNS). Sacubitril / valsartan has been widely used in the treatment of HF; therefore, from existing research and theories, we can predict these two positive results, and despite the low heterogeneity, we performed the subgroup analysis to find the relationship between hospitalization for HF and dosages and follow-up durations. We found that the dosage of sacubitril / valsartan of 50-100 mg bid and longer follow-up durations were more beneficial for patients with AMI. Most patients (61.5%) were enrolled in the trials after HF, which may have affected the outcome of this meta-analysis.

Similar to the other negative primary outcomes such as all-cause mortality, stroke, nonfatal MI, malignant cardiac event or cardiac death, angina pectoris, malignant arrhythmia, and coronary artery reconstruction, significant differences were not considered between ACEI/ARBs and ARNI in terms of these negative primary outcomes in the patients of AMI. However, the effect of ARNI in reducing the incidence of recurrent MI and arrhythmia has been shown in many studies and trials by inhibiting the inflammatory response, myocardial fibrosis and hypertrophy, ventricular remodeling, and left ventricular scar [21-23]. The sample size is too small and the follow-up duration is too short, which could be responsible for the negative outcomes; therefore, further research and trials are required to confirm this conclusion. Regarding the secondary outcomes, due to paucity of other research findings, we could not perform the meta-analysis. More evidence needs to be provided in the future in terms of these outcomes.

The limitations in this meta-analysis: first, because of several studies and trials were ongoing, insufficient data were available to perform the meta-analysis. Second, the dosage and types of ACEI/ARBs used in this meta-analysis were different, which may have influenced the results. Third, the sample size was small, and most of the patients recruited for the trials were diagnosed with HF after AMI. Finally, the studies included were mostly from China, meaning that there may have been regional and ethnic differences in the results.

## 5. Conclusion

In summary, according to this meta-analysis, we believe that sacubitril/valsartan decreased the hospitalization rate of HF and re-admission for cardiovascular diseases and that there is no obvious effects with respect to others MACEs compared with ACEI/ARBs in patients with AMI. For the additional outcomes, more studies and trials are needed to assess the effects of ARNI in the future.

## Acknowledgments

We wish to thank Yafei Chen in Zhoukou Central Hospital of Henan Province for his advice in this meta-analysis.

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