

Sacubitril/Valsartan Versus Valsartan in Elderly Patients With Acute Myocardial Infarction and Hypertension: Effects on Ventricular Remodeling and Short-term Prognosis After PCI: A Prospective Randomized Controlled Study

Yong WANG

The First People's Hospital of Shangqiu

Zichang LIU

The First People's Hospital of Shangqiu

Xuesheng XU

The First People's Hospital of Shangqiu

Wenkun GE

610587321@qq.com

The First People's Hospital of Shangqiu

Research Article

Keywords: Acute myocardial infarction, Sacubitril/valsartan, Ventricular remodeling, Hypertension, Percutaneous coronary intervention

Posted Date: August 31st, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10401751/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

In older adults, acute myocardial infarction (AMI) complicated by hypertension promotes adverse ventricular remodeling, impairs cardiac function, and increases the risk of unfavorable outcomes despite percutaneous coronary intervention (PCI). Although renin–angiotensin–aldosterone system inhibition is central to post-AMI management, residual cardiovascular risk remains. Whether early angiotensin receptor–neprilysin inhibition provides benefit in this high-risk population remains insufficiently defined. This study compared the efficacy and safety of sacubitril/valsartan with valsartan in elderly patients with AMI and hypertension after PCI.

Methods

This prospective, randomized, controlled trial enrolled 200 patients aged ≥ 65 years with AMI and hypertension who underwent PCI. Within 24 hours after PCI, participants were randomly assigned to receive sacubitril/valsartan or valsartan and were followed for 12 weeks. The primary outcome was the total effective rate, defined by improvement in left ventricular ejection fraction (LVEF) or New York Heart Association functional class. Secondary outcomes included LVEF, left ventricular end-diastolic diameter (LVEDD), inflammatory biomarkers, hypotension, and major adverse cardiovascular events (MACE). Between-group comparisons were performed using independent-samples *t* tests, Mann–Whitney U tests, chi-square tests, or Fisher's exact tests, as appropriate. Repeated measures were evaluated using repeated-measures analysis of variance with Greenhouse–Geisser and Bonferroni corrections when indicated, and time-to-event outcomes were assessed using Kaplan–Meier analysis and the log-rank test.

Results

At 12 weeks, the total effective rate was significantly higher with sacubitril/valsartan than with valsartan (91% vs. 79%; $P = 0.017$). Sacubitril/valsartan was associated with greater improvement in LVEF (46.50% vs. 42.22%; $P < 0.001$) and a smaller LVEDD (49.25 vs. 49.91 mm; $P = 0.028$). Inflammatory biomarker levels were significantly lower in the sacubitril/valsartan group. MACE occurred less frequently with sacubitril/valsartan (5.1% vs. 14.4%; $P = 0.026$), whereas hypotension rates did not differ significantly between groups.

Conclusions

Early initiation of sacubitril/valsartan after PCI improved cardiac function, attenuated ventricular remodeling and systemic inflammation, and reduced short-term MACE compared with valsartan, without a significant increase in hypotension. These findings support further evaluation of early angiotensin receptor–neprilysin inhibition in this vulnerable population.

Trial registration:

This trial was registered on Chinese Clinical Trial Registry, ChiCTR2300074600; registration date: 10 August 2023. This trial was retrospectively registered.

Introduction

Acute myocardial infarction (AMI) complicated by hypertension is common among older adults and is associated with a substantial burden of morbidity and adverse cardiovascular outcomes. Epidemiological evidence indicates that hypertension affects approximately half of patients presenting with AMI and significantly increases the risk of recurrent cardiovascular events [1]. Large registry studies have likewise identified hypertension as a major modifiable risk factor in this population [2].

Admission blood pressure also appears to have prognostic significance, with lower values inversely associated with long-term survival [3]. The coexistence of hypertension and AMI may exert additive or synergistic adverse effects on cardiac structure and function by accelerating ventricular remodeling and promoting progressive deterioration in myocardial performance. Specifically, the chronic hemodynamic load imposed by hypertension, together with acute ischemic injury, facilitates left ventricular hypertrophy, myocardial fibrosis, and maladaptive changes in ventricular geometry. These processes can further impair systolic and diastolic function and contribute to a less favorable clinical course [4]. This interaction may be particularly consequential in very elderly patients, in whom it contributes to a complex and potentially paradoxical risk profile for mechanical complications [5]. Accordingly, the management of older patients with both AMI and hypertension remains challenging because the combined pathophysiological effects of these conditions may attenuate the benefits of conventional post-AMI treatment and adversely affect functional recovery and survival [6, 7].

Inhibition of the renin–angiotensin–aldosterone system is a cornerstone of pharmacological treatment after AMI because of its established role in limiting adverse ventricular remodeling and improving prognosis. Angiotensin receptor blockers (ARBs), including valsartan, are widely used for this purpose and have been associated with reductions in mortality and cardiovascular events in patients with heart failure and atrial fibrillation [8, 9]. Nevertheless, the effectiveness of conventional renin–angiotensin–aldosterone system inhibitors (RAASi) remains suboptimal in some clinical populations. For example, among patients with heart failure with reduced ejection fraction (HFrEF), only 47.1% were receiving at least 50% of the recommended target ARB dose at the 6-month follow-up [10]. In addition, preclinical evidence showing that combined treatment with valsartan and spironolactone can substantially attenuate myocardial dysfunction suggests that complementary therapeutic strategies may be needed to overcome the limitations of renin–angiotensin–aldosterone system inhibition alone [11]. These considerations have stimulated interest in therapies capable of simultaneously modulating multiple neurohormonal pathways and thereby providing broader cardiovascular protection.

Angiotensin receptor–neprilysin inhibitors (ARNIs), particularly sacubitril/valsartan, have consequently emerged as an important therapeutic class that provides more comprehensive neurohormonal modulation than conventional ARB therapy [12]. Sacubitril/valsartan has demonstrated superiority over traditional RAASi in reducing hospitalization for heart failure and cardiovascular mortality across a broad range of left ventricular ejection fractions [13]. Although its efficacy in HFrEF is well established, the comparative effects of sacubitril/valsartan on systemic inflammation and adverse cardiovascular outcomes in older patients with AMI and concomitant hypertension remain insufficiently characterized. Most previous studies have focused on younger patients with chronic heart failure or have relied on composite outcomes that may not fully reflect the distinct risk–benefit profile of very elderly patients, including octogenarians [14]. Furthermore, prospective randomized trials directly comparing the safety of ARNIs and ARBs during the early post-AMI period are limited, particularly with respect to clinically important outcomes such as hypotension and major adverse cardiovascular events (MACE) after primary percutaneous coronary intervention (PCI) [15]. The use of potent blood pressure-lowering therapies in this setting is additionally complicated by continued debate regarding a possible J-shaped relationship between blood pressure and prognosis after AMI [16]. Consequently, it remains uncertain whether the potentially superior antiremodeling and anti-inflammatory effects of ARNIs confer a meaningful net clinical benefit over ARBs without producing an unacceptable increase in treatment-related adverse events among older hypertensive patients during the immediate post-AMI period.

A comprehensive assessment of therapeutic benefit in this population should extend beyond conventional measures of cardiac function. Ventricular remodeling, reflected by alterations in left ventricular geometry and performance, is a major determinant of heart failure progression but has not been evaluated consistently as a primary outcome in comparative studies of ARNIs and ARBs after AMI [17]. Likewise, the inflammatory cascade is critically involved in myocardial injury, healing, and subsequent adverse outcomes after ischemia, yet inflammatory biomarkers are frequently assessed in isolation rather than as part of an integrated evaluation of treatment efficacy [18]. The effects of these interventions on short-term MACE, including cardiac death and rehospitalization for heart failure, have also often been examined only as secondary or exploratory outcomes, thereby limiting the strength of the evidence regarding their broader prognostic value [19]. Studies that concurrently evaluate left ventricular functional recovery, reverse remodeling, systemic inflammation, and early cardiovascular events are therefore needed to more fully characterize the clinical effects of sacubitril/valsartan in this setting.

Against this background, the present prospective, randomized, controlled trial was designed to directly compare the efficacy and safety of early sacubitril/valsartan initiation with those of valsartan in patients aged ≥ 65 years with AMI and hypertension following PCI. The study hypothesis was that sacubitril/valsartan would provide greater improvements in cardiac function and short-term clinical outcomes than valsartan over a 12-week treatment period. Previous investigations have not specifically examined the simultaneous and systematic recovery of left ventricular function, reversal of ventricular remodeling, and changes in inflammatory biomarkers within this timeframe in older patients with AMI and comorbid hypertension [20, 21]. Management of blood pressure after AMI is particularly complex because therapeutic targets may be influenced by the potential J-shaped association, while adequate neurohormonal modulation remains essential for promoting favorable ventricular remodeling [16]. In addition, the interaction between hypertension-related systemic inflammation and the local myocardial inflammatory response to infarction provides a strong rationale for assessing inflammatory biomarkers in this population [22]. This study therefore sought to address these unresolved questions by providing an integrated evaluation of early sacubitril/valsartan therapy in a clinically vulnerable, high-risk subgroup and to generate evidence that may inform optimization of post-infarction treatment strategies.

Materials and Methods

1.1 Study Design and Ethical Considerations

This prospective, randomized, controlled study was approved by the Ethics Committee of The First People's Hospital of Shangqiu (approval no. HS2021005). Written informed consent was obtained from all participants or their authorized family members before enrollment. The trial was registered with the Chinese Clinical Trial Registry under registration number ChiCTR2300074600.

This prospective randomized controlled trial was designed, conducted and reported strictly in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2025 guidelines for randomized controlled trials. All core items required by the CONSORT statement have been fully supplemented and clarified throughout the manuscript to ensure transparent and complete reporting of trial methodology, participant flow, outcomes and safety data.

1.2 Study Population

Consecutive patients aged ≥ 65 years with AMI and concomitant hypertension who were admitted to the Department of Cardiology at The First People's Hospital of Shangqiu between October 2021 and October 2025 were screened for eligibility. All enrolled patients had successfully undergone percutaneous coronary intervention (PCI). The inclusion criteria were as follows: (1) AMI diagnosed according to the Fourth Universal Definition of Myocardial Infarction; (2) a documented history of essential hypertension or newly diagnosed hypertension after hospital admission, defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg; (3) age ≥ 65 years; and (4) PCI performed within 12 hours after AMI onset. The exclusion criteria were as follows: (1) a history of myocardial infarction, heart failure, or severe valvular heart disease; (2) severe hepatic or renal dysfunction, defined as an alanine aminotransferase level > 3 times the upper limit of normal or an estimated glomerular filtration rate < 30 mL/min/1.73 m²; (3) known hypersensitivity to sacubitril/valsartan, valsartan, or another angiotensin receptor–neprilysin inhibitor; and (4) a severe psychiatric disorder or inability to adhere to the scheduled follow-up procedures.

1.3 Treatment Regimens and Randomization

Before PCI, all patients received loading doses of antiplatelet therapy consisting of aspirin 300 mg plus either clopidogrel 600 mg or ticagrelor 180 mg, together with intravenous unfractionated heparin 70–100 U/kg. PCI was performed within 12 hours of AMI onset in both groups, and intervention was restricted to the culprit vessel. The decision to perform thrombus aspiration or intracoronary thrombolysis was made by the treating operator according to lesion complexity and thrombus burden. After PCI, patients received aspirin 100 mg/day and either clopidogrel 75 mg/day or ticagrelor 90 mg twice daily. Statins and beta-blockers were also administered as standard therapy unless contraindicated. Participants were subsequently randomized in a 1:1 ratio using a random-number table to one of the following treatment groups:

The sacubitril/valsartan group included 100 patients. Sacubitril/valsartan tablets were administered orally within 24 hours after PCI at an initial dose of 25–50 mg twice daily. The dose was subsequently titrated according to blood pressure and tolerability to a maximum tolerated dose of 100–200 mg twice daily. The tablets had a labeled strength of 100 mg and were manufactured by Beijing Novartis Pharmaceutical Co., Ltd., under National Drug Approval Number J20171054.

The valsartan group included 100 patients. Valsartan capsules were administered orally within 24 hours after PCI at an initial dose of 40–80 mg once daily. The dose was subsequently titrated according to blood pressure and tolerability to 80–160 mg once daily. The capsules had a labeled strength of 80 mg and were manufactured by Beijing Novartis Pharmaceutical Co., Ltd., under National Drug Approval Number H20040217.

Both treatment regimens were continued until completion of the 12-week study period.

1.4 Outcomes and Follow-up

The primary outcome was the overall efficacy rate after 12 weeks of treatment. Treatment was considered effective when the patient achieved either an increase in left ventricular ejection fraction (LVEF) of $\geq 5\%$ from baseline or an improvement of ≥ 1 New York Heart Association functional class from baseline. Secondary outcomes included echocardiographic indices, inflammatory biomarkers, and clinical adverse events. Echocardiographic outcomes comprised LVEF and left ventricular end-diastolic diameter. Inflammatory biomarkers included high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). Safety and clinical outcomes included hypotension, defined as systolic blood pressure < 90 mmHg, and major adverse cardiovascular events, comprising cardiac death, nonfatal myocardial infarction, and rehospitalization for heart failure. All patients underwent echocardiographic assessment and laboratory testing at baseline and after 12 weeks of treatment. Follow-up was conducted through outpatient visits or telephone interviews over 12 weeks, corresponding to 90 days. Losses to follow-up and all clinical events occurring during the follow-up period were recorded.

1.5 Statistical Analysis

Statistical analyses were performed using SPSS version 26.0. Normally distributed continuous variables were presented as the mean $\pm$ standard deviation and were compared between groups using independent-samples *t* tests. Non-normally distributed continuous variables were presented as the median and interquartile range and were compared using the Mann–Whitney *U* test. Categorical variables were presented as numbers and percentages and were compared using the chi-square test or Fisher's exact test, as appropriate. Ordinal variables were analyzed using rank-sum tests. Repeated-measures data were evaluated using repeated-measures analysis of variance. The Greenhouse–Geisser correction was applied when necessary, and post hoc pairwise comparisons were adjusted using the Bonferroni method. Time-to-event outcomes were analyzed using the Kaplan–Meier method, and survival distributions were compared using the log-rank test. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

2.1 Baseline Characteristics

Baseline demographic and clinical characteristics were well balanced between the treatment groups. No statistically significant between-group differences were observed in age, sex, body mass index, time from symptom onset, New York Heart Association functional class, infarct location, smoking status, or history of type 2 diabetes mellitus ($P > 0.05$), indicating comparability of the groups before treatment (Table 1).

2.2 Clinical Efficacy

After 12 weeks of treatment, the overall efficacy rate was significantly higher in the sacubitril/valsartan group than in the valsartan group. A treatment response was observed in 91 of 100 patients receiving sacubitril/valsartan, corresponding to an overall efficacy rate of 91%, compared with 79 of 100 patients receiving valsartan, corresponding to a rate of 79% ($\chi^2 = 5.647$, $P = 0.017$; Table 2).

2.3 Cardiac Function and Ventricular Remodeling

At baseline, LVEF, left ventricular end-diastolic diameter (LVEDD), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels did not differ significantly between the two groups (all $P > 0.05$). At both 4 and 12 weeks after treatment initiation, LVEF increased, whereas LVEDD and NT-proBNP levels decreased in both groups. However, patients treated with sacubitril/valsartan exhibited significantly greater improvements in LVEF and significantly larger reductions in LVEDD and NT-proBNP than those treated with valsartan (all $P < 0.05$; Table 3).

Table 3
Cardiac function and ventricular remodeling parameters by treatment group, mean $\pm$ standard deviation

Group	n	LVEF (%)			LVEDD (mm)			NT-proBNP (pg/ml)		
		Pre-treatment	4 weeks	12 weeks	Pre-treatment	4 weeks	12 weeks	Pre-treatment	4 weeks	12 weeks
Observation	100	38.11 $\pm$ 4.39	40.67 $\pm$ 4.22	42.22 $\pm$ 3.96	50.83 $\pm$ 2.45	49.58 $\pm$ 1.67	49.91 $\pm$ 2.24	3267.67 $\pm$ 116.66	2124.46 $\pm$ 80.93	1236.08 $\pm$ 74.85
Control	100	38.44 $\pm$ 4.92	42.37 $\pm$ 4.19	46.50 $\pm$ 3.33	51.05 $\pm$ 2.43	50.41 $\pm$ 1.86	49.25 $\pm$ 1.86	3275.84 $\pm$ 116.95	1651.67 $\pm$ 68.03	876.81 $\pm$ 61.74
t		0.500	2.859	8.266	0.638	3.321	2.289	0.495	44.720	18.948
P		0.617	0.005	< 0.001	0.524	0.001	0.023	0.621	< 0.001	< 0.001

2.4 Inflammatory Biomarkers

Baseline concentrations of hs-CRP, IL-6, and IL-1 β were comparable between the treatment groups, with no statistically significant differences observed before treatment ($P > 0.05$). At 4 and 12 weeks, all three inflammatory biomarkers decreased in both groups. The reductions were significantly greater in the sacubitril/valsartan group than in the valsartan group at both follow-up assessments (all $P < 0.001$; Table 4).

Table 4
Inflammatory biomarker levels by treatment group, mean $\pm$ standard deviation

Group	n	Hs-CRP (ng/mL)			IL-6 (pg/mL)			IL-1 β (pg/mL)		
		Pre-treatment	4 weeks	12 weeks	Pre-treatment	4 weeks	12 weeks	Pre-treatment	4 weeks	12 weeks
Observation	100	42.62 $\pm$ 3.71	28.14 $\pm$ 2.50	21.23 $\pm$ 2.01	14.38 $\pm$ 1.00	10.16 $\pm$ 0.57	0.49 $\pm$ 0.09	21.11 $\pm$ 2.48	15.68 $\pm$ 1.37	10.74 $\pm$ 0.75
Control	100	42.11 $\pm$ 3.47	16.65 $\pm$ 2.64	10.90 $\pm$ 2.65	14.42 $\pm$ 0.97	6.08 $\pm$ 0.54	0.43 $\pm$ 0.06	20.76 $\pm$ 2.36	10.58 $\pm$ 1.04	7.36 $\pm$ 0.47
t		1.009	31.553	30.980	0.263	51.982	5.985	1.024	29.670	38.324
P		0.314	< 0.001	< 0.001	0.793	< 0.001	< 0.001	0.307	< 0.001	< 0.001

2.5 Hypotension and Major Adverse Cardiovascular Events

During follow-up, hypotension occurred in 12 patients in the sacubitril/valsartan group and 5 patients in the valsartan group. Although hypotension was numerically more frequent with sacubitril/valsartan, the between-group difference was not statistically significant ($RR = 2.40$, 95% $CI = 0.88-6.56$, $\chi^2 = 3.150$, $P = 0.076$). MACE occurred in 5 patients receiving sacubitril/valsartan and 14 patients receiving valsartan. This difference was statistically significant and favored sacubitril/valsartan ($RR = 0.36$, 95% $CI = 0.13-0.95$, $\chi^2 = 4.939$, $P = 0.026$).

2.6 Kaplan–Meier Survival Analysis

Kaplan–Meier curves were generated using all-cause mortality as the time-to-event endpoint. Over the 90-day follow-up period, 3 of the 100 patients assigned to valsartan and 2 of the 100 patients assigned to sacubitril/valsartan were lost to follow-up. The mean survival time was 86.23 days in the valsartan group and 88.62 days in the sacubitril/valsartan group. Kaplan–Meier analysis showed a significantly higher survival probability among patients treated with sacubitril/valsartan than among those treated with valsartan ($\chi^2 = 4.906$, $P = 0.027$; Fig. 1).

[Figure 1. Kaplan–Meier survival curves by treatment group]

Discussion

The present study demonstrates that, among older patients with AMI and concomitant hypertension who underwent PCI, early initiation of sacubitril/valsartan was associated with greater improvements in cardiac function, more favorable ventricular remodeling, and larger reductions in systemic inflammatory activity than valsartan alone. These findings are consistent with a growing body of evidence suggesting that sacubitril/valsartan provides broader cardiovascular benefits than conventional angiotensin receptor blockade across a range of clinical settings [23]. The therapeutic effects of sacubitril/valsartan derive from its dual mechanism of action, which combines renin–angiotensin–aldosterone system (RAAS) inhibition with neprilysin blockade. This approach enhances the biological activity of natriuretic peptides and thereby promotes vasodilation, natriuresis, and inhibition of myocardial fibrosis and hypertrophy [24]. Preclinical investigations have further shown that sacubitril/valsartan may confer superior cardiovascular protection in heart failure by increasing nitric oxide bioavailability [25] and attenuating pressure overload-induced cardiac remodeling through suppression of pyruvate dehydrogenase kinase 4 signaling [26]. In experimental models of hypertension, sacubitril/valsartan has also improved ventricular remodeling and reduced susceptibility to atrial fibrillation more effectively than valsartan alone, with these benefits attributed to favorable effects on both electrical and structural remodeling [27]. Evidence from clinical populations supports these observations. In perimenopausal women with hypertension, sacubitril/valsartan reduced left ventricular mass index and downregulated fibrosis-associated mediators, including transforming growth factor- β and α -smooth muscle actin [28]. Similarly, the REVERSE-LVH trial demonstrated a greater reduction in myocardial interstitial fibrosis volume with sacubitril/valsartan than with valsartan despite comparable blood pressure control [29]. Collectively, these findings support the interpretation that the clinical effects of sacubitril/valsartan extend beyond blood pressure lowering and may be mediated, at least in part, by direct antifibrotic and anti-inflammatory actions that are particularly relevant during post-AMI myocardial healing [30].

The structural and functional improvements observed in the sacubitril/valsartan group, including greater recovery of LVEF and a larger reduction in LVEDD, are consistent with more effective attenuation of myocardial fibrosis, ventricular dilation, and maladaptive remodeling. These results accord with both experimental and clinical evidence indicating that angiotensin receptor–neprilysin inhibitor (ARNI) therapy exerts stronger antifibrotic and reverse-remodeling effects than RAAS blockade alone. In a post-myocardial infarction heart failure model, dual inhibition of the angiotensin II type 1 receptor and neprilysin prevented interstitial fibrosis in the remote myocardium and reduced cardiomyocyte hypertrophy more effectively than valsartan monotherapy [31]. The antifibrotic effects of sacubitril/valsartan have been proposed to represent direct myocardial protection that is at least partly independent of its hemodynamic actions [32]. Improvement in LVEF is a well-established indicator of reverse cardiac remodeling during ARNI therapy and is generally attributed to attenuation of adverse structural changes within the ventricle [33]. Similar functional and anatomical recovery has been reported across several clinical contexts. For example, among patients who developed new-onset heart failure after valvular surgery, ARNI therapy produced significantly greater improvements in LVEF and reductions in LVEDD than comparator treatment [34]. Meta-analyses of randomized trials have likewise shown that early ARNI initiation after AMI is more effective than ARB therapy in increasing LVEF and reducing left ventricular dimensions [35]. Favorable changes in ventricular geometry and systolic performance may represent an important mechanistic pathway through which sacubitril/valsartan lowers the risk of major adverse cardiovascular events and hospitalization for heart failure [36, 37]. By more effectively interrupting the pathological remodeling process that contributes to progressive clinical deterioration after myocardial injury, sacubitril/valsartan may translate structural cardiac recovery into improved short-term and longer-term prognosis [38].

The favorable effects of sacubitril/valsartan on cardiac function and ventricular remodeling observed in the present study are broadly consistent with findings from the PARADIGM-HF and PARAGON-HF trials, which established the therapeutic role of sacubitril/valsartan in heart failure across reduced and preserved ejection fraction phenotypes. Although the mechanisms underlying these benefits have not been fully elucidated, simultaneous inhibition of neprilysin and the angiotensin II type 1 receptor is likely to provide complementary neurohormonal effects. Neprilysin inhibition increases the bioavailability of natriuretic and other vasoactive peptides, thereby promoting vasodilation, attenuating sympathetic activation, and exerting antifibrotic and antihypertrophic effects. These actions extend beyond those of valsartan alone, which primarily inhibits the RAAS [39]. The greater improvement in LVEF and reduction in LVEDD observed with sacubitril/valsartan in the present study are consistent with this broader pharmacological profile. The significantly lower concentrations of inflammatory biomarkers, including hs-CRP, IL-6, and TNF- α , in the sacubitril/valsartan group are also clinically relevant, as experimental evidence suggests that neprilysin inhibition may attenuate the inflammatory response triggered by myocardial ischemia [40]. Although hypotension occurred more frequently in the sacubitril/valsartan group, the difference was not statistically significant. This numerical increase is biologically plausible given the more potent vasodilatory effects of angiotensin receptor–neprilysin inhibition and is consistent with findings from large comparative studies of sacubitril/valsartan and ARBs [41, 42].

The marked reductions in hs-CRP, IL-6, and TNF- α observed in patients receiving sacubitril/valsartan further suggest that attenuation of systemic inflammation may contribute to the associated improvements in cardiac function and ventricular remodeling. Inflammation is a central mediator of adverse remodeling after myocardial infarction, and elevated concentrations of proinflammatory cytokines have been associated with impaired myocardial recovery and poorer clinical outcomes. The present clinical findings are consistent with preclinical studies indicating that ARNI therapy suppresses the expression of inflammatory mediators. Experimental evidence suggests that sacubitril/valsartan may attenuate myocardial remodeling through inhibition of the MAPK/ERK signaling pathway, which regulates inflammatory cytokine transcription [40]. In an animal model of post-myocardial infarction heart failure, sacubitril/valsartan also limited left ventricular contractile dysfunction and interstitial fibrosis more effectively than valsartan alone, supporting a potentially stronger combined antifibrotic and anti-inflammatory effect [31]. This benefit is likely attributable to its dual mechanism, comprising RAAS inhibition through valsartan and augmentation of the natriuretic peptide system through sacubitril-mediated neprilysin inhibition [43]. Because RAAS activation promotes NF- κ B signaling and downstream inflammatory responses, its suppression may reduce inflammatory cytokine production. The lower inflammatory burden observed in the sacubitril/valsartan group therefore provides a plausible pathophysiologic link between treatment and the concurrent improvements in systolic function and left ventricular dimensions, underscoring the importance of inflammatory regulation during post-infarction myocardial healing.

The potential clinical importance of these findings is further supported by evidence associating the anti-inflammatory and antifibrotic effects of sacubitril/valsartan with improved long-term outcomes. A meta-analysis of patients with AMI found that early initiation of ARNI therapy was associated with lower risks of major adverse cardiovascular events and rehospitalization for heart failure, consistent with the direction of the findings observed in the present study [35]. In addition, PARADIGM-HF demonstrated that sacubitril/valsartan reduced the risk of sudden cardiac death, an effect that may be partly mediated by favorable changes in myocardial fibrosis and electrical remodeling [44]. Recent reviews have also highlighted the potential antiarrhythmic properties of sacubitril/valsartan, suggesting that neprilysin inhibition may stabilize the myocardial substrate and reduce susceptibility to ventricular arrhythmias [45]. This mechanism is particularly relevant after AMI, when malignant arrhythmias remain an important cause of mortality. Sacubitril/valsartan may additionally confer renoprotective effects, which have been reported to vary according to dose in patients with heart failure and may be especially beneficial in older hypertensive patients, among whom renal impairment is common [46]. Improvements in renal function reported in previous studies may contribute to better overall cardiovascular outcomes, given that renal dysfunction is a well-established predictor of poor prognosis after AMI [47].

Limitations

Several limitations should be considered when interpreting the present findings. First, this was a single-center trial with a relatively modest sample size, which may limit the external validity and generalizability of the results. Larger multicenter

studies are therefore required to confirm these observations across more diverse clinical settings and patient populations. Second, the 12-week follow-up period was adequate for evaluating early therapeutic effects but may have been insufficient to capture late adverse events, sustained changes in ventricular remodeling, or longer-term clinical outcomes. Studies incorporating extended follow-up are needed to determine whether the observed benefits persist over time. Furthermore, the composite primary endpoint, which combined improvement in LVEF with improvement in NYHA functional class, may not have captured the full spectrum of clinically meaningful recovery. Future investigations should incorporate more granular and patient-centered outcomes, including health-related quality of life and biomarkers of myocardial fibrosis [48, 49]. The exclusion of patients with severe comorbid conditions, including cardiogenic shock or advanced renal dysfunction, also restricts the applicability of the findings to these particularly high-risk groups [50]. Although established treatment regimens were used, the possibility of residual confounding cannot be excluded, particularly with respect to interoperator variation in procedural technique and differences in medication adherence after hospital discharge [51]. Finally, although a statistically significant between-group difference in MACE was observed, the study was not specifically powered for this secondary outcome. Accordingly, this result should be interpreted cautiously and confirmed in larger, prospectively designed studies capable of evaluating both clinical events and the mechanisms underlying differential effects on systemic inflammation and ventricular remodeling [52].

Additional methodological issues may have affected the internal validity of the study. Although participants were randomly assigned to treatment, neither patients nor treating clinicians were blinded, introducing the potential for performance and detection bias. Knowledge of treatment allocation may have influenced patient behavior, clinical decision-making, or the assessment of outcomes, particularly those with subjective components [53]. The pragmatic, open-label design may therefore have affected interpretation of certain endpoints, and the absence of blinded endpoint adjudication or a double-dummy strategy represents an important limitation because these approaches are commonly used to reduce bias in pharmacological trials [54]. The drug-titration protocol also warrants consideration. Doses of sacubitril/valsartan and valsartan were adjusted according to office blood pressure measurements and physician judgment rather than a prespecified, protocol-driven titration algorithm or individualized therapeutic drug monitoring. Although blood pressure-guided titration reflects routine clinical practice [55], it does not account for interindividual pharmacokinetic variability or ensure that patients receive biologically equivalent or individually optimized doses. Consequently, differences in dose exposure may have influenced both comparative efficacy and safety outcomes.

Future research should further define the role of sacubitril/valsartan after AMI. Larger, multicenter, double-blind, randomized controlled trials with longer follow-up periods are needed to determine whether early treatment improves mortality and reduces hospitalization for heart failure over the long term. Additional studies should evaluate clinically relevant subgroups, including patients with heart failure with preserved ejection fraction or those with mildly to moderately reduced ejection fraction, for whom the current evidence remains less definitive [56]. Potential drug–drug interactions, particularly with antiplatelet agents routinely administered after PCI, also require further investigation to optimize treatment safety and efficacy [57]. The use of sacubitril/valsartan in patients with advanced kidney disease or those receiving dialysis warrants particular attention because preliminary evidence suggests possible benefit accompanied by an increased risk of hyperkalemia [58, 59]. Incorporating advanced imaging techniques, including cardiac magnetic resonance imaging, may also permit more precise quantification of myocardial fibrosis and ventricular remodeling and provide deeper mechanistic insight into the effects of treatment [60].

Conclusion

Early initiation of sacubitril/valsartan after PCI in older patients with AMI and hypertension was associated with greater improvement in cardiac function, more favorable ventricular remodeling, lower inflammatory biomarker levels, and fewer short-term major adverse cardiovascular events than valsartan, without a statistically significant increase in hypotension. These findings suggest that early angiotensin receptor–neprilysin inhibition may represent a promising therapeutic strategy for this vulnerable population. However, given the single-center design, limited sample size, short follow-up, and lack of power for

major adverse cardiovascular events, larger multicenter trials with longer-term follow-up are required to confirm the durability, safety, and prognostic significance of these results.

Declarations

Funding: This work was supported by the Henan Medical Science and Technology Research Project (Joint Co-construction Project; Grant No. LHGJ20210987).

Author biography: Yong Wang was born in July 1985 and is an associate chief physician with a PhD. His research focuses on basic and clinical investigations of coronary artery disease.

Authors' contributions: Yong Wang drafted the manuscript. Yong Wang and Zichang Liu performed the data analyses and biochemical assays. Wenkun Ge coordinated the study and revised the manuscript in his capacity as corresponding author. All authors read and approved the final manuscript.

Compliance with ethical standards

Competing interests: The authors declare that they have no competing interests or other disclosures.

Availability of data and materials: The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Consent for publication: Not applicable.

Acknowledgments

We thank Phoebe Chi, MD, from Liwen Bianji (Edanz) (www.liwenbianji.cn), for editing a draft of this manuscript.

References

1. Wang Y, Li J, Zheng X, Jiang Z, Hu S, Wadhera RK, et al. Risk factors associated with major cardiovascular events 1 year after acute myocardial infarction. *JAMA Netw open*. 2018;1:e181079. <https://doi.org/10.1001/jamanetworkopen.2018.1079>.
2. Komici K, Vitale DF, Mancini A, Bencivenga L, Conte M, Provenzano S, et al. Impact of malnutrition on long-term mortality in elderly patients with acute myocardial infarction. *Nutrients*. 2019;11. <https://doi.org/10.3390/nu11020224>.
3. Roth D, Tulder RV, Heidinger B, Herkner H, Schreiber W, Havel C. Admission blood pressure and 1-year mortality in acute myocardial infarction. *Int J Clin Pract*. 2015;69:812–9. <https://doi.org/10.1111/ijcp.12588>.
4. Huang X, Wang H, Yuan W. Fibrinogen-to-albumin ratio predicts acute kidney injury in very elderly acute myocardial infarction patients. *Biomedicines*. 2025;13. <https://doi.org/10.3390/biomedicines13081909>.
5. Yan L, Yuan W. Risk factors for mechanical complications in very elderly patients with acute myocardial infarction. *Front Med*. 2025;12:1714080. <https://doi.org/10.3389/fmed.2025.1714080>.
6. Acar RD, Bulut M, Ergün S, Yesin M, Eren H, Akçakoyun M. Does cardiac rehabilitation improve left ventricular diastolic function of patients with acute myocardial infarction? *Türk Kardiyoloji Dernegi arsivi: Turk Kardiyoloji Derneginin yayin organidir*. 2014;42:710–6. <https://doi.org/10.5543/tkda.2014.76282>.
7. Yoon HJ, Kim KH, Kim JY, Cho JY, Yoon NS, Park HW, et al. Impaired diastolic recovery after acute myocardial infarction as a predictor of adverse events. *J Cardiovasc ultrasound*. 2015;23:150–7. <https://doi.org/10.4250/jcu.2015.23.3.150>.
8. Menichelli D, Poli D, Antonucci E, Palareti G, Pignatelli P, Pastori D. Renin-angiotensin-aldosterone system inhibitors and mortality risk in elderly patients with atrial fibrillation. Insights from the nationwide START registry. *Eur J Intern Med*. 2024;119:84–92. <https://doi.org/10.1016/j.ejim.2023.08.019>.

9. van Dissel AC, Winter MM, van der Bom T, Vliegen HW, van Dijk APJ, Pieper PG, et al. Long-term clinical outcomes of valsartan in patients with a systemic right ventricle: Follow-up of a multicenter randomized controlled trial. *Int J Cardiol.* 2019;278:84–7. <https://doi.org/10.1016/j.ijcard.2018.11.027>.
10. Mohanty AF, Levitan EB, King JB, Dodson JA, Vardeny O, Cook J, et al. Sacubitril/valsartan initiation among veterans who are renin-angiotensin-aldosterone system inhibitor naïve with heart failure and reduced ejection fraction. *J Am Heart Association.* 2021;10:e020474. <https://doi.org/10.1161/JAHA.120.020474>.
11. Chang W-T, Lin Y-W, Chen C-Y, Hong C-S, Chen Z-C, Lin Y-C, et al. The combination of valsartan and spironolactone mitigated mitral regurgitation-induced cardiac dysfunction in a novel rat model. *J Cardiovasc Pharmacol.* 2024;84:410–7. <https://doi.org/10.1097/FJC.0000000000001614>.
12. Hernandez AV, Pasupuleti V, Scarpelli N, Malespini J, Banach M, Bielecka-Dabrowa AM. Efficacy and safety of sacubitril/valsartan in heart failure compared to renin-angiotensin-aldosterone system inhibitors: A systematic review and meta-analysis of randomised controlled trials. *Archives Med science: AMS.* 2023;19:565–76. <https://doi.org/10.5114/aoms/159113>.
13. Solomon SD, Vaduganathan M, Claggett BL, Packer M, Zile M, Swedberg K, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation.* 2020;141:352–61. <https://doi.org/10.1161/CIRCULATIONAHA.119.044586>.
14. Park CS, Park J, Bae NY, Kwak S, Choi H-M, Yoon YE, et al. Characteristics, predictors, and clinical outcomes in heart failure with reduced ejection fraction according to a 1-year left ventricular ejection fraction following sacubitril/valsartan treatment. *J Am Heart Association.* 2024;13:e036763. <https://doi.org/10.1161/JAHA.124.036763>.
15. Wachter R, Senni M, Belohlavek J, Straburzynska-Migaj E, Witte KK, Kobalava Z, et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: Primary results of the randomised TRANSITION study. *Eur J Heart Fail.* 2019;21:998–1007. <https://doi.org/10.1002/ejhf.1498>.
16. Volpe M, Gallo G, Guzik TJ, Williams B, Messerli FH. Blood pressure management in secondary prevention after myocardial infarction. *Cardiovascular Res.* 2025;121:1989–96. <https://doi.org/10.1093/cvr/cvaf145>.
17. Chiang C-Y, Huang S-C, Chen M, Shih J-Y, Hong C-S, Wu N-C, et al. Effects of renal impairment on cardiac remodeling and clinical outcomes after myocardial infarction. *Int J Med Sci.* 2021;18:2842–8. <https://doi.org/10.7150/ijms.61891>.
18. Liu Q, Zhao C, Dang P, Li Y, Yan Y. Prognostic value of pulmonary hypertension with a nomogram in acute myocardial infarction patients with reduced left ventricular function. *Front Cardiovasc Med.* 2024;11:1368139. <https://doi.org/10.3389/fcvm.2024.1368139>.
19. Coisne A, Fourdinier V, Lemesle G, Delsart P, Aghezzaf S, Lamblin N, et al. Clinical significance of myocardial work parameters after acute myocardial infarction. *Eur heart J open.* 2022;2:oeac037. <https://doi.org/10.1093/ehjopen/oeac037>.
20. Salem HSE, El-Mawardy RM, Zahran ME, Bastawy IM, Aziz MF, Attia AE. Early dapagliflozin in non-diabetic acute myocardial infarction patients post-PCI: Effects on cardiovascular outcomes and left ventricular remodeling (EARLY DAPA-AMI). *J Saudi Heart Association.* 2025;37:9. <https://doi.org/10.37616/2212-5043.1464>.
21. Pan Y, Zhou Z, Zhang H, Zhou Y, Li Y, Li C, et al. The ATRQβ-001 vaccine improves cardiac function and prevents postinfarction cardiac remodeling in mice. *Hypertens research: official J Japanese Soc Hypertens.* 2019;42:329–40. <https://doi.org/10.1038/s41440-018-0185-3>.
22. Bandoni RL, Choque PNB, Dellê H, de Moraes TL, Porter MHM, Silva BD et al. da,. Cholinergic stimulation with pyridostigmine modulates a heart-spleen axis after acute myocardial infarction in spontaneous hypertensive rats. *Scientific reports.* 2021;11:9563. <https://doi.org/10.1038/s41598-021-89104-8>.
23. Ambrosy AP, Mentz RJ, Fiuzat M, Cleland JGF, Greene SJ, O'Connor CM, et al. The role of angiotensin receptor-neprilysin inhibitors in cardiovascular disease-existing evidence, knowledge gaps, and future directions. *Eur J Heart Fail.* 2018;20:963–72. <https://doi.org/10.1002/ejhf.1159>.
24. Pagel PS, Hang D, Freed JK, Crystal GJ. Advances in cardiovascular pharmacotherapy. VI. Sacubitril-valsartan, an angiotensin receptor-neprilysin inhibitor. *J Cardiothorac Vasc Anesth.* 2026;40:960–84.

<https://doi.org/10.1053/j.jvca.2025.12.003>.

25. Trivedi RK, Polhemus DJ, Li Z, Yoo D, Koiwaya H, Scarborough A, et al. Combined angiotensin receptor-neprilysin inhibitors improve cardiac and vascular function via increased NO bioavailability in heart failure. *J Am Heart Association*. 2018;7. <https://doi.org/10.1161/JAHA.117.008268>.
26. Shen M, Zheng C, Chen L, Li M, Huang X, He M, et al. LCZ696 (sacubitril/valsartan) inhibits pulmonary hypertension induced right ventricular remodeling by targeting pyruvate dehydrogenase kinase 4. *Biomed pharmacotherapy = Biomedecine pharmacotherapie*. 2023;162:114569. <https://doi.org/10.1016/j.biopha.2023.114569>.
27. Li Q, Fang Y, Peng D-W, Li L-A, Deng C-Y, Yang H, et al. Sacubitril/valsartan reduces susceptibility to atrial fibrillation by improving atrial remodeling in spontaneously hypertensive rats. *Eur J Pharmacol*. 2023;952:175754. <https://doi.org/10.1016/j.ejphar.2023.175754>.
28. Chen J, Pei Y, Wang Q, Li C, Liang W, Yu J. Effect of sacubitril/valsartan or valsartan on ventricular remodeling and myocardial fibrosis in perimenopausal women with hypertension. *J Hypertens*. 2023;41:1077–83. <https://doi.org/10.1097/HJH.0000000000003430>.
29. Lee V, Dalakoti M, Zheng Q, Toh D-F, Boubertakh R, Bryant JA, et al. Effects of sacubitril/valsartan on hypertensive heart disease: The REVERSE-LVH randomized phase 2 trial. *Nat Commun*. 2025;16:6981. <https://doi.org/10.1038/s41467-025-62203-0>.
30. Liu Y, Zhong C, Si J, Chen S, Kang L, Xu B. The impact of sacubitril/valsartan on cardiac fibrosis early after myocardial infarction in hypertensive rats. *J Hypertens*. 2022;40:1822–30. <https://doi.org/10.1097/HJH.0000000000003230>.
31. Pfau D, Thorn SL, Zhang J, Mikush N, Renaud JM, Klein R, et al. Angiotensin receptor neprilysin inhibitor attenuates myocardial remodeling and improves infarct perfusion in experimental heart failure. *Sci Rep*. 2019;9:5791. <https://doi.org/10.1038/s41598-019-42113-0>.
32. Stanko P, Repova K, Baka T, Krajcirovicova K, Aziriova S, Barta A, et al. Sacubitril/valsartan alleviates cardiac remodeling and dysfunction in I-NAME-induced hypertension and hypertensive heart disease. *Biomedicines*. 2024;12. <https://doi.org/10.3390/biomedicines12040733>.
33. Abboud A, Januzzi JL. Reverse cardiac remodeling and ARNI therapy. *Curr Heart Fail Rep*. 2021;18:71–83. <https://doi.org/10.1007/s11897-021-00501-6>.
34. Yuqian C, Qinghua H, Fanyan L, Lingjin H, Xuliang C, Chengliang Z. Heart failure with reduced ejection fraction developed from valvular surgery: Risk factors and therapeutic effects of sacubitril valsartan. *Int J Cardiol Heart vasculature*. 2025;57:101634. <https://doi.org/10.1016/j.ijcha.2025.101634>.
35. Yang P, Han Y, Lian C, Wu X. Efficacy and safety of sacubitril/valsartan vs. Valsartan in patients with acute myocardial infarction: A meta-analysis. *Front Cardiovasc Med*. 2022;9:988117. <https://doi.org/10.3389/fcvm.2022.988117>.
36. Ye S, Guo N, Li J, Zhao J, Zong D, Wang L. Early sacubitril/valsartan therapy reduces ventricular remodeling and cardiac events in patients with acute anterior myocardial infarction. *Eur J Pharmacol*. 2025;1007:178188. <https://doi.org/10.1016/j.ejphar.2025.178188>.
37. Pietro GD, Improta R, Severino P, D'Amato A, Birtolo LI, Filippo OD, et al. The in-hospital administration of sacubitril/valsartan in acute myocardial infarction: A meta-analysis. *ESC heart Fail*. 2025;12:998–1012. <https://doi.org/10.1002/ehf2.15082>.
38. Zheng C, Dai H, Huang J, Lin M, Zheng Q, Tang P, et al. The efficacy and safety of sacubitril/valsartan in the treatment of chronic heart failure: A meta-analysis. *Am J translational Res*. 2021;13:12114–28.
39. Lin LM, Wu Y, Wu MF, Lin JX. Focus on the novel cardiovascular drug LZC696: From evidence to clinical consideration. *Cardiovasc Drugs Ther*. 2016;30:623–33. <https://doi.org/10.1007/s10557-016-6699-5>.
40. Zhang X, Yan C, Zheng M. Sacubitril-valsartan ameliorates heart failure by inhibiting cardiac remodeling potentially via MAPK/ERK signaling. *Annals of clinical and laboratory science*. 2022;52:391–938.
41. Li D, Li Y, Yao L, Li J, Zhou X, Gui M, et al. Comparative analysis of adverse events between sacubitril/valsartan and valsartan using the FAERS database: A disproportionality analysis. *Exp Opin Drug Saf*. 2025;1–11. <https://doi.org/10.1080/14740338.2025.2591388>.

42. McCormack PL. Sacubitril/valsartan: A review in chronic heart failure with reduced ejection fraction. *Drugs*. 2016;76:387–96. <https://doi.org/10.1007/s40265-016-0544-9>.
43. Zhang R, Sun X, Li Y, He W, Zhu H, Liu B, et al. The efficacy and safety of sacubitril/valsartan in heart failure patients: A review. *J Cardiovasc Pharmacol Therap*. 2022;27:10742484211058681. <https://doi.org/10.1177/10742484211058681>.
44. Silva-Cardoso J, Brás D, Canário-Almeida F, Andrade A, Oliveira L, Pádua F, et al. Neurohormonal modulation: The new paradigm of pharmacological treatment of heart failure. *Rev Port Cardiol*. 2019;38:175–85. <https://doi.org/10.1016/j.repc.2018.10.011>.
45. Huang E, Bernard ML, Hiltbold AE, Khatib S, Polin GM, Rogers PA, et al. Sacubitril/valsartan: An antiarrhythmic drug? *J Cardiovasc Electrophys*. 2022;33:2375–81. <https://doi.org/10.1111/jce.15670>.
46. Kato T, Nakano Y, Yasukawa N, Oonishi M, Hamada Y. Dose-dependent renoprotective effects of sacubitril/valsartan in heart failure: A retrospective study. *Ren Fail*. 2025;47:2538830. <https://doi.org/10.1080/0886022X.2025.2538830>.
47. Uijl E, Roksnoer LCW, Hoorn EJ, Danser AHJ. From ARB to ARNI in cardiovascular control. *Curr Hypertens Rep*. 2016;18:86. <https://doi.org/10.1007/s11906-016-0694-x>.
48. Buckley SA, Lee SJ, Walter RB. Measuring quality of life in acute myeloid leukemia: Limitations and future directions. *Expert Rev Hematol*. 2016;9:821–3. <https://doi.org/10.1080/17474086.2016.1211006>.
49. Koohsari MJ, Oka K. Neighbourhood environments and risk of incident atrial fibrillation: Limitations and future directions. *Eur J Prev Cardiol*. 2020;27:1438–9. <https://doi.org/10.1177/2047487319878378>.
50. Rawal HA, Kocheril AG. Sacubitril/valsartan in heart failure: Cardiogenic shock. *Case reports in cardiology*. 2018;2018:8231576. <https://doi.org/10.1155/2018/8231576>.
51. Massaad E, Fatima N, Hadzipasic M, Alvarez-Breckenridge C, Shankar GM, Shin JH. Predictive analytics in spine oncology research: First steps, limitations, and future directions. *Neurospine*. 2019;16:669–77. <https://doi.org/10.14245/ns.1938402.201>.
52. Norwood TA, Seliske LM, De P. Mapping the occurrence of acute myeloid leukemia: Methodological limitations and future direction. *Cancer*. 2020;126:1354–5. <https://doi.org/10.1002/cncr.32673>.
53. Cashin AG, Lee H. An introduction to mediation analyses of randomized controlled trials. *J Clin Epidemiol*. 2021;133:161–4. <https://doi.org/10.1016/j.jclinepi.2021.02.014>.
54. Uhl K, Cravero JP. Measuring behavioral and emotional changes in children following hospitalization: Limitations and future directions. *Paediatr Anaesth*. 2019;29:1083–5. <https://doi.org/10.1111/pan.13746>.
55. Matsumura K, Ijichi T, Morimoto J, Takabayashi K, Miho M, Ueno K, et al. Up-titration of sacubitril/valsartan among patients with heart failure and preserved ejection fraction. *J Cardiovasc Pharmacol Therap*. 2023;28:10742484221146375. <https://doi.org/10.1177/10742484221146375>.
56. Villani A, Ravaro S, Cerea P, Caravita S, Ciambellotti F, Branzi G, et al. Do the remodeling effects of sacubitril/valsartan treatment depend upon heart failure duration? *J Cardiovasc Med (Hagerstown Md)*. 2020;21:682–7. <https://doi.org/10.2459/JCM.0000000000001000>.
57. Rao BR, Speight CD, Allen LA, Halpern SD, Ko Y-A, Matlock DD, et al. Impact of financial considerations on willingness to take sacubitril/valsartan for heart failure. *J Am Heart Association*. 2022;11:e023789. <https://doi.org/10.1161/JAHA.121.023789>.
58. Wen Y, Xia Y, Gong Y. Effects and safety of sacubitril/valsartan (SV) on heart function and blood pressure in maintenance hemodialysis (MHD) patients. *Am J translational Res*. 2022;14:3439–47.
59. Heyse A, Manhaeghe L, Mahieu E, Vanfraechem C, Durme FV. Sacubitril/valsartan in heart failure and end-stage renal insufficiency. *ESC heart Fail*. 2019;6:1331–3. <https://doi.org/10.1002/ehf2.12544>.
60. Lee V, Zheng Q, Toh D-F, Pua CJ, Bryant JA, Lee C-H, et al. Sacubitril/valsartan versus valsartan in regressing myocardial fibrosis in hypertension: A prospective, randomized, open-label, blinded endpoint clinical trial protocol. *Front Cardiovasc Med*. 2023;10:1248468. <https://doi.org/10.3389/fcvm.2023.1248468>.

Table 1 and 2

Table 1 and 2 are available in the Supplementary Files section.

Figures

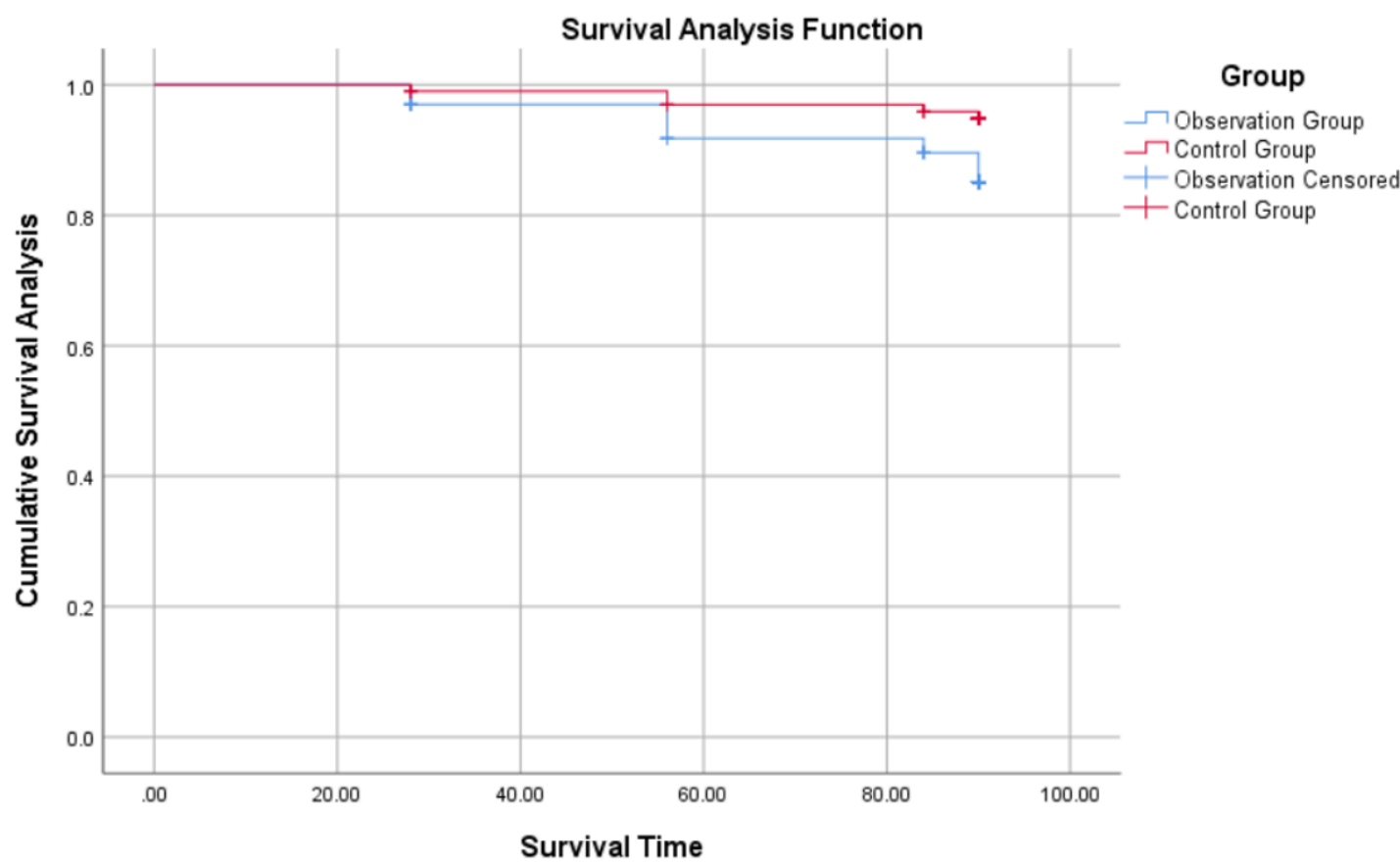


Figure 1

Kaplan–Meier survival curves by treatment group

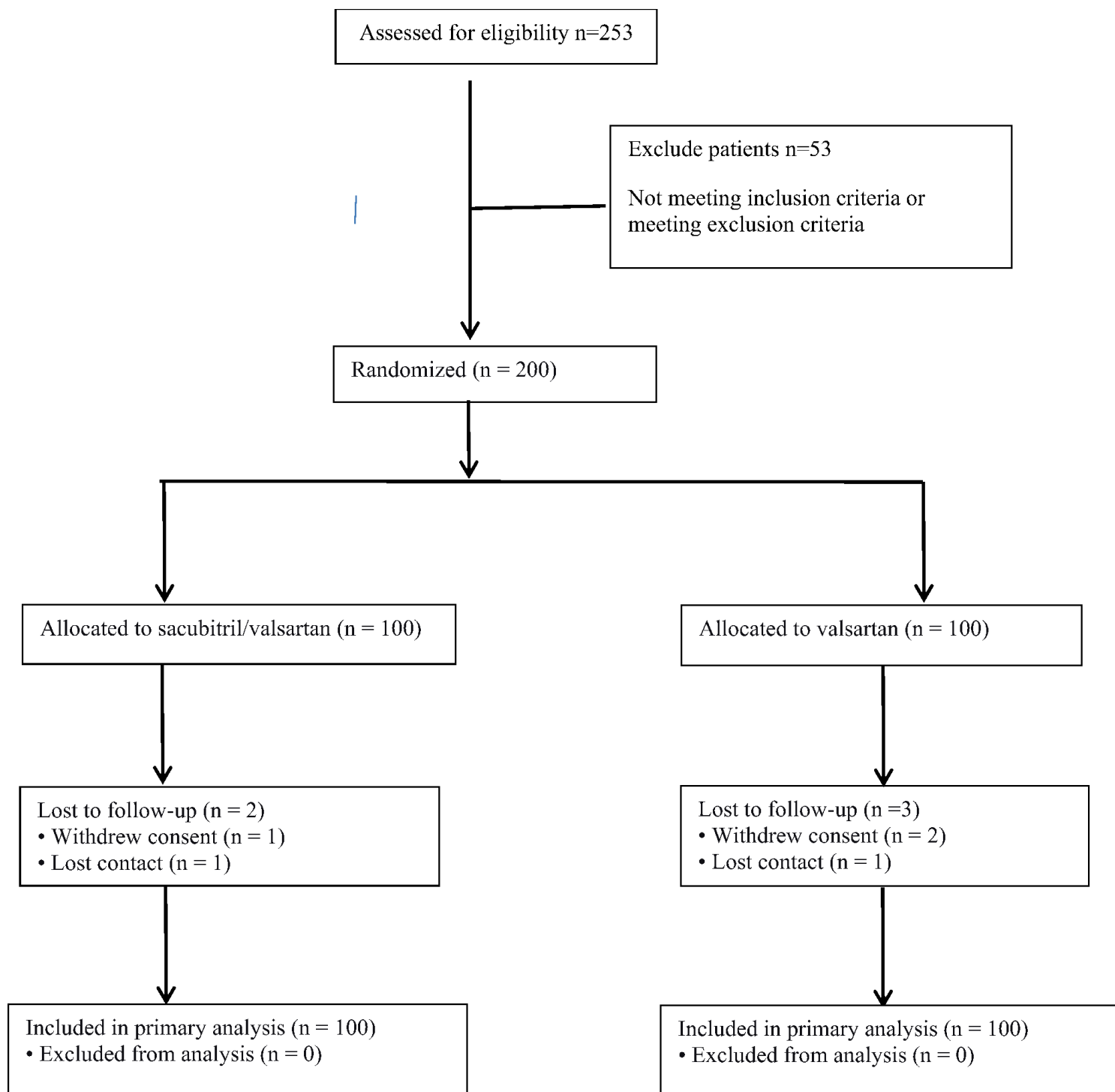


Figure 2

Figure 1. CONSORT 2025 flow diagram of participant recruitment, randomization, follow-up, and analysis.

Abbreviations: ITT, intention-to-treat.

Note: Missing data due to loss to follow-up (2 in the sacubitril/valsartan group and 3 in the valsartan group) were handled using appropriate statistical models without excluding participants from the primary ITT analysis. All 200 randomized participants were included in the final analysis according to their original assigned groups.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table12.docx](#)