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ORIGINAL RESEARCH ARTICLE

The Effects of Angiotensin Receptor-Neprilysin Inhibition on Major Coronary Events in Patients With Acute Myocardial Infarction: Insights From the PARADISE-MI Trial

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BACKGROUND: In patients who survive an acute myocardial infarction (AMI), angiotensin-converting enzyme inhibitors decrease the risk of subsequent major cardiovascular events. Whether angiotensin-receptor blockade and neprilysin inhibition with sacubitril/valsartan reduce major coronary events more effectively than angiotensin-converting enzyme inhibitors in high-risk patients with recent AMI remains unknown. We aimed to compare the effects of sacubitril/valsartan on coronary outcomes in patients with AMI.

METHODS: We conducted a prespecified analysis of the PARADISE-MI trial (Prospective ARNI vs ACE Inhibitors Trial to Determine Superiority in Reducing Heart Failure Events After MI), which compared sacubitril/valsartan (97/103 mg twice daily) with ramipril (5 mg twice daily) for reducing heart failure events after myocardial infarction in 5661 patients with AMI complicated by left ventricular systolic dysfunction, pulmonary congestion, or both. In the present analysis, the prespecified composite coronary outcome was the first occurrence of death from coronary heart disease, nonfatal myocardial infarction, hospitalization for angina, or postrandomization coronary revascularization.

RESULTS: Patients were randomly assigned at a median of 4.4 [3.0–5.8] days after index AMI (ST-segment–elevation myocardial infarction 76%, non–ST-segment–elevation myocardial infarction 24%), by which time 89% of patients had undergone coronary reperfusion. Compared with ramipril, sacubitril/valsartan decreased the risk of coronary outcomes (hazard ratio, 0.86 [95% CI, 0.74–0.99], P=0.04) over a median follow-up of 22 months. Rates of the components of the composite outcomes were lower in patients on sacubitril/valsartan but were not individually significantly different.

CONCLUSIONS: In survivors of an AMI with left ventricular systolic dysfunction and pulmonary congestion, sacubitril/valsartan—compared with ramipril—reduced the risk of a prespecified major coronary composite outcome. Dedicated studies are necessary to confirm this finding and elucidate its mechanism.

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Key Words: myocardial infarction ■ neprilysin ■ sacubitril and valsartan sodium hydrate drug combination

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Clinical Perspective

What Is New?

- Among patients with a recent acute myocardial infarction and left ventricular systolic dysfunction, heart failure, or both, sacubitril/valsartan decreased the risk of coronary-related events by 14% compared with ramipril.
- The benefits of sacubitril/valsartan, in terms of nonfatal myocardial infarction and coronary revascularization risk reduction, were mostly observed in the long term.
- The reduction in coronary events occurred with a favorable safety profile.

What Are the Clinical Implications?

- Given the high risk of coronary events after acute myocardial infarction, novel therapeutic strategies for secondary prevention should be considered in these patients.
- In addition to antiplatelet and lipid-lowering therapies, sacubitril/valsartan should be explored as a potential agent to mitigate the residual risk in survivors of acute myocardial infarction.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
AMI	acute myocardial infarction
CAD	coronary artery disease
EVALUATE-HF	Effects of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction
HF	heart failure
LVSD	left ventricular systolic dysfunction
MI	myocardial infarction
PARADIGM-HF	Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure.
PARAGON-HF	Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction
PCI	percutaneous coronary intervention
STEMI	ST-segment–elevation myocardial infarction

Patients who survive an acute myocardial infarction (AMI) complicated by left systolic dysfunction (LVSD), heart failure (HF), or both are at high risk of subsequent hospitalization for HF and death.[1–4] Early large-scale randomized trials showed that use of angiotensin-converting enzyme (ACE) inhibitors decreased the rate of hospital admission for HF and improved survival in such patients.[5–8] These trials also showed that ACE inhibitors significantly reduced the risk of recurrent myocardial infarction (MI) and other cardiovascular events; the additional benefit of ACE inhibitors was confirmed in other trials in related populations, including those with an established atherothrombotic disease with or without HF.[5–12] Subsequently, angiotensin receptor blockers were found to have benefits similar to ACE inhibitors in patients with an AMI, complicated by LVSD, HF, or both, and other high-risk cardiovascular groups.[9,13,14] Since these landmark trials, ACE inhibitors or angiotensin receptor blockers have become a cornerstone for the treatment of HF with reduced ejection fraction and survivors of AMI.[15,16]

More recently, the angiotensin receptor neprilysin inhibitor (sacubitril/valsartan) was shown to be superior to a renin-angiotensin system blocker alone (enalapril) in preventing cardiovascular death or hospitalization for HF in patients with HF with reduced ejection fraction enrolled in the PARADIGM-HF trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure).[17] The double effect of angiotensin receptor blockade and neprilysin inhibition has a major effect on the natriuretic peptide axis, increasing the levels of B-type natriuretic peptide and atrial natriuretic peptide.[18] Infusion of either molecules in patients with anterior MI resulted in reduced cardiac sympathetic nerve activation, less left ventricular remodeling, and improved left ventricular ejection fraction.[19,20] A subsequent analysis of the PARADIGM-HF trial revealed a reduced risk of coronary events with sacubitril/valsartan compared with enalapril.[21] Clinical guidelines have since provided a class I recommendation to sacubitril/valsartan as a replacement for ACE inhibitors in patients with HF with reduced ejection fraction.[22,23] Furthermore, in patients who have HF with preserved ejection fraction enrolled in the PARAGON-HF trial (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction), sacubitril/valsartan was associated with lower rates of hospitalization and cardiac death than valsartan, although statistically nonsignificant.[24] On the basis of the PARAGON-HF and PARADIGM-HF trials, the US Food and Drug Administration expanded labeling for sacubitril/valsartan for use in patients with chronic HF and a lower than normal left ventricular ejection fraction.

The PARADISE-MI trial (Prospective ARNI vs ACE Inhibitors Trial to Determine Superiority in Reducing Heart Failure Events After MI) was designed to investigate whether the benefits of sacubitril/valsartan over a renin-angiotensin system blocker alone could be

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extended to high-risk survivors of AMI.[25] Compared with ramipril, sacubitril/valsartan did not reduce the risk of adjudicated cardiovascular death or HF in a time-to-first event analysis. However, in a subsequent subanalysis of the trial taking into account first and recurrent events using both clinical end point committee adjudications and investigator reports, a significant reduction in the primary outcome was noted with sacubitril/valsartan versus ramipril.[26] Here, we report the effect of sacubitril/valsartan versus ramipril on the incidence of the prespecified coronary outcome and other coronary artery disease (CAD)-related events in the PARADISE-MI trial.

METHODS

The data and study materials will be made available to other researchers on a reasonable request to the study investigators.

Study Population

The design and main results of the PARADISE-MI trial have been previously reported.[25,27] In brief, PARADISE-MI was an international, multicenter, randomized, and double-blind trial designed to compare sacubitril/valsartan with ramipril in patients without a history of HF and who had an AMI associated with LVSD, pulmonary congestion, or both.[25] Key inclusion criteria were (1) age of at least 18 years; (2) diagnosis of spontaneous acute MI; (3) evidence of LVSD (left ventricular ejection fraction ≤40%), or pulmonary congestion, or both (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}·1.73 m^{-2}, diabetes, previous MI, atrial fibrillation, left ventricular ejection fraction <30%, Worst Killip class III or IV, and ST-segment–elevation MI (STEMI) without reperfusion therapy within the first 24 hours after presentation). Those individuals who were hemodynamically unstable (within the first 24 hours preceding randomization) or had an estimated glomerular filtration rate <30 mL·min^{-1}·1.73 m^{-2}, serum potassium >5.2 mmol/L, a history of angioedema, intolerance to an ACE inhibitor or angiotensin receptor blocker, or coronary artery bypass graft surgery planned or performed for index MI were excluded from the study. Patients were randomly assigned between 12 hours and 7 days after index presentation to either sacubitril/valsartan (97–103 mg twice daily) or ramipril (5 mg twice daily).[25,27] The study was approved by the ethics committees at each participating trial center. All the patients provided written informed consent before enrollment.

Clinical Outcomes

The primary outcome of the PARADISE-MI trial was the first occurrence of cardiovascular death, outpatient development of HF, or hospitalization for HF. Secondary outcomes included cardiovascular death, hospitalization for HF, outpatient HF, and a composite of cardiovascular death, nonfatal MI, or nonfatal stroke. In the present analysis, the prespecified exploratory coronary outcome was a composite of death from coronary heart disease (including fatal MI or death attributable to coronary revascularization), nonfatal MI, hospitalization for angina, or postrandomization coronary revascularization. Standardized end points definitions are listed in Table S1. We further analyzed the effect of sacubitril/valsartan on each of the individual components of this coronary outcome. All prespecified outcomes were adjudicated by a clinical-events classification committee whose members were unaware of the group assignments.

Statistical Analysis

PARADISE-MI was designed as an event-driven trial. Clinical and procedural characteristics are summarized by randomized group and by occurrence of the primary end point using means±SD and frequencies for continuous and categorical variables, respectively. The treatment groups were compared on an intention-to-treat basis, and hazard ratios 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.[25] The assumption of proportional hazards was assessed through Schoenfeld residuals. The cumulative event rate curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Given that our end point included only death from coronary heart disease, we conducted a sensitivity analysis substituting cardiovascular death for CAD death to address any competing risk issue that may arise because of the effects of HF-related death. All analyses were performed using STATA version 14.2 (StataCorp) and R version 4.1.0 (R Foundation for Statistical Computing).

RESULTS

Baseline Characteristics

A total of 5661 patients from 495 sites in 41 countries were randomly assigned to either sacubitril/valsartan (n=2830) or ramipril (n=2831) at a median of 4.4 [3.0–5.8] days after index MI. Baseline clinical and procedural characteristics were well-balanced between the experimental and control arms (Table S2). Overall, the mean age of patients was 63.7 years, 24.1% were women, and 42% had diabetes. Among the 4291 patients who presented with a STEMI, 3759 (87.6%) underwent reperfusion with PCI within 24 hours, with an average time from presentation to PCI of 70 [31–178] minutes. Likewise, 1023 (74.7%) patients with non-STEMI underwent PCI, 496 patients (73.3% of non-STEMIs) in the sacubitril/valsartan group, and 527 patients (76.1% of non-STEMIs) in the ramipril group. Patients received high rates of evidence-based secondary prevention agents, including dual antiplatelet therapy (92%), statins (95%), and β-blockers (85%). Table 1 summarizes the baseline clinical characteristics of patients according to the occurrence of the primary composite coronary outcome. In brief, patients who experienced a coronary event were more likely to have hypertension, diabetes, a history of cardiovascular events, multivessel disease, but less likely to have STEMI as index event.

CAD-Related Outcomes

The effects of sacubitril/valsartan, compared with ramipril, on the prespecified coronary outcome and its

Table 1. Baselines Characteristics of Patients According to the Occurrence of the Prespecified Composite Coronary Outcome

Baseline characteristics	Free of postrandomization coronary event n=4928	Postrandomization coronary event n=733	*P* value
Age, y	63.6±11.6	64.4±11.1	0.10
Female sex, n (%)	1208 (24.5)	155 (21.1)	0.05
Race/ethnicity, n (%)			<0.001
Asian	877 (17.8)	76 (10.4)	
Black	63 (1.3)	12 (1.6)	
White	3650 (74.1)	613 (83.6)	
Other	338 (6.9)	32 (4.4)	
Body mass index, kg/m^2	28.1±5.0	28.3±4.9	0.44
Medical history, n (%)			
Previous myocardial infarction	757 (15.4)	163 (22.2)	<0.001
Previous revascularization	754 (15.3)	180 (24.6)	<0.001
Previous stroke	222 (4.5)	41 (5.6)	0.02
Hypertension	3140 (63.7)	536 (73.1)	<0.001
Diabetes	2047 (41.5)	354 (48.3)	<0.001
Current smoking	1019 (20.7)	177 (24.1)	0.03
Atrial fibrillation/flutter	682 (13.8)	102 (13.9)	0.01
Estimated glomerular filtration rate, mL·min^{-1}·1.73 m^{-2}	72.2±22.3	69.4±22.8	0.002
Left ventricular ejection fraction, %	36.6±9.3	36.2±10.0	0.37
Qualifying myocardial infarction, n (%)			
ST-segment–elevation myocardial infarction	3799 (77.1)	492 (67.1)	<0.001
Non–ST-segment–elevation myocardial infarction/other	1129 (22.9)	241 (32.9)	
Reperfusion, n (%)	4406 (89.4)	631 (86.1)	0.01
Thrombolytics	235 (4.8)	18 (2.5)	<0.001
Percutaneous coronary intervention	4357 (88.4)	623 (85.0)	0.008
Drug-eluting stent	3909 (91.9)	549 (91.0)	0.46
Location of myocardial infarction, n (%)			<0.001
Anterior	3407 (69.1)	446 (60.8)	
Inferior	900 (18.3)	153 (20.9)	
Other	621 (12.6)	134 (18.3)	
Multivessel disease, n (%)	2493 (50.6)	515 (70.3)	<0.001
Time from symptom onset to hospital arrival, min	128 [43–373] n=4520	149 [47–417] n=645	0.22
Time from presentation to revascularization (ST-segment–elevation myocardial infarction), min	68 [30–174] n=3314	70 [33–148] n=408	0.91
Killip class ≥II, n (%)	2774 (58.1)	427 (60.3)	0.27
Medical treatment at randomization, n (%)			
Dual antiplatelet therapy	4549 (92.3)	673 (91.8)	0.64
β-Blocker	4197 (85.2)	630 (85.9)	0.58
Mineralocorticoid receptor antagonist	2024 (41.1)	314 (42.8)	0.36
Diuretics	2147 (43.6)	374 (51.0)	<0.001
Statin	4671 (94.8)	699 (95.4)	0.51
Angiotensin-converting-enzyme inhibitor/angiotensin-receptor blocker*	3828 (77.7)	608 (82.9)	0.001

Values are n (%), mean±SD, or median [interquartile range].
*Angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker use within 7 days before randomization.

Table 2. Time-to-First Event Analysis of the Prespecified Composite Coronary Outcome and Its Components

Outcome	Events and event rate (per 100 patient-years)		Hazard ratio (95% CI)	*P* value
	Sacubitril/valsartan (n=2830)	Ramipril (n=2831)		
Death from coronary heart disease, nonfatal myocardial infarction, hospitalization for angina, or coronary revascularization	340 [6.9]	393 [8.1]	0.86 (0.74–0.99)	0.04
Death from coronary heart disease, nonfatal myocardial infarction, or coronary revascularization	335 [6.8]	391 [8.1]	0.85 (0.73–0.98)	0.03
Death from coronary heart disease or nonfatal myocardial infarction	161 [3.1]	186 [3.6]	0.86 (0.70–1.07)	0.18
Components of composite coronary events				
Death from coronary heart disease	46 [0.9]	58 [1.1]	0.79 (0.54–1.17)	0.24
Nonfatal myocardial infarction	116 [2.2]	133 [2.6]	0.87 (0.68–1.12)	0.27
Hospitalization for angina	12 [0.2]	6 [0.1]	1.97 (0.74–5.26)	0.17
Coronary revascularization	230 [4.6]	265 [5.4]	0.86 (0.72–1.03)	0.09
Percutaneous coronary intervention	201 [4.0]	233 [4.7]	0.86 (0.71–1.03)	0.11
Coronary artery bypass graft	35 [0.7]	38 [0.7]	0.92 (0.58–1.45)	0.71
Additional outcomes				
All-cause death	213 [4.0]	242 [4.5]	0.88 (0.73–1.05)	0.16
Cardiovascular death	168 [3.1]	191 [3.6]	0.87 (0.71–1.08)	0.20
Stroke (fatal and nonfatal)	57 [1.1]	59 [1.1]	0.96 (0.67–1.39)	0.84

individual components are listed in Table 2. After a median of 22 months of follow-up, sacubitril/valsartan reduced the risk of coronary events, compared with ramipril (hazard ratio [HR], 0.86 [95% CI, 0.74–0.99], *P*=0.04), with a relatively late divergence of the curves (Figure 1). The patient-year rates of individual components of the coronary outcome, including death from coronary heart disease (0.9 versus 1.1 per 100 patient-years), nonfatal MI (2.2 versus 2.6 per 100 patient-years; Figure 2A), and coronary revascularization (4.6 versus 5.4 per 100 patient-years; Figure 2B), were each numerically lower in the sacubitril/valsartan group, except for the rather infrequent hospitalization for angina (0.2 versus 0.1 per 100 patient-years; Table 2).

Type 1 MI accounted for most nonfatal spontaneous MI occurring after randomization (Table S3). The vast majority of the coronary revascularization procedures performed after randomization were done by PCI and on an elective basis (Table 2 and Table S4). Overall, the median time to postrandomization revascularization was 103 [35–302] days. In the sacubitril/valsartan arm, it was 87.5 [35–293] days, and in the ramipril arm, it was

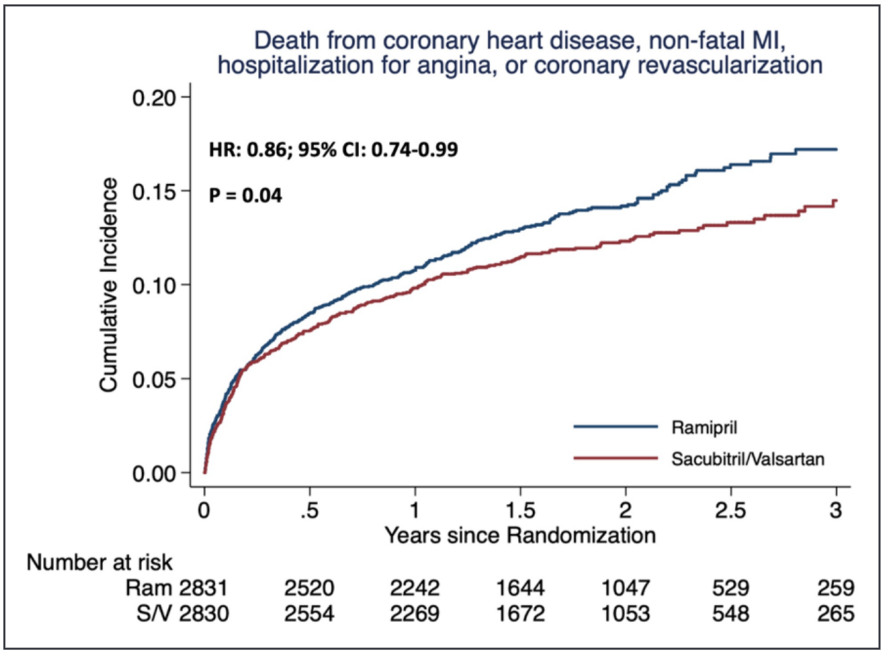

Figure 1. Cumulative incidence of the prespecified composite coronary outcome.
HR indicates hazard ratio; MI, myocardial infarction; Ram, ramipril; and S/V, sacubitril/valsartan.

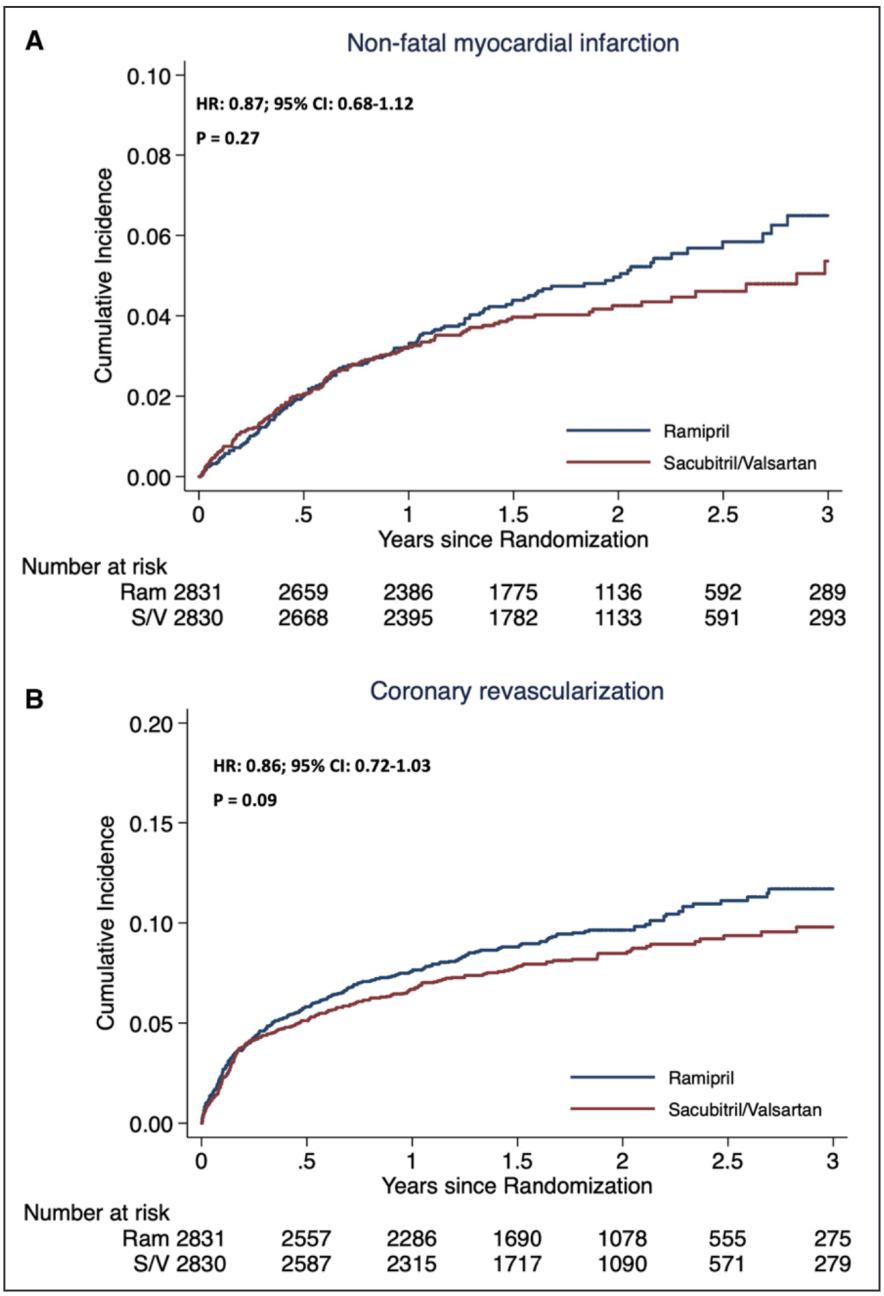

Figure 2. Cumulative incidence of coronary events.
A, Cumulative incidence of nonfatal myocardial infarction. **B**, Cumulative incidence of coronary revascularization. HR indicates hazard ratio; Ram, ramipril; and S/V, sacubitril/valsartan.

113 [35–302] days. As a sensitivity analysis, the point estimates for treatment effects were similar when including either death from CAD or cardiovascular death in the composite coronary outcome (Table S5).

There was no evidence that the effect of sacubitril/valsartan versus ramipril on coronary events differed across prespecified subgroups (Figure 3).

DISCUSSION

In this prespecified analysis of the PARADISE-MI trial, sacubitril/valsartan, compared with ramipril, reduced the risk of coronary-related events by 14% in patients with a recent AMI and LVSD, heart failure, or both. In absolute terms, ≈83 patients would need to be treated with sacubitril/valsartan to prevent 1 major coronary event. The reduction in coronary events, including nonfatal MI and the need for coronary revascularization, was primarily observed in the long term. It is important to note that this benefit occurred with a favorable safety profile.

The management of AMI has significantly evolved since the publication of landmark trials that demonstrated the coronary benefits of ACE inhibitors nearly 30 years ago. In particular, therapies such as prompt revascularization with PCI, statins, and antithrombotic agents have significantly improved prognosis in patients who survive an AMI. Despite the broad use of these evidence-based therapies in PARADISE-MI, sacubitril/valsartan led to a statistically significant risk reduction in major coronary events compared with the proven ACE inhibitor ramipril.

There is uncertainty regarding how neprilysin inhibition brings about a benefit with respect to coronary

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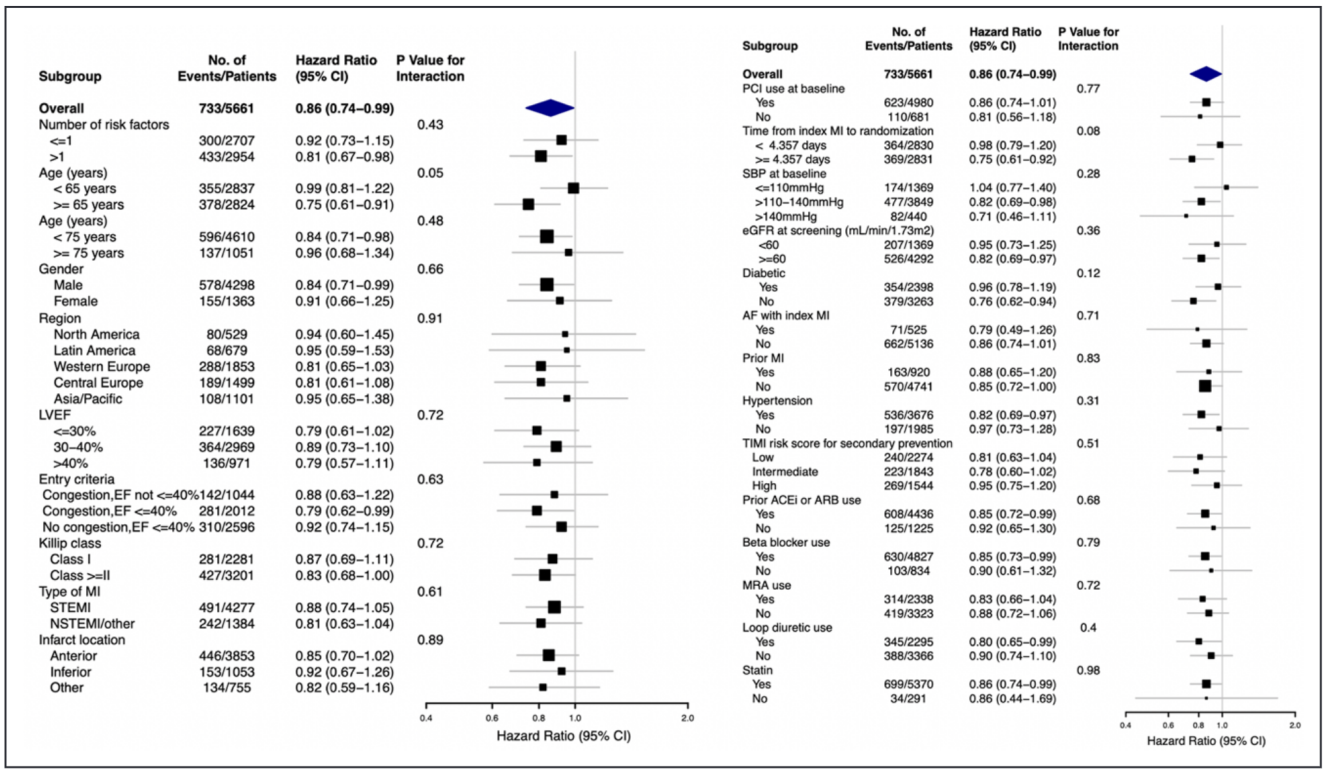

Figure 3. Coronary composite outcome, according to prespecified subgroup.
ACEi indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blockers; EF, ejection fraction; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonists; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-segment–elevation myocardial infarction; and TIMI, thrombolysis in myocardial infarction.

events. Although the vasoactive peptide substrates for neprilysin inhibition are remarkably broad, animal experiments suggest several possibilities. In an apolipoprotein E–deficient mouse model, both valsartan and sacubitril inhibited the formation of atherosclerotic plaques by reducing plaque lipid content and cross-sectional area, raising plaque's collagen content, and increasing fibrous cap thickness.[28] Compared with the experimental group (ie, sacubitril/valsartan), plaques in the control group (ie, valsartan) had relatively higher levels of proinflammatory cytokines (ie, interleukin-6, matrix metallopeptidase-8, and monocyte chemoattractant protein-1). Plaque stabilization and proinflammatory gene inhibition were more marked with dual pathway inhibition with sacubitril/valsartan than with valsartan alone.

Another plausible mechanism is a favorable effect of neprilysin inhibition on coronary circulation and thus myocardial ischemia. The drug combination inhibits the breakdown of C-type natriuretic peptide, an important substrate for neprilysin, through intracellular cyclic guanosine monophosphate concentration increases. C-type natriuretic peptide is an essential biomolecule that regulates coronary arterial tone, increases blood flow, and acts as an inhibitor of atherosclerosis through antiproliferative/antimigratory effects.[29,30] Furthermore, neprilysin inhibition also increases bradykinin levels, which is well-known to mediate the flow-dependent vasodilation of the coronary arteries through nitric oxide and prostacyclin production.[31–33] A more pronounced systolic blood pressure lowering (and reduced pulse pressure) with sacubitril/valsartan may have contributed to reduced coronary events.[34] Increased pulse pressure has been related to an increased risk of myocardial infarction.[34] Last, improvement in hemodynamic parameters with sacubitril-valsartan versus ramipril may reduce demand ischemia and thus improve coronary outcomes. In fact, in the EVALUATE-HF randomized trial (Effects of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction), treatment with sacubitril-valsartan, compared with enalapril, improved atrial and ventricular remodeling, lowered brain natriuretic peptide levels, and decreased filling pressures.[35]

Sacubitril/valsartan showed a safety profile similar to ramipril. The study drug was discontinued because of an adverse event in 12.6% of patients in the sacubitril/valsartan group versus 13.4% of those in the ramipril group (P=0.39).[27] The most notable adverse events were hypotension (28.3% in sacubitril/valsartan group versus 21.9% in ramipril group, P<0.001) and cough (9.0% in sacubitril/valsartan group versus 13.1% in ramipril group, P<0.001).[27]

The hypothesis-generating findings from this prespecified analysis of the PARADISE-MI trial may have important clinical and research implications. Given the magnitude of

the benefit achieved and the relative safety of the treatment, and the fact that this benefit is above and beyond the known benefits of ramipril, these results suggest that sacubitril/valsartan should be explored as a potential additional pathway to reduce residual risk after MI in addition to antiplatelet and lipid-lowering therapies. Large and adequately powered trials are needed to confirm the potential benefits of sacubitril/valsartan in reducing coronary events among patients after an AMI. Furthermore, these studies should include the measurement of biomarker molecules to better understand the molecular and cellular mechanisms that mediate the favorable effects of sacubitril/valsartan in preventing CAD-related events.

Several limitations should be considered while interpreting the study findings. First, the primary end point of the PARADISE-MI trial was not met. Second, although the present analysis was prespecified, it was exploratory, that is, no α was assigned, and the findings can only be considered hypothesis-generating. Third, the study was underpowered to detect an effect of treatment on individual coronary events (ie, death from coronary heart disease, nonfatal MI, hospitalization for angina, or postrandomization coronary revascularization).

Conclusions

In survivors of an AMI who were at high risk because of HF, LVSD, or both, sacubitril/valsartan, compared with the ACE inhibitor ramipril, appears to reduce the risk of major coronary events. These findings support the hypothesis that neprilysin inhibition may reduce CAD-associated outcomes after AMI. Further studies are warranted to validate this hypothesis.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Table S1–S5

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