doi.org/10.36721/PJPS/2026.40.16612.1

Effect of early administration of sacubitril/valsartan in ST-elevation myocardial infarction patients undergoing PCI: Impact on infarct size and ventricular remodeling

Lei Sun[1], Haibin Jin[1], Xiaoqin Wen[1] and Xingyu Huo[2]*
[1]Department of Cardiology, Tianjin Hospital, Tianjin 300210, China
[2]Department of Emergency, Tianjin Chest Hospital, Tianjin 300000, China

Abstract: **Background**: Adverse left ventricular remodeling remains a major determinant of heart failure and mortality in patients with ST-elevation myocardial infarction (STEMI) despite successful primary percutaneous coronary intervention (PCI). Sacubitril/valsartan has shown beneficial effects on ventricular remodeling in heart failure populations; however, evidence regarding its early initiation following STEMI remains limited. **Objectives**: To evaluate the association of early sacubitril/valsartan initiation with infarct-size markers and ventricular remodeling outcomes in STEMI patients undergoing primary PCI. **Methods**: This retrospective observational cohort study included 150 consecutive STEMI patients treated with primary PCI at Tianjin Hospital, China, between January 2020 and December 2024. Patients were categorized into an angiotensin receptor–neprilysin inhibitor (ARNI) group receiving sacubitril/valsartan within 7 days of STEMI or a control group receiving standard ACEI/ARB therapy. Ventricular remodeling was assessed using serial echocardiographic measurements including left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV). Clinical outcomes were evaluated with a minimum follow-up of 6 months. **Results**: Baseline demographic and procedural characteristics were comparable between groups. Patients receiving early sacubitril/valsartan demonstrated lower peak cardiac biomarker levels and greater improvement in follow-up LVEF compared with the control group. Adverse ventricular remodeling occurred less frequently in the ARNI group. Heart failure–related hospitalizations were lower among patients receiving sacubitril/valsartan, whereas all-cause mortality and adverse event rates were comparable between groups. Multivariable analysis demonstrated that early sacubitril/valsartan initiation was associated with favorable ventricular remodeling. **Conclusion**: Early sacubitril/valsartan initiation after STEMI treated with primary PCI was associated with improved ventricular remodeling and better recovery of left ventricular systolic function in this retrospective cohort. These findings should be considered hypothesis-generating and require confirmation in larger prospective randomized studies.

Keywords: Angiotensin receptor–neprilysin inhibitors; Infarct size; Left ventricular ejection fraction; Primary percutaneous coronary intervention; Sacubitril/valsartan; ST-elevation myocardial infarction; Ventricular remodeling

Submitted 17-04-2026 – Revised 15-06-2026 – Accepted 07-08-2026

INTRODUCTION

ST-elevation myocardial infarction (STEMI) remains a significant cause of cardiovascular morbidity and mortality in the world despite the remarkable advances in reperfusion interventions and pharmacological treatment. The basis of STEMI treatment is primary percutaneous coronary intervention (PCI) which has considerably improved short term mortality outcomes. Nevertheless, following effective and timely revascularization, a relatively high percentage of patients undergo unfavorable remodeling of the left ventricle (LV) (Ibanez *et al*., 2018; O'Gara *et al*., 2013). Adverse ventricular remodeling is a major predictor of heart failure, frequent hospitalizations, and mortality, and this is why therapeutic interventions to limit the size of the infarct and preserve ventricular function are crucial (Pfeffer and Braunwald, 1990; Sutton and Sharpe, 2000). Ventricular remodeling following acute myocardial infarction is a multifactorial process, comprising myocyte necrosis, neurohormonal responses, inflammatory reactions, and extracellular matrix changes. Among these mechanisms, the most important is the activation of the renin-angiotensin-aldosterone system (RAAS), which leads to vasoconstriction, sodium and water retention, myocardial fibrosis and progressive ventricular dilation (Pfeffer and Braunwald, 1990; Sutton and Sharpe, 2000). Consequently, the early initiation of RAAS inhibition with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) has now become a standard part of post-STEMI care and is effective for ventricular remodeling and survival (Pfeffer et al., 2003; Køber *et al*., 1995). However, despite the ideal RAAS blockade, residual risk of adverse remodeling and heart failure progression does exist in a major proportion of patients. Sacubitril/valsartan is another angiotensin receptor-neprilysin inhibitor (ARNI), a new therapeutic intervention that combines RAAS inhibition with neprilysin inhibition. This dual mechanism augments endogenous natriuretic peptides and reduces maladaptive

**Corresponding author:* e-mail: mattdd2013@126.com

Article in Press

neurohormonal responses, leading to vasodilation, natriuresis, reduced myocardial fibrosis, and improved cardiac remodeling (McMurray *et al*., 2014; Solomon *et al*., 2019).

Sacubitril/valsartan has been demonstrated to have clinical advantages in patients with heart failure and low ejection fraction and demonstrates superiority over conventional ACEI therapy in reducing cardiovascular mortality and heart failure hospitalization (Velazquez *et al*., 2019). This encouraging finding has brought about the urge to use sacubitril/valsartan earlier during myocardial injury like during the acute and early post-infarction era. Emergent experimental and clinical data indicate that early post-infarction sacubitril/valsartan reduces the infarct size, improves the left ventricular systolic function, and ameliorates the undesirable ventricular remodeling, in comparison to the standard RAAS inhibition alone (Pfeffer *et al*., 2021; Liu *et al*., 2024). A trial named PARADISE-MI was conducted to evaluate the effectiveness of sacubitril/valsartan in patients with acute myocardial infarction and left ventricular dysfunction or pulmonary congestion and reported a propensity toward improved outcomes, but did not show a significant advantage compared with ramipril (Pfeffer *et al*., 2021). Nevertheless, the specialist research and subgroup results suggest the potential benefit of selected patient cohorts and the need for further real-life research (Zhang *et al*., 2021). It is important to note that there is a paucity of information on the comparison of sacubitril/valsartan use in patients with STEMI undergoing primary PCI, particularly in the absence of randomized controlled trials. Practical retrospective studies could be valuable regarding the usefulness of early ARNI initiation in routine clinical practice, especially regarding infarct size reduction and ventricular remodeling parameters, both of which are strong predictors of long-term prognosis (Jhund and McMurray, 2021; Bozkurt *et al*., 2021).

As a mechanism of action, sacubitril/valsartan (LCZ696) acts as an RAAS blocker. Post-STEMI triggers both the pro-natriuretic peptide (NP) and RAAS neurohormonal systems, which oppose each other in their activation of the renin-angiotensin-aldosterone (RAAS) system (Fig. 1). The RAAS stimulation facilitates vasoconstriction, sodium retention, sympathetic stimulation, myocardial fibrosis and hypertrophy, which leads to negative ventricular remodeling and the development of heart failure. The NP system, conversely, has positive physiological influences, such as vasodilation, natriuresis, inhibition of sympathetic tone and aldosterone release, and myocardial fibrosis and hypertrophy. Sacubitril/valsartan (LCZ696) is a dual neurohormonal inhibitor, preventing neprilysin (NEP) and angiotensin II type-1 (AT1) receptor (to inhibit RAAS signaling), respectively (White *et al*., 1987; Xiong *et al*., 2021; Rezq *et al*., 2021). This dual blockage reinstates neurohormonal homeostasis, reduces stress on the myocardial wall, limits infarct growth, and inhibits adverse left ventricular remodeling, ultimately resulting in improved cardiac performance and delaying heart failure progression after myocardial infarction.

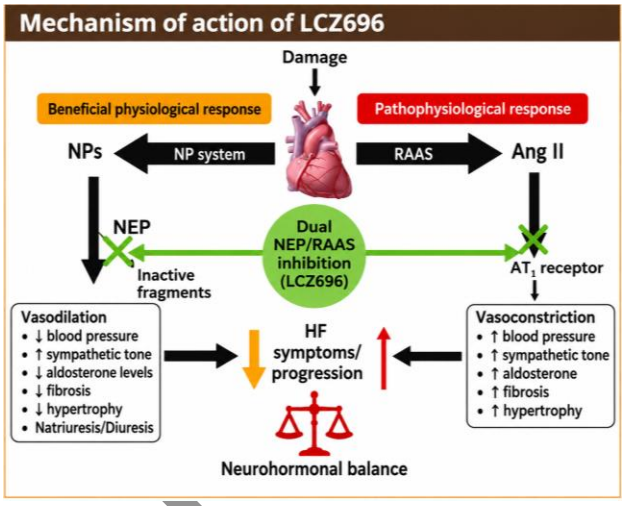


Fig. 1: Mechanism of action of sacubitril/valsartan (LCZ696).

In that regard, this research paper sought to evaluate the impact of early sacubitril/valsartan intervention in patients with STEMI undergoing primary PCI. This study used a four-year retrospective cohort (2020-2024) to assess the effects of early sacubitril/valsartan initiation on infarction size and ventricular remodeling compared with conventional post-STEMI medical therapy. This paper aims to build on the growing body of evidence and to inform prospective trials and clinical decision-making about the early use of sacubitril/valsartan in patients with STEMI by exploiting real-world data from a current population of PCI patients. Although several randomized trials, systematic reviews, and meta-analyses have evaluated sacubitril/valsartan following acute myocardial infarction, important gaps remain. First, much of the available evidence has been derived from highly selected trial populations, which may not fully reflect routine clinical practice. Second, data regarding the timing of sacubitril/valsartan initiation during the early post-STEMI period, particularly among patients undergoing contemporary primary PCI, remain relatively limited. Third, real-world information on treatment feasibility, dose titration, persistence and ventricular remodeling outcomes outside controlled trial settings is still evolving. Furthermore, the PARADISE-MI trial demonstrated favorable trends. Still, it did not establish clear superiority of sacubitril/valsartan over ramipril for its primary composite endpoint, leaving uncertainty regarding the magnitude of benefit in unselected post-myocardial infarction populations. Therefore, additional observational studies from contemporary clinical practice may provide complementary evidence regarding the implementation

Article in Press

and potential effectiveness of early sacubitril/valsartan therapy following STEMI.

Accordingly, the present study was designed not to establish a novel therapeutic effect of sacubitril/valsartan, but to evaluate its early use in a contemporary real-world cohort of STEMI patients undergoing primary PCI. Specifically, the association between early initiation of sacubitril/valsartan and infarct-related biomarkers, ventricular remodeling parameters, left ventricular functional recovery, and short-term clinical outcomes during routine clinical care was examined.

MATERIALS AND METHODS

Study design and study period

This study was conducted at Tianjin Hospital, Tianjin, China, a tertiary-care cardiovascular referral center with an established primary PCI program for the management of acute myocardial infarction. This study was designed as a single-center, retrospective observational cohort study. Medical records of patients presenting with STEMI and undergoing primary PCI were reviewed over a four-year period from January 2020 to December 2024. The study was reported in accordance with the STROBE recommendations for cohort studies (von Elm *et al*., 2007).

Study population

A total of 150 consecutive patients with STEMI who underwent primary PCI during the study period were included in the analysis. STEMI was defined according to standard electrocardiographic criteria, including persistent ST-segment elevation in at least two contiguous leads or new-onset left bundle branch block, in the presence of clinical features consistent with acute myocardial infarction (Ibanez *et al*., 2018; O'Gara *et al*., 2013). All patients underwent coronary angiography followed by PCI of the culprit vessel. Because of the retrospective observational design, formal prospective sample-size calculation was not performed. All consecutive eligible STEMI patients undergoing primary PCI during the study period were included to minimize selection bias and maximize statistical power.

Inclusion and exclusion criteria

Patients were eligible for inclusion if they met the following criteria:

Age ≥18 years
Diagnosis of STEMI and treatment with primary PCI
Availability of complete clinical, procedural, and follow-up data; initiation of guideline-directed medical therapy following PCI:

Patients were excluded if they had a prior history of chronic heart failure with reduced ejection fraction, cardiogenic shock at presentation, previous myocardial infarction within six months, significant valvular heart disease, end-stage renal disease requiring dialysis, contraindications to sacubitril/valsartan, or incomplete medical records.

Definition of early sacubitril/valsartan administration

Early sacubitril/valsartan administration was defined as initiation of the drug within 7 days of index STEMI during the index hospitalization or at early post-discharge follow-up, once the patient was hemodynamically stable. Patients who received sacubitril/valsartan formed the ARNI group, while those treated with standard RAAS inhibition (ACEI or ARB) served as the control group. Dose initiation and titration were performed at the discretion of the treating physician based on blood pressure, renal function and clinical stability.

PCI procedure and peri-procedural management

Primary PCI was performed according to standard institutional protocols and current guideline recommendations (Ibanez *et al*., 2018; O'Gara *et al*., 2013). Procedural details, including culprit vessel, pre- and post-procedural Thrombolysis in Myocardial Infarction (TIMI) flow grade, stent type and use of adjunctive pharmacotherapy, were documented. All patients received guideline-directed antiplatelet therapy, statins, beta-blockers and anticoagulation unless contraindicated.

Data collection and study variables

Data were extracted retrospectively from electronic medical records and catheterization laboratory databases. Collected variables included demographic characteristics, cardiovascular risk factors, clinical presentation, laboratory parameters, echocardiographic findings, angiographic characteristics and pharmacological treatments. Follow-up data were obtained from outpatient records and echocardiographic reports.

Assessment of infarct size

Infarct size was primarily estimated from peak cardiac biomarker levels, including creatine kinase–MB and cardiac troponin, obtained during index hospitalization. Imaging-based assessment of infarct size using echocardiographic surrogates or cardiac magnetic resonance imaging was available in a subset of patients and analyzed separately where applicable. Because initiation of sacubitril/valsartan occurred after reperfusion therapy in many patients, biomarker differences were interpreted cautiously and not considered definitive evidence of direct treatment-related infarct-size reduction.

Evaluation of ventricular remodeling

Ventricular remodeling was evaluated using transthoracic echocardiography performed during index hospitalization and at follow-up. Parameters assessed included LVEF, LVEDV and LVESV. Adverse ventricular remodeling was defined according to established echocardiographic criteria as an increase in LVEDV ≥20% from baseline and/or

Article in Press

failure of LVEF improvement during follow-up after myocardial infarction.

Study outcomes

The primary outcomes of the study were infarct size and changes in ventricular remodeling parameters during follow-up. Secondary outcomes included changes in LVEF, incidence of heart failure hospitalization and all-cause mortality during the follow-up period. Heart failure hospitalization was defined as hospital admission requiring intravenous diuretics or escalation of heart failure therapy in the presence of physician-confirmed symptoms and signs of congestion.

Follow-up

Patients were followed for at least 6 months after the index STEMI event. Clinical and echocardiographic follow-up data were collected from outpatient visits or hospital readmissions. Follow-up assessments included evaluation of blood pressure, renal function, serum potassium, medication tolerance and echocardiographic ventricular remodeling parameters at standardized outpatient intervals.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median with interquartile range, as appropriate, while categorical variables were presented as frequencies and percentages. Between-group comparisons were performed using the independent Student's t-test or Mann–Whitney U test for continuous variables and chi-square test or Fisher's exact test for categorical variables. Kaplan–Meier survival analysis with log-rank testing was used for analyses of all-cause mortality and heart failure hospitalizations. Multivariable logistic regression analysis, adjusted for baseline infarct size, baseline LVEF, age, diabetes mellitus, and clinical stability variables, was performed to identify predictors of favorable ventricular remodeling. A propensity score-adjusted analysis was also performed to reduce treatment-selection bias associated with clinician-directed ARNI initiation. Given multiple subgroup analyses, the findings should be interpreted as exploratory and hypothesis-generating. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA).

Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Tianjin Hospital Ethics Committee (Approval No. 2025-0110). Given the study's retrospective nature, informed consent was waived.

RESULTS

Baseline demographic and clinical characteristics

A total of 150 patients with STEMI undergoing primary PCI were included in the final analysis. Patients were stratified into two groups: early initiation of sacubitril/valsartan (ARNI group) or standard RAAS inhibitor therapy (control group). Baseline demographic and clinical characteristics of the study population are summarized in table 1. The two groups were comparable with respect to age, sex distribution, cardiovascular risk factors, infarct location, Killip class at presentation and baseline LVEF.

Angiographic and procedural characteristics

Angiographic and procedural characteristics are presented in table 2 and figure 2. There were no statistically significant differences between the ARNI and control groups in terms of culprit vessel distribution, pre- and post-procedural TIMI flow, stent type, number of stents deployed, or procedural success rates. Door-to-balloon time and use of adjunctive pharmacotherapy during PCI were also comparable between groups.

Infarct size assessment

Markers of infarct size are summarized in table 3 and Figure 3. Patients receiving early sacubitril/valsartan had lower peak cardiac biomarker levels than those receiving standard therapy. Imaging-based measures of infarct size, where available, showed a similar trend favoring the ARNI group.

Ventricular remodeling and left ventricular function

Changes in ventricular remodeling parameters during follow-up are shown in figures 4 and 5. Patients in the ARNI group showed greater improvement in LVEF and smaller increases in left ventricular end-diastolic and end-systolic volumes than those in the control group. The proportion of patients demonstrating adverse ventricular remodeling was lower in the ARNI group.

Patient selection and group allocation

The patient screening process, exclusions and final group allocation are illustrated in figure 6 and table 4.

Clinical outcomes and adverse events

During the follow-up period, patients receiving early sacubitril/valsartan experienced fewer heart failure–related hospitalizations compared with the control group. Rates of all-cause mortality and adverse events, including hypotension, renal dysfunction and hyperkalemia, were similar between the two groups as shown in Figures 7-8.

Early initiation of sacubitril/valsartan was feasible in the majority of patients, with over one-third starting therapy within 48 hours after PCI.

Most patients tolerated treatment well and nearly 90% remained on therapy at six months, with successful dose up-titration achieved in over 40% of cases (Table 5).

Article in Press

Table 1: Baseline demographic and clinical characteristics of the study population.

Variable	ARNI group (n=75)	Control group (n=75)	p-value
Age (years)	58.4 ± 10.2	59.6 ± 9.8	0.48
Male sex (%)	77.3	74.7	0.71
Hypertension (%)	52.0	54.7	0.74
Diabetes mellitus (%)	42.7	45.3	0.75
Dyslipidemia (%)	58.7	61.3	0.74
Current smoker (%)	41.3	38.7	0.74
Killip class ≥ II (%)	22.7	25.3	0.71
Baseline LVEF (%)	41.8 ± 6.4	42.1 ± 6.2	0.76

Continuous variables were compared using the independent Student's t-test, while categorical variables were analyzed using the chi-square test or Fisher's exact test.

Table 2: Angiographic and procedural characteristics of patients undergoing primary PCI.

Variable	ARNI Group	Control group	p-value
LAD culprit vessel (%)	56.0	58.7	0.74
Pre-PCI TIMI 0–1 (%)	77.3	80.0	0.68
Post-PCI TIMI 3 (%)	93.3	90.7	0.56
Door-to-balloon time (min)	64 ± 18	66 ± 20	0.52
Drug-eluting stent use (%)	96.0	94.7	0.65
Procedural success (%)	97.3	96.0	0.65
LAD culprit vessel (%)	56.0	58.7	0.74
Pre-PCI TIMI 0–1 (%)	77.3	80.0	0.68
Post-PCI TIMI 3 (%)	93.3	90.7	0.56
Door-to-balloon time (min)	64 ± 18	66 ± 20	0.52

Continuous variables were analyzed using the independent Student's t-test, while categorical variables were compared using the chi-square test or Fisher's exact test.

in Press

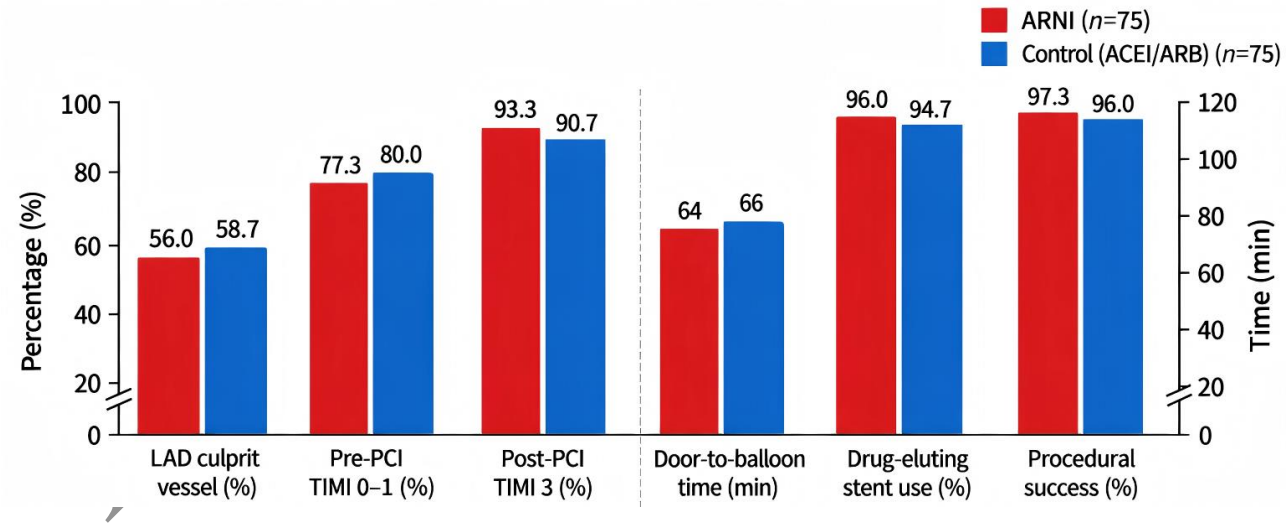


Fig. 2: Angiographic and procedural characteristics of patients undergoing primary percutaneous coronary intervention..

Among patients discontinuing sacubitril/valsartan therapy, the most common reasons included symptomatic hypotension, worsening renal function, persistent dizziness and patient preference related to medication tolerance and financial considerations. Stratified analysis by timing of sacubitril/valsartan initiation showed numerically greater improvement in ventricular remodeling parameters among patients initiated within 48 hours of PCI compared with those initiated between 3 and 7 days. However, given the limited sample size within subgroups, these findings should be interpreted cautiously and considered exploratory.

Table 3: Infarct size and ventricular remodeling parameters at follow-up.

Parameter	ARNI group	Control group	p-value
Peak troponin (ng/mL)	38.6 ± 12.4	46.9 ± 14.1	0.002
Peak CK-MB (U/L)	212 ± 68	261 ± 74	0.001
Infarct size (% LV mass)	18.2 ± 5.6	22.7 ± 6.1	<0.001
Follow-up LVEF (%)	49.6 ± 7.1	45.2 ± 6.8	0.001
Adverse LV remodeling (%)	18.7	38.7	0.008
Peak troponin (ng/mL)	38.6 ± 12.4	46.9 ± 14.1	0.002
Peak CK-MB (U/L)	212 ± 68	261 ± 74	0.001

Continuous variables were compared using the independent Student's t-test. Categorical variables were analyzed using the chi-square test.

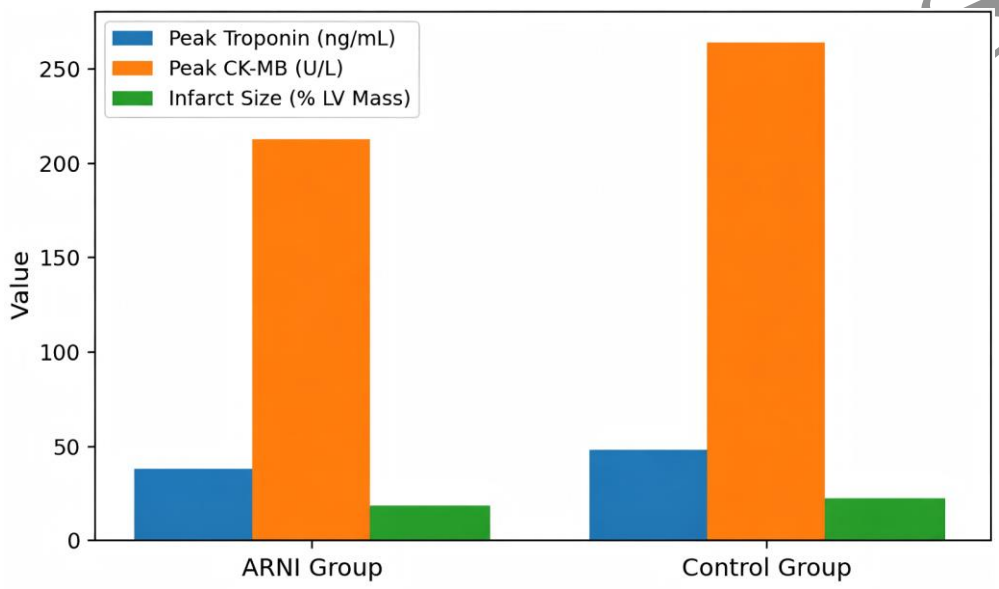


Fig. 3: Comparison of infarct size markers between the ARNI and Control groups. Peak cardiac troponin and creatine kinase-myocardial band (CK-MB) levels were significantly lower in patients receiving early sacubitril/valsartan (ARNI group) compared with those receiving standard ACEI/ARB therapy (Control group), indicating a lower biomarker-estimated infarct burden. Data are presented as mean ± standard deviation. Statistical comparisons were performed using the independent Student's t-test.

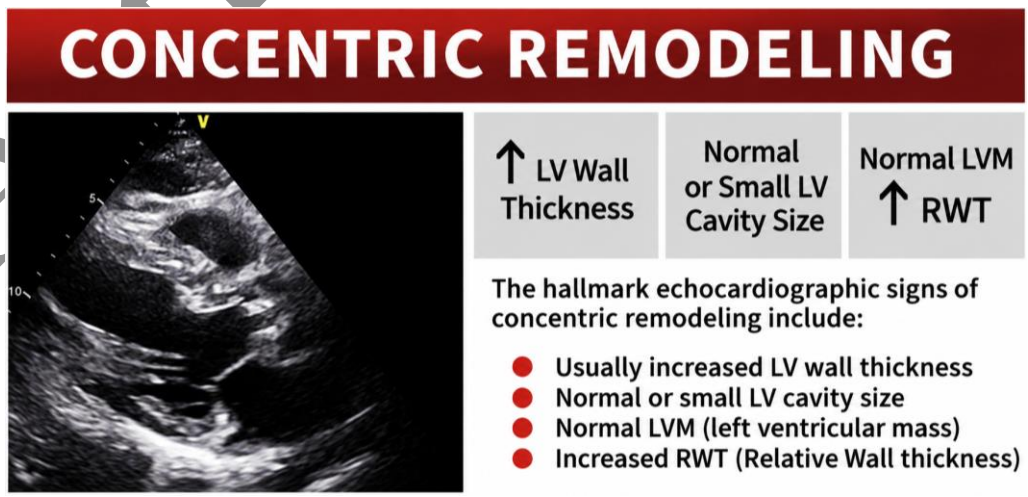


Fig. 4: Ventricular remodelling and left ventricular function.

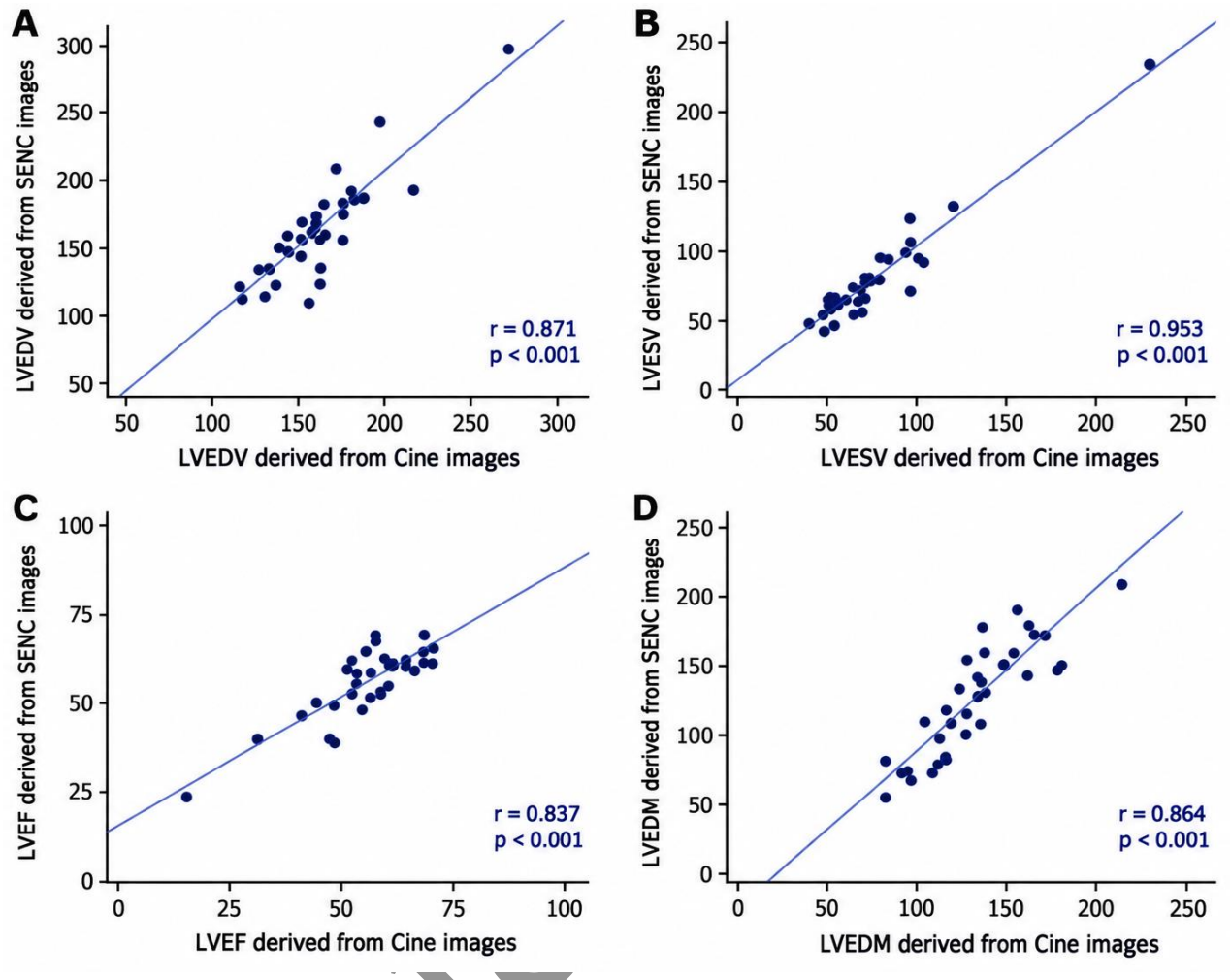


Fig. 5: Forest plot.

Table 4: Patient selection, exclusions and group allocation.

Study flow variable	Number of patients (n)
STEMI patients undergoing primary PCI screened	182
Excluded – Incomplete clinical or follow-up data	14
Excluded – Prior chronic heart failure (HFrEF)	7
Excluded – Cardiogenic shock at presentation	6
Excluded – Previous myocardial infarction (<6 months)	5
Total excluded	32
Final study population included	150
Early sacubitril/valsartan (ARNI group)	75
Standard ACEI/ARB therapy (Control group)	75

Predictors of favorable ventricular remodeling

Multivariable logistic regression analysis demonstrated that early initiation of sacubitril/valsartan was independently associated with favorable ventricular remodeling. Patients receiving early sacubitril/valsartan had 2.84-fold higher odds of favorable ventricular remodeling compared with those receiving standard ACEI/ARB therapy (OR = 2.84, 95% CI: 1.42–5.67, p = 0.003). In addition, lower baseline infarct size was independently associated with favorable ventricular remodeling. Specifically, patients with smaller baseline infarct size had a 1.91-fold higher odds of achieving favorable ventricular remodeling compared with those with larger infarct size (OR = 1.91, 95% CI: 1.18–3.09, p = 0.008). Furthermore, patients with baseline LVEF ≥40% had a 2.36-fold higher odds of favorable ventricular remodeling compared with patients with baseline LVEF <40% (OR = 2.36, 95% CI: 1.21–4.61, p = 0.012) as shown in table 6 and figure 9.

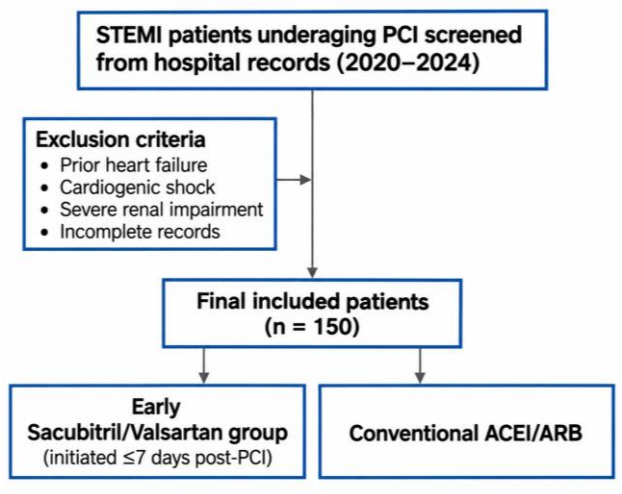


Fig. 6. Flow diagram of patient selection and study group allocation.

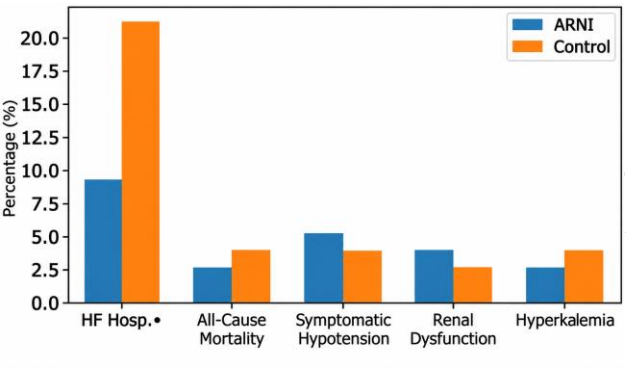


Fig. 7: Clinical outcomes and adverse events during the 6-month follow-up period in STEMI patients undergoing primary PCI. Patients receiving early sacubitril/valsartan (ARNI group) had significantly fewer heart failure hospitalizations than those in the Control group. Rates of all-cause mortality, symptomatic hypotension, renal dysfunction and hyperkalemia were comparable between groups. Note: * indicates a statistically significant difference between groups ($p < 0.05$).

Early initiation of sacubitril/valsartan was associated with approximately 2.8-fold greater odds of favorable ventricular remodeling compared with standard ACEI/ARB therapy, after adjustment for baseline clinical variables.

Subgroup analyses showed that the positive ventricular remodeling response to early initiation of sacubitril/valsartan was observed in clinically relevant subgroups, all of which showed stronger effects in patients with anterior wall STEMI, lower baseline LVEF, diabetes mellitus and early reperfusion (Table 7).

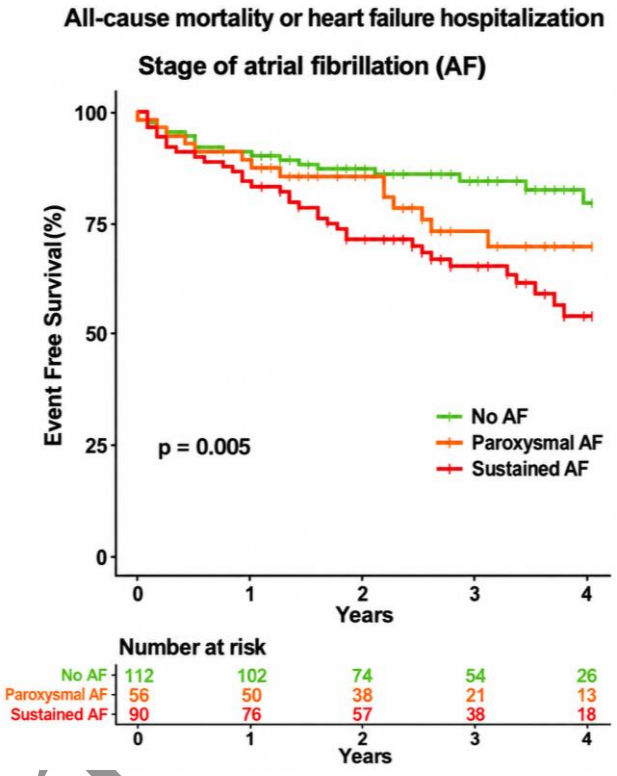


Fig. 8: All-cause mortality.

DISCUSSION

This retrospective cohort study examined the effect of early treatment with sacubitril/valsartan in patients presenting with STEMI undergoing PCI. Early use of sacubitril/valsartan was associated with reduced infarct-related biomarker levels, improved left ventricular systolic function, and less adverse ventricular remodeling during follow-up period compared with conventional ACEI/ARB treatment.

These findings confirm the potential to consider early angiotensin receptor-neprilysin inhibition as an additional intervention to optimize myocardial outcomes following STEMI in the clinical setting (Liu *et al*., 2024; Vitale *et al*., 2019). Patients in this study who were treated with early sacubitril/valsartan demonstrated lower peak levels of cardiac biomarkers and a smaller estimated infarct size compared to control patients who underwent standard RAAS inhibition. One of the main predictors of STEMI prognosis in the long term is infarct size, which is associated with a higher risk of heart failure, ventricular remodeling, and mortality (Zhang *et al*., 2022; Xiong *et al*., 2021). Despite the fact that timely reperfusion by primary PCI can greatly reduce myocardial necrosis, a secondary pharmacological approach to post-ischemic neurohormonal activation can be used to minimize myocardial injury.

Article in

Table 5: Sacubitril/Valsartan initiation timing, dose titration and treatment persistence.

Parameter	ARNI group (n=75)	Control group (n=75)	p-value
Timing of therapy initiation			
Initiation within 48 h post-PCI, n (%)	29 (38.7)	31 (41.3)	0.74
Initiation 3–7 days post-PCI, n (%)	46 (61.3)	44 (58.7)	0.74
Initial prescribed dose			
Low-dose therapy, n (%)	51 (68.0)	49 (65.3)	0.73
Standard-dose therapy, n (%)	24 (32.0)	26 (34.7)	0.73
Dose status at 6 months			
Maintained initial dose, n (%)	34 (45.3)	39 (52.0)	0.41
Successfully up-titrated, n (%)	31 (41.3)	28 (37.3)	0.62
Dose reduced due to intolerance, n (%)	10 (13.4)	8 (10.7)	0.61
Treatment persistence at 6 months			
Continued therapy, n (%)	66 (88.0)	68 (90.7)	0.59
Discontinued therapy, n (%)	9 (12.0)	7 (9.3)	0.59
Reasons for discontinuation			
Symptomatic hypotension, n (%)	4 (5.3)	3 (4.0)	0.70
Renal dysfunction, n (%)	3 (4.0)	2 (2.7)	0.65
Persistent dizziness/cough, n (%)	0 (0.0)	1 (1.3)	0.32
Patient preference/non-adherence, n (%)	2 (2.7)	1 (1.3)	0.56

Data are presented as number (percentage). Comparisons between groups were performed using the chi-square test or Fisher's exact test, as appropriate. ARNI = Angiotensin Receptor–Neprilysin Inhibitor; PCI = Percutaneous Coronary Intervention; ACEI = Angiotensin-Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker.

Table 6: Multivariate logistic regression analysis for predictors of favourable ventricular remodelling.

Variable	Odds ratio (OR)	95% Confidence interval	p-value
Early sacubitril/valsartan initiation	2.84	1.42 – 5.67	0.003
Lower baseline infarct size	1.91	1.18 – 3.09	0.008
Baseline LVEF ≥40%	2.36	1.21 – 4.61	0.012
Age (per 10-year increase)	0.89	0.71 – 1.12	0.34
Diabetes mellitus	0.78	0.41 – 1.49	0.46
Anterior wall MI	0.93	0.50 – 1.74	0.82
Door-to-balloon time <90 min	1.27	0.66 – 2.43	0.48

Note: Favourable ventricular remodelling was coded as the dependent variable (1 = favourable remodelling, 0 = unfavourable remodelling). OR >1 indicates increased odds of favourable ventricular remodelling.

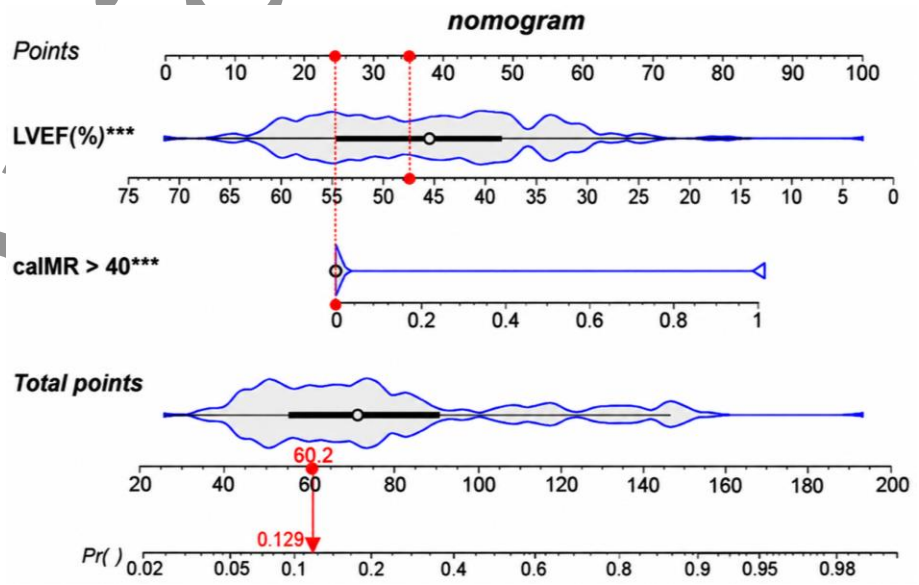


Fig. 9: Multivariate prediction & mechanistic model.

Article in Press

Table 7: Subgroup analysis of favourable ventricular remodelling associated with early sacubitril/valsartan.

Subgroup	Odds ratio (OR)	95% Confidence interval	p-value
Age < 65 years	3.12	1.41 – 6.91	0.005*
Age ≥ 65 years	1.94	0.88 – 4.29	0.10
Anterior wall STEMI	3.48	1.52 – 7.96	0.003*
Non-anterior STEMI	2.01	0.91 – 4.45	0.08
Baseline LVEF < 40%	3.67	1.58 – 8.54	0.002*
Baseline LVEF ≥ 40%	1.88	0.86 – 4.11	0.11
Diabetes mellitus present	2.91	1.21 – 6.99	0.017*
Diabetes mellitus absent	2.62	1.14 – 6.04	0.024*
PCI within 90 min	3.21	1.39 – 7.44	0.006*
PCI > 90 min	2.05	0.89 – 4.72	0.09

Subgroup comparisons were analyzed using multivariable logistic regression. * indicates statistically significant p-value (<0.05).

The described reduction in infarct size in the sacubitril/valsartan group may be attributed to the drug's dual action, i.e., its capacity to block angiotensin II receptors and, at the same time, neprilysin. This triggers increased concentrations of natriuretic peptides and other vasoactive substances that have vasodilatory, anti-inflammatory, antifibrotic, and anti-hypertrophic properties, and simultaneously inhibit myocardial injury induced by the RAAS (Xiong *et al*., 2021). Preliminary and preclinical studies have shown that these pleiotropic effects can inhibit the growth of the infarct and enhance myocardial repair if the therapy is initiated early after acute myocardial infarction (Rezq *et al*., 2021; Jia *et al*., 2025). Consistent with these observations, recent meta-analyses and retrospective studies have demonstrated reduced infarct size and improved biomarker profiles with early use of sacubitril/valsartan after STEMI (Liu *et al*., 2024). Negative ventricular remodeling has been found to be an important aspect in the occurrence of post-infarction heart failure despite the current reperfusion and guideline-based medical care. In the present study, follow-up with early therapy using sacubitril/valsartan was associated with improvement in LVEF and reduced changes in left ventricular end-diastolic and end-systolic volumes. In addition, the proportion of patients who developed adverse ventricular remodeling was significantly lower in the sacubitril/valsartan group. The results of the above are in line with the emerging studies that have shown that angiotensin receptorneprilysin inhibition positively remodels postinfarction remodeling by inhibiting myocardial fibrosis, alleviating wall stress and improving ventricular compliance (Garg and Yusuf, 1995; Pascual-Figal *et al*., 2021). Clinical trials have still indicated improvements in echocardiographic measurements with sacubitril/ valsartan compared to ACEI/ARB therapy in post-MI populations, particularly during the initial hospitalization, or in the immediate post-revascularization period (Pfeffer *et al*., 2021). Although the PARADISE-MI trial did not show a statistically significant reduction in the primary composite endpoint compared to ramipril, postulation of positive effects on ventricular remodeling and heart failure-related outcomes in the sampled high-risk patients (Yin *et al*., 2025) have been postulated based on secondary analyses and real-world data. The present analysis showed that early sacubitril/valsartan initiation was associated with approximately 2.8-fold higher odds of favorable ventricular remodeling compared with standard ACEI/ARB therapy after adjustment for baseline characteristics. However, because treatment allocation was clinician-directed in this retrospective cohort, these findings should be interpreted as an association. These findings should be interpreted in the context of the PARADISE-MI trial, which did not demonstrate statistically significant superiority of sacubitril/valsartan over ramipril for the primary composite endpoint despite favorable trends in ventricular remodeling and heart failure outcomes.

Therefore, the present observational results should not be interpreted as confirmatory evidence of superiority but rather as supportive real-world data suggesting potential benefit that warrants further prospective validation. The clinical implications of these findings warrant further investigation. Early application of sacubitril/valsartan after STEMI and PCI may help preserve left ventricular function and limit adverse remodeling; however, the observational design does not establish causality or long-term benefit. Given the cardiac failure burden in low- and middle-income countries, including low- and middle-income settings, the post-MI environment is a key focus and, thus, the maximization of early pharmacological treatment can have positive effects on overall population health. However, close monitoring and observation of hypotension and renal failure remain to be used in managing the acute post-infarction population (Wei *et al*., 2025; Zhao *et al*., 2025). Importantly, peak cardiac biomarker levels may largely reflect baseline infarct severity because ARNI initiation occurred after reperfusion therapy in many patients. Therefore, biomarker differences should not be interpreted as definitive evidence of direct infarct-size reduction attributable to sacubitril/valsartan therapy.

Article in Press

Importantly, the present study does not seek to redefine the established role of sacubitril/valsartan after myocardial infarction. Rather, it provides real-world evidence regarding early ARNI initiation following primary PCI and describes treatment patterns, feasibility and ventricular remodeling outcomes in routine clinical practice. Therefore, the results should be viewed as complementary to existing randomized and meta-analytic evidence rather than as independent proof of therapeutic superiority.

Several limitations should be acknowledged. First, the retrospective observational design introduces potential selection bias and residual confounding because treatment allocation was clinician-directed rather than randomized. Although multivariable and propensity score-adjusted analyses were performed, unmeasured confounding related to infarct territory extent, collateral circulation, completeness of revascularization and early post-PCI clinical stability cannot be excluded. Second, infarct size was primarily assessed using cardiac biomarkers, whereas imaging-based assessment was available only in a subset of patients. Third, subgroup analyses and multiple comparisons were exploratory in nature and were not adjusted for multiplicity. Fourth, the six-month follow-up duration captures early ventricular remodeling changes but is insufficient to determine long-term outcomes, including mortality and heart failure progression. Finally, the single-center design and relatively modest sample size may limit generalizability.

CONCLUSION

Early initiation of sacubitril/valsartan following STEMI treated with primary PCI was associated with favorable ventricular remodeling and improved recovery of left ventricular systolic function compared with conventional ACEI/ARB therapy in this retrospective observational cohort. Because treatment allocation was clinician-directed and infarct size was primarily estimated from biomarker assessment, these findings should be considered hypothesis-generating rather than confirmatory evidence of treatment superiority. Larger, prospective, randomized studies with long-term follow-up and standardized imaging-based assessment are necessary to further clarify the optimal role and timing of initiating sacubitril/valsartan after STEMI.

Acknowledgments
None

Authors' contributions
Lei Sun: Conceptualization, study design, data collection, analysis, manuscript drafting and interpretation of results; Haibin Jin: Data acquisition, statistical analysis, interpretation of findings and manuscript revision; Xiaoqin Wen: Clinical data assessment, literature review and manuscript editing; Xingyu Huo: Supervision of the study, critical revision of the manuscript and final approval of the submitted version.

Funding
There was no funding.

Data availability statement
The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
This study was approved by Tianjin Hospital Ethics Committee (NO. 2025-0110). This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflicts of interest
The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Consent to publish
The manuscript has neither been previously published nor is under consideration by any other journal. The authors have all approved the content of the paper.

REFERENCES

Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, Drazner MH, Felker GM, Filippatos G, Fonarow GC, Fiuzat M, Gomez-Mesa JE, Heidenreich P, Imamura T, Januzzi J, Jankowska EA, Khazanie P, Kinugawa K, Lam CSP, Matsue Y, Metra M, Ohtani T, Piepoli MF, Ponikowski P, Rosano GMC, Sakata Y, Seferović P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J and Zieroth S (2021). Universal definition and classification of heart failure. *J Card Fail*, **27**(4): 387-413.

Garg R and Yusuf S (1995). Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA*, **273**(18): 1450-1456.

Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P and Widimský P (2018). 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*, **39**(2): 119-177.

Article in Press

Jhund PS and McMurray JJV (2021). Does sacubitril/valsartan have a role in acute myocardial infarction? *Eur Heart J*, 42(38): 3866-3869.

Jia Y, Zhao C, Cui K, Zhang Y, Wang G, Yao Q and Zhang Y (2025). The effect of sacubitril/valsartan sodium on cardiac function and ventricular remodeling in patients with heart failure after PCI for acute myocardial infarction. *Am J Transl Res*, **17**(6): 4713-4722.

Køber L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, Videbæk J, Cole DS, Auclert L, Pauly NC, Aliot E, Persson S and Camm AJ (1995). A clinical trial of trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*, **333**(25): 1670-1676.

Liu Y, Sun Y and Dai W (2024). Effect of sacubitril-valsartan on left ventricular remodeling in patients with acute myocardial infarction after primary percutaneous coronary intervention: A systematic review and meta-analysis. *Front Pharmacol.*, **15**: 1366035.

McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K and Zile MR (2014). Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*, **371**(11): 993-1004.

O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ and Zhao DX (2013). 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *Circulation*, **127**(4): e362-e425.

Pascual-Figal D, Bayés-Genis A, Beltrán-Troncoso P, Caravaca-Pérez P, Conde-Martel A, Crespo-Leiro MG, Delgado JF, Díez J, Formiga F and Manito N (2021). Sacubitril-valsartan, clinical benefits and related mechanisms of action in heart failure with reduced ejection fraction: A review. *Front Cardiovasc Med*, **8**: 754499.

Pfeffer MA and Braunwald E (1990). Ventricular remodeling after myocardial infarction: Experimental observations and clinical implications. *Circulation*, **81**(4): 1161-1172.

Pfeffer MA, Claggett B, Lewis EF, Granger CB, Køber L, Maggioni AP, Mann DL, McMurray JJV, Rouleau JL, Solomon SD, Steg PG, Berwanger O, Cikes M, De Pasquale CG, East C, Fernandez A, Jering K, Landmesser U, Mehran R, Merkely B, Mody FV, Petrie MC, Petrov I, Schou M, Senni M, Sim D, van der Meer P, Lefkowitz M, Zhou Y, Gong J and Braunwald E (2021). Angiotensin receptor-neprilysin inhibition in acute myocardial infarction. *N Engl J Med*, **385**(20): 1845-1855.

Pfeffer MA, McMurray JJV, Velazquez EJ, Rouleau JL, Køber L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA and Califf RM (2003). Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*, **349**(20): 1893-1906.

Rezq A, Saad M and El Nozahi M (2021). Comparison of the efficacy and safety of sacubitril/valsartan versus ramipril in patients with ST-segment elevation myocardial infarction. *Am J Cardiol*, **143**: 7-13.

Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC and Lefkowitz MP (2019). Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*, **381**(17): 1609-1620.

Sutton MGSJ and Sharpe N (2000). Left ventricular remodeling after myocardial infarction: Pathophysiology and therapy. *Circulation*, **101**(25): 2981-2988.

Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E and PIONEER-HF Investigators (2019). Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*, **380**(6): 539-548.

Vitale G, Romano G, Di Franco A, Caccamo G, Nugara C, Ajello L, Storniolo S, Sarullo S, Agnese V, Giallauria F, Novo G, Clemenza F and Sarullo FM (2019). Early effects of sacubitril/valsartan on exercise tolerance in patients with heart failure with reduced ejection fraction. *J Clin Med*, **8(**2): 262.

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC and Vandenbroucke JP (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *PLoS Med*, **4**(10): e296.

Wei W, Xu G, Gao J, Wang G, Wang Y, Li C, Zheng J, Lu H, Lu Y, Wang K, Xu H, Wang C and Pan X (2025). Sacubitril/valsartan partially alleviates myocardial infarction injury by activating the FGF21 signaling pathway via PPARs. *Cardiovasc Diabetol*, **24**(1): 89.

White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM and Wild CJ (1987). Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation*, **76**(1): 44-51.

Xiong B, Nie D, Qian J, Yao Y, Yang G, Rong S, Zhu Q, Du Y, Jiang Y and Huang J (2021). The benefits of sacubitril-valsartan in patients with acute myocardial

Article in Press

infarction: A systematic review and meta-analysis. *ESC Heart Fail*, **8**(6): 4852-4862.

Yin H, Zhou Y, Zhou Y, Ren L and Ma L (2025). Early sacubitril/valsartan use associated with reduced atrial fibrillation risk in patients with acute myocardial infarction complicated by mitral regurgitation: A retrospective cohort study. *Front Cardiovasc Med*, **12**: 1658746.

Zhang L, Yan K, Zhao H, Shou Y, Chen T and Chen J (2022). Therapeutic effects and safety of early use of sacubitril/valsartan after acute myocardial infarction: A systematic review and meta-analysis. *Ann Palliat Med*, **11**(3): 1017-1027.

Zhang Y, Wu Y, Zhang K, Ke Z, Hu P and Jin D (2021). Benefits of early administration of sacubitril/valsartan in patients with ST-elevation myocardial infarction after primary percutaneous coronary intervention. *Coron Artery Dis*, **32**(5): 427-431.

Zhao YM, Luo JT, Pang KF, Feng Y, Tan JP, Liu M and Lin ZH (2025). Clinical efficacy of sacubitril/valsartan combined with cardiac rehabilitation in patients with heart failure after acute myocardial infarction: A single-center randomized trial. *BMC Cardiovasc Disord*, **25**(1): 246.

Article in Press