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Therapeutic Role of Sacubitril/Valsartan after Myocardial Infarction: A Systematic Review and Meta-Analysis

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1. Abstract

Background: Acute Myocardial Infarction (AMI) is among the most common causes of morbidity and mortality. Although there is contradictory data about sacubitril/valsartan's clinical efficacy and safety, it may lower the risk of AMI. The focus of this research is to carefully analyse and summarise data from randomised controlled trials (RCTs) to ascertain whether early sacubitril/valsartan treatment after AMI is safe and efficacious.

Methodology: English databases like PubMed, Embase and Google Scholar were searched from inception up to June; 2025 using terms: acute non-ST-segment elevation myocardial infarction (NSTEMI), AMI, sacubitril/valsartan, acute ST-segment elevation myocardial infarction (STEMI). The studies included compared sacubitril/valsartan (experimental group) to ACEI or ARBs (control group). With a random effect model, generic inverse variance was utilized to pool the mean differences (MDs) and risk ratios (RR) for continuous and dichotomous outcomes, respectively, along with 95% confidence intervals (CIs). The bias was assessed using Cochrane's 5.1.0 tool and conducted meta-analysis using RevMan 5.4.

Results: Nine RCTs involving 6774 myocardial infarction patients were included, 3399 were given Sacubitril/Valsartan and 3375 received ACEIs or ARBs. Comparing the treatment group to the heart failure death risk, the results indicated that sacubitril/valsartan treatment was substantially linked with a lower risk of heart failure death (RR = 0.83, 95% CI = 0.70-0.98, I2 = 0, P = 0.03), increased LVEF (MD = 3.41, 95% CI = 2.51-4.32, I2 = 37%, P = 0.0001), lower incidence of MI (RR = 0.96, 95% CI = 0.37-2.47, P = 0.93, I2 = 0%), and lower hospitalization rates for heart failure (RR = 0.52, 95% CI = 0.28-0.95, P = 0.03, I2 = 72%), decreased NT-proBNP (RR = -290.41, 95%CI = -508.93_ -71.90, I2 = 99, P = 0.009), increased 6MWD(RR = 81.05, 95% CI = -37.43-199.53, I2 = 98%, P = 0.18), reduced incidence of all adverse events (RR = 0.91, 95% CI = 0.80-1.04, I2 = 0%, P = 0.16) and reduced incidence of MACE (RR = 0.58, 95%CI = 0.45-0.75, I2 = 0%, P<0.0001).

Conclusion: Early sacubitril/valsartan administration significantly reduces myocardial infarction, heart failure-related mortality, hospitalization, cardiovascular deaths, and adverse cardiac events in post-AMI patients. Furthermore, it raises the left ventricular ejection fraction.

2. Keywords: Angiotensin Receptor-Neprilysin Inhibitors, Sacubitril/Valsartan, Enalapril, Heart failure, Valsartan, Systematic review, Meta-analysis

3. Introduction

Myocardial infarction (MI) can be described as an acute event in which there is occlusion of the coronary arteries that results in ischemia or necrosis of the myocardium tissue [1]. Heart failure is treated with medications such as ACEIs (angiotensin converting enzyme inhibitors), MRAs (mineralocorticoid receptor antagonists), and angiotensin receptor blockers (ARB) [2]. Heart failure (HF) is primarily caused by acute MI, even with the wide range of medication available [3]. Recent research indicates that the hospitalization rate for heart failure (HF) was 13.6% for patients with non-ST-elevation myocardial infarction (NSTEMI) and 14.8% for patients with acute ST-segment elevation myocardial infarction (STEMI). Heart failure incidence was 25.4% and 23.4% at one year, respectively [4]. The onset of heart failure (HF) after an acute myocardial infarction has been closely linked to the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, which increases blood pressure [5]. In addition, as a compensatory mechanism, the natriuretic peptide system is also triggered simultaneously that causes vasodilation, natriuresis, and diuresis thus lowering the blood pressure. It operates in antagonistic relationship with the RAAS and positively impacts on the pathophysiology of cardiac failure. The neprilysin enzyme degrades these natriuretic peptides [6].

The sole drug in the class of pharmaceuticals known as angiotensin receptor neprilysin inhibitors (ARNI) is sacubitril/valsartan combination. While valsartan is an angiotensin receptor blocker (ARB), sacubitril is an inhibitor of neprilysin, delaying the breakdown of these natriuretic peptides and extending their therapeutic effects [7]. This combination medication blocks the RAAS system and concurrently prevents the breakdown of natriuretic peptides that lowers blood pressure through the principal events of vasodilation and diuresis. On the other hand, blocking neprilysin will cause angiotensin II to build up because neprilysin breaks down angiotensin II. Because of this, a neprilysin inhibitor cannot be used alone to counteract the effects of excess angiotensin II; it must be taken in conjunction with an ARB.

The European Society of Cardiology recently issued guidelines for the diagnosis and treatment of acute and chronic heart failure suggest that in ambulatory patients with heart failure with reduced ejection fraction (HFrEF) who are still experiencing symptoms after receiving optimal care from an ACEI, a beta-blocker, and a mineralocorticoid receptor antagonist (MRA), sacubitril/valsartan should be used instead of an ACEI.

Early administration of ACEI's following acute MI has demonstrated a 7% reduction in HF during the first month just [8]. Sacubitril/valsartan has been approved as a substitute for ACEIs or ARBs in those patients with have symptomatic heart failure with reduced ejection fraction (HFrEF) [9,10].

Growing amounts of evidence in recent years have indicated possible advantages of giving individuals who have had an acute myocardial infarction (AMI) sacubitril/valsartan as soon as possible. Nevertheless, a significant gap in the availability of pertinent clinical evidence remains apparent. The current meta-analysis was prompted by the lack of comprehensive data and is intended to thoroughly examine and provide light on the effectiveness and safety profile of promptly starting sacubitril/valsartan in patients who have had an acute MI.

To inform evidence-based clinical judgement and enhance patient outcomes, it is imperative to assess such a significant therapeutic intervention in this high-risk patient population.

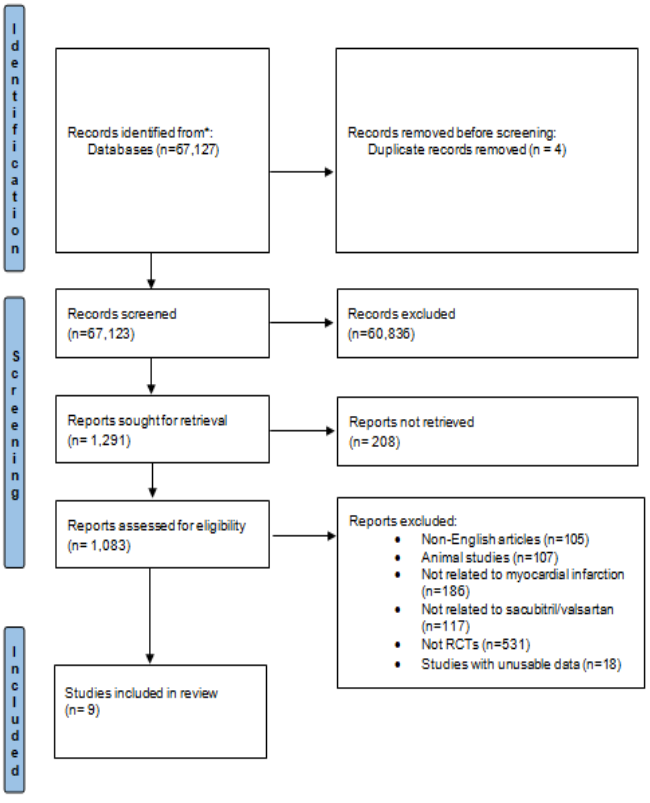
4. Methods

On the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11], this systematic review and meta-analysis was carried out [11].

4.1. Search strategy and study selection

From the beginning to June 2025, an electronic search was conducted on Pub Med, EMBASE, and Google Scholar utilising medical subject heading (MeSH) phrases and pertinent key words for (myocardial infarction) AND (sacubitril/valsartan combo) AND (ACEIs). Supplementary **Table 1** contains the detailed search strategy. The search was done using the Boolean operators "OR" and "AND". All of the articles were transferred into Endnote v20 and duplicates were eliminated. The titles and abstracts of every article that was retrieved were screened independently by two writers, who eliminated the ones that did not meet the inclusion requirements. The remaining articles' full texts were examined in light of the eligibility requirements. Disagreements or conflicts were discussed about and settled with a third author. The details of search and study selection process is illustrated in PRISMA flow diagram (**Figure1**).

Figure 1: PRISMA flow diagram showing the search strategy and study selection process for meta-analysis.



4.2. Eligibility criteria

Our meta-analysis's inclusion criteria were; i) Double blind randomized controlled trials (RCTs); ii) Patients diagnosed with acute MI; iii) Sacubitril/valsartan combination therapy administered as experimental group while ACEIs or valsartan alone used as control group; iv) Studies published in English language and reporting our outcomes. In case of multiple publications reporting the same clinical research, the one with most complete publication data was considered.

The exclusion criterion was; i) Studies other than randomized controlled trials (RCTs) that comprise observational research (case reports, cohort, cross-sectional, and case-control studies), Abstracts from conferences, editorials, review papers, and animal studies; ii) Trials not matching our PICO; iii) Non clinical studies and those with no full text availability.

4.3. Data extraction

Two researchers worked independently on the data extraction. A third researcher was consulted regarding any discrepancies found in the data. Using a standard data extraction form, the first author of the studies, the publication year, the nation, the study design, sample size, patient characteristics (age, sex ratio), intervention details, and clinical outcomes were all included in the data extracted from the eligible studies. The primary outcomes were death from cardiac death (heart failure) and cardiovascular deaths, adverse events and left ventricular ejection fraction (LVEF) while the secondary outcomes were myocardial infarction occurrence, NT-pro BNP, hospitalization for heart failure and 6MWD. For categorical outcomes, we retrieved the total number of patients and the number of incidents for each outcome; for continuous outcomes, we recovered the sample size, averages, and standard deviations.

4.4. Quality assessment

In accordance with chapter 8 of the Cochrane Handbook [12], a risk of bias table was created by two reviewers who evaluated the quality of the included studies and calculated the risk of bias for each one [12].

2.5. Statistical analysis

The statistical analysis was done through Review Manager (ReMan, Version 5.4; The Cochrane Collaboration, Copenhagen, Denmark). A random effect model and generic inverse variance were used to combine mean differences (MDs) and risk ratios (RR) for continuous and dichotomous outcomes, respectively, with 95% confidence intervals (CIs).Forest plots were used to illustrate the combined results.

The I^2 statistic and the Chi^2 test were used by the authors to categorise the degree of heterogeneity among the studies as low, moderate, or high. The Cochrane Handbook for Systematic Reviews of Interventions, section 10.10, was followed in evaluating I^2 values [13]. A leave-one-out sensitivity analysis was conducted, omitting a single study at a time, to ascertain the impact of individual studies on the overall conclusions when considerable heterogeneity (> 75%) was detected. Subgroup analysis was done, presenting the subgroups according to MI type. For the Chi^2 test, $P < 0.1$ was regarded as statistically significant. We used funnel plots for primary outcomes to visualize publication bias.

5. Results

3.1 Search results and population characteristics;

The literature search strategy is depicted in Fig 1using the PRISMA diagram. 67,126 studies were found in our preliminary search. Four records that were found to be duplicates were deleted. Because of the relevance to the topic, 1083 studies were chosen for additional evaluation. Following that, 50,836 papers were eliminated since they were non-RCTs and systematic reviews. In turn, nine RCTs were included in the final selection [14-22] for meta-analysis.

These 9 randomized controlled trials (RCTs) selected for our meta-analysis involved 6774 myocardial infarction diagnosed patients, of whom 3399 were given Sacubitril/Valsartan and 3375 received ACEIs or valsartan alone. The patients' average age across all studies was 55 years, with most of them being obese or overweight having BMI greater than 24 kg/m^2. Six months was the average follow up period [14-16,19-21] with variations of 23 weeks in [17], 52 weeks in [18], and 3 months [22]. Patients with acute myocardial infarction were enrolled in these studies. **Table 1** provides specifics on the research features of the randomised control trials that were part of the meta-analysis.

A significant number of patients were on mineralocorticoid antagonists, beta blockers and other medications at baseline and had diabetes mellitus, hypertension or a history of myocardial infarction. The study population detailed baseline characteristic are shown in supplementary **Table 1**, moreover, baseline cardiovascular parameters and co-morbidities of patients in included studies are summarized in supplementary tables S3 and S4.

3.2. Quality assessment and Publication bias

Using the Cochrane Collaboration's risk of bias assessment tool [12], we rigorously evaluated quality of the included studies and found that they were generally of moderate to high quality. The selected studies were all described as randomized and double blinded. Rezq, et al. [19] detailed that random numbers were generated through computer-based methods.

The study by Jering, et al. [17] was randomized double blind and they disclosed that patient randomization was conducted utilizing interactive web response technology. Wang, et al. [15] specifically indicated that patients were allocated to groups through the envelope method. Lin, et al. [14] employed a simple random sampling technique. Similarly, all the studies exhibited low risk of bias across all the domains except the study by Zhang, et al. 2020 that showed “Some concerns” of bias in the domains of measurement of outcomes and selection of reported results leading to overall “Some concerns” of bias. Also, the study by Abdelnabi, et al. 2023 showed an overall “Some concern” due to bias in selection of reported results. The assessment of risk of bias incorporated in the RCTs is displayed in supplementary **Figures S1** (a) and (b).

Notably, the funnel plots of the primary outcomes (Supplementary **Figures S2, Figures S3** and **Figures S4**) show that our results were not impacted by publication bias, as evidenced by the symmetric distribution of the studies on both the sides of the vertical axis.

Table1: Study characteristics of the included randomised controlled trials in meta-analysis.

Study	County	Patients	N (I/C)	Age (I/C, years old)	Drugs (T/C)	Duration
Lin, et al. (2022) [4]	China	Patients with acute MI	55/54	61.38±12.31/59.74±11.53	Sacubitril-Valsartan/Valsartan	6 months
Wang, et al. (2021) [5]	China	Patients with left ventricular systolic dysfunction following acute anterior wall MI	68/69	59.13±7.15/60.56±7.62	Sacubitril-Valsartan/ Enalapril	6 months
Zhang, et al. (2020) [6]	China	Patients with STEMI	79/77	60.3±11.7/60.0±10.9	Sacubitril-Valsartan/ACEI	6 months
Jering, et al. (2022) [7]	41 countries	Patients with acute MI	2380/2381	64/64	Sacubitril-Valsartan/ACEI	
Docherty, et al (2021) [8]	UK	Patients with MI	47/46	61.8±10.6/59.7±10.1	Sacubitril-Valsartan/Valsartan	52 weeks
Rezq, et al. (2021) [9]	Egypt	Patients with STEMI	100/100	52±9.2/57±11.6	Sacubitril-Valsartan/Ramipril	23 weeks
Pei Yang, et al. (2023) [0]	China	Patients with acute MI	85/63	59.07±11.532/59.92±12.019	Sacubitril-Valsartan/Valsartan	6 months
Abdelnabi, et al. (2021) [1]	Egypt	Patients with revascularized STEMI and reduced left ventricular systolic function	96/96	58±11.7/58±11.3	Sacubitril-Valsartan/Valsartan	6 months
Hai Fan, et al. (2023) [22]	China	Patients with acute MI	39/39	71.33±10.52/68.00±11.45	Sacubitril-Valsartan/ Irbesartan	3 months

I = Intervention arm, C = Control arm, MI: Myocardial infarction, STEMI: ST-segment elevation myocardial infarction.

3.2. Quality assessment and Publication bias

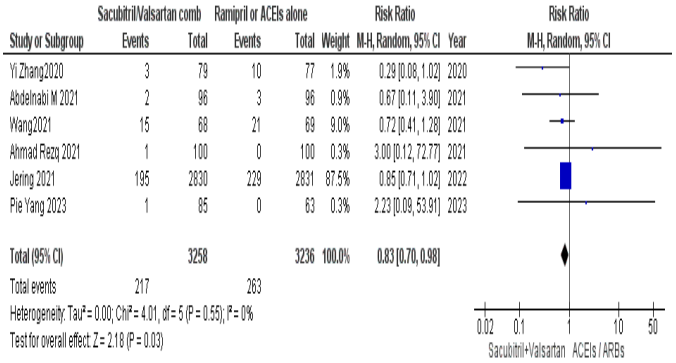
Using the Cochrane Collaboration's risk of bias assessment tool [12], we rigorously evaluated quality of the included studies and found that they were generally of moderate to high quality. The selected studies were all described as randomized and double blinded. Rezq, et al. [19] detailed that random numbers were generated through computer-based methods. The study by Jering, et al. [17] was randomized double blind and they disclosed that patient randomization was conducted utilizing interactive web response technology. Wang, et al. [15] specifically indicated that patients were allocated to groups through the envelope method. Lin, et al. [14] employed a simple random sampling technique. Similarly, all the studies exhibited low risk of bias across all the domains except the study by Zhang, et al. 2020 that showed "Some concerns" of bias in the domains of measurement of outcomes and selection of reported results leading to overall "Some concerns" of bias. Also, the study by Abdelnabi, et al. 2023 showed an overall "Some concern" due to bias in selection of reported results.

The assessment of risk of bias incorporated in the RCTs is displayed in supplementary figures S1 (a) and (b). Notably, the funnel plots of the primary outcomes (Supplementary Figures S2, **Figures S3** and **Figures S4**) show that our results were not impacted by publication bias, as evidenced by the symmetric distribution of the studies on both the sides of the vertical axis.

5. 3. Primary outcomes

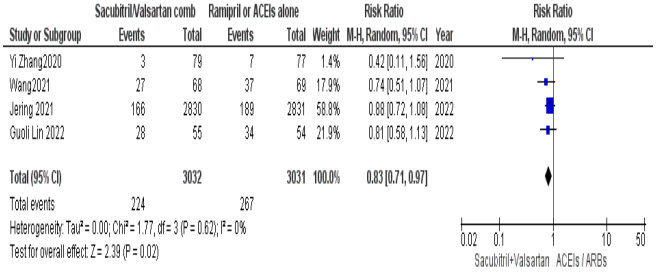
5.3.1. Mortality: Six trials provided data on the incidence of heart failure-related deaths. The pooled analysis revealed that treatment with sacubitril/valsartan was substantially associated with a lower risk of heart failure-related deaths when compared to the control group (RR = 0.83, 95% CI = 0.70-0.98, I2 = 0, P = 0.03 Figure 2). Simultaneously, there existed a significant difference between the mortality resulting from cardiovascular causes within treatment and control group. The combined data from four trials indicated a reduced incidence of cardiovascular deaths associated with the use of sacubitril/ valsartan combination treatment (RR = 0.83, 95% CI = 0.71-0.97, I2 = 0, P = 0.02 Figure 3).

Figure 2: Forest plot of death from cardiac death (heart failure).



It shows the significant result of pooled analysis comparing the effect of sacubitril/valsartan combination treatment to the control group on death from cardiac failure risk. ACIEs-Angiotensin converting enzyme inhibitor; RR-Relative risk; CI-Confidence interval; M-H-Mantel Hansel. Sources: References [15-17,19-21].

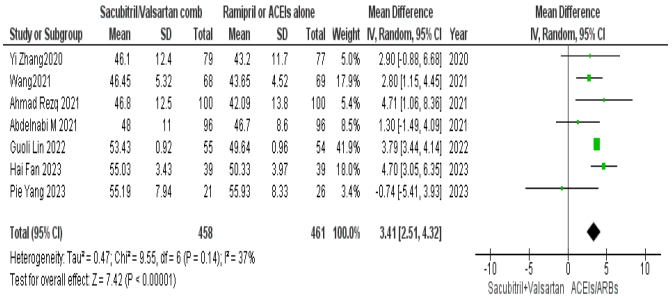
Figure 3: Forest plot for the outcome of cardiovascular death.



It shows the significant result of pooled analysis comparing the effect of sacubitril/valsartan combination treatment to the control group on cardiovascular death risk. ACIEs-Angiotensin converting enzyme inhibitor; RR-Relative risk; CI-Confidence interval; M-H-Mantel Hansel. Sources: References [14-17].

5.3.2. Left ventricular ejection fraction (LVEF): LVEF data from the two groups were compared and studied in seven trials. The combined risk ratio indicated that treatment with sacubitril/valsartan group was significantly related with higher LVEF values in comparison to the control group (MD = 3.41, 95% CI = 2.51-4.32, I2 = 37%, P = 0.0001 **Figure 4**).

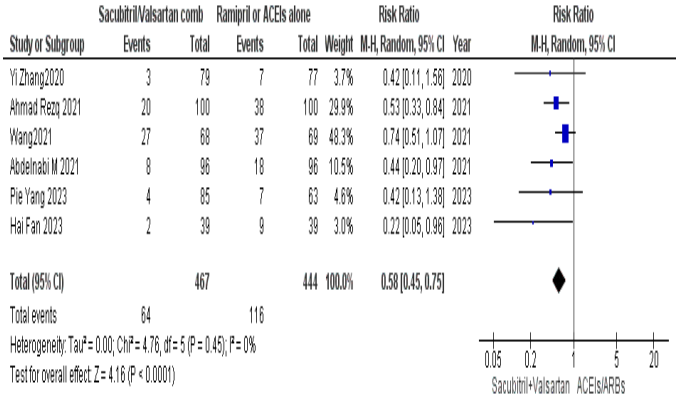
Figure 4: Forest plot for the outcome of left ventricular ejection fraction.



It shows the significant result of pooled analysis comparing the effect of sacubitril/valsartan combination treatment to the control group on left ventricular ejection fraction. ACIEs-Angiotensin converting enzyme inhibitor; MD-Mean difference; CI-Confidence interval; M-H-Mantel Hansel. Sources: References [14-16,19-22].

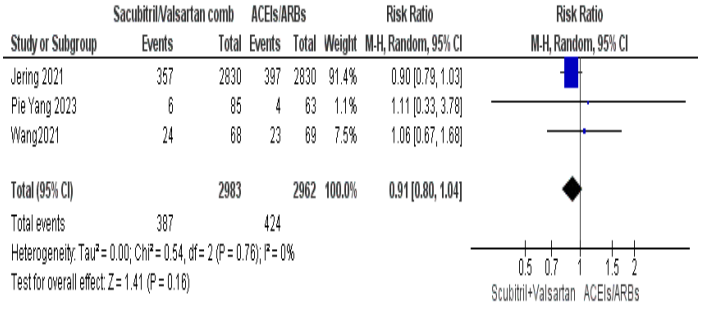
5.3.3. Adverse events: Major adverse cardiac events and any adverse events were analyzed to assess the safety of sacubitril/valsartan treatment for acute myocardial infarction. According to the results of six trials, patients who were administered sacubitril/valsartan treatment had a lower incidence of major adverse cardiac events than those in the control group (RR = 0.58, 95% CI = 0.45-0.75, I2 = 0%, P < 0.0001 Figure 5). Likewise, there was also a lower incidence of any adverse events for sacubitril/valsartan treatments compared to ACEIs or ARBs (RR = 0.91, 95% CI = 0.80-1.04, I2 = 0%, P = 0.16 **Figure 6**).

Figure 5: Forest plot for the outcome of major adverse cardiac events (MACE).



It shows the significant result of pooled analysis comparing the effect of sacubitril/valsartan combination treatment to the control group on major adverse cardiac events. ACIEs; Angiotensin converting enzyme inhibitor, RR; Relative risk, CI; Confidence interval, M-H; Mantel Hansel. Sources: References [15,16,19-22].

Figure 6: Forest plot for the outcome of any adverse events.

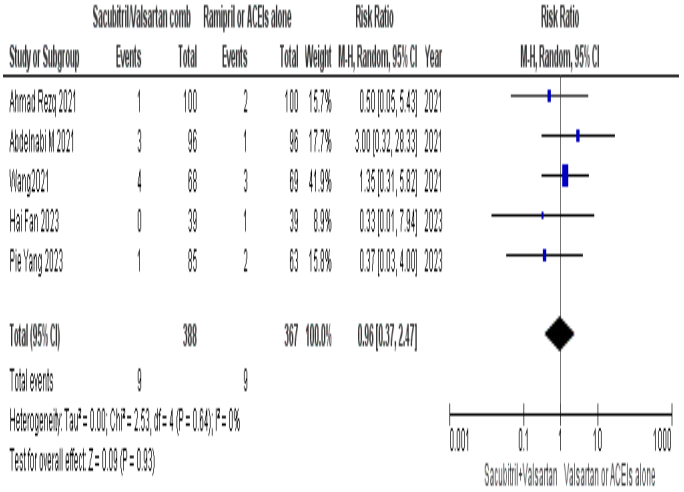


It shows the significant result of pooled analysis comparing the effect of sacubitril/valsartan combination treatment to the control group on any adverse events. ACIEs-Angiotensin converting enzyme inhibitor; MD-Mean difference; CI-Confidence interval; M-H-Mantel Hansel. Sources: References [15,17,20].

5.4. Secondary outcomes

5.4.1. Myocardial infarction (MI): Based on data from five investigations, the result of myocardial infarction occurrence was assessed. The forest plot demonstrated had a lower incidence of MI in sacubitril/valsartan group relative to the ACEI/ARB treatment (RR = 0.96, 95% CI = 0.37-2.47, P = 0.93, I2 = 0% **Figure7**).

Figure 7: Forest plot for the outcome of myocardial infarction.

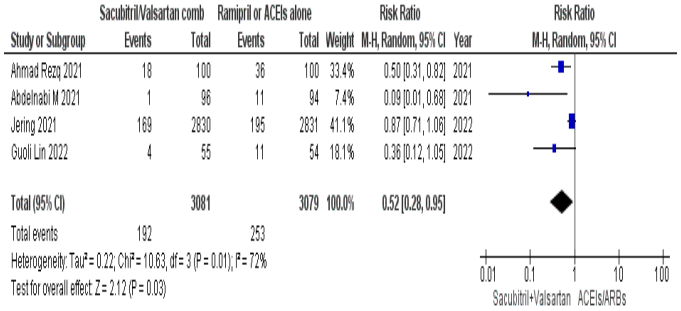


It shows the non significant result of pooled analysis comparing the effect of sacubitril/valsartan combination treatment to the control group on myocardial infarction risk. ACIEs-Angiotensin converting enzyme inhibitor; RR-Relative risk; CI-Confidence interval; M-H-Mantel Hansel. Sources: References [15,19-22].

5.4.2. Hospitalization for heart failure: According to the combined outcomes of three trials, patients receiving sacubitril/valsartan had a significantly reduced rate of heart failure hospitalizations than those in the control group (RR = 0.52, 95% CI = 0.28-0.95, P = 0.03, I2 = 72%, **Figure 8**).

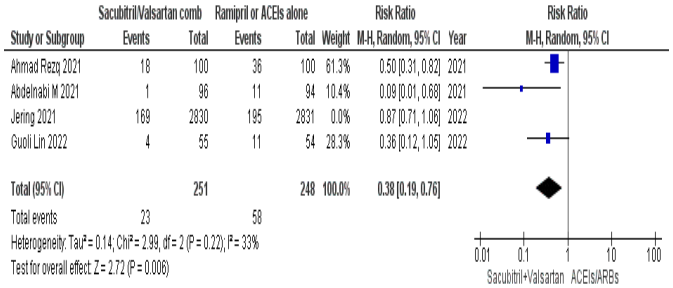
A leave one out sensitivity analysis was performed in order to identify the reason for the high heterogeneity. The results indicated that the heterogeneity significantly decreased to 33% when the study by Jering, et al. was excluded, and this decrease had no effect on the statistical significance of the result (RR = 0.38, 95% CI = 0.19-0.38, I2 = 33%, P = 0.006 **Figure 9**).

Figure 8: Forest plot for the outcome of heart failure hospitalization.



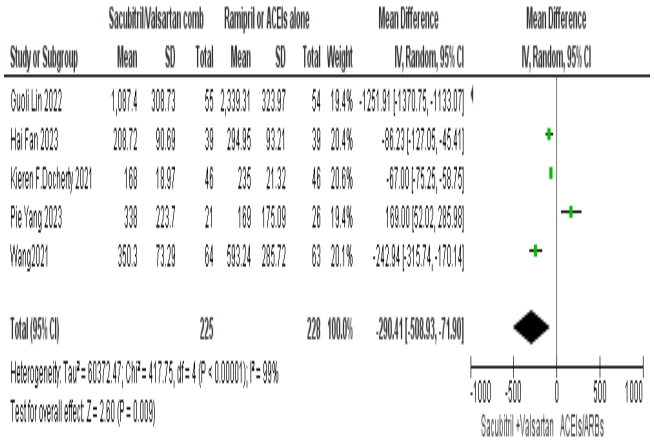
It shows the significant result of pooled analysis comparing the effect of sacubitril/valsartan combination treatment to the control group on hospitalization for heart failure risk. ACIEs-Angiotensin converting enzyme inhibitor; RR-Relative risk; CI-Confidence interval; M-H-Mantel Hansel. Sources: References [14,17,19,21].

Figure 9: Leave-one out sensitivity analysis of hospitalization for heart failure.



3.4.3. NT-pro BNP: For assessing the outcome of NT-proBNP, we combined the data from 5 studies and the pooled result showed that sacubitril/valsartan treatment renders a significantly decreased value of NT-proBNP in reference to the control group (RR = -290.41, 95%CI = -508.93_ -71.90, I2 = 99, P = 0.009 figure10). The considerably high heterogeneity in this outcome can be attributed to the differences in the values of NT-proBNP reported by individual studies, methodological and baseline characteristic difference among the included trials.

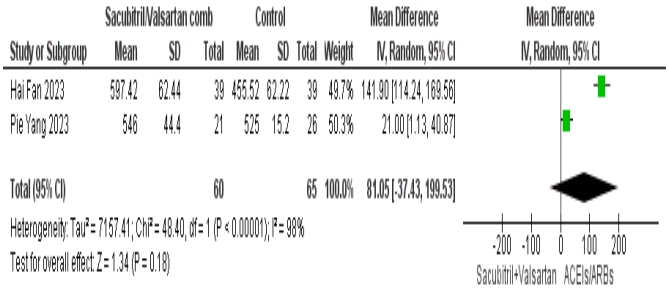
Figure10: Forest plot for the outcome of Nt-pro-BNP.



It shows the result of pooled analysis comparing the effect of sacubitril/valsartan combination treatment to the control group on the level of NT-proBNP. ACIEs-Angiotensin converting enzyme inhibitor, MD; mean difference, CI-Confidence interval, IV; inverse variance. Sources: References [14,15,18,20,22].

4.4. 6 MWD: This outcome was addressed by two of the included trials and the combined result demonstrated a higher value of 6MWD for the patients treated with sacubitril/valsartan group with respect to the control group (RR = 81.05, 95% CI = -37.43-199.53, I2 = 98%, P = 0.18 **Figure 11**).

Figure 11: Forest plot for the outcome of Six Minutes' Walk Distance (6MWD).



Forest 6 MWD; it shows the result of pooled analysis comparing the effect of sacubitril/valsartan combination treatment to the control group on the value of 6MWD. ACIEs-Angiotensin converting enzyme inhibitor; MD; Mean difference; CI-Confidence interval; IV; Inverse variance. Sources; References [20,22].

6. Discussion

Although the clinical use of PCI and other therapeutic advancements has greatly reduced the complications of AMI, still the burden is high [23]. Studies reveal that excessive RAAS activation in STEMI patients results in myocardial hypertrophy, fibroblast proliferation, and differentiation, which in turn promotes ventricular remodeling and heart failure [17]. The traditional approach to treating AMI patients involved the early administration of beta blockers or ACEI/ARBs [13]; however, a more recent line of medications called sacubitril/valsartan has shown promising results as alternative to ACEI/ARB treatment.

Sacubitril/valsartan medication has also been recommended by the European Society of Cardiology in their updated guidelines for the management of chronic heart failure. There are important practical implications for sacubitril/valsartan in the realm of cardiovascular treatment. It is a useful therapeutic alternative for individuals recuperating from an acute myocardial infarction (MI) together with patients who heart failure with decreased ejection fraction (HFrEF).

Its unique combination of neprilysin inhibition and angiotensin II receptor blockade addresses multiple facets of heart failure pathophysiology, including vasodilation, preload and afterload reduction, and neurohormonal modulation [7].

We carried out this study for evaluation of the safety and effectiveness of sacubitril/valsartan in the treatment of acute myocardial infarction, which includes the largest pool of studies and cases to date, using the knowledge and evidence currently available from the randomised controlled trials in the literature. Sacubitril/valsartan administration in patients with acute MI appears to lower the risk of death from heart failure, cardiovascular death, significant adverse cardiac events, and any adverse event, according to the primary outcome analysis. Compared to the control group, it enhanced LVEF, and all of the effects were statistically significant. The occurrence of MI, hospitalization for heart failure, NT-proBNP level and 6MWD were pooled under

secondary outcome analysis where they all showed a decreasing trend for sacubitril/valsartan treatment in comparison to ACEIs/ARBs treatment. Compared to our meta- analysis, several research projects have produced variable findings. We identified a meta-analysis conducted by Liu, et al. [25] that examined the outcomes relevant to our article, and the findings were consistent with our study's findings. In their results, sacubitril/valsartan treatment in comparison to ACEIs/ARBs renders a greater value for LVEF (MD = 2.99), while significantly reducing NT-proBNP (Std. MD = -1.33), HF (OR = 0.49) and MACE (OR = 0.47).

Cosentino, et al. [26] observed a 20% reduction in cardiovascular mortality as well as a drop in the heart failure hospitalization rate in the active arm compared to the standard of treatment (enalapril) arm (RR = 0.80; 95% confidence interval [CI], 0.71 – 0.89; p <.001). Similarly, in their meta analysis, Zhao, et al. [27] also reported an increase in the LVEF and a decline in MACE for patients receiving Sacubitril/Valsartan than the ACEI group. Contrary to our findings, in Zhou, et al. [28] results there was no discernible contrast in the occurrence of cardiac mortality between the ACEI group and the Sacubitril/Valsartan group (RR: 1.00). In the same way, the result of our meta analysis regarding LVEF and NT-proBNP were inconsistent with the findings of Docherty, et al. [18].

Compared to valsartan, sacubitril/valsartan did not significantly lower LVEF or NT-proBNP in their randomized controlled trial. A study by Kaplinsky, et al. [29] showed a relationship between a decline in LVEF and a higher chance of heart failure hospitalization or cardiovascular death. The study found that for every five points' lower LVEF, there was a 9% increase in the chance of cardiovascular death or heart failure hospitalization. Another study conducted by Lin, et al. [14] reported increased LVEF with sacubitril/valsartan co-therapy compared to valsartan alone but showed no statistical significance regarding cardiovascular death outcome. However, our data and results suggest that it does lower the risk of cardiovascular death outcome in relation to the control group (RR = 0.86, P = 0.004). According to Rezq, et al. [19], in 6 months, compared to the control group, the sacubitril/valsartan group showed 1 cardiac death out of 100 patients. However, we reported that there was a lower risk of death from heart failure and the difference was statistically significant. The same study also reported lower heart failure hospitalization rate (18% Vs 38%, P = 0.044) and MI occurrence (1% Vs 2%) for sacubitril/valsartan treatment compared to control arm which supported the findings of our study.

All the primary outcomes in our study demonstrated a very low heterogeneity which enhances the overall strength of our findings. Moderate to high heterogeneity was found in the secondary outcomes which can be attributed to differences in baseline parameters, ethnicity and follow up times. We also introduced subgroups and performed sensitivity analysis as well to know about the studies and factors imparting heterogeneity in the analysis.

Our meta-analysis has several strengths. Firstly, we cast a wide net, encompassing diverse databases and study designs, ensuring a holistic representation of available evidence. Our study incorporated the largest number of trials and outcomes compared to the similar literature available. The additional outcomes are death from cardiac failure, NT-proBNP, cardiovascular death, MI occurrence, and 6MWD. In contrast to the previous meta-analysis, we only include the original trial in case of multiple publications based on same clinical data. All these factors thus enhance our conclusions validity. Secondly, we included randomized controlled trails that enrolled different populations; the study by Jering et al. have included patients from 41 different countries, hence our results can be generalized and the findings could be useful for different demographics or situation. Thirdly, no publishing bias was discovered through the use of a number of plots and tests, such as the funnel plot; this enhances the robustness of our findings. Fourthly, the pooled analysis of our primary outcomes displays a very low heterogeneity, which makes our results more consistent, precise and generalized. We also conducted sensitivity analysis and subgroup analysis for some secondary outcomes to assess the effect of various studies on the combined estimate.

The overall intermediate quality of the trials and the difference in sample sizes and follow up periods are the study limitations. The variations in sample sizes, ethnicities and baseline characteristics could contribute to clinical heterogeneity. For studies where the baseline values of some efficacy end points were not reported, we included only the final post treatment values of those outcomes instead of change in values of those parameters due to the treatment.

Overall, current evidence suggests potential benefits in reducing adverse cardiovascular events, but more comprehensive and dedicated studies are warranted to establish its definitive role and guidelines in managing acute MI. Clinicians should continue to weigh the available evidence and individual patient characteristics when considering the incorporation of sacubitril/valsartan into treatment strategies for acute MI, focusing on optimizing patient outcomes and enhancing overall care.

7. Conclusion

In conclusion, the early administration of sacubitril/valsartan exerts a noteworthy influence, significantly reducing the incidence of myocardial infarction, heart failure-related mortality, heart failure hospitalization, cardiovascular-related deaths, and potentially serious adverse cardiac events in individuals suffering from heart failure following an acute myocardial infarction. Furthermore, this treatment demonstrated a substantial improvement in left ventricular ejection fraction. Based on the extensive meta-analysis, it is evident that sacubitril/valsartan is not only generally safe but also holds substantial therapeutic benefits, particularly when initiated promptly following an acute myocardial infarction. These findings underscore the clinical significance of early sacubitril/valsartan intervention in enhancing patient outcomes in this specific context.

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9. Competing Interests

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

10. Author Contribution

[Muhammad Aqib Faizan, Saher Bano and Tooba Rehman]

pitched in with valuable contributions towards the experimental designs of the study, sequencing of the data, created tables along with drafting the manuscript and reviewing the manuscript thoroughly. [Rabia Nawaz and Aliza Jamshid] did tidy of data according to the relevant outcome of the drugs that were administered and extensive analyzes of the data and interpreted its result and helped others out in drafting the manuscript. [Ahmad Mustafa Khalid, Abdul Basit Khan, Hamza Sardar and Muneeb ullah Khan] did immense contribution towards the concept of the manuscript by doing extensive literature search, pooling all the relevant studies onto one place, did their data extraction and did a critical review of the whole manuscript to look for any anomalies.

11. Ethics approval

Not applicable. This is a meta-analysis.

12. Data Availability Statement

The data used in this meta-analysis were extracted from publicly available sources, including published randomized controlled trials. All relevant data supporting the findings of this study are included within the manuscript and supplementary materials. Due to the nature of this analysis, no new primary data were generated. Additional details can be made available upon reasonable request to the corresponding author.

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Supplementary files:

Supplementary Table S1: Supplementary table S1 Detailed search strategies employed for each data base.

Database	Search strategy	Results
Pubmed	((((((((((Myocardial Infarction"[Mesh]) OR (Infarction, Myocardial)) OR (Myocardial Infarctions)) OR (Cardiovascular Stroke)) OR (Cardiovascular Strokes)) OR (Myocardial Infarct)) OR (Myocardial Infarcts)) OR (Heart Attack)) OR (Heart Attacks)) AND ((((((((((((("sacubitril and valsartan sodium hydrate drug combination" [Supplementary Concept]) OR (sacubitril valsartan sodium hydrate)) OR (sacubitril-valsartan sodium hydrate drug combination)) 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)) OR (sacubitril and valsartan drug combination)) OR (sacubitril valsartan drug combination)) OR (sacubitril-valsartan)) OR (3-(1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-3'-methyl-2'-(pentanoyl(2'-(tetrazol-5-ylate)biphenyl-4'-ylmethyl)amino)butyrate)) OR (sacubitril and valsartan sodium anhydrous drug combination)) OR (sacubitril valsartan sodium anhydrous)) OR (sacubitril-valsartan sodium anhydrous drug combination)) OR (LCZ 696)) OR (LCZ696)) OR (LCZ-696)) OR (Entresto))) AND ((((((((((("Ramipril"[Mesh]) OR (Vesdil)) OR (Triatec)) OR (Altace)) OR (Zabien)) OR (Ramace)) OR (Tritace)) OR (Acovil)) OR (Delix)) OR (Carasel)) OR (HOE-498)) OR (HOE 498)) OR (HOE498))) OR ((((((((((((((((((("Angiotensin-Converting Enzyme Inhibitors"[Mesh]) OR (Angiotensin Converting Enzyme Inhibitors)) OR (Inhibitors, Angiotensin-Converting Enzyme)) OR (Inhibitors, Angiotensin Converting Enzyme)) OR (Kininase II Antagonists)) OR (Kininase II Inhibitors)) OR (Angiotensin-Converting Enzyme Antagonists)) OR (Angiotensin Converting Enzyme Antagonists)) OR (Kininase II Inhibitor)) OR (II Inhibitor, Kininase)) OR (Antagonists, Kininase II)) OR (ACE Inhibitors)) OR (Angiotensin I-Converting Enzyme Inhibitors)) OR (Angiotensin I Converting Enzyme Inhibitors)) OR (Angiotensin Converting Enzyme Inhibitor)) OR (ACE Inhibitor)) OR (Angiotensin I-Converting Enzyme Inhibitor)) OR (Angiotensin I Converting Enzyme Inhibitor)) OR (Angiotensin-Converting Enzyme Inhibitor)) OR (Antagonists, Angiotensin-Converting Enzyme)) OR (Antagonists, Angiotensin Converting Enzyme))	66,957
Embase	(Myocardial infarction OR MI) AND (sacubitril and valsartan drug combination OR Angiotensin receptor–neprilysin inhibitors) AND (angiotensin-converting enzyme inhibitor OR ACEI OR ramipril OR enalapril)	43
Google scholar	(Myocardial infarction OR MI) AND (sacubitril and valsartan drug combination OR Angiotensin receptor–neprilysin inhibitors) AND (angiotensin-converting enzyme inhibitor OR ACEI OR ramipril OR enalapril)	127

MI; Myocardial infarction, ACEI; Angiotensin-Converting Enzyme Inhibitor, ANRI; Angiotensin receptor–neprilysin inhibitors.

Supplementary table S2: Baseline characteristics of included studies.

Study And Year	Type Of Study	Intervention Name	Control Name	Disease	Follow Up (Months)	Total No. Participant	No. Of Patients		Age (Mean ±Sd)		Male No. (%)		BMI (Kg/m^2) (Mean ±Sd)		Smoking		EGFR. ml/min/1.73 m2	
							Sac/Val	Control	Sac/Val	Control	Sac/Val	Control	Sac/Val	Control	Sac/Val	Control	Sac/Val	Control

Lin et al. (2022) [14]	RCT	Sac/Val	Valsartan	Acute MI	6	109	55	54	61.38±12.31	93.00±27.78	86.92±32.57	47 (87.0)	24.17±2.69	23.68±3.18	16 (29.1)	13 (24.1)	93.00±27.78	86.92±32.57
Wang et al. (2021) [15]	RCT	Sac/Val	Enalapril	LVSD Post-Acute MI	6	137	68	69	59.13 ± 7.15	N/A	N/A	54 (78.30	26.54 (24.07, 28.49)	25.24 (23.81, 27.44)	N/A	N/A	N/A	N/A
Zhang et al. (2020) [16]	RCT	Sac/Val	ACEI (Perindopril, Acertil, Servier)	STEMI Post PPCI	6	186	79	77	60.3 ± 11.7	N/A	N/A	55 (71.4 %)	24.77±2.65	24.49±3.38	N/A	N/A	N/A	N/A
Jering t al. (2022) [17]	RCT	Sac/Val	ACEI Ramipril	Acute MI	6	5,661	2380	2381	64	72(22)	72(23)	N/A	N/A	N/A	22	21	72(22)	72(23)
Docherty et al. (2021) [18]	RCT	Sac/Val	Valsartan	MI	12	93	47	46	61.8 ± 10.6	87.3(15.4)	88.2 (15.0)	43(93.5)	N/A	N/A	N/A	N/A	87.3(15.4)	88.2 (15.0)
Rezq et al. (2021) [19]	RCT	Sac/Val	Ramipril	STEMI	5.9	200	100	100	52 ± 9.2	N/A	N/A	88%	28.7± 4.3	29.2± 3.5	66%	74%	N/A	N/A
Pei Yang et al. (2023) [20]	RCT	Sac/Val	Valsartan	Acute MI	6	148	85	63	59.07±11.532	59.92±12.019	75(88.2)	57(90.5)	22.96± 2.195	23.00 ±2.540	46(54.1)	32(50.8)	94.80±20.132	95.72 ± 15.510
Abdelnabi et al. (2021) [21]	RCT	Sac/Val	Valsartan	Post-acute MI	6	192	96	96	58±11.7	58±11.3	64(66.67)	63(65.6)	N/A	N/A	50(52)	46(48)	N/A	N/A
Hai Fan et al. (2023) [22]	RCT	Sac/Val	Irbesartan	Acute MI	3	78	39	39	71.33±10.52	68.00±11.45	28	31	22.12± 2.52	22.27 ±2.31	N/A	N/A	N/A	N/A

RCT: Randomized Controlled Trial, MI: Myocardial Infarction, STEMI: ST-segment elevation myocardial infarction, SD: Standard Deviation, BMI: Body mass index, EGFR: estimated glomerular filtration rate, N/A: Not available.

Supplementary table S3: Baseline Characteristics of cardiovascular parameters

Study And Year	LVEF (%)	Killip Class >Ii (N%)	Coronary Reperfusion	Location Of MI		
				Anterior	Inferior	Other

	Sac/Val	Control	Sac/Val	Control	Sac/Val	Control	Sac/Val	Control	Sac/Val	Control	Sac/Val	Cont
Lin et al. (2022)[14]	45.76±5.11	45.11±4.93	I-29(52.7) II-18(32.7) III-8(14.5)	I-30(55.6) II-21(38.9) III-3(5.6)	N/A	N/A	N/A	N/A	N/A	Inferior	N/A	N/A
Wang et al. (2021)[15]	41.91±3.28	41.68±2.82	N/A	N/A	N/A	N/A	N/A	N/A	N/A	12 (24%)	N/A	N/A
Zhang et al. (2020)[16]	54.7±10.8	53.9±13.2	5(6.3%)	3(3.9%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Jering et al. (2022)[17]	36	37	56	57	89(88/4)	89(88/5)	68	N/A	19	N/A	N/A	18
Docherty et al. (2021)[18]	36.0(6.4)	37.7(7.6)	N/A	N/A	N/A	N/A	44(93.6)	44(95.7)	2(4.3)	N/A	1(2.1)	1(2.2
Rezq et al (Jan2021)[19]	N/A	N/A	N/A	N/A	631 (86.1)	4406 (89.4)	72%/78%	N/A	N/A	1(2.2)	N/A	N/A
Pei Yang et al. (2023)[20]	546±44.4	525±15.2	I-67(78.8) II-13(15.3) III-5(5.9)	I-54(85.7) II-7(11.1) III-2(3.2)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Abdelnabi et al. (2021)[21]	48±11	46.7±8.6	N/A	N/A	N/A	N/A	68(70.1)	67(69.8)	N/A	N/A	N/A	N/A
Hai Fan et al. (2023)[22]	55.09±3.43	50.33±3.97	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

LVEF: left ventricular ejection fraction, MI: Myocardial infarction, N/A: Not available

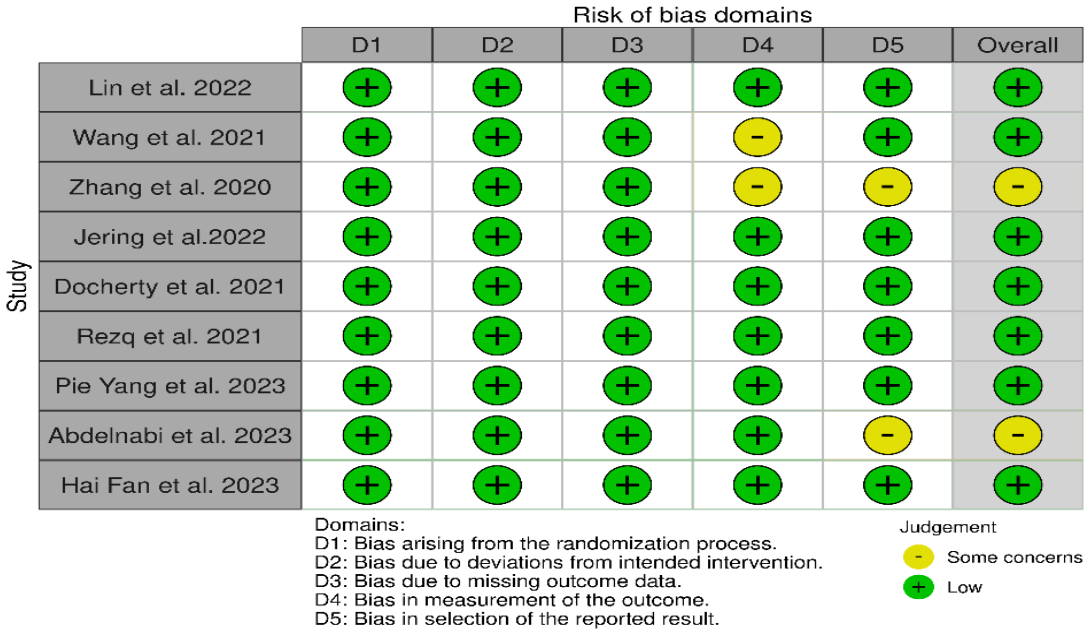
Supplementary table S4: Co-morbidities of the patients in the included studies

Study and Year	Myocardial Infarction		Previous stroke no. (%)		Hypertension no. (%)		DM No. (%)		STEMI No. (%)		NSTEMI No. (%)	
	Sac/Val	Control	Sac/Val	Control	Sac/Val	Control	Sac/Val	Control	Sac/Val	Control	Sac/Val	Con
Lin et al. (2022)[14]	N/A	N/A	N/A	N/A	23(41.8)	20(37.0)	15(27.3)	12(22.2)	N/A	N/A	N/A	N/A
Wang et al. (2021)[15]	N/A	N/A	N/A	N/A	32(47.10)	28(40.60)	15(22.10)	20(29.00)	N/A	N/A	N/A	N/A
Zhang et al. (2020)[16]	N/A	N/A	N/A	N/A	54(68.4%)	51(66.2%)	25(31.6%)	28(35.4%)	N/A	N/A	N/A	N/A
Jering et al. (2022)[17]	16	16	4	5	65	65	43	42	N/A	N/A	N/A	N/A
Docherty et al. (2021)[18]	N/A	N/A	N/A	N/A	12(25.5)	8(17.4)	9(19.1)	6(13.0)	N/A	N/A	N/A	N/A
Rezq et al. (Jan2021)[19]	N/A	N/A	N/A	N/A	34%	38%	40%	34%	N/A	N/A	N/A	N/A
Pei Yang et al. (2023)[20]	7(8.2)	3(4.8)	7(8.2)	7(11.1)	44(51.8)	36(57.1)	18(21.2)	17(27)	51(60.0)	39(61.9)	N/A	N/A
Abdelnabi et al. (2021)[21]	3(3.1)	1(1.1)	2(2.1)	2(2.1)	67(69.8)	71(74)	47(49)	42(44)	68(70.1)	67(69.8)	N/A	N/A
Hai Fan et al. (2023)[22]	0(0)	1(2.5)	N/A	N/A	23	20	11	13	N/A	N/A	N/A	N/A

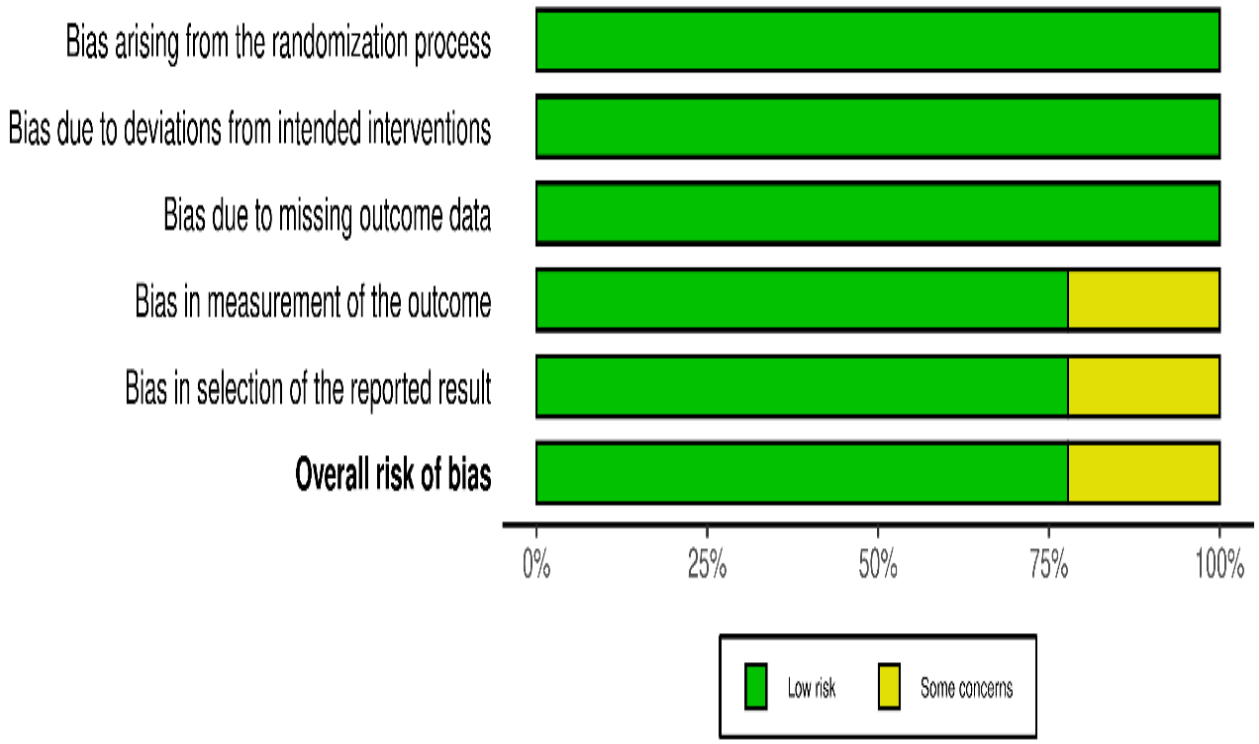
DM: Diabetes mellitus, STEMI: ST-segment elevation myocardial infarction, NSTEMI: Non-ST-elevation myocardial infarction, N/A: not available.

Supplementary figureS1 (a,b). Risk of bias assessment of the included randomized controlled trials in meta-analysis

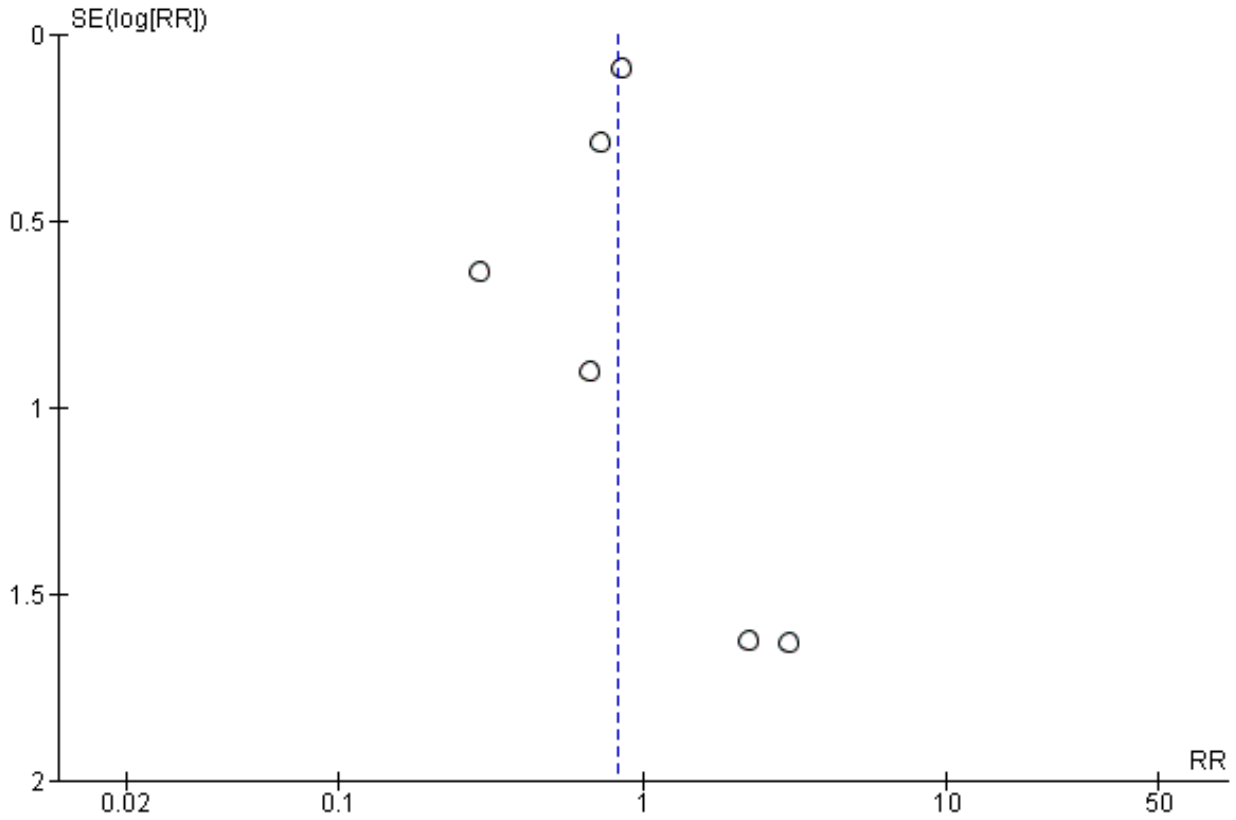
(a)



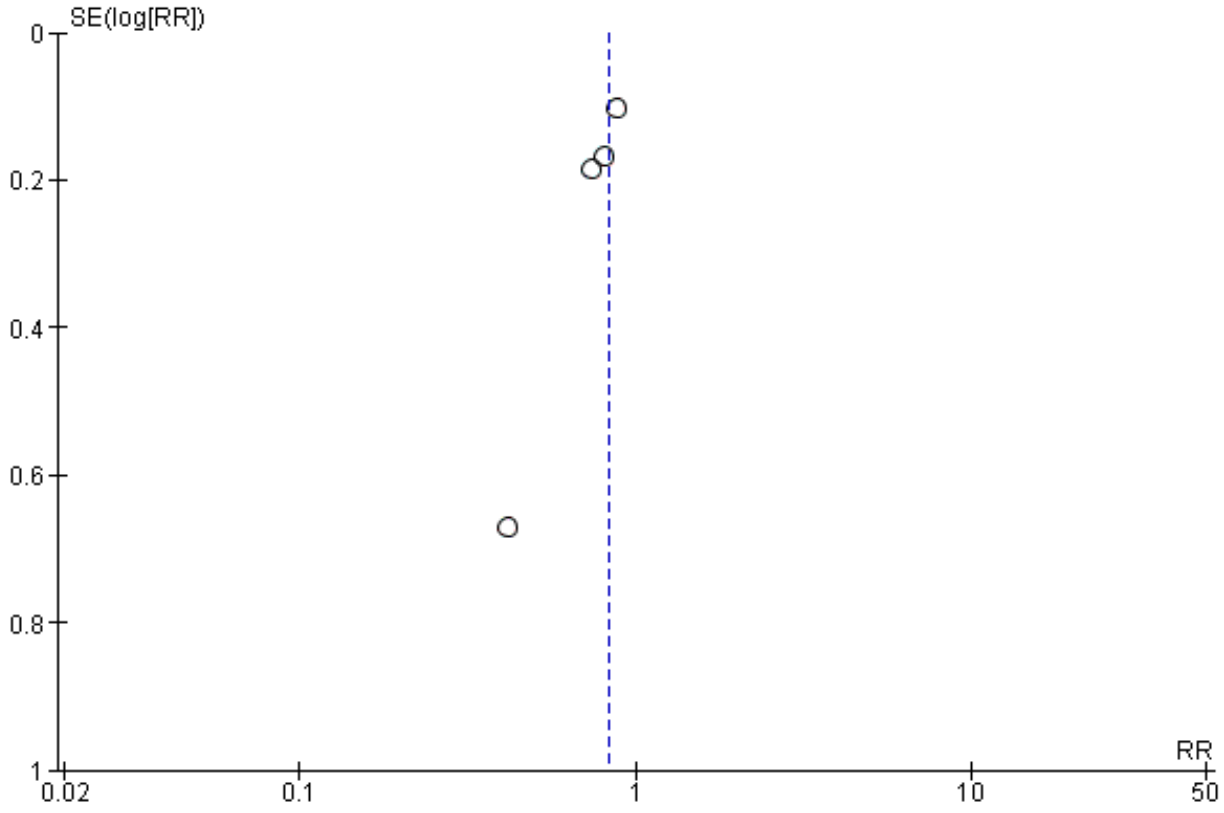
(b)



Supplementary figure S2. Funnel plot for the outcome of death from heart failure.



Supplementary figure S3. Funnel plot for the outcome of death from cardiovascular mortality.



Supplementary figure S4. Funnel plot for the outcome of LVEF