Effect Sacubitril/Valsartan in patients with Acute Myocardial Infarction (AMI): a systematic review and meta-analysis

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ABSTRACT

Background: Acute Myocardial Infarction (AMI) is a type of coronary heart disease with high morbidity and mortality. The renin-angiotensin-aldosterone system (RAAS) is an important endocrine system in controlling blood pressure and cardiovascular homeostasis and is responsible for AMI. In patients with AMI or a heart attack, sacubitril/valsartan has been shown to reduce the risk of heart failure and death. This study aims to evaluate the effect of sacubitril/valsartan in AMI patients.

Methods: In order to evaluate the effects of sacubitril/valsartan in patients with AMI, three databases, including PubMed, Cochrane Library, and the ClinicalTrials website, were searched. The final search was performed in January 2023. The meta-analysis was subsequently performed with Revman 5.4 software.

Results: The results of the main outcomes showed that sacubitril/valsartan has no significant reduction in major adverse cardiovascular and cerebrovascular events (MACCEs) odds ratio (OR), 0.70; 95% confidence interval (CI), 0.38-1.30; P=0.26 and incidence of acute heart failure (AHF) (OR, 0.52; 95% CI, 0.24-1.15; P=0.11). The secondary outcomes showed no effect of sacubitril/valsartan to increase left ventricular remodeling.

Conclusion: In conclusion, the present meta-analysis revealed that sacubitril/valsartan could not effectively reduce the incidence of MACCEs and AHF in patients with AMI. In the future, a meta-analysis study will be designed with many studies to reduce the incidence of MACCEs and AHF effectively.

Keywords: Sacubitril, Valsartan, AMI, MACCEs.


INTRODUCTION

Acute myocardial infarction (AMI) is a serious health problem because of its high incidence and poor prognosis. The principle of therapy is to protect and improve the patient's cardiac function, save the dying myocardium, and reduce the infarct area. Also, actively prevent and treat possible complications. Immediate revascularization in patients suffering from AMI and drug treatment is necessary to reduce mortality.3

The renin-angiotensin-aldosterone system (RAAS) is an important endocrine system in controlling blood pressure and cardiovascular homeostasis. Hemodynamic changes in the period after myocardial infarction stimulate intense activation of the circulating and local RAAS. This occurs through its end products, angiotensin II and aldosterone, to increase sodium and fluid retention, cardiac contractility, and systemic vascular tone. In the long term, this adaptive response may be harmful and contribute to developing some of the complications seen after infarction. Angiotensin II can induce coronary and systemic vasoconstriction and, therefore, can prolong the duration of ischemia. RAAS response after infarction can be modified pharmacologically. Angiotensin-converting enzyme (ACE) inhibitor drugs have become a mainstay of treating heart failure and have now been shown to have an important role in preventing ventricular remodeling after myocardial infarction.4

There are 2 classes of antihypertensive drugs that inhibit the renin-angiotensin-aldosterone system (RAAS), were Angiotensin Receptor Blockers (ARB) and Angiotensin-Converting Enzyme Inhibitors (ACEI). The two RAAS inhibitory agents (ARB & ACEI) have...
vascular protective effects by enhancing endothelial function and preventing vascular remodeling.\(^6\)

Sacubitril/valsartan is a medication used to treat heart failure and is a combination of two drugs: sacubitril, an angiotensin receptor-neprilysin inhibitor (ARNI), and valsartan, an angiotensin receptor blocker (ARB). Many trials confirmed that the sacubitril–valsartan in treating patients with heart failure reduced ejection fraction (HFrEF). However, there are insufficient data to register the effects of mandatory discontinuation of sacubitril-valsartan, either because of financial shortage and switching to standard therapy, including an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).\(^6\)

Sacubitril/valsartan is the first angiotensin receptor-neprilysin inhibitor combining the valsartan with sacubitril, a neprilysin inhibitor. In the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, ARNI therapy significantly reduced the risk of death and hospitalization for worsening HF compared with enalapril. Lots of studies have confirmed that in HF patients with reduced ejection fraction, sacubitril/valsartan can reduce N-terminal B-type natriuretic peptide levels, increase left ventricular ejection fraction (LVEF), and reverse ventricular remodeling, exerting more clinical and symptomatic benefits as compared to ACEI/ARB.\(^7\)

Several clinical trials compared the benefits of sacubitril–valsartan and ACEI/ARB in AMI patients and identified that sacubitril–valsartan could improve the Left Ventricular (LV) ejection fraction (LVEF) and significantly reduce the major adverse cardiac events (MACE), HF re-hospitalization risk, as well as LV dimensions. In patients with acute myocardial infarction (AMI), or a heart attack, sacubitril/valsartan has been shown to reduce the risk of heart failure and death. It works by inhibiting the activity of certain enzymes that contribute to the development of heart failure and by blocking the effects of a hormone called angiotensin II that constricts blood vessels and increases blood pressure.\(^8\)

Based on those mentioned above, this study aims to evaluate the effect of Sacubitril/Valsartan in patients with Acute Myocardial Infarction (AMI) through systematic review and meta-analysis.

**MATERIALS AND METHODS**

The inclusion criteria of relevant literature were defined according to the Population, Intervention, Comparison, Outcome and Study (PICOs) design tools such as:

1. **Population:** patients with AMI after coronary revascularization, including percutaneous transluminal coronary intervention (PCI).
2. **Intervention:** the sacubitril/valsartan group was administered sacubitril/valsartan,
3. **Comparison:** the control group was treated with ACEI or ARB on the basis
4. **Outcome:** the main outcomes were major adverse cardiovascular and cerebrovascular events (MACCEs) and acute heart failure (AHF). The secondary outcome is LVEF (Left Ventricular Ejection Fraction)
5. **Study design:** randomized controlled trials (RCTs) were included.

The exclusion criteria (regarding the publications) were republished studies, studies with no available data, studies in which the full text was unavailable, and studies written in a language other than English. The search was performed by entering the following keywords: acute myocardial infarction and sacubitril/valsartan. The literature search start date was October 2021 until January 2023. Databases from PubMed, Cochrane Library and the ClinicalTrials. The flow diagram showed in Figure 1.

A total of 3 studies were included in the systematic review. The studies extracted from the information table were author, year, country, research, characteristic, sample size, type of AMI, AMI treatment, intervention, doses of sacubitril/valsartan, intervention, and follow-up. It is presented in Table 1. Statistical analysis was performed using Review Manager 5.3 and Odds Ratio (OR) as effect analysis statistics for dichotomous variables of effect measurement indicators, and each effect size provided its 95% CI.
RESULTS

Literature search results obtained 152 articles by searching the databases, and 138 articles were retrieved after removing duplicates. Then, 124 articles were not selected based on inclusion and exclusion criteria. A total of 14 articles were examined and 11 articles were not RCTs. Ultimately, 3 studies were included in the meta-analysis (Figure 1).

The basic information of the included studies is shown in Table 1. The cases involved Egypt, China, and the US. The three studies comprised one Prospective multicenter RCT and two Active-controlled randomized. Regarding the type of AMI involved, all studies assessed ST-elevation myocardial infarction (STEMI) treated with PCI. The intervention used for all experimental groups was sacubitril and valsartan, although the time between the onset of AMI and the intervention varied.

Overall analysis for the primary outcomes was presented in Figure 2. The results of the meta-analysis revealed no significant differences were identified in MACCEs (OR, 0.70; 95% CI, 0.38-1.30; P=0.26) and AHF (OR, 0.52; 95% CI, 0.24-1.15; P=0.11). The secondary outcome is presented in Figure 3. The result of the meta-analysis revealed no significant differences were identified in LVEF (OR, 0.26; 95% CI, -0.05-0.58; P=0.10).

DISCUSSION

In this analysis, when RCT studies were included in the meta-analysis showed that sacubitril/valsartan does not affect patients with acute myocardial infarction. Other studies showed no statistically significant difference in the overall incidence of cardiovascular events between the 2 groups of intervention. This may be due to the follow-up time or sample size being insufficiently long or large.

Although in this study, the sacubitril/valsartan has no effect in patients with acute myocardial infarction, other studies have expected results. A meta-analysis by Liu S et al. revealed the sacubitril/valsartan reduction in MACCEs and the incidence of AHF. Since the appearance of sacubitril/valsartan, its benefits for Heart Failure (HF) patients have been confirmed in most studies. Research conducted by Zhao et al. found that sacubitril/valsartan is superior to ACEI in reducing the risk of major cardiac events and increased left ventricular ejection fraction.

In this meta-analysis study, there was no effect of sacubitril/valsartan to increase left ventricular remodeling. Although many studies show that early application of sacubitril/valsartan following emergency PCI in patients with AMI can effectively improve left ventricular remodeling. In addition, a meta-analysis performed by Zhao et al. present study revealed a significant reduction in MACCEs, readmission and incidence of AHF without any statistically significant differences in adverse events between the sacubitril/valsartan group and the control group. Other studies showed 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.

There were limitations in this meta-analysis. First, the sample size of most included RCTs was small and may put our estimates at risk of bias. Second, regarding sacubitril/valsartan administration, the initial time, dosage, and duration were variable in each RCT, which might produce confound bias for the evaluation.

It is important to note that sacubitril/valsartan is not recommended for use in the acute phase of a heart attack but rather for patients with stable heart failure or reduced ejection fraction (HFrEF) or after the acute phase has resolved. Sacubitril/valsartan can cause side effects and may not be appropriate for all patients. It is important to consult a healthcare professional to determine if sacubitril/valsartan is the right treatment for a specific patient.

CONCLUSION

In summary, this meta-analysis showed that sacubitril/valsartan does not affect patients with acute myocardial infarction. But other studies suggest that early administration of sacubitril-valsartan maybe can decrease the risk of hospitalization for HF and improve the cardiac function in AMI patients. In the future, the PARADISE-MI study will design RCT with a large sample size.
size, confirm our findings and further investigate whether sacubitril/valsartan could improve the long-term prognosis of patients following AMI.

CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

ETHICS CONSIDERATION

Ethical consideration of publication followed COPE and ICMJE protocols before the study was published.

FUNDING

None.

AUTHOR CONTRIBUTION

All authors equally contribute to the study from the conceptual framework, data acquisition, and data analysis until reporting the study results through publication.

REFERENCES


