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Angiotensin Receptor-Neprilysin Inhibition in Patients With STEMI vs NSTEMI

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ABSTRACT

BACKGROUND Patients who sustain an acute myocardial infarction (AMI), including ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), remain at high risk for heart failure (HF), coronary events, and death. Angiotensin-converting enzyme inhibitors have been shown to significantly decrease the risk for cardiovascular events in both STEMI and NSTEMI patients.

OBJECTIVES The objectives were to determine whether angiotensin-receptor blockade and neprilysin inhibition with sacubitril/valsartan, compared with ramipril, has impact on reducing cardiovascular events according to the type of AMI.

METHODS The PARADISE-MI (Prospective ARNI versus ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction) trial enrolled patients with AMI complicated by left ventricular dysfunction and/or pulmonary congestion and at least 1 risk-enhancing factor. Patients were randomized to either sacubitril/valsartan or ramipril. The primary endpoint was death from cardiovascular causes or incident HF. In this prespecified analysis, we stratified patients according to AMI type.

RESULTS Of 5,661 enrolled patients, 4,291 (75.8%) had STEMI. These patients were younger and had fewer comorbidities and cardiovascular risk factors than NSTEMI patients. After adjustment for potential confounders, the risk for the primary outcome was marginally higher in NSTEMI vs STEMI patients (adjusted HR: 1.19; 95% CI: 1.00-1.41), with borderline statistical significance ($P = 0.05$). The primary composite outcome occurred at similar rates in patients randomized to sacubitril/valsartan vs ramipril in STEMI (10% vs 12%; HR: 0.87; 95% CI: 0.73-1.04; $P = 0.13$) and NSTEMI patients (17% vs 17%; HR: 0.97; 95% CI: 0.75-1.25; $P = 0.80$; P interaction $= 0.53$).

CONCLUSIONS Compared with ramipril, sacubitril/valsartan did not significantly decrease the risk for cardiovascular death and HF in patients with AMI complicated by left ventricular dysfunction, irrespective of the type of AMI. (Prospective ARNI vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI; NCT02924727) (J Am Coll Cardiol 2024;83:904-914) Crown Copyright © 2024 Published by Elsevier on behalf of the American College of Cardiology Foundation. All rights reserved.

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Patients surviving an acute myocardial infarction (AMI) complicated by left ventricular systolic dysfunction (LVSD) remain at an increased risk for heart failure (HF), coronary events, and death.[1] Early studies revealed that angiotensin-converting enzyme inhibitors (ACEI) are particularly effective in mitigating this risk and improving patients' outcomes after AMI.[2,3] A systematic review of 4 trials including 100,000 patients showed that the absolute benefits of ACEI in patients with ST-segment elevation myocardial infarction (STEMI) were greater in high-risk subsets of patients such as those with anterior myocardial infarction (MI).[4] Given that angiotensin receptor blockers (ARBs) provide a more selective blockade of the renin-angiotensin-aldosterone system (RAAS) than ACEI, it was hypothesized that ARBs would provide greater clinical benefits in high-risk AMI patients. Nonetheless, 2 large randomized clinical trials conducted in survivors of AMI showed that ARBs were not superior to ACEI. In 1 of these studies, the comparison of ARB and an ACEI met the prespecified criteria for noninferiority,[5] whereas in a second smaller trial the noninferiority criteria for an ARB as compared with an ACEI were not met.[6]

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Recently, the angiotensin receptor-neprilysin inhibitor, sacubitril/valsartan, has emerged as a novel first-in-class therapy that improves clinical outcomes for patients with HF through combined inhibition of RAAS and decreased degradation of natriuretic peptides.[7] Current HF guidelines provide a Class I recommendation for sacubitril/valsartan in patients with HF with reduced ejection fraction and NYHA functional class II to III symptoms.[8,9] The PARADISE-MI (Prospective ARNI versus ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction) trial showed that sacubitril/valsartan did not reduce the incidence of cardiovascular (CV) death or HF in survivors of AMI.[10] However, a recent prespecified analysis of the PARADISE-MI study showed that sacubitril/valsartan, compared with ramipril, reduced the risk of a composite coronary outcome, which included the first occurrence of death from coronary heart disease, nonfatal MI, hospitalization for angina, or postrandomization coronary revascularization.[11] PARADISE-MI enrolled patients with recent AMI, including STEMI and non-ST-segment elevation myocardial infarction (NSTEMI), complicated by LVSD and/or pulmonary congestion. STEMI and NSTEMI patients have distinct risk profiles, management, as well as prognoses.[12] Historically, STEMI was associated with high mortality rates and complications in the acute phase, which also impacted the long-term prognosis. However, the advancements and wide availability of reperfusion strategies have substantially improved outcomes after STEMI over the past years. In contrast, NSTEMI patients are generally older and have age-related risk factors and comorbidities, limiting the benefits of pharmacotherapy and delayed invasive revascularization strategies. Due to these inherent differences in risk profiles and management of patients with STEMI and NSTEMI, we hypothesized that the treatment effects of sacubitril/valsartan vs ramipril might differ according to the type of MI. In this study, we report the treatment effects of sacubitril/valsartan vs ramipril in the PARADISE-MI trial according to the type of MI.

ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

AMI = acute myocardial infarction

ARBs = angiotensin receptor blockers

CV = cardiovascular

HF = heart failure

LVEF = left ventricular ejection fraction

LVSD = left ventricular systolic dysfunction

MI = myocardial infarction

NSTEMI = non-ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

RAAS = renin-angiotensin-aldosterone system

STEMI = ST-segment elevation myocardial infarction

METHODS

Data will be made available upon a reasonable request to the study investigators.

STUDY POPULATION. The PARADISE-MI trial study design has been previously described.[10,13] Briefly, PARADISE-MI was an international, multicenter, double-blind, randomized trial comparing sacubitril/valsartan with ramipril in patients without a history of HF who had an AMI complicated by LVSD, pulmonary congestion, or both.[13] The main inclusion criteria were as follows: 1) age of at least 18 years;

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2) diagnosis of spontaneous AMI; 3) evidence of LVSD (left ventricular ejection fraction [LVEF] ≤40%) and/or pulmonary congestion (associated with the index MI) requiring treatment; and 4) at least 1 risk-enhancing factor (ie, age ≥70 years, estimated glomerular filtration rate <60 mL/min/1.73 m^2, diabetes mellitus, prior MI, atrial fibrillation, LVEF <30%, Worst Killip class III or IV, and STEMI without reperfusion therapy within the first 24 hours after presentation). Exclusion criteria were as follows: 1) hemodynamic instability within the first 24 hours preceding randomization; 2) estimated glomerular filtration rate <30 mL/min/1.73 m^2; 3) serum potassium >5.2 mmol/L; 4) a history of angioedema; 5) intolerance to an ACEI or ARB; or 6) coronary artery bypass graft surgery planned or performed for index MI. Patients who fulfilled enrollment criteria were randomized between 12 hours and 7 days after index presentation to either sacubitril/valsartan (97-103 mg twice daily) or ramipril (5 mg twice daily).[10,13] Randomization was stratified by the type of AMI (STEMI vs NSTEMI) and by geographic area.

The study was approved by ethics committees at each participating trial center. All patients participating in the trial provided written informed consent before enrollment.

CLINICAL OUTCOMES. The primary outcome of the PARADISE-MI trial was a composite of CV death, outpatient development of HF, or hospitalization for HF. Secondary outcomes included time-to-first occurrence of all-cause death and the composite of CV death, nonfatal MI, or nonfatal stroke. We also examined the prespecified coronary composite endpoint of death from coronary heart disease, nonfatal MI, hospitalization for angina, or post-randomization coronary revascularization. The endpoint of outpatient HF was defined as clinical development of symptomatic HF (either urgent/unscheduled or nonurgent) in the outpatient setting with symptoms and signs requiring initiation or intensification of intravenous or qualifying oral HF treatment. A blinded clinical events classification committee adjudicated all prespecified outcomes.

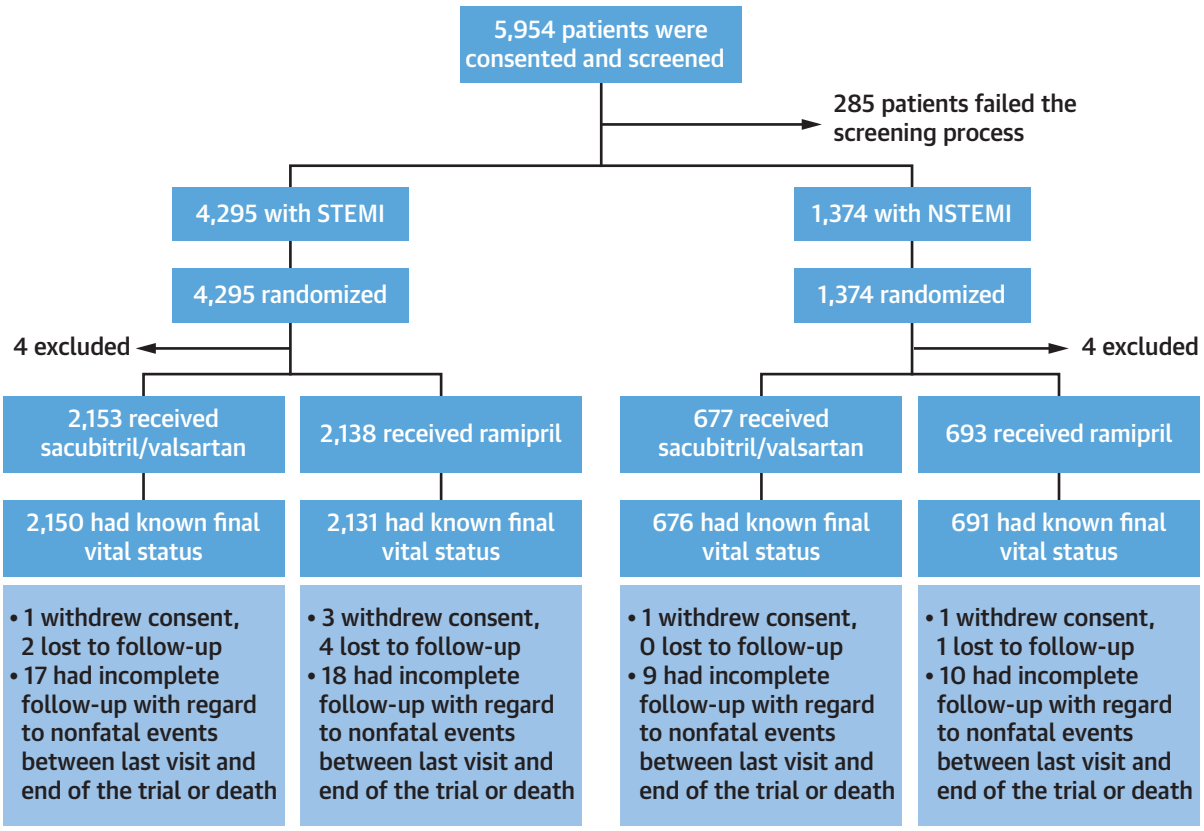
STATISTICAL ANALYSIS. Baseline clinical and procedural characteristics are summarized by the type of AMI using mean ± SD and frequencies for continuous and categorical variables, respectively. Treatment groups were compared on an intention-to-treat basis, and HRs with 95% CIs were generated using the Cox proportional hazards model, stratified by type of MI, with treatment, percutaneous coronary intervention (PCI) at baseline, and geographic region included as factors in the model.[13] These variables were predetermined at the time of the design of the study and were used during randomization. Other clinically relevant variables, known to significantly impact outcomes, were included in the model that assessed the risk of adverse events in the overall STEMI and NSTEMI populations: sex, age (years), pulmonary congestion, PCI use, LVEF (%), and hypertension. The assumption of proportional hazards was assessed via Schoenfeld residuals. The Kaplan-Meier method was used to determine the cumulative event rate curves, which were then compared with the log-rank test. All analyses were performed using STATA version 14.2 (StataCorp) and R version 4.1.0 (R Foundation for Statistical Computing).

RESULTS

BASELINE CHARACTERISTICS. Among 5,661 patients enrolled in the PARADISE-MI trial, 4,291 (75.8%) had STEMI, and 1,370 (24.2%) had NSTEMI (**Figure 1**). Patients presenting with STEMI were generally younger, less often females, and had a lower burden of comorbidities and CV risk factors (ie, diabetes mellitus, hypertension, and history of prior MI) than their counterparts presenting with NSTEMI (**Table 1**). Furthermore, STEMI patients were more likely to have an anterior wall MI and to undergo coronary reperfusion and percutaneous revascularization than NSTEMI patients. With respect to medical therapy at discharge, STEMI patients were more likely to be on dual antiplatelet therapy and statins but less likely on diuretics than NSTEMI patients. Although most baseline characteristics were well-balanced across treatment arms, in the setting of STEMI, patients randomized to the sacubitril/valsartan arm were older than those randomized to the ramipril arm (63.1 ± 11.5 vs 62.3 ± 11.4; $P = 0.02$) (Supplemental Table 1). In contrast, in the NSTEMI cohort, racial disparities (fewer Caucasian and Black patients and more Asian and other races in the sacubitril/valsartan arm) existed among patients randomized to either sacubitril/valsartan or ramipril (Supplemental Table 2).

CLINICAL OUTCOMES BY TYPE OF MI. The incidence of the primary endpoint of death from CV causes or incident HF was 9.8 per 100 person-years in the NSTEMI group and 6.2 per 100 person-years in the STEMI group (HR: 1.56; 95% CI: 1.33-1.82; $P < 0.001$) (**Figure 2**). After adjustment for potential confounders, a borderline significant increase in the risk for the primary endpoint was noted in the NSTEMI vs STEMI group (adjusted HR [adjHR]: 1.19; 95% CI: 1.00-1.41; $P = 0.05$). Among the components of the primary composite outcome, the adjusted risk of CV death

FIGURE 1 Disposition of Study Participants



Flowchart showing distribution of study participants. Eight patients (4 in each group), who were determined to not meet the trial inclusion criteria, were excluded after randomization but before administration of the trial drug. The number of patients categorized under STEMI and NSTEMI in the current report differs from the numbers presented in the primary paper.[10] This discrepancy is attributable to the misclassification of the MI types during the initial stratification for randomization in the primary paper, which has been corrected in the current paper to provide more accurate groupings. MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

(**Table 2**, Supplemental Figure 1) was significantly higher in the NSTEMI group, whereas there were no significant differences in the adjusted risk for HF hospitalization or outpatient HF events (**Table 2**, Supplemental Figures 2 and 3). The prespecified composite coronary outcome of the first occurrence of death from coronary heart disease, nonfatal MI, hospitalization for angina, or postrandomization coronary revascularization remained significantly higher in the NSTEMI than in the STEMI group (10.7 per 100 person-years in NSTEMI vs 6.6 per 100 person-years in STEMI) even after adjusting for potential confounders ($_{adj}$HR: 1.48; 95% CI: 1.25-1.74; $P < 0.001$) (**Table 2**, Supplemental Figure 4). This was mainly driven by an increased risk for nonfatal MI ($_{adj}$HR: 1.60; 95% CI: 1.23-2.07; $P < 0.001$) and postrandomization coronary revascularization ($_{adj}$HR: 1.51; 95% CI: 1.24-1.85; $P < 0.001$) in NSTEMI vs STEMI patients (**Table 2**). Last, the adjusted risks for the secondary outcomes of all-cause death ($_{adj}$HR: 1.28; 95% CI: 1.03-1.58; $P = 0.02$) and the composite of CV death, nonfatal MI, or nonfatal stroke ($_{adj}$HR: 1.46; 95% CI: 1.23-1.74; $P < 0.001$) were both significantly higher in NSTEMI patients as compared with STEMI patients.

CLINICAL OUTCOMES BY TREATMENT ARM. In the STEMI cohort, the primary composite outcome of CV death or incident HF occurred in 224 (10%) patients in the sacubitril/valsartan arm and 254 (12%) patients in the ramipril arm (HR: 0.87; 95% CI: 0.73-1.04; $P = 0.13$). The primary outcome rates did not differ in NSTEMI patients with 114 (17%) events in the sacubitril/valsartan arm and 119 (17%) events in the

TABLE 1 Characteristics of the Patients at Baseline

	NSTEMI (n = 1,370)	STEMI (n = 4,291)	*P* Value
Age, y	67.1 ± 11.1	62.7 ± 11.4	<0.001
Female	400 (29.2)	963 (22.4)	<0.001
Race			0.04
Asian	232 (16.9)	721 (16.8)	
Black	26 (1.9)	49 (1.1)	
Caucasian	1,038 (75.8)	3,225 (75.2)	
Other	74 (5.4)	296 (6.9)	
Heart rate, beats/min	73.7 ± 11.6	76.3 ± 11.8	<0.001
Systolic blood pressure, mm Hg	125.4 ± 14.7	119.5 ± 12.5	<0.001
Diastolic blood pressure, mm Hg	73.7 ± 10.5	73.8 ± 9.5	0.87
Body mass index, kg/m^2	28.5 ± 5.3	28.0 ± 4.9	<0.001
LVEF, %	38.3 ± 11.0	36.0 ± 8.8	<0.001
Pulmonary congestion	878 (64.1)	2,178 (50.8)	<0.001
1 or more risk augmenting factors	901 (65.8)	2,053 (47.8)	<0.001
Medical history			
Prior MI	384 (28.0)	536 (12.5)	<0.001
Prior CABG or PCI	384 (28.0)	550 (12.8)	<0.001
Prior stroke	94 (6.9)	169 (3.9)	<0.001
Hypertension	1,068 (78.0)	2,608 (60.8)	<0.001
Diabetes	704 (51.4)	1,697 (39.5)	<0.001
Current smoking	259 (18.9)	937 (21.8)	0.021
Atrial fibrillation/flutter	247 (18.0)	537 (12.5)	<0.001
Estimated GFR, mL/min/1.73 m^2	67.7 ± 21.6	73.2 ± 22.5	<0.001
Coronary reperfusion	1,038 (75.8)	3,999 (93.2)	<0.001
STEMI without reperfusion within 24 h	-	496 (11.6)	-
Thrombolytic therapy	5 (0.4)	248 (5.8)	<0.001
PCI	1,023 (74.7)	3,957 (92.2)	<0.001
Drug-eluting stent	919 (67.1)	3,539 (82.5)	<0.001
Location of MI			<0.001
Anterior	625 (45.6)	3,228 (75.2)	
Inferior	230 (16.8)	823 (19.2)	
Other	515 (37.6)	240 (5.6)	
Killip class ≥II	867 (65.1)	2,334 (56.2)	<0.001
Time to randomization, d	4.6 ± 1.7	4.2 ± 1.8	<0.001
Medical treatment at randomization			
Dual-antiplatelet therapy	1,209 (88.2)	4,013 (93.5)	<0.001
Beta-blocker	1,156 (84.4)	3,671 (85.6)	0.29
MRA	531 (38.8)	1,807 (42.1)	0.028
Diuretics	727 (53.1)	1,794 (41.8)	<0.001
Statin	1,268 (92.6)	4,102 (95.6)	<0.001
ACEI/ARB	1,108 (80.9)	3,328 (77.6)	0.009

Values are mean ± SD or n (%). Percentages may not total 100 because of rounding.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft surgery; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid-receptor antagonist; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

ramipril arm (HR: 0.97; 95% CI: 0.75-1.25; $P = 0.80$), yielding an interaction P value of 0.53 (Figure 3). Similar patterns were found for secondary endpoints (CV death, HF hospitalization, outpatient HF, all-cause death, and a composite of CV death, nonfatal MI, or stroke) with comparable risk estimates for either treatment arms in both types of AMI (Figure 3). Interestingly, there was no significant interaction between treatment arm (sacubitril/valsartan vs ramipril) and type of AMI (STEMI vs NSTEMI) with respect to the risk for the prespecified coronary composite endpoint (Supplemental Figure 5). Nonetheless, the risk of coronary events with sacubitril/valsartan vs ramipril was numerically lower among NSTEMI patients (HR: 0.76; 95% CI: 0.59-0.98) but not STEMI patients (HR: 0.91; 95% CI: 0.76-1.08). This was mainly driven by a significant reduction in the risk for nonfatal MI (HR: 0.61; 95% CI: 0.40-0.91) and post-randomization coronary revascularization (HR: 0.68; 95% CI: 0.49-0.93) among NSTEMI patients (Figure 4).

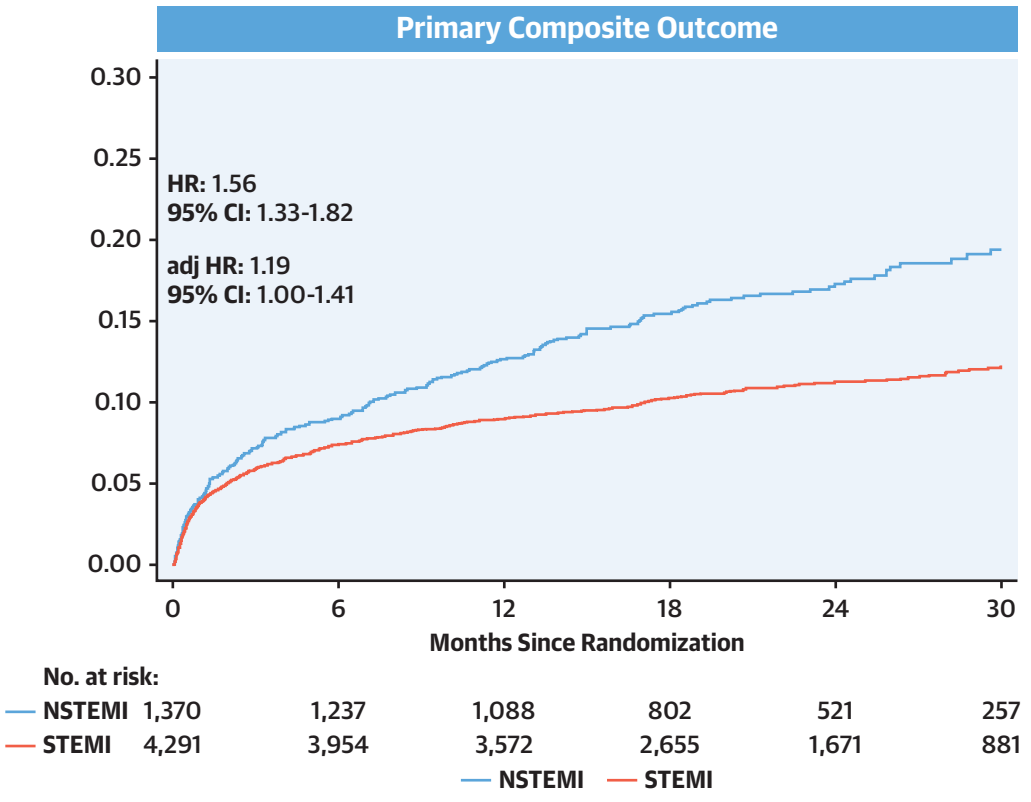
SAFETY PROFILE. As compared with ramipril, sacubitril/valsartan was relatively safe in both STEMI and NSTEMI patients (Supplemental Tables 3 and 4). Hypotension was a common side effect of sacubitril/valsartan in both subsets, occurring in up to 28% of patients. Nonetheless, ramipril was associated with more hepatotoxicity than sacubitril/valsartan in STEMI patients (5.9% vs 4.4%; $P = 0.02$).

DISCUSSION

In this prespecified subgroup analysis of the PARADISE-MI trial, we report the following 2 main findings: 1) NSTEMI patients had higher event rates than STEMI patients, which was largely explained by differences in the prevalence of comorbidities and invasive management between groups; and 2) sacubitril/valsartan vs ramipril did not significantly decrease the rates of CV death, HF hospitalization, or HF requiring treatment on an outpatient basis in patients presenting with STEMI or NSTEMI (Central Illustration).

CLINICAL OUTCOMES IN STEMI VS NSTEMI. Major advances in the diagnosis and management of AMI during the past decades have led to a significant decrease in subsequent mortality and hospitalization for HF.[14,15] This includes prompt revascularization and coronary stenting with state-of-the-art second-generation drug-eluting stents, widespread use of potent antithrombotic therapy and statins, and introduction of new agents for hypertension, hypercholesterolemia, and diabetes mellitus.[16-18] These advances have led to significant improvement in the prognosis of AMI survivors. Indeed, this is reflected in our study by the low overall event rates in patients with STEMI and NSTEMI, despite that the trial design required the presence of at least 1 prespecified risk-augmenting factor. Furthermore, the categorization of patients as "high-risk" post-AMI in the PARADISE-MI trial may have been determined prematurely, thereby allowing some patients to benefit from early reperfusion strategies and consequently

FIGURE 2 Cumulative Incidence of the Primary Outcome by Type of MI



The cumulative event of the primary composite outcomes was compared between patients who had NSTEMI and those who had STEMI. HRs were adjusted for sex, age (years), pulmonary congestion, PCI use, LVEF (%), and hypertension. adj HR = adjusted hazard ratio; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; other abbreviations as in Figure 1.

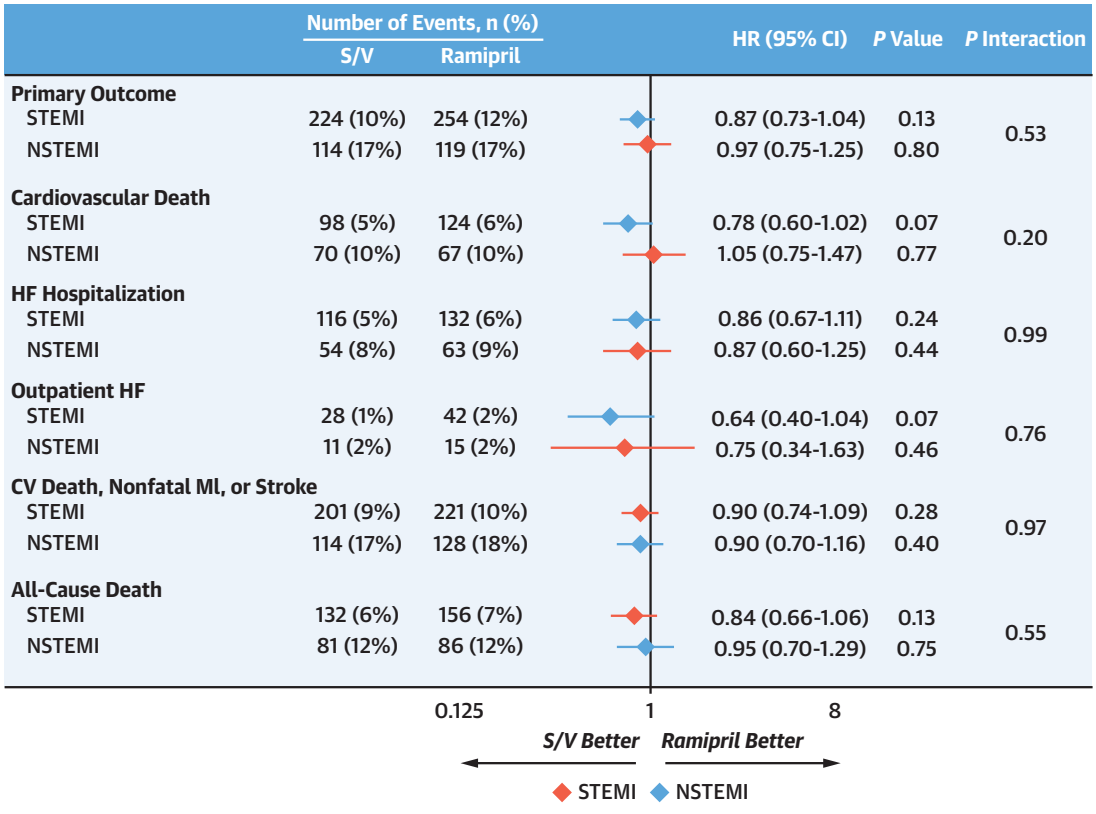
TABLE 2 Clinical Outcomes by Type of AMI

	NSTEMI (n = 1,370)		STEMI (n = 4,291)		Unadjusted Outcomes		Adjusted Outcomes[a]	
	No. of Events	Incidence (per 100 py)	No. of Events	Incidence (per 100 py)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Primary composite outcome	233	6.2	478	6.2	1.56 (1.33-1.82)	<0.001	1.19 (1.00-1.41)	0.05
CV death	137	5.4	222	2.7	1.96 (1.58-2.42)	<0.001	1.37 (1.08-1.74)	0.008
HF hospitalization	117	4.9	248	3.2	1.51 (1.21-1.88)	<0.001	1.20 (0.95-1.53)	0.13
Outpatient HF	26	1.0	70	0.9	1.18 (0.75-1.85)	0.47	0.98 (0.60-1.60)	0.70
Composite coronary outcome	241	10.7	492	6.6	1.60 (1.37-1.86)	<0.001	1.48 (1.25-1.74)	<0.001
Death from CHD	36	1.4	68	0.8	1.67 (1.12-2.51)	0.01	1.25 (0.81-1.94)	0.31
Nonfatal MI	99	4.1	190	2.4	1.69 (1.32-2.15)	<0.001	1.60 (1.23-2.07)	<0.001
Revascularization	159	6.8	336	4.4	1.53 (1.27-1.85)	<0.001	1.51 (1.24-1.85)	<0.001
Secondary outcomes								
All-cause death	167	6.5	288	3.5	1.84 (1.52-2.22)	<0.001	1.28 (1.03-1.58)	0.02
CV death, nonfatal MI, or nonfatal stroke	242	10.1	422	5.4	1.85 (1.58-2.17)	<0.001	1.46 (1.23-1.74)	<0.001

[a]Adjusted for sex, age (y), pulmonary congestion, PCI use, LVEF (%), and hypertension.

CHD = coronary heart disease; CV = cardiovascular; HF = heart failure; py = person-years; other abbreviations as in Table 1.

FIGURE 3 Clinical Outcomes by Treatment Arm, According to Type of MI

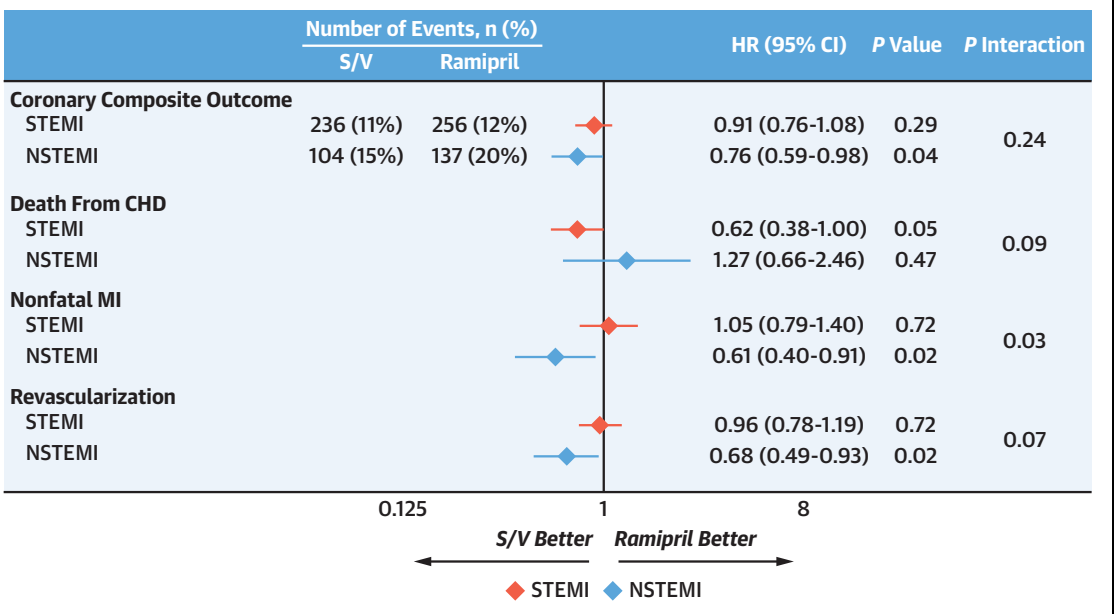


Forest plot showing the risk for the primary and secondary outcomes according to the treatment arm, S/V vs ramipril, in both STEMI and NSTEMI patients. HF = heart failure; S/V = sacubitril/valsartan; other abbreviations as in Figure 1.

improve their outcomes. This early classification could have resulted in lower event rates. Had the risk assessment been conducted after a more extended period after the AMI, a more precise identification of patients truly progressing toward HF might have yielded different results. In addition, the inclusion of well-established biomarkers such as N-terminal prohormone of brain natriuretic peptide in the trial's inclusion criteria could have led to the identification of high-risk patients who might derive larger benefits from sacubitril/valsartan vs ramipril.[19] Data from large registries during the past decades suggest a trend in the risk profile of patients presenting with AMI.[20,21] In general, NSTEMI patients are older and present with more comorbidities and risk factors (ie, diabetes mellitus, hypertension, kidney disease, and prior AMI) than STEMI patients. Therefore, although the extent of myocardial damage is larger after STEMI, NSTEMI patients often have a poorer prognosis after the index event. In addition, NSTEMI patients are less likely to undergo prompt revascularization and to be discharged on optimal medical therapy. Our results are largely consistent with the notion that differences in outcomes in survivors of STEMI and NSTEMI are strongly related to differences in patients' clinical characteristics and treatment modalities rather than the type of infarction. More importantly, our findings highlight the need for further research to improve outcomes in NSTEMI patients.

SACUBITRIL/VALSARTAN AFTER AMI. Studies exploring various therapeutic strategies after AMI, predominantly in STEMI patients, have focused on translating the benefits of RAAS inhibition from the bench to the bedside. Experiments conducted in wild-type mice subjected to ligation of the left anterior descending artery and then assigned to sacubitril/valsartan or enalapril showed more effective suppression of proinflammatory cytokines (interleukin-1β and

FIGURE 4 Coronary Outcome by Treatment Arm, According to Type of MI



Forest plot showing the risk for the coronary composite outcome and its components according to the treatment arm, S/V vs ramipril, in both STEMI and NSTEMI patients. CHD = coronary heart disease; other abbreviations as in Figures 1 and 3.

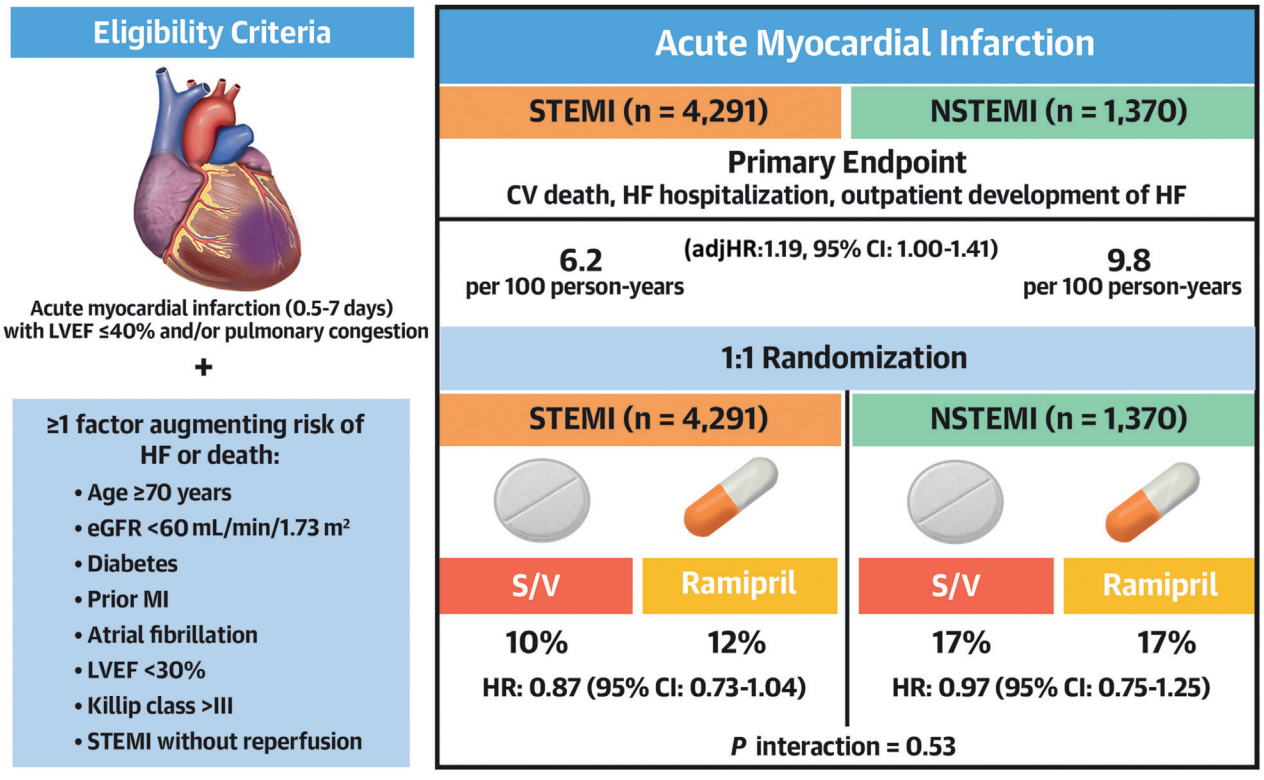
interleukin-6) and extracellular matrix degradation in macrophages post-AMI with the former.[22] Based on these observations and the results of trials conducted in HF patients, the PARADISE-MI trial was designed to assess the safety and efficacy of sacubitril/valsartan vs ramipril in post-AMI patients.[23-25] The main findings from the PARADISE-MI trial did not support the routine use of sacubitril/valsartan over ramipril in patients with AMI complicated by HF. However, the number of events for the primary endpoint was lower with sacubitril/valsartan vs ramipril, although statistically not significant (11.9% vs 13.2%; $P = 0.17$). Given the overall safety profile of sacubitril/valsartan compared with ramipril, we asked whether there were important treatment effects of sacubitril/valsartan when compared with ramipril with respect to type of MI at presentation. In this subanalysis, we found that sacubitril/valsartan is not different from ramipril in the prevention of cardiac death and HF after either STEMI or NSTEMI.

HF complicating STEMI is common and is associated with a substantial increase in mortality rates.[26,27] Relevant to this discussion, the SAVE-STEMI trial was a small, single-center study involving 200 patients with STEMI randomized to sacubitril/valsartan or ramipril immediately after percutaneous revascularization.[28] Although no differences in major adverse cardiac events were observed at 30 days, at 6 months those treated with sacubitril/valsartan had a significant decrease in major adverse cardiac events mainly driven by a decrease in HF hospitalizations (18% vs 36%; OR: 0.40; 95% CI: 0.22-0.75; $P = 0.004$). Similarly, the SAVE-SHOCK trial randomized 100 patients who received PCI for STEMI complicated by cardiogenic shock to either sacubitril/valsartan or ramipril.[29] The primary outcome of all-cause death, cardiac death, hospitalization due to HF, MI, and stroke occurred at similar rates in both groups at 30-day and 6-month follow-up. Nonetheless, sacubitril/valsartan significantly decreased the risk of hospitalization for HF, compared with ramipril.

The evidence for sacubitril/valsartan use across the spectrum of HF patients is currently recommended by European and American guidelines.[8,9] In contrast, the data on its safety and efficacy in patients with complicated AMI are scarce. Despite the high efficacy of contemporary medical therapy, there is a clear unmet need for additional risk reduction after AMI, especially among NSTEMI patients, to prevent the occurrence of coronary events, HF, and death.

STUDY LIMITATIONS. Although prespecified, our analysis has several limitations that must be considered. First, the primary endpoint of the main trial was not met, therefore, the findings of this analysis

CENTRAL ILLUSTRATION **Clinical Outcomes With Sacubitril/Valsartan vs Ramipril According to Acute Myocardial Infarction Type**



Mann DL, et al. J Am Coll Cardiol. 2024;83(9):904-914.

In this prespecified analysis of the PARADISE-MI trial, patients with NSTEMI had higher rates of cardiovascular events than patients with STEMI. There was no significant difference in the risk for the primary composite outcome between patients randomized to S/V and those randomized to ramipril, irrespective of the type of acute myocardial infarction. eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PARADISE-MI = Prospective ARNI versus ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction; STEMI = ST-segment elevation myocardial infarction; S/V = sacubitril/valsartan.

should be viewed as hypothesis generating. Second, the null effects with respect to the primary outcome in STEMI patients warrant cautious interpretation as a type II error and is possible in the context of an underpowered subgroup analysis. Third, our results do not apply to all STEMI or NSTEMI patients but only to those with LVSD and/or pulmonary congestion in addition to at least 1 high-risk criterion as mentioned in the Methods section. Fourth, our adjustment model only includes some but not all clinically relevant variables. This deliberate exclusion was undertaken with the primary objective of mitigating the risk of overfitting the data. Fifth, our findings may not be generalizable to patients treated with ACEI other than ramipril, an important consideration given the slight variation in pharmacodynamics across the different types of ACEI.

CONCLUSIONS

In patients with AMI complicated by LVSD with or without pulmonary congestion, sacubitril/valsartan did not significantly decrease the primary endpoint of CV death or incident HF compared with ramipril, irrespective of the type of MI.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Compared with ramipril, treatment with sacubitril/valsartan did not reduce the risk of cardiovascular events in high-risk patients with either STEMI or NSTEMI complicated by left ventricular dysfunction.

TRANSLATIONAL OUTLOOK: Additional studies are needed to improve outcomes in high-risk patients surviving AMI, especially NSTEMI.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.