THE EFFECTS OF ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITION ON MAJOR CORONARY EVENTS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION: INSIGHTS FROM THE PARADISE-MI TRIAL

RUNNING TITLE: EFFECTS OF SACUBITRIL/VALSARTAN ON CORONARY EVENTS

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ABSTRACT

Background

In patients who survive an acute myocardial infarction (AMI), angiotensin-converting enzyme (ACE) 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 ACE inhibitors in high-risk patients with recent AMI remains unknown. We sought to compare the effects of sacubitril/valsartan on coronary outcomes in patients with AMI.

Methods

We conducted a pre-specified analysis of the PARADISE-MI trial, 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 (LVSD), pulmonary congestion, or both. In the present analysis, the pre-specified composite coronary outcome was the first occurrence of death from coronary heart disease, non-fatal myocardial infarction, hospitalization for angina, or post-randomization coronary revascularization.

Results

Patients were randomized at a median of 4.4 [3.0, 5.8] days following index AMI (STEMI 76%, NSTEMI 24%), by which time 89% of patients had undergone coronary reperfusion. Compared with ramipril, sacubitril/valsartan decreased the risk of coronary outcomes (HR 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 LVSD and/or pulmonary congestion, sacubitril/valsartan, compared with ramipril, reduced the risk of a pre-specified major coronary composite outcome. Dedicated studies are necessary to confirm this finding and elucidate its mechanism.

Clinical trial registration: The trial was registered with ClinicalTrials.gov, NCT02924727.

Key Words: sacubitril/valsartan; neprilysin inhibition; acute myocardial infarction; coronary events.

Non-Standard Abbreviations and Acronyms

ACE: angiotensin converting enzyme.

AMI: acute myocardial infarction.

CNP: c-type natriuretic peptide.

EVALUATE-HF: Effects of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction.

LVSD: left ventricular systolic dysfunction.

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.

CLINICAL PERSPECTIVE

What is new?

- Among patients with a recent acute myocardial infarction (AMI) and left ventricular systolic dysfunction, heart failure, or both, sacubitril/valsartan decreased the risk of coronary-related events by 14% as compared with ramipril.
- The benefits of sacubitril/valsartan, in terms of non-fatal 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 post-AMI, 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 AMI.

INTRODUCTION

Patients surviving 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 (ARB) were found to have similar benefits to ACE inhibitors in patients with an AMI, complicated by LVSD, HF, or both, and other high-risk cardiovascular groups.[9,13,14] Following these landmark trials, ACE inhibitors or ARBs have become a cornerstone for the treatment of HF with reduced ejection fraction (HFrEF) 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 (CV) death or hospitalization for HF in patients with HFrEF enrolled in the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial.[17] The double effect of angiotensin receptor blockade and neprilysin inhibition has a major impact 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 myocardial infarction resulted in reduced cardiac sympathetic nerve activation, less left ventricular remodeling, and improved left ventricular ejection fraction

(LVEF).[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 HFrEF.[22,23] Furthermore, in HF patients with preserved ejection fraction enrolled in the PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction) trial, sacubitril/valsartan was associated with lower rates of hospitalization and cardiac death than valsartan, though statistically non-significant.[24] Based on the PARAGON-HF and PARADIGM-HF trials, the United States Food and Drug Administration expanded labeling for sacubitril/valsartan for use in patients with chronic HF and a lower than normal LVEF.

The PARADISE-MI (Prospective ARNI vs. ACE inhibitors trial to determine superiority in reducing heart failure events after myocardial infarction) trial was designed to investigate whether the benefits of sacubitril/valsartan over a renin-angiotensin system blocker alone could be extended to high-risk survivors of AMI.[25] Compared to ramipril, sacubitril/valsartan did not reduce the risk of adjudicated CV death or HF in a time-to-first event analysis. However, in a subsequent sub-analysis 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 vs. ramipril.[26] Here we report the impact of sacubitril/valsartan vs. ramipril on the incidence of the pre-specified coronary outcome and other coronary artery diseases (CAD)-related events in the PARADISE-MI trial.

METHODS

The data and study materials will be made available to other researchers upon 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] Briefly, 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) an age of at least 18 years, 2) diagnosis of spontaneous acute MI, 3) evidence of LVSD (LVEF ≤ 40%) and/or pulmonary congestion (associated with the index MI) requiring treatment, and 4) at least one risk-enhancing factor (i.e., 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 ST-elevation MI (STEMI) without reperfusion therapy within the first 24 hours after presentation). Those who were hemodynamically unstable (within the first 24 hours preceding randomization) or had an eGFR <30ml/min/1.73m^2, serum potassium >5.2 mmol/L, a history of angioedema, intolerance to an ACE-I or angiotensin receptor blocker (ARB), or coronary artery bypass graft surgery planned or performed for index MI were excluded from the study. Patients 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).[25,27] The study was approved by the ethics committees at each participating trial center. All patients provided written informed consent before enrollment.

CLINICAL OUTCOMES

The primary outcome of the PARADISE-MI trial was the first occurrence of CV death, outpatient development of HF, or hospitalization for HF. Secondary outcomes included CV death, hospitalization for HF, outpatient HF, and a composite of CV death, non-fatal MI, or non-fatal stroke. In the present analysis, the pre-specified exploratory coronary outcome was a composite of death from coronary heart disease (including fatal MI or death due to coronary revascularization), non-fatal MI, hospitalization for angina, or post-randomization coronary revascularization. Standardized endpoints definitions are listed in **Table S1**. We further analyzed the impact of sacubitril/valsartan on each of the individual components of this coronary outcome. All pre-specified 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 endpoint using means (± standard deviation) and frequencies for continuous and categorical variables, respectively. The treatment groups were compared on an intention-to-treat basis, and hazard ratios with 95% confidence intervals (CI) 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 via Schoenfeld residuals. The cumulative event rate curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Given that our endpoint included only death from coronary heart disease, we conducted a sensitivity analysis substituting CV death for CAD death to address any competing risk issue that may arise due to the effects of HF-related death.

All analyses were performed using STATA version 14.2 (StataCorp, College Station, Texas) and R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

A total of 5,661 patients from 495 sites in 41 countries were randomized to either sacubitril/valsartan (n=2,830) or ramipril (n=2,831) 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 mellitus. 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. Similarly, 1023 (74.7%) of non-ST-elevation MI (NSTEMI) patients underwent PCI, 496 patients (73.3% of NSTEMIs) in the sacubitril/valsartan group, and 527 patients (76.1% of NSTEMIs) in the ramipril group. Patients received high rates of evidence-based secondary prevention agents, including dual antiplatelet therapy (92%), statins (95%), and beta-blockers (85%). **Table 1** summarizes the baseline clinical characteristics of patients according to the occurrence of the primary composite coronary outcome. Briefly, patients who experienced a coronary event were more likely to have hypertension, diabetes mellitus, a prior history of cardiovascular events, multivessel disease, but less likely to have STEMI as index event.

Coronary artery disease-related outcomes

The effects of sacubitril/valsartan, compared with ramipril, on the pre-specified coronary outcome and its 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 vs. 1.1 per 100 patient-years), non-fatal MI (2.2 vs. 2.6 per 100 patient-years) (**Figure 2A**), and coronary revascularization (4.6 vs. 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 vs. 0.1 per 100 patient-years) (**Table 2**).

Type 1 MI accounted for most non-fatal spontaneous MI occurring after randomization (**Table S3**). The vast majority of the coronary revascularization procedures performed after randomization was done by PCI and on an elective basis (**Table 2** and **Table S4**). Overall, the median time to post-randomization 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 113 [35, 302] days. As a sensitivity analysis, the point estimates for treatment effects were similar when including either death from CAD or CV death in the composite coronary outcome (**Table S5**).

There were no evidence that the effect of sacubitril/valsartan vs. ramipril on coronary events differed across pre-specified subgroups **(Figure 3)**.

DISCUSSION

In this pre-specified 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, about 83 patients would need to be treated with sacubitril/valsartan to prevent one major coronary event. The reduction in coronary events,

including non-fatal MI and the need for coronary revascularization, was primarily observed in the long term. Importantly, 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 thirty 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 events. While 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 plaques lipid content and cross-sectional area, raising plaque's collagen content, and increasing fibrous cap thickness.[28] Compared with the experimental group (i.e., sacubitril/valsartan), plaques in the control group (i.e., valsartan) had relatively higher levels of proinflammatory cytokines (i.e., interleukin-6, matrix metallopeptidase-8, and monocyte chemoattractant protein-1). Indeed, plaque stabilization and pro-inflammatory genes inhibition were more marked with dual pathway inhibition with sacubitril/valsartan than with valsartan alone.

Another plausible mechanism is a favorable impact of neprilysin inhibition on coronary circulation and thus myocardial ischemia. The drug combination inhibits the breakdown of C-type natriuretic peptide (CNP), an important substrate for neprilysin, through intracellular cyclic

guanosine monophosphate concentration increases. CNP 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 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] Lastly, improvement in hemodynamic parameters with sacubitril-valsartan vs. ramipril may reduce demand ischemia and thus improve coronary outcomes. In fact, in the EVALUATE-HF (Effects of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction) randomized trial, treatment with sacubitril-valsartan, as compared with enalapril, improved atrial and ventricular remodeling, lowered brain natriuretic peptide levels, and decreased filling pressures.[35]

Sacubitril/valsartan showed a similar safety profile as compared with ramipril. The study drug was discontinued due to an adverse event in 12.6% of patients in the sacubitril/valsartan group vs. 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 vs. 21.9% in ramipril group, $p<0.001$) and cough (9.0% in sacubitril/valsartan group vs. 13.1% in ramipril group, $p<0.001$).[27]

The hypothesis-generating findings from this pre-specified 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 post-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 post-AMI patients. 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 taken into consideration while interpreting the study findings. First, the primary endpoint of the PARADISE-MI trial was not met. Second, although the present analysis was pre-specified, it was exploratory, i.e., no alpha 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 (i.e., death from coronary heart disease, non-fatal MI, hospitalization for angina, or post-randomization coronary revascularization).

CONCLUSIONS

In survivors of an AMI who were at high risk because of HF, LVSD, or both, sacubitril/valsartan, compared with 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.

SOURCES OF FUNDING

Funded by Novartis.

DISCLOSURES

Dr. Berwanger reports research grants from AstraZeneca, Pfizer, Bayer, Amgen, Servier, Bristol-Myers Squibb, and Boehringer-Ingelheim paid to his institution, and advisory board and personal fees from Pfizer and Novartis outside of the submitted work.

Dr. Mann reports consulting fees from Bristol-Myers Squibb and Novo-Nordisk.

Dr. Depasquale reports speaker honoraria and consulting fees from AstraZeneca, Novartis, Vifor, Otsuka, St Jude, Boehringer Ingelheim, Bayer, Lilly, Roche, Servier, American Regent.

Dr. Ducrocq reports speaker and/or consulting fees from Abbott, Amgen, Astra Zeneca, Bayer, BMS, Sanofi; proctoring fees from Boston scientific; CEC fees from Novo-Nordisk.

Dr. Kober reports speaker fees from Novartis, Novo, AstraZeneca, Boehringer and Bayer.

Dr. Landmesser reports institutional research grants from Amgen, Bayer and Novartis; consulting or speaker honorary from Abbott, Amgen, Bayer, Novartis, Pfizer, Sanofi, The Medicines Company.

Dr. Lefkowitz is an employeee of Novartis Pharmaceutcal Corporation.

Dr Maggioni reports personal fees for participation in committees of studies supported by Bayer, Novartis, Astra Zeneca, Fresenius, outside the present work.

Dr. Mehran reports institutional research payments from Abbott, Abiomed, Alleviant Medical, AM-Pharma, Applied Therapeutics, Arena, AstraZeneca, BAIM, Bayer, Beth Israel Deaconess, Biosensors, Biotronik, Boston Scientific, Bristol-Myers Squibb, CardiaWave, CellAegis, CeloNova, CERC, Chiesi, Concept Medical, CSL Behring, Cytosorbents, DSI, Duke University, Element Science, Faraday, Humacyte, Idorsia, Insel Gruppe AG, Magenta, Medtronic, Novartis, OrbusNeich, Philips, RenalPro, Vivasure, Zoll; personal fees from Cine-Med Research, WebMD; consulting fees paid to the institution from Abbott, Janssen, Medtronic, Novartis; Equity <1% in Applied Therapeutics, Elixir Medical, STEL, CONTROLRAD (spouse); Scientific Advisory Board for AMA, ACC (BOT Member), SCAI (Women in Innovations Committee Member), JAMA Associate Editor; Faculty CRF (no fee).

Dr Petrie reports research funding – Boehringer Ingelheim, Roche, SQ Innovations, Astra Zeneca, Novartis, Novo Nordisk, Medtronic, Boston Scientific, Pharmacosmos, 3R LifeSciences. Consultancy and Clinical Trials Committees committees - Boehringer Ingelheim, Novartis, Roche, Corvia, Astra Zeneca, Novo Nordisk, Medtronic, Abbvie, Bayer, Takeda, Cardiorentis, Pharmacosmos, Siemens. Dr Petrie is supported by the British Heart Foundation (BHF) Centre of Research Excellence Award (RE/13/5/30177 and RE/18/6/34217+).

Dr. Rouleau reports consultant fees from Novartis, BMS, Bayer, and AstraZeneca.

Dr. Sim reports speaker and/or consulting fees from Abbott, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Medtronic, Menarini, Merck, Novartis, Otsuka, Pfizer, Roche, Servier, Vifor Pharma.

Dr. Steg reports receiving research grants from Amarin, Bayer, Sanofi, and Servier; serving on clinical trials (Steering Committee, Clinical Endpoint Committee, Data Safety Monitoring Board) for Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Idorsia, Lexicon, PhaseBio, Novartis,

Pfizer, Sanofi, and Servier; and receiving consultant or speaker fees from Amarin, Amgen, BMS/Myokardia, Merck, Novo-Nordisk, and Regeneron.

Dr. Zhou is an employeee of Novartis Pharmaceutcal Corporation.

The other authors have nothing to disclose.

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Table 1. Baselines characteristics of patients according to the occurrence of the pre-specified composite coronary outcome.

Baseline characteristics	Free of Post-Randomization Coronary Event N=4928	Post-Randomization Coronary Event N=733	p-value
Age – years	63.6 ± 11.6	64.4 ± 11.1	0.10
Female sex	1208 (24.5%)	155 (21.1%)	0.05
Race			<0.001
Asian	877 (17.8%)	76 (10.4%)	
Black	63 (1.3%)	12 (1.6%)	
Caucasian	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			
Prior MI	757 (15.4%)	163 (22.2%)	<0.001
Prior revascularization	754 (15.3%)	180 (24.6%)	<0.001
Prior stroke	222 (4.5%)	41 (5.6%)	0.02
Hypertension	3140 (63.7%)	536 (73.1%)	<0.001
Diabetes mellitus	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 GFR - $ml/min/1.73m^2$	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 MI			
STEMI	3799 (77.1%)	492 (67.1%)	<0.001
NSTEMI/other	1129 (22.9%)	241 (32.9%)	
Reperfusion	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 MI			<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	2493 (50.6%)	515 (70.3%)	<0.001
Time from symptom onset to hospital arrival - minutes	128 [43, 373] n=4520	149 [47, 417] n=645	0.22
Time from presentation to revascularization (STEMI) - minutes	68 [30, 174] n=3314	70 [33, 148] n=408	0.91
Killip class ≥II	2774 (58.1%)	427 (60.3%)	0.27
Medical treatment at randomization			
Dual antiplatelet therapy	4549 (92.3%)	673 (91.8%)	0.64
Beta 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
ACE inhibitor/ARB*	3828 (77.7%)	608 (82.9%)	0.001

Values are presented as n (%), means ± standard deviation, or median [interquartile range].

ACE: angiotensin-converting-enzyme; **ARB**: angiotensin-receptor blocker; **GFR**: glomerular filtration rate; **IQR**: interquartile range; **MI**: myocardial infarction; **NSTEMI**: non-ST-elevation myocardial infarction; **STEMI**: ST-elevation myocardial infarction.

*ACE inhibitor or ARB use within seven days before randomization.

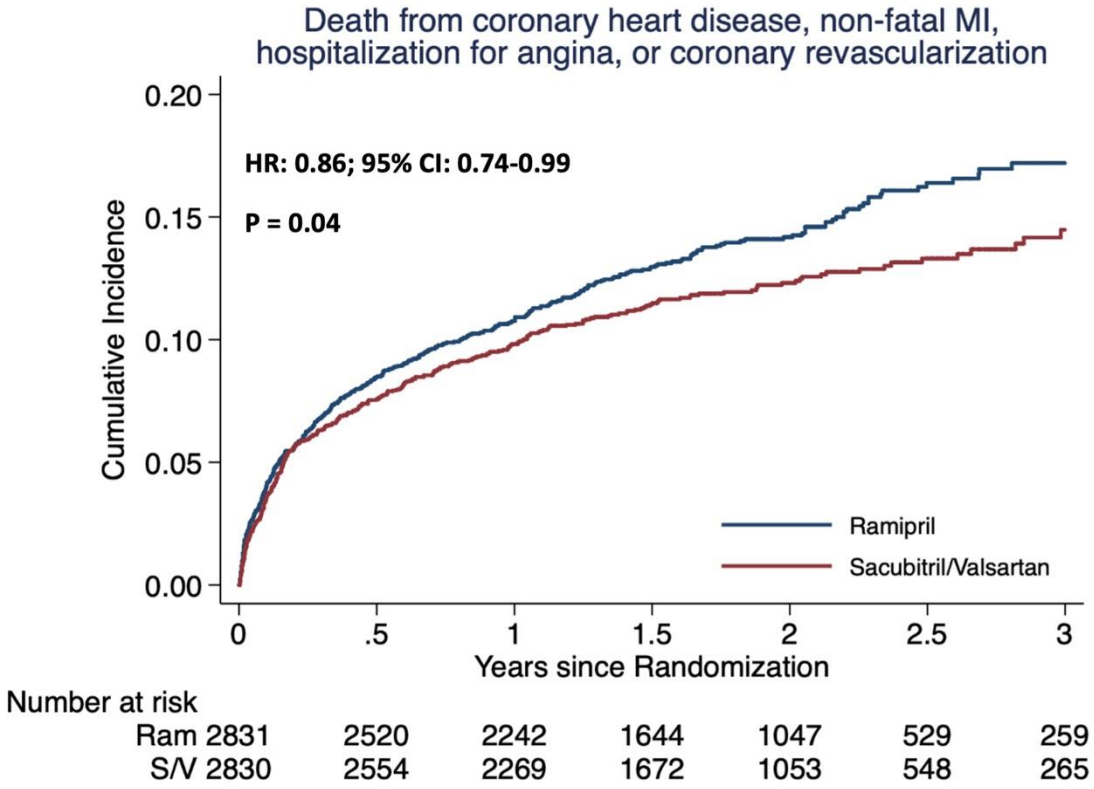
Table 2. Time-to-first event analysis of the pre-specified composite coronary outcome and its components.

Outcome	Events and Event Rate [per 100 pt-yrs]		Hazard Ratio (95% CI)	p-value
	Sacubitril/ valsartan (N=2830)	Ramipril (N=2831)		
Death from coronary heart disease, non-fatal 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, non-fatal 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 non-fatal 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
Non-fatal 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
PCI	201 [4.0]	233 [4.7]	0.86 (0.71-1.03)	0.11
CABG	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 non-fatal)	57 [1.1]	59 [1.1]	0.96 (0.67-1.39)	0.84

PCI: percutaneous coronary intervention; **CABG:** coronary artery bypass graft

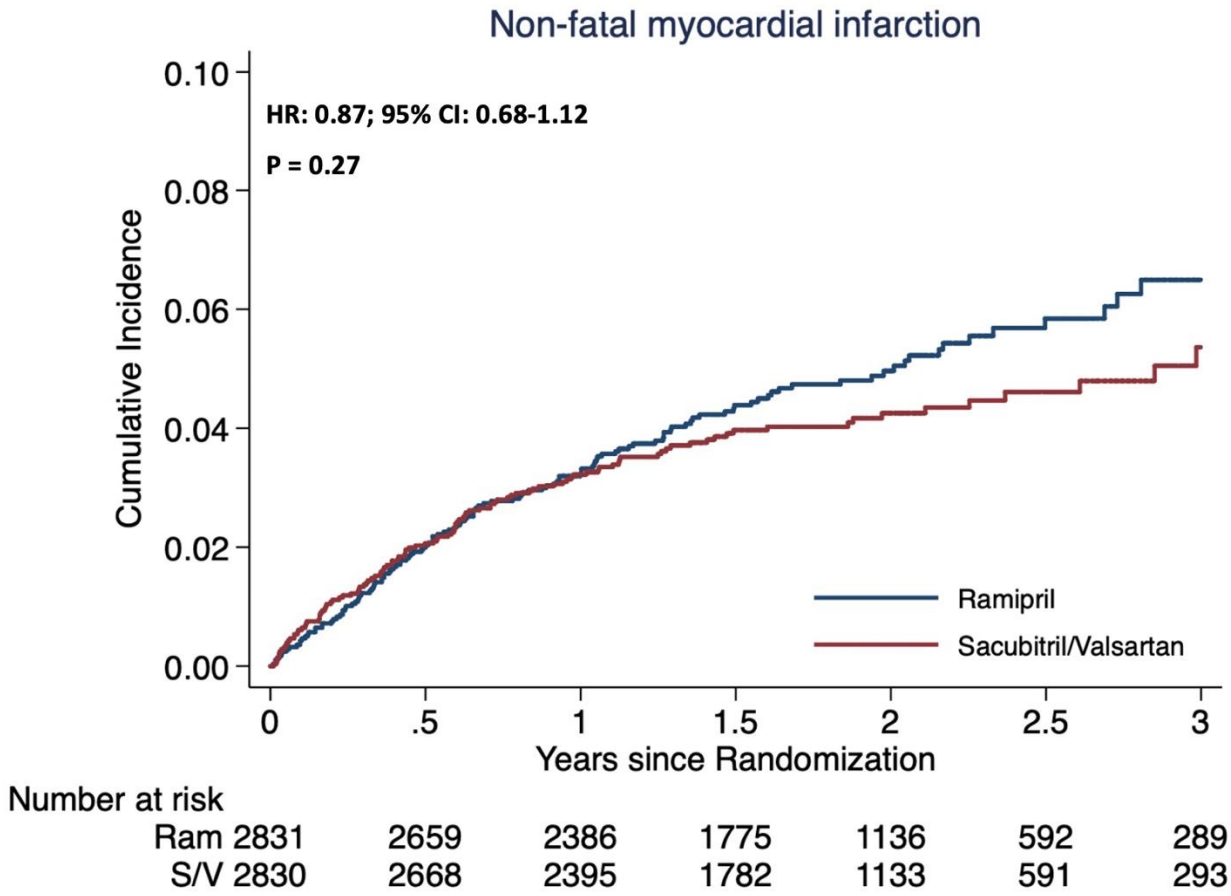
FIGURES

Figure 1. Cumulative incidence of coronary outcomes.



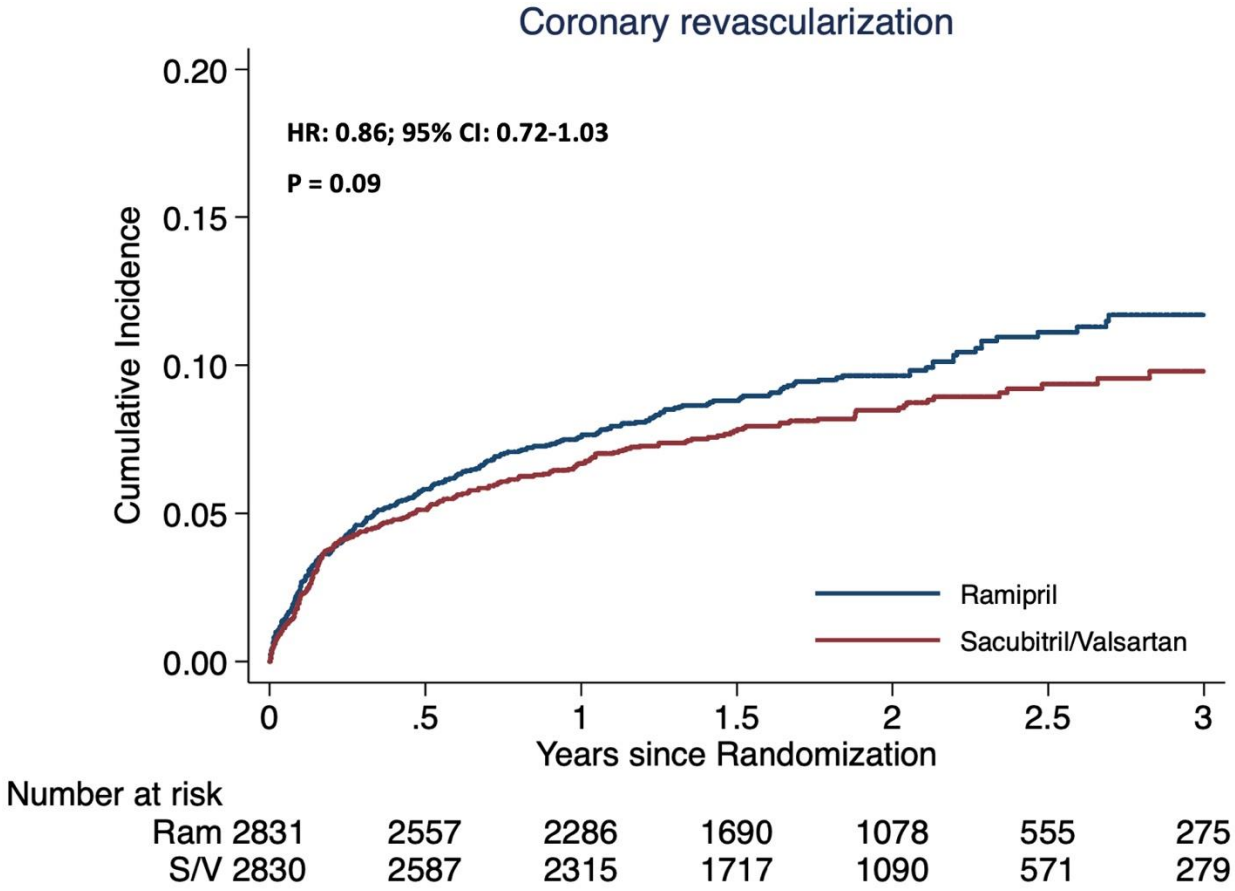
CI: confidence interval; **HR**: hazard ratio; **Ram**: ramipril; **S/V**: sacubitril/valsartan.

Figure 2A. Cumulative incidence of non-fatal myocardial infarction.



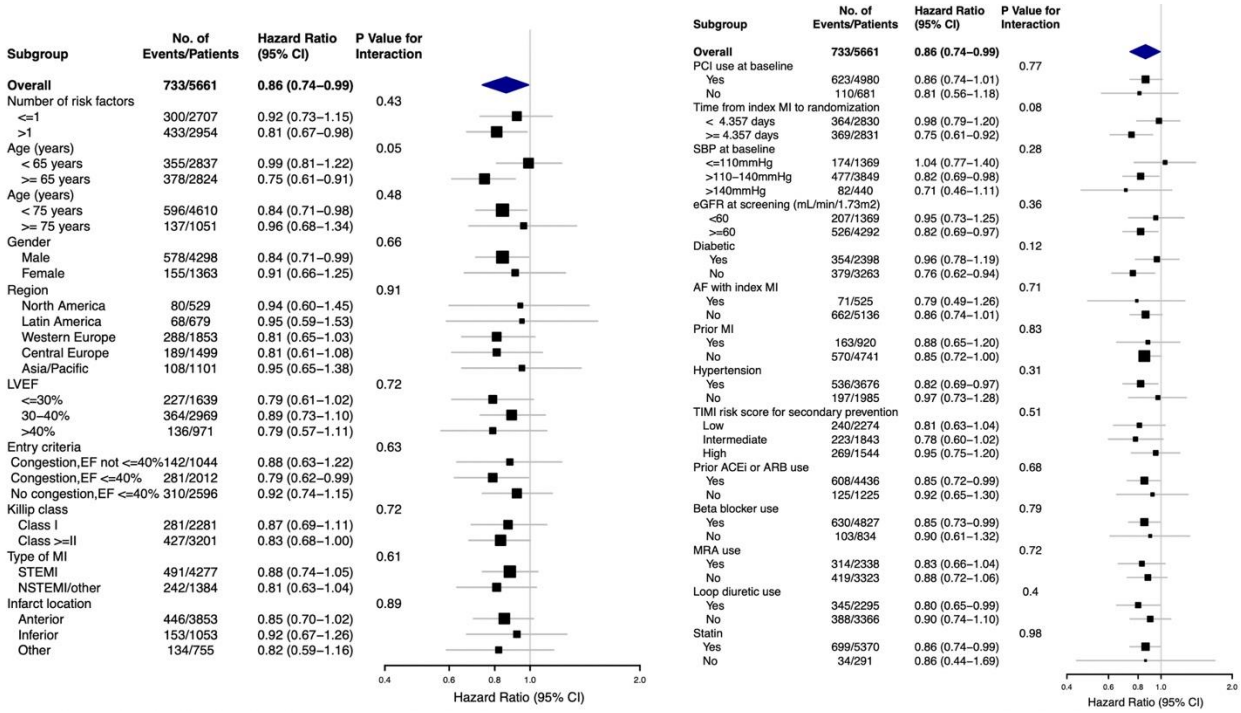
CI: confidence interval; **HR**: hazard ratio; **Ram**: ramipril; **S/V**: sacubitril/valsartan.

Figure 2B. Cumulative incidence of coronary revascularization.



CI: confidence interval; **HR**: hazard ratio; **Ram**: ramipril; **S/V**: sacubitril/valsartan.

Figure 3. Coronary composite outcome, according to pre-specified subgroup.



LVEF: left ventricular ejection fraction; **EF**: ejection fraction; **MI**: myocardial infarction; **STEMI**: ST-segment elevation myocardial infarction; **NSTEMI**: non-ST-segment elevation myocardial infarction; **PCI:** percutaneous coronary intervention; **SBP**: systolic blood pressure; **eGFR**: estimated glomerular filtration rate; **AF**: atrial fibrillation; **TIMI**: thrombolysis in myocardial infarction; **ACEi**: angiotensin-converting enzyme inhibitor; **ARB**: angiotensin receptor blockers; **MRA**: mineralocorticoid receptor antagonists.