ORIGINAL ARTICLE

Angiotensin Receptor–Neprilysin Inhibition in Acute Myocardial Infarction

M.A. Pfeffer, B. Claggett, E.F. Lewis, C.B. Granger, L. Køber, A.P. Maggioni, D.L. Mann, J.J.V. McMurray, J.-L. Rouleau, S.D. Solomon, P.G. Steg, O. Berwanger, M. Cikes, C.G. De Pasquale, C. East, A. Fernandez, K. Jering, U. Landmesser, R. Mehran, B. Merkely, F. Vaghaiwalla Mody, M.C. Petrie, I. Petrov, M. Schou, M. Senni, D. Sim, P. van der Meer, M. Lefkowitz, Y. Zhou, J. Gong, and E. Braunwald, for the PARADISE-MI Investigators and Committees*

ABSTRACT

BACKGROUND

In patients with symptomatic heart failure, sacubitril–valsartan has been found to reduce the risk of hospitalization and death from cardiovascular causes more effectively than an angiotensin-converting–enzyme inhibitor. Trials comparing the effects of these drugs in patients with acute myocardial infarction have been lacking.

METHODS

We randomly assigned patients with myocardial infarction complicated by a reduced left ventricular ejection fraction, pulmonary congestion, or both to receive either sacubitril–valsartan (97 mg of sacubitril and 103 mg of valsartan twice daily) or ramipril (5 mg twice daily) in addition to recommended therapy. The primary outcome was death from cardiovascular causes or incident heart failure (outpatient symptomatic heart failure or heart failure leading to hospitalization), whichever occurred first.

RESULTS

A total of 5661 patients underwent randomization; 2830 were assigned to receive sacubitril–valsartan and 2831 to receive ramipril. Over a median of 22 months, a primary-outcome event occurred in 338 patients (11.9%) in the sacubitril–valsartan group and in 373 patients (13.2%) in the ramipril group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; P=0.17). Death from cardiovascular causes or hospitalization for heart failure occurred in 308 patients (10.9%) in the sacubitril–valsartan group and in 335 patients (11.8%) in the ramipril group (hazard ratio, 0.91; 95% CI, 0.78 to 1.07); death from cardiovascular causes in 168 (5.9%) and 191 (6.7%), respectively (hazard ratio, 0.87; 95% CI, 0.71 to 1.08); and death from any cause in 213 (7.5%) and 242 (8.5%), respectively (hazard ratio, 0.88; 95% CI, 0.73 to 1.05). Treatment was discontinued because of an adverse event in 357 patients (12.6%) in the sacubitril–valsartan group and 379 patients (13.4%) in the ramipril group.

CONCLUSIONS

Sacubitril–valsartan was not associated with a significantly lower incidence of death from cardiovascular causes or incident heart failure than ramipril among patients with acute myocardial infarction. (Funded by Novartis; PARADISE-MI ClinicalTrials.gov number, NCT02924727.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Pfeffer can be contacted at mpfeffer@rics.bwh.harvard.edu or at the Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

*The PARADISE-MI investigators and committees are listed in the Supplementary Appendix, available at NEJM.org.

This article was updated on November 11, 2021, at NEJM.org.

N Engl J Med 2021;385:1845-55.
DOI: 10.1056/NEJMoa2104508

CME at NEJM.org

A Quick Take is available at NEJM.org

The use of a proven effective inhibitor of the renin–angiotensin system is an important guideline-based component of contemporary comprehensive management of acute myocardial infarction that is assessed in clinical performance measures.[1-4] The greatest absolute and relative benefits of these agents in reducing the risk of nonfatal and fatal cardiovascular events after myocardial infarction have been obtained with early initiation and sustained administration to patients at higher risk.[5] This evidence is based on randomized, controlled trials that have evaluated several individual angiotensin-converting–enzyme (ACE) inhibitors in comparison with placebo and on an active-controlled trial evaluating the angiotensin-receptor blocker (ARB) valsartan as compared with the ACE inhibitor captopril, as well as the combination of both agents as compared with captopril alone.[6]

The angiotensin receptor–neprilysin inhibitor sacubitril–valsartan simultaneously blocks the renin–angiotensin system and inhibits the breakdown of several vasoactive peptides.[7] In patients with symptomatic heart failure, sacubitril–valsartan reduced the risk of episodes of clinical deterioration of heart failure leading to hospitalizations or urgent ambulatory visits more effectively than a renin–angiotensin inhibitor alone and prolonged survival among those with a reduced left ventricular ejection fraction.[8] We tested whether treatment with sacubitril–valsartan would result in a lower incidence of death from cardiovascular causes or symptomatic heart failure than the ACE inhibitor ramipril, when initiated shortly after acute myocardial infarction in patients with no previous heart failure but with a reduced left ventricular ejection fraction, transient pulmonary congestion, or both conditions.

Methods

Trial Design and Oversight

We conducted the Prospective ARNI versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction (PARADISE-MI), an international, multicenter, randomized, double-blind, active-comparator trial designed to determine whether sacubitril–valsartan would be superior to ramipril in reducing the risk of death from cardiovascular causes or incident heart failure.[9] The executive committee designed and oversaw the conduct of the trial and data analysis, in collaboration with the sponsor, Novartis. The protocol was approved by the ethics committee at each trial center. An independent data and safety monitoring committee monitored trial conduct and patient safety and performed two interim analyses. Data were collected, managed, and analyzed by the sponsor and corroborated by an independent academic statistician. The first draft of the manuscript was prepared by the first and last authors with assistance from the academic statistician, who had complete access to the data. The sponsor could not require changes to the manuscript. The authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and statistical analysis plan, available with the full text of this article at NEJM.org. The trial committee members, independent statistician, and participating investigators are listed in the Supplementary Appendix, available at NEJM.org.

Trial Population

Adults without a history of heart failure were eligible if they had had a spontaneous myocardial infarction within 0.5 to 7 days before presentation in association with a reduced left ventricular ejection fraction (left ventricular ejection fraction ≤40%), pulmonary congestion (associated with the index myocardial infarction) that was judged on the basis of clinical or radiologic assessment to require intravenous treatment, or both conditions and had at least one of eight prespecified risk-augmenting factors (age ≥70 years, diabetes mellitus, previous myocardial infarction, an estimated glomerular filtration rate [eGFR] of <60 ml per minute per 1.73 m^2 of body-surface area at screening, atrial fibrillation, a left ventricular ejection fraction of <30% associated with the index myocardial infarction, Killip class III or IV, or ST-segment elevation myocardial infarction without reperfusion within 24 hours after presentation). Patients were excluded for clinical instability (defined as receipt of treatment with intravenous diuretics, vasodilators, vasopressors, or inotropes) during the 24 hours preceding randomization, an eGFR of less than 30 ml per minute per 1.73 m^2, a serum potassium level greater than 5.2 mmol per liter, a history of

angioedema, or an inability to take an ACE inhibitor or ARB. Details of the inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix. All the patients provided written informed consent before enrollment.

TRIAL PROCEDURES

Eligible patients were randomly assigned in a 1:1 ratio to receive treatment, in a double-blind manner, with either sacubitril–valsartan or ramipril; randomization was performed with the use of interactive-response technology, with stratification according to geographic region and type of myocardial infarction (ST-segment or non–ST-segment elevation).[9] Treatment with ACE inhibitors and ARBs was discontinued at randomization.

To minimize the risk of angioedema for patients who had received an ACE inhibitor within 36 hours before randomization, if the patients were assigned to receive sacubitril–valsartan, their first two doses of trial medication consisted of valsartan alone, given in a manner that maintained blinding. Clinical evaluations were scheduled for weeks 1, 2, and 4; months 2 and 4; and every 4 months thereafter. Three doses of each drug were available to the investigators (1.25 mg, 2.5 mg, or 5 mg of ramipril administered twice daily; or 24 mg of sacubitril plus 26 mg of valsartan, 49 mg of sacubitril plus 51 mg of valsartan, or 97 mg of sacubitril plus 103 mg of valsartan administered twice daily), with the highest dose of each drug as the target. At treatment initiation, one of the two lower doses could be used, and the dose could be adjusted at the discretion of the investigator.

TRIAL OUTCOMES

The composite primary outcome was death from cardiovascular causes or incident heart failure, whichever occurred first. Incident heart failure included hospitalization for heart failure and outpatient episodes of symptomatic heart failure treated with intravenous or sustained oral diuretic therapy. Secondary outcomes that were included in a hierarchical testing strategy were a composite of death from cardiovascular causes or hospitalization for heart failure; a composite of hospitalization for heart failure or an outpatient episode of symptomatic heart failure; a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; and the total number of (first or recurrent) nonfatal cardiovascular events (hospitalizations for heart failure, myocardial infarction, or stroke). Additional secondary outcomes included the number of deaths from cardiovascular causes and the total number of deaths. All prespecified outcomes were adjudicated by a clinical outcome committee, the members of which were unaware of the treatment-group assignment, with the use of definitions listed in Table S2.

Data on all reported adverse events and serious adverse events were compiled for safety assessments. Hypotension, hyperkalemia, renal dysfunction, cough, and angioedema were prespecified adverse events of interest, with reports of angioedema adjudicated by a separate committee (Table S3).

STATISTICAL ANALYSIS

Our trial was designed to be event-driven. We determined that 708 primary-outcome events would provide the trial with 80% power to detect a hazard ratio of 0.81 for the primary composite outcome in a time-to-event analysis, with the use of a two-sided alpha level of 0.05. We estimated that 592 deaths from cardiovascular causes or hospitalizations for heart failure would provide 77% power to detect a hazard ratio of 0.80 for this secondary outcome. We estimated that following 5650 patients for a mean duration of 19 months would provide the target number of primary events. An initial sample-size calculation (described in the Supplemental Methods section in the Supplementary Appendix) called for enrollment of 4650 patients, but the number was revised on the basis of a prespecified blinded assessment of cumulative incidence that was performed when approximately half the patients had undergone randomization and had reached the 3-month time point.

The treatment groups were compared on an intention-to-treat basis with the use of a Cox proportional hazards regression model, stratified according to type of myocardial infarction, with treatment, percutaneous coronary intervention at baseline, and geographic region included as factors in the model.[9] The assumption of proportional hazards was assessed with Schoenfeld residuals. Cumulative-incidence curves were generated according to the method of Kaplan and Meier. The timing and occurrence of recurrent

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Sacubitril–Valsartan (N=2830)	Ramipril (N=2831)
Age — yr	64.0±11.6	63.5±11.4
Female sex — no. (%)	663 (23.4)	700 (24.7)
Race — no. (%)†		
Asian	475 (16.8)	478 (16.9)
Black	35 (1.2)	40 (1.4)
White	2125 (75.1)	2138 (75.5)
Other	195 (6.9)	175 (6.2)
Region — no. (%)‡		
Asia–Pacific and other	551 (19.5)	551 (19.5)
Central Europe	750 (26.5)	749 (26.5)
Latin America	339 (12.0)	340 (12.0)
North America	264 (9.3)	264 (9.3)
Western Europe	926 (32.7)	927 (32.7)
Heart rate — beats/min	75.6±11.8	75.7±11.7
Systolic blood pressure — mm Hg	120.8±13.4	121.0±13.2
Diastolic blood pressure — mm Hg	73.8±9.9	73.7±9.7
Body-mass index§	28.2±5.0	28.1±5.1
Left ventricular ejection fraction — %	36.4±9.3	36.6±9.6
Pulmonary congestion — no. (%)	1508 (53.3)	1548 (54.7)
One or more risk-augmenting factors — no. (%)¶	1490 (52.7)	1464 (51.7)
Medical history — no. (%)		
Previous heart failure	0	0
Previous myocardial infarction	463 (16.4)	457 (16.1)
Previous coronary-artery bypass grafting or percutaneous coronary intervention	471 (16.6)	463 (16.4)
Previous stroke	121 (4.3)	142 (5.0)
Previous or current hypertension	1845 (65.2)	1831 (64.7)
Previous or current diabetes	1221 (43.1)	1180 (41.7)
Previous or current atrial fibrillation or flutter	402 (14.2)	382 (13.5)
Current smoking	613 (21.7)	583 (20.6)
Serum creatinine level — mg/dl	1.1±0.3	1.1±0.3
eGFR — ml/min/1.73 m^2	71.7±21.7	71.9±23.1
Qualifying myocardial infarction — no. (%)		
Type of myocardial infarction — no. (%)		
STEMI	2153 (76.1)	2138 (75.5)
NSTEMI or other	677 (23.9)	693 (24.5)
Coronary reperfusion — no. (%)	2524 (89.2)	2513 (88.8)
STEMI without reperfusion within 24 hours — no. (%)	235 (8.3)	261 (9.2)
Thrombolytics	124 (4.4)	129 (4.6)
Percutaneous coronary intervention	2490 (88.0)	2490 (88.0)
Drug-eluting stent	2225 (78.6)	2233 (78.9)

Table 1. (Continued.)

Characteristic	Sacubitril–Valsartan (N=2830)	Ramipril (N=2831)
Location of myocardial infarction — no. (%)		
Anterior	1919 (67.8)	1934 (68.3)
Inferior	535 (18.9)	518 (18.3)
Other	376 (13.3)	379 (13.4)
Killip class ≥II — no. (%)	1595 (56.4)	1606 (56.7)
Time to randomization — days	4.3±1.8	4.3±1.7
Medical treatment at randomization — no. (%)		
Dual antiplatelet therapy	2608 (92.2)	2614 (92.3)
Beta-blocker	2414 (85.3)	2413 (85.2)
Mineralocorticoid-receptor antagonist	1155 (40.8)	1183 (41.8)
Diuretic	1271 (44.9)	1250 (44.2)
Statin	2674 (94.5)	2696 (95.2)
ACE inhibitor or ARB‖	2216 (78.3)	2220 (78.4)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert values for creatinine to micromoles per liter, multiply by 88.4. NSTEMI denotes non–ST-segment elevation myocardial infarction.
† Race was reported by the patients.
‡ Asia–Pacific and other included Australia, China, India, Israel, Korea, the Philippines, Singapore, South Africa, Taiwan, and Thailand; Central Europe included Bulgaria, Croatia, the Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, and Turkey; Latin America (including Central America) included Argentina, Brazil, Colombia, Mexico, and Peru; North America included Canada and the United States; and Western Europe included Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and the United Kingdom.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ The prespecified risk-augmenting factors were an age of 70 years or greater, diabetes mellitus, previous myocardial infarction, an estimated glomerular filtration rate (eGFR) of less than 60 ml per minute per 1.73 m^2 of body-surface area at screening, atrial fibrillation or a left ventricular ejection fraction lower than 30% associated with the index myocardial infarction, Killip class III or IV, or ST-segment elevation myocardial infarction (STEMI) without reperfusion within 24 hours.
‖ This category includes patients who used an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) within 7 days before randomization.

events were analyzed with the use of a negative binomial regression model with a Weibull baseline intensity function,[10] with inclusion of treatment, type of myocardial infarction, percutaneous coronary intervention at baseline, and geographic region included as factors in the model. Censoring rules are described in the Supplemental Methods section in the Supplementary Appendix.

The unanticipated coronavirus disease 2019 pandemic prompted a protocol amendment for an additional interim analysis, which was performed by the data and safety monitoring committee when approximately 80% of the anticipated primary-outcome events had occurred, with a two-sided alpha level of 0.01. To account for this analysis and the originally planned interim analysis, the significance level was set at 0.0484 for the final analysis of the primary outcome (see the Supplemental Methods section in the Supplementary Appendix).

To control the type I error for the secondary outcomes, a hierarchical test sequence was prespecified; significance testing was to be terminated with the first nonsignificant result. All other secondary outcomes (those after the first nonsignificant test in the hierarchy and those not included in the hierarchy) were considered to be exploratory.

All P values reported are two-sided. P values are not reported for the exploratory outcomes or for subgroup analyses because no adjustment for multiple testing was prespecified. The widths of the confidence intervals have also not been adjusted for multiple comparisons, so these intervals should not be used to infer definitive treatment effects for the secondary outcomes.

Table 2. Primary and Secondary Outcomes.

Outcome	Sacubitril–Valsartan (N=2830)	Ramipril (N=2831)	Hazard Ratio or Rate Ratio (95% CI)*	P Value
Primary composite outcome — no. (%)†	338 (11.9)	373 (13.2)	0.90 (0.78–1.04)	0.17
Components of primary outcome — no./total no. (%)‡				
Death from cardiovascular causes	137/338 (40.5)	136/373 (36.5)		
Hospitalization for heart failure	164/338 (48.5)	187/373 (50.1)		
Outpatient episode of symptomatic heart failure	37/338 (10.9)	50/373 (13.4)		
Secondary outcomes				
Death from cardiovascular causes or hospitalization for heart failure — no. (%)	308 (10.9)	335 (11.8)	0.91 (0.78–1.07)	
Hospitalization for heart failure or outpatient heart failure — no. (%)	201 (7.1)	237 (8.4)	0.84 (0.70–1.02)	
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke — no. (%)	315 (11.1)	349 (12.3)	0.90 (0.77–1.05)	
Deaths from cardiovascular causes and total hospitalizations for heart failure, myocardial infarction, or stroke — no.§	591	682	0.84 (0.70–1.00)¶	
Death from cardiovascular causes — no. (%)§‖	168 (5.9)	191 (6.7)	0.87 (0.71–1.08)	
Death from any cause — no. (%)	213 (7.5)	242 (8.5)	0.88 (0.73–1.05)	

* The widths of the confidence intervals have not been adjusted for multiple comparisons, and therefore these intervals should not be used to infer definitive treatment effects on the secondary outcomes.
† The primary outcome was a composite of death from cardiovascular causes or incident heart failure (hospitalization for heart failure or outpatient symptomatic heart failure), whichever occurred first. Numbers represent patients with each respective outcome.
‡ For the components of the primary outcome, percentages of primary-outcome events are shown.
§ The total number of hospitalizations for heart failure, myocardial infarction, or stroke, and the total number of deaths from cardiovascular causes was analyzed by means of negative binomial regression with Weibull baseline intensity function.
¶ This value is a rate ratio derived from a negative binomial regression with Weibull baseline intensity function.
‖ Death from cardiovascular causes was not prespecified as a separate outcome.

RESULTS

PATIENTS

Trial enrollment began on December 9, 2016, and was completed on March 16, 2020; all events that occurred through December 31, 2020, were included in the efficacy analysis. Of the 5954 patients who underwent screening, 285 were excluded (Table S4) and 5669 underwent randomization. After randomization but before administration of the trial drug, 8 patients were determined to not meet the trial inclusion criteria. Per protocol, these patients were prospectively excluded from all analyses.

The remaining 5661 patients underwent randomization in accordance with the protocol; 2830 were assigned to receive sacubitril–valsartan and 2831 to receive ramipril. The median follow-up duration was 22 months in each group. At the end of the trial, vital status was available for all except 13 patients — 4 (0.1%) in the sacubitril–valsartan group and 9 (0.3%) in the ramipril group. Additional details regarding enrollment and follow-up are provided in Figure S1, and information regarding incomplete follow-up is provided in the Supplemental Results section in the Supplementary Appendix.

As shown in Table 1, the baseline characteristics of the patients were well-balanced between the two treatment groups. The mean age of the patients was 63.7 years, and 24.1% were women. Patients underwent randomization a mean of 4.3 days after presenting with their qualifying myocardial infarction. Coronary reperfusion, predominantly percutaneous coronary intervention, had been attempted in 89.0% of the patients; the left ventricular ejection fraction was 40% or lower in 81.4% of the patients, 54.0% had pul-

monary congestion, and 35.5% had both baseline features. Dual antiplatelet therapy was prescribed in 92.2% of the patients, 94.9% were treated with a statin, and 41.3% were treated with a mineralocorticoid-receptor antagonist at baseline. Either an ACE inhibitor or an ARB was used in 78.4% of patients before being discontinued at randomization.

CLINICAL EFFICACY OUTCOMES

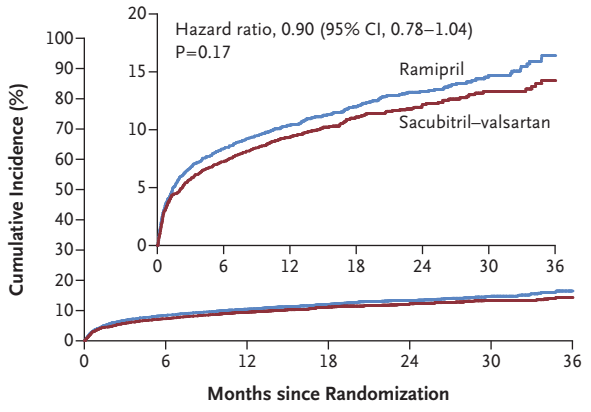
A total of 338 positively adjudicated primary-outcome events occurred among patients assigned to receive sacubitril–valsartan (137 deaths from cardiovascular causes, 164 first hospitalizations for heart failure, and 37 first outpatient episodes of symptomatic heart failure), and 373 occurred among those assigned to receive ramipril (136 deaths from cardiovascular causes, 187 first hospitalizations for heart failure, and 50 first outpatient episodes of symptomatic heart failure) (11.9% and 13.2% of the patients, respectively; hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; P=0.17) (Table 2 and Fig. 1). No violation of the proportional hazards assumption was detected (P=0.30). An assessment of competing risks is provided in the Supplemental Methods section in the Supplementary Appendix. The results for the primary outcome in the 23 prespecified subgroups are shown in Figure 2.

Because the result for the primary outcome was not significant, subsequent analyses were considered to be exploratory (Table 2). Death from cardiovascular causes or hospitalization for heart failure occurred in 308 patients (10.9%) in the sacubitril–valsartan group and in 335 patients (11.8%) in the ramipril group (hazard ratio, 0.91; 95% CI, 0.78 to 1.07). Death from cardiovascular causes occurred in 168 patients (5.9%) in the sacubitril–valsartan group and in 191 patients (6.7%) in the ramipril group (hazard ratio, 0.87; 95% CI, 0.71 to 1.08). Death from any cause occurred in 213 patients (7.5%) in the sacubitril–valsartan group and in 242 patients (8.5%) in the ramipril group (hazard ratio, 0.88; 95% CI, 0.73 to 1.05).

SAFETY AND SIDE EFFECTS

Treatment with the trial drug was permanently discontinued for any reason other than death in 501 patients (17.7%) in the sacubitril–valsartan group and in 517 patients (18.3%) in the ramipril group, and treatment was discontinued because of an adverse event in 357 patients (12.6%) and in 379 patients (13.4%), respectively. Patients in the sacubitril–valsartan group were more likely to have hypotension-related adverse events and were less likely to have cough-related adverse events than those in the ramipril group (Table 3).

At the final assessment, 1437 patients in the sacubitril–valsartan group (50.8% of all patients, 67.5% of those receiving the trial drug) and 1606 patients in the ramipril group (56.7% of all patients, 76.5% of those receiving the trial drug) were receiving the target dose. The percentages of patients with elevated serum creatinine, potassium, alanine aminotransferase, or aspartate aminotransferase levels were similar in the two groups (Table 3). Confirmed angioedema occurred in 14 patients in the sacubitril–valsartan group and in 17 patients in the ramipril group, with no patient having severe airway compromise (Table S3). Adverse events of special inter-



No. at Risk							
Ramipril	2831	2577	2318	1725	1091	570	278
Sacubitril–valsartan	2830	2614	2342	1732	1101	568	280

Figure 1. Cumulative Incidence of the Primary Composite Outcome.

Shown are the Kaplan–Meier event curves for the primary composite outcome of death from cardiovascular causes or incident heart failure (hospitalization for heart failure or an outpatient episode of symptomatic heart failure). The hazard ratio and 95% confidence interval were estimated with the use of a Cox proportional hazards regression model, stratified according to type of myocardial infarction, with treatment-group assignment, percutaneous coronary intervention at baseline, and geographic region as factors in the model. The graphs are truncated at 3 years, at which time less than 10% of the patients remained at risk. The inset shows the same data on an enlarged y axis.

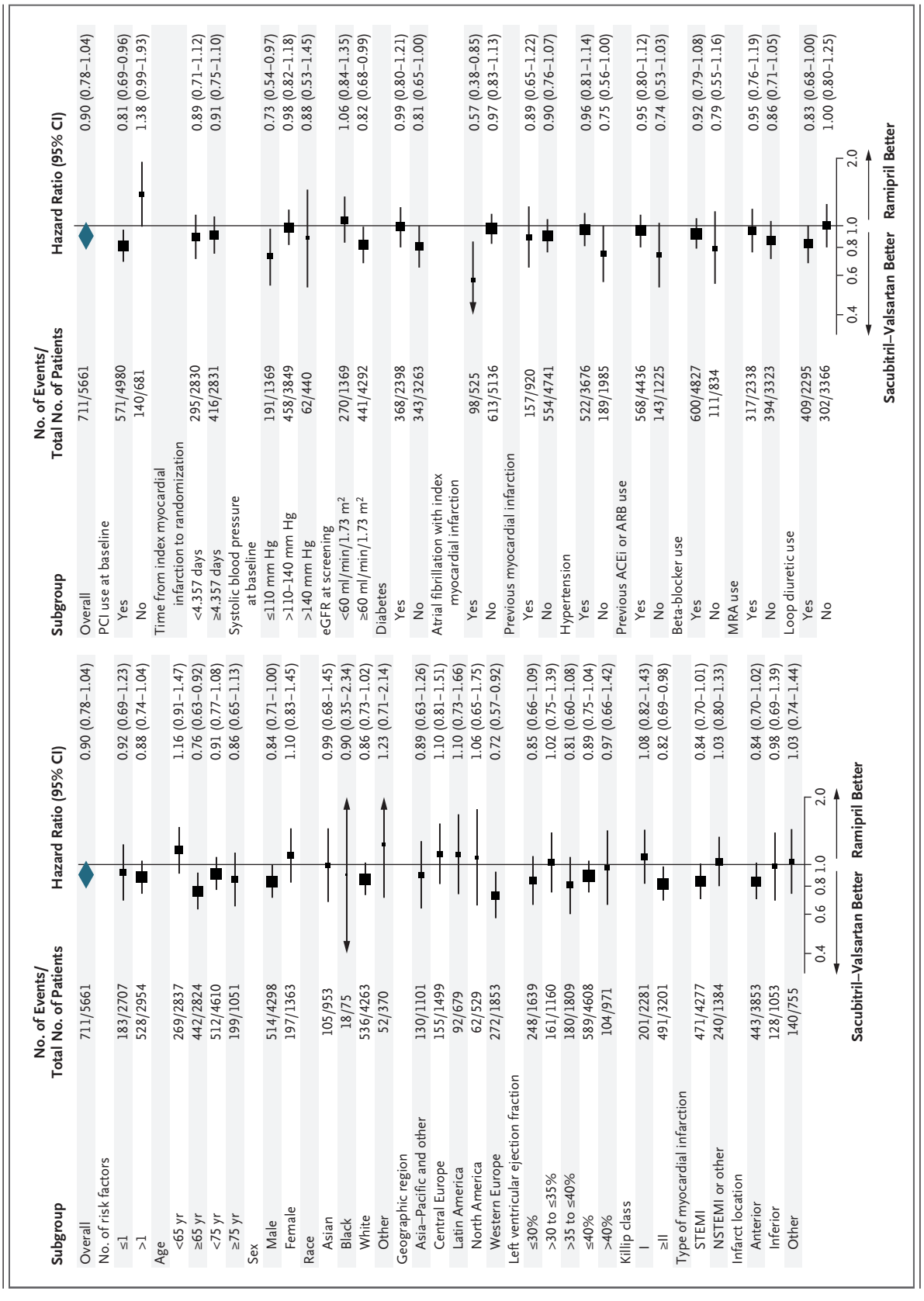


Figure 2 (facing page). Primary Composite Outcome Analyzed According to Prespecified Subgroup.

Shown are the results for the primary outcome of the trial in prespecified subgroups. The diamond denotes the overall effect, the sizes of the boxes are proportional to the number of patients in each subgroup, and arrows indicate that the upper or lower boundary of the 95% confidence interval exceeds the scale of the x axis. Race was reported by the patients. Asia–Pacific and other included Australia, China, India, Israel, Korea, the Philippines, Singapore, South Africa, Taiwan, and Thailand; Central Europe included Bulgaria, Croatia, the Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, and Turkey; Latin America (including Central America) included Argentina, Brazil, Colombia, Mexico, and Peru; North America included Canada and the United States; and Western Europe included Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and the United Kingdom. ACEi denotes angiotensin-converting–enzyme inhibitor, ARB angiotensin-receptor blocker, eGFR estimated glomerular filtration rate, MRA mineralocorticoid-receptor antagonist, NSTEMI non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.

est and serious adverse events are summarized in Tables S5 and S6, respectively.

DISCUSSION

In this randomized, double-blind, active-controlled trial, we compared sacubitril–valsartan with ramipril in patients who had acute myocardial infarction complicated by a reduced left ventricular ejection fraction, pulmonary congestion, or both, and no history of heart failure. Because both ramipril and valsartan have been shown to reduce the risk of death or the development of heart failure in this patient population, our trial assessed the potential incremental benefits, as well as risks, of adding the neprilysin inhibitor sacubitril to an effective renin–angiotensin system blocking regimen.[11] Treatment with sacubitril–valsartan did not result in a significantly lower risk of the primary composite outcome of death from cardiovascular causes or incident heart failure than did treatment with ramipril.

The fact that we initiated treatment with either an ACE inhibitor or an angiotensin receptor–neprilysin inhibitor in a blinded manner, within days after presentation with acute myocardial infarction without a run-in phase, provides new information on the relative safety and side-effect profile of these two therapies. The overall incidence of adverse effects attributed to the therapies was similar in the two groups, as was the safety profile obtained from extensive serum monitoring for renal function and liver-enzyme abnormalities. Although the percentage of patients who discontinued their assigned medication was similar in the two groups, we did observe the expected pattern of more discontinuations attributed to hypotension and fewer attributed to cough with sacubitril–valsartan than with ramipril.

In patients with established symptomatic heart failure with a reduced left ventricular ejection fraction, sacubitril–valsartan is more effective than an ACE inhibitor in reducing the risk of death and hospitalization for heart failure.[8] Our objective, which was not met, was to show superiority of sacubitril–valsartan over ramipril in preventing the development of incident heart failure in this post–myocardial infarction population. Several considerations are relevant when any major trial does not show a significant result with respect to the primary outcome, including the appropriateness of the trial population, the anticipated treatment effect, the primary outcome chosen, deficiencies in trial conduct, and the expected and actual statistical power.[12] Survivors of an acute myocardial infarction with a reduced left ventricular ejection fraction, transient pulmonary congestion, or both conditions were a relevant patient group because they remain at substantial risk for symptomatic chronic heart failure despite treatment advances, including prompt coronary reperfusion and treatment with statins. With the proven effectiveness of ACE inhibitors in this population, superiority to an active control therapy such as ramipril was required. We believe that the conduct of our trial was satisfactory, with adequate adherence and minimal loss of data. The trial also had sufficient power to detect the treatment effect size we had anticipated.

In this clinical trial, patients with acute myocardial infarction complicated by a reduced left ventricular ejection fraction, pulmonary congestion, or both were randomly assigned to receive either sacubitril–valsartan or ramipril. There was no significant benefit of sacubitril–

Table 3. Adverse Events during Treatment.*

Safety Outcome	Sacubitril–Valsartan (N=2830)	Ramipril (N=2831)	P Value
	number (percent)		
Treatment discontinuation because of adverse event	357 (12.6)	379 (13.4)	0.39
Serious adverse event	1146 (40.5)	1126 (39.8)	0.58
Adverse event	2352 (83.1)	2325 (82.1)	0.33
Adverse events of interest			
Hypotension	802 (28.3)	620 (21.9)	<0.001
Cough	255 (9.0)	371 (13.1)	<0.001
Angioedema	14 (0.5)	17 (0.6)	0.59
Hepatotoxic effect	132 (4.7)	167 (5.9)	0.04
Hyperkalemia	301 (10.6)	285 (10.1)	0.48
Cognitive impairment†	54 (1.9)	60 (2.1)	0.57
Hypersensitivity†	322 (11.4)	296 (10.5)	0.27
Cancer	85 (3.0)	71 (2.5)	0.25
Renal impairment†	329 (11.6)	326 (11.5)	0.90
Statin drug–drug interaction	106 (3.7)	129 (4.6)	0.13
Laboratory abnormalities			
Elevated serum creatinine level			
≥2.0 mg/dl	162 (5.7)	171 (6.0)	0.61
≥2.5 mg/dl	67 (2.4)	65 (2.3)	0.86
≥3.0 mg/dl	23 (0.8)	34 (1.2)	0.14
Elevated serum potassium level			
>5.5 mmol/liter	403 (14.2)	361 (12.8)	0.10
>6.0 mmol/liter	92 (3.3)	95 (3.4)	0.83
Elevated aspartate aminotransferase level			
>3× upper limit of reference range	23 (0.8)	27 (1.0)	0.57
>5× upper limit of reference range	8 (0.3)	13 (0.5)	0.27
Elevated alanine aminotransferase level			
>3× upper limit of reference range	32 (1.1)	38 (1.3)	0.47
>5× upper limit of reference range	11 (0.4)	12 (0.4)	0.84

* To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for potassium to milligrams per deciliter, divide by 0.2558.
† The broad standardized *Medical Dictionary for Regulatory Activities* queries (SMQs) are shown. Corresponding narrow SMQs are provided in Table S5.

valsartan with respect to the primary outcome of death from cardiovascular causes, first hospitalization for heart failure, or first outpatient episode of symptomatic heart failure.

Supported by Novartis.
Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.
A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Marc A. Pfeffer, M.D., Ph.D., Brian Claggett, Ph.D., Eldrin F. Lewis, M.D., M.P.H., Christopher B. Granger, M.D., Lars Køber, M.D., Aldo P. Maggioni, M.D., Douglas L. Mann, M.D., John J.V. McMurray, M.D., Jean-Lucien Rouleau, M.D., Scott D. Solomon, M.D., Philippe G. Steg, M.D., Otavio Berwanger, M.D., Ph.D., Maja Cikes, M.D., Ph.D., Carmine G. De Pasquale, B.M., B.S., Ph.D., Cara East, M.D., Alberto Fernandez, M.D., Karola Jering, M.D., Ulf Landmesser, M.D., Roxana Mehran, M.D., Béla Merkely, M.D., Ph.D., Freny Vaghaiwalla Mody, M.D., Mark C. Petrie, M.D., Ivo Petrov, M.D., Ph.D., Morten Schou, M.D., Ph.D., Michele Senni, M.D., David Sim, M.B., B.S., M.Med., Peter van der Meer, M.D., Ph.D., Martin Lefkowitz, M.D., Yinong Zhou, M.D., Jianjian Gong, Ph.D., and Eugene Braunwald, M.D.

The authors' affiliations are as follows: the Cardiovascular Division (M.A.P., B.C., S.D.S., K.J., E.B.) and the Thrombolysis in Myocardial Infarction Study Group, Cardiovascular Division (E.B.), Brigham and Women's Hospital and Harvard Medical School, Boston; the Division of Cardiovascular Medicine, Stanford University School of Medicine, Palo Alto (E.F.L.), and the Heart Failure and Preventive Cardiology Programs, Department of Veterans Affairs Greater Los Angeles, University of California, Los Angeles, Los Angeles (F.V.M.) — both in California; Duke University Medical Center, Durham, NC (C.B.G.); Rigshospitalet, Blegdamsvej, University of Copenhagen (L.K.), and the Department of Cardiology, Herlev-Gentofte University Hospital (M. Schou) — both in Copenhagen; National Association of Hospital Cardiologists Research Center, Florence (A.P.M.), and the Cardiovascular Department, Hospital Papa Giovanni XXIII, Bergamo (M. Senni) — both in Italy; Washington University School of Medicine, St. Louis (D.L.M.); British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M., M.C.P.); Montreal Heart Institute, University of Montreal, Montreal (J.-L.R.); Université de Paris, Assistance Publique–Hôpitaux de Paris, French Alliance for Cardiovascular Trials and INSERM Unité 1148, Paris (P.G.S.); Academic Research Organization, Hospital Israelita Albert Einstein, São Paulo (O.B.); the Department of Cardiovascular Diseases, University Hospital Center Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia (M.C.); the Department of Cardiovascular Medicine, Flinders Medical Centre, Adelaide, SA, Australia (C.G.D.P.); Baylor Soltero CV Research Center, Baylor Scott and White Heart and Vascular Hospital, Dallas (C.E.); Cardiology Service, Sanatorio Modelo Quilmes, Quilmes, Argentina (A.F.); the Department of Cardiology, German Center for Cardiovascular Research Partner Site Berlin, Berlin Institute of Health, Charité–Universitätsmedizin Berlin, Berlin (U.L.); Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York (R.M.); the Heart and Vascular Center, Semmelweis University, Budapest, Hungary (B.M.); Acibadem City Clinic Cardiovascular Center, Sofia, Bulgaria (I.P.); National Heart Center Singapore, Singapore (D.S.); the Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (P.M.); and Novartis, East Hanover, NJ (M.L., Y.Z., J.G.).

REFERENCES

1. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:485-510.
2. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:2354-94.
3. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77.
4. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021;42:1289-367.
5. Flather MD, Yusuf S, Køber L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet 2000;355:1575-81.
6. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893-906.
7. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. JACC Heart Fail 2014;2:663-70.
8. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
9. Jering KS, Claggett B, Pfeffer MA, et al. Prospective ARNI vs. ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction (PARADISE-MI): design and baseline characteristics. Eur J Heart Fail 2021;23:1040-8.
10. Lawless JF. Regression methods for Poisson process data. J Am Stat Assoc 1987;82:808-15.
11. McMurray JJV. Neprilysin inhibition to treat heart failure: a tale of science, serendipity, and second chances. Eur J Heart Fail 2015;17:242-7.
12. Pocock SJ, Stone GW. The primary outcome fails — what next? N Engl J Med 2016;375:861-70.