

ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H.,
Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D.,
Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D.,
for the PIONEER-HF Investigators*

ABSTRACT

BACKGROUND

Acute decompensated heart failure accounts for more than 1 million hospitalizations in the United States annually. Whether the initiation of sacubitril–valsartan therapy is safe and effective among patients who are hospitalized for acute decompensated heart failure is unknown.

METHODS

We enrolled patients with heart failure with reduced ejection fraction who were hospitalized for acute decompensated heart failure at 129 sites in the United States. After hemodynamic stabilization, patients were randomly assigned to receive sacubitril–valsartan (target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily) or enalapril (target dose, 10 mg twice daily). The primary efficacy outcome was the time-averaged proportional change in the N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration from baseline through weeks 4 and 8. Key safety outcomes were the rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema.

RESULTS

Of the 881 patients who underwent randomization, 440 were assigned to receive sacubitril–valsartan and 441 to receive enalapril. The time-averaged reduction in the NT-proBNP concentration was significantly greater in the sacubitril–valsartan group than in the enalapril group; the ratio of the geometric mean of values obtained at weeks 4 and 8 to the baseline value was 0.53 in the sacubitril–valsartan group as compared with 0.75 in the enalapril group (percent change, –46.7% vs. –25.3%; ratio of change with sacubitril–valsartan vs. enalapril, 0.71; 95% confidence interval [CI], 0.63 to 0.81; $P < 0.001$). The greater reduction in the NT-proBNP concentration with sacubitril–valsartan than with enalapril was evident as early as week 1 (ratio of change, 0.76; 95% CI, 0.69 to 0.85). The rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly between the two groups.

CONCLUSIONS

Among patients with heart failure with reduced ejection fraction who were hospitalized for acute decompensated heart failure, the initiation of sacubitril–valsartan therapy led to a greater reduction in the NT-proBNP concentration than enalapril therapy. Rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly between the two groups. (Funded by Novartis; PIONEER-HF ClinicalTrials.gov number, NCT02554890.)

From the Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT (E.J.V.); the Thrombolysis in Myocardial Infarction Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston (D.A.M., E.B.); Duke Clinical Research Institute, Duke University, Durham, NC (A.D.D.); Novartis Pharmaceuticals, East Hanover, NJ (C.I.D., K.M., R.R.); and the Division of Cardiology, Permanente Medical Group, San Francisco, and the Division of Research, Kaiser Permanente Northern California, Oakland — both in California (A.P.A.). Address reprint requests to Dr. Velazquez at Yale University School of Medicine, P.O. Box 208017, New Haven, CT 06520-8017, or at eric.velazquez@yale.edu.

*A complete list of the PIONEER-HF investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 11, 2018, at NEJM.org.

DOI: 10.1056/NEJMoa1812851

Copyright © 2018 Massachusetts Medical Society.

ACUTE DECOMPENSATED HEART FAILURE accounts for more than 1 million hospitalizations in the United States annually.¹ Rates of short-term unplanned rehospitalization and death associated with acute decompensated heart failure are high (21% and 12%, respectively).² Despite multiple trials of promising therapies, the standard of care, which consists of decongestion with intravenous diuretics and hemodynamic support with vasodilators and inotropes, has remained largely unchanged during the past 45 years.³⁻⁵

Sacubitril–valsartan is an angiotensin receptor–neprilysin inhibitor that is indicated for the treatment of patients with symptomatic heart failure with reduced ejection fraction. In the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial,^{6,7} the use of sacubitril–valsartan resulted in a lower risk of death from cardiovascular causes or hospitalization for heart failure than the use of enalapril in this population. Patients who were eligible for inclusion in the PARADIGM-HF trial were ambulatory outpatients who had received an angiotensin-converting–enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB), at stable doses equivalent to a dose of enalapril of 10 mg daily, for a minimum of 4 weeks. In addition, the trial had sequential run-in periods during which all patients received high-dose enalapril and sacubitril–valsartan before they underwent randomization. Patients with acute decompensated heart failure, which was defined by the presence of signs and symptoms that may lead to the use of intravenous therapy, were excluded from the trial.

Whether the initiation of sacubitril–valsartan therapy is effective and safe among patients who are hospitalized for acute decompensated heart failure is unknown.⁸ Therefore, we designed the PIONEER-HF (Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) trial to assess the efficacy and safety of the initiation of sacubitril–valsartan therapy, as compared with enalapril therapy, after hemodynamic stabilization among patients who were hospitalized for acute decompensated heart failure.

METHODS

TRIAL DESIGN

Details of the trial design have been published previously.⁹ We conducted a multicenter, randomized, double-blind, active-controlled trial of the in-hospital initiation of sacubitril–valsartan therapy, as compared with enalapril therapy, among patients who had been admitted for acute decompensated heart failure with reduced ejection fraction. The trial protocol (available with the full text of this article at NEJM.org) was approved by ethics committees at participating centers. Novartis was the sole sponsor and conducted the trial in collaboration with the Duke Clinical Research Institute (DCRI) and the Thrombolysis in Myocardial Infarction (TIMI) Study Group.

The academic leadership committee (see the Supplementary Appendix, available at NEJM.org) designed the protocol, identified the participating centers, and oversaw implementation of the protocol in conjunction with the trial sponsor. United BioSource Corporation (UBC), a contract research organization, was involved in trial operations. All statistical analyses were completed by UBC and were verified independently by the DCRI and the sponsor. An independent data and safety monitoring board (see the Supplementary Appendix) monitored safety data during the trial. The first draft of the manuscript was written by the first author, and all the authors critically reviewed and revised the manuscript at every stage before acceptance. All the authors had full access to the data and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

TRIAL PATIENTS

Patients 18 years of age or older were eligible for inclusion in the trial if they had a left ventricular ejection fraction of 40% or less and an N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration of 1600 pg per milliliter or more or a B-type natriuretic peptide (BNP) concentration of 400 pg per milliliter or more and had received a primary diagnosis of acute decompensated heart failure, including signs and symptoms of fluid overload. Patients were enrolled no less than 24 hours and up to 10 days after initial presentation to the hospital, while they were still hospitalized.

Before randomization, patients were required to be hemodynamically stable, which was defined by maintenance of a systolic blood pressure of at least 100 mm Hg for the preceding 6 hours, with no increase in the dose of intravenous diuretics and no use of intravenous vasodilators during the preceding 6 hours and no use of intravenous inotropes during the preceding 24 hours. A complete list of the inclusion and exclusion criteria is provided in Table S1 in the Supplementary Appendix. All the patients provided written informed consent.

TRIAL PROCEDURES

Patients were randomly assigned to receive either sacubitril-valsartan or enalapril. Randomization was performed with the use of an interactive Web-based response system. The initial dose of sacubitril-valsartan (either 24 mg of sacubitril with 26 mg of valsartan or 49 mg of sacubitril with 51 mg of valsartan as a fixed-dose combination) or enalapril (either 2.5 mg or 5 mg) was administered orally twice daily, with dosing selected on the basis of the systolic blood pressure at randomization, according to a prespecified algorithm (Fig. S1 in the Supplementary Appendix). To ensure blinding, with each dose patients also received a placebo that resembled the other trial drug. Patients in the enalapril group received the assigned trial drug and placebo starting with the first dose. Patients in the sacubitril-valsartan group received two doses of placebo alone (with tablets that resembled both trial drugs), to ensure a washout period of a minimum of 36 hours before the initiation of sacubitril-valsartan, and then received the assigned trial drug and placebo starting with the third dose. All the patients were monitored for a minimum of 6 hours after the third dose was administered before they were discharged from the hospital.

During the 8-week trial period, the dose of sacubitril-valsartan was adjusted with a target of 97 mg of sacubitril with 103 mg of valsartan twice daily, and the dose of enalapril was adjusted with a target of 10 mg twice daily. Dose adjustment was guided by an algorithm that was based on the systolic blood pressure and by the investigator's assessment of side effects (Fig. S1 in the Supplementary Appendix). Follow-up visits were to be scheduled for weeks 1 and 2 and every 2 weeks thereafter. Hematologic, chemical, and biomarker

analyses of blood and urine samples were performed at a central laboratory. The last dose of the assigned trial drug was administered on the morning of the week 8 visit.

TRIAL OUTCOMES

The primary efficacy outcome was the time-averaged proportional change in the NT-proBNP concentration from baseline through weeks 4 and 8. Key safety outcomes were the incidences of worsening renal function (an increase in the serum creatinine concentration of ≥ 0.5 mg per deciliter [≥ 44 μmol per liter] and a decrease in the estimated glomerular filtration rate of $\geq 25\%$), hyperkalemia (a serum potassium concentration of ≥ 5.5 mmol per liter), symptomatic hypotension, and angioedema. Any angioedema-like event that was reported by a site investigator was reviewed by an angioedema adjudication committee whose members were unaware of the treatment assignments (see the Supplementary Appendix). Secondary biomarker outcomes included time-averaged proportional changes in the high-sensitivity troponin T concentration, BNP concentration, and ratio of BNP to NT-proBNP. We also conducted analyses of exploratory clinical outcomes, including the incidence of a composite of death, rehospitalization for heart failure, implantation of a left ventricular assist device, inclusion on the list of patients eligible for heart transplantation, an unplanned visit for acute heart failure that led to the use of intravenous diuretics, an increase in the dose of diuretics of more than 50%, or the use of an additional drug for heart failure.

STATISTICAL ANALYSIS

We calculated that a sample of 882 patients would provide the trial with 85% power to detect an 18 percentage-point greater time-averaged proportional reduction in the NT-proBNP concentration, from the baseline value to the geometric mean of values obtained at weeks 4 and 8, in the sacubitril-valsartan group than in the enalapril group, at a two-sided significance level of 0.05. This calculation was based on the assumption of a ratio of the NT-proBNP concentration at week 8 as compared with baseline of 0.95 in the enalapril group, a geometric standard deviation of the log normal distribution of 0.85, and a rate at which samples are missing or cannot be evaluated of 25%.

All efficacy analyses were performed according to the intention-to-treat principle, with the use of all available data through the 8-week trial period. The analyses were based on the likelihood method, with the assumption that data were missing at random. The analyses included all enrolled patients except those who underwent randomization inappropriately.

The primary analysis of the proportional change in the NT-proBNP concentration from baseline on a logarithmic scale was performed with the use of an analysis of covariance model, with adjustment for the baseline value. A similar method was used to analyze the secondary biomarker outcomes. The incidences of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema were calculated along with relative risks and associated 95% confidence intervals. Cumulative clinical-event rates were calculated according to the Kaplan–Meier method; the differences in clinical outcomes between the two treatment groups were assessed with the log-rank test, and hazard ratios and associated 95% confidence intervals were calculated with a Cox proportional-hazards model. Confidence intervals for all outcomes except the primary efficacy outcome have not been adjusted for multiple comparisons, and therefore, inferences drawn from these intervals may not be reproducible. The consistency of treatment effect was examined across six prespecified subgroups and six additional exploratory subgroups. All analyses were performed with the use of SAS software, version 9.3 or higher (SAS Institute).

RESULTS

TRIAL POPULATION

From May 2016 to May 2018, a total of 887 patients were enrolled at 129 participating centers in the United States. A total of 6 patients (0.7%) underwent randomization inappropriately; these patients did not receive any doses of a trial drug and were prospectively omitted from all analyses. The efficacy analyses included 881 patients, of whom 440 were randomly assigned to receive sacubitril–valsartan and 441 to receive enalapril (Fig. 1). The trial database was locked on August 21, 2018.

Patients were enrolled in the trial a median of 68 hours (interquartile range, 48 to 98) after initial presentation to the hospital. At the time of

randomization, signs and symptoms of heart failure were highly prevalent; 61.7% of the patients had peripheral edema and 32.9% had rales on auscultation of the lungs. Baseline characteristics of the patients are shown in Table 1, and in Table S2 in the Supplementary Appendix. The mean (\pm SD) age of the patients was 61 \pm 14 years; 635 patients (72.1%) were male, and 316 (35.9%) were black. The index hospitalization was for the first diagnosis of heart failure in 303 patients (34.4%). Of the 576 patients (65.4%) who had previously received a diagnosis of heart failure, 343 (59.5%) had had at least one hospitalization for heart failure during the previous year. At the time of admission to the hospital, 459 patients (52.1%) were not receiving treatment with an ACE inhibitor or ARB.

At randomization, the median systolic blood pressure was 118 mm Hg (interquartile range, 110 to 132), and 23.4% of the patients had a systolic blood pressure of less than 110 mm Hg. At screening, the median NT-proBNP concentration was 4812 pg per milliliter (interquartile range, 3050 to 8745) and the median BNP concentration was 1063 pg per milliliter (interquartile range, 718 to 1743). During the index hospitalization and before randomization, 814 patients (93.0%) received intravenous furosemide, 97 (11.0%) received care in an intensive care unit, and 68 (7.7%) received an intravenous inotrope. The median duration of the index hospitalization was 5.20 days (interquartile range, 4.09 to 7.24).

TRIAL TREATMENTS AND FOLLOW-UP

At least one dose of a trial drug was administered in 875 patients (439 in the sacubitril–valsartan group and 436 in the enalapril group); these patients were included in the safety analyses (i.e., analyses of adverse events). With the exclusion of discontinuation owing to death, the trial drug was discontinued prematurely in 87 patients (19.6%) in the sacubitril–valsartan group and in 90 patients (20.3%) in the enalapril group (Table S3 in the Supplementary Appendix). A total of 4 patients (3 in the sacubitril–valsartan group and 1 in the enalapril group) were lost to follow-up, with no data on vital status at 8 weeks; data for these patients were censored at a median of 37 days (Fig. 1). By the week 8 visit, 243 patients (55.2%) in the sacubitril–valsartan group and 268 (60.8%) in the enalapril group were receiving the target dose of the assigned trial drug. Data for

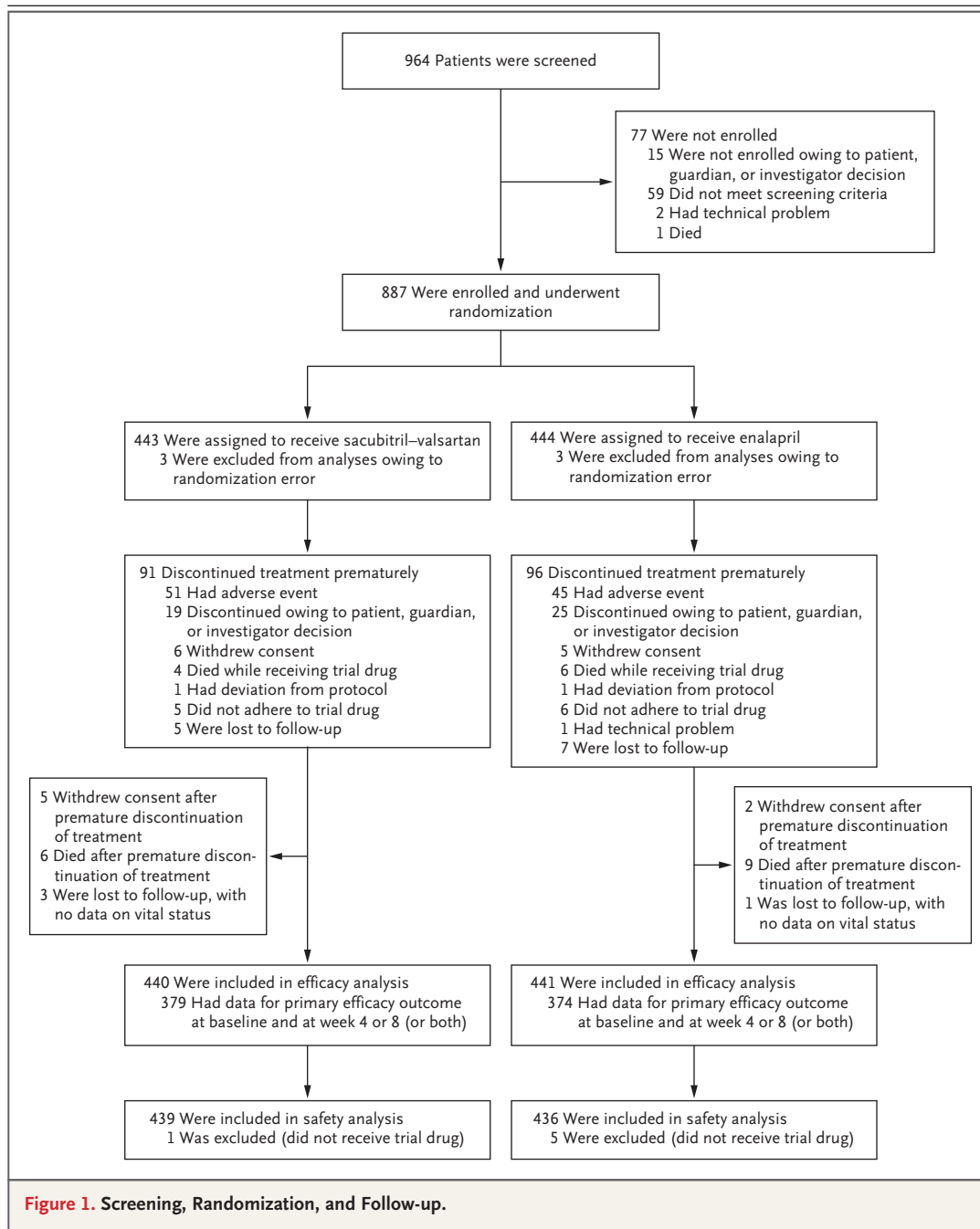


Figure 1. Screening, Randomization, and Follow-up.

the primary efficacy outcome were available through week 8 for 349 patients (79.3%) in the sacubitril-valsartan group and for 348 patients (78.9%) in the enalapril group.

PRIMARY EFFICACY OUTCOME

The NT-proBNP concentration decreased in both treatment groups. The time-averaged reduction in

the NT-proBNP concentration was significantly greater in the sacubitril-valsartan group than in the enalapril group; the ratio of the geometric mean of values obtained at weeks 4 and 8 to the baseline value was 0.53 in the sacubitril-valsartan group as compared with 0.75 in the enalapril group (percent change, -46.7% vs. -25.3%; ratio of change with sacubitril-valsartan vs. enalapril,

Table 1. Characteristics of the Patients at Baseline.*

Variable	Sacubitril–Valsartan (N = 440)	Enalapril (N = 441)
Age — yr		
Median	61	63
Interquartile range	51–71	54–72
Female sex — no. (%)	113 (25.7)	133 (30.2)
Race — no. (%)†		
Black	158 (35.9)	158 (35.8)
White	261 (59.3)	254 (57.6)
Body-mass index‡		
Median	30.5	30.0
Interquartile range	25.9–37.1	25.8–36.3
Previous heart failure — no. (%)	298 (67.7)	278 (63.0)
Previous use of medication — no. (%)		
ACE inhibitor or ARB	208 (47.3)	214 (48.5)
Beta-blocker	262 (59.5)	263 (59.6)
MRA	48 (10.9)	40 (9.1)
Loop diuretic	262 (59.5)	240 (54.4)
Hydralazine	30 (6.8)	33 (7.5)
Nitrate	43 (9.8)	40 (9.1)
Digoxin	41 (9.3)	35 (7.9)
NYHA class — no. (%)		
I	4 (0.9)	5 (1.1)
II	100 (22.7)	122 (27.7)
III	283 (64.3)	269 (61.0)
IV	39 (8.9)	36 (8.2)
Not assessed	14 (3.2)	9 (2.0)
Systolic blood pressure — mm Hg§		
Median	118	118
Interquartile range	110–133	109–132
Pulse — beats per min§		
Median	81	80
Interquartile range	72–92	72–91
Left ventricular ejection fraction — %¶		
Median	24	25
Interquartile range	18–30	20–30
NT-proBNP at screening — pg/ml¶		
Median	4821	4710
Interquartile range	3109–8767	2966–8280
NT-proBNP at randomization — pg/ml§		
Median	2883	2536
Interquartile range	1610–5403	1363–4917
Serum creatinine — mg/dl§		
Median	1.28	1.27
Interquartile range	1.07–1.51	1.05–1.50
Estimated GFR — ml/min/1.73 m ² §		
Median	58.4	58.9
Interquartile range	47.5–71.5	47.4–70.9
Serum potassium — mmol per liter§		
Median	4.20	4.25
Interquartile range	4.00–4.50	3.90–4.60

* There were no significant differences between the two groups with respect to baseline characteristics, with the exception of the N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration at randomization (P=0.04). ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, GFR glomerular filtration rate, and MRA mineralocorticoid-receptor antagonist.
† Information on race was reported by the patient.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The value was obtained at the central laboratory at randomization.
¶ The value was obtained at the site laboratory at screening.

0.71; 95% confidence interval [CI], 0.63 to 0.81; P<0.001) (Fig. 2, and Table S4 in the Supplementary Appendix). The greater reduction in the NT-proBNP concentration with sacubitril–valsartan than with enalapril was evident as early as week 1 (ratio of change, 0.76; 95% CI, 0.69 to 0.85). The results remained robust in a multiple imputation analysis that was performed to account for missing data (ratio of change, 0.73; 95% CI, 0.64 to 0.82).

SECONDARY EFFICACY AND SAFETY OUTCOMES

The rates of worsening renal function, hyperkalemia, and symptomatic hypotension did not differ significantly between the sacubitril–valsartan group and the enalapril group (Table 2). Figure S2 in the Supplementary Appendix shows the mean serum creatinine concentration, potassium concentration, and systolic blood pressure throughout the trial period in each group; Table S5 in the Supplementary Appendix shows the number of patients who had a systolic blood pressure of less than 100 mm Hg at each time point in each group. On blinded adjudication, there was one confirmed angioedema event in the sacubitril–valsartan group (in a white patient) and there were six in the enalapril group (all in black patients) (Table 2). Secondary biomarker outcomes and exploratory clinical outcomes are shown in Table 2. Table S6 in the Supplementary Appendix shows the most common adverse events (occurring in >5% of the patients in either treatment group). The rate of permanent discontinuation of the trial drug owing to any adverse event did not differ significantly between the two treatment groups (Table S3 in the Supplementary Appendix).

SUBGROUP ANALYSES

Results of analyses of subgroups that were defined according to demographic and clinical characteristics of interest reflected a consistently beneficial

effect of sacubitril-valsartan, as compared with enalapril, with regard to the primary efficacy outcome (Fig. 3). In addition, subgroup analyses showed no significant differences between the two treatments with regard to the key safety outcomes (Fig. S3 in the Supplementary Appendix).

DISCUSSION

The PIONEER-HF trial was performed to evaluate the use of a neprilysin inhibitor added to a renin-angiotensin system inhibitor, as compared with a renin-angiotensin system inhibitor alone, in the treatment of patients who were hospitalized for acute heart failure. The initiation of sacubitril-valsartan therapy after hemodynamic stabilization led to a greater reduction in the NT-proBNP concentration than enalapril therapy, a difference that was evident by the first week.

The beneficial effect of sacubitril-valsartan on the concentration of NT-proBNP, which is a biomarker of neurohormonal activation, hemodynamic stress, and subsequent cardiovascular events, was accompanied by a reduction in the concentration of high-sensitivity cardiac troponin T, which is a biomarker of myocardial injury associated with abnormalities of cardiac structure and function and with a worse prognosis among patients with heart failure. The rates of renal dysfunction, hyperkalemia, and symptomatic hypotension did not differ significantly between the sacubitril-valsartan group and the enalapril group. Furthermore, in an analysis of exploratory clinical outcomes, the in-hospital initiation of sacubitril-valsartan therapy was associated with a lower rate of rehospitalization for heart failure at 8 weeks than enalapril therapy.

The results of the PIONEER-HF trial extend the evidence base regarding the use of sacubitril-valsartan to populations for which there had been limited or no data, including patients who are hospitalized for acute decompensated heart failure, patients who have new heart failure, patients who have not been exposed to high doses of guideline-directed medications for heart failure, and patients who are not receiving conventional renin-angiotensin system inhibitors.⁸ In addition, 35.9% of the patients in our trial identified as black, and there is limited evidence from previous clinical studies regarding the use of sacubitril-valsartan among black patients. The favorable effect of sacubitril-valsartan, as compared with enalapril, was evident from the in-hospital

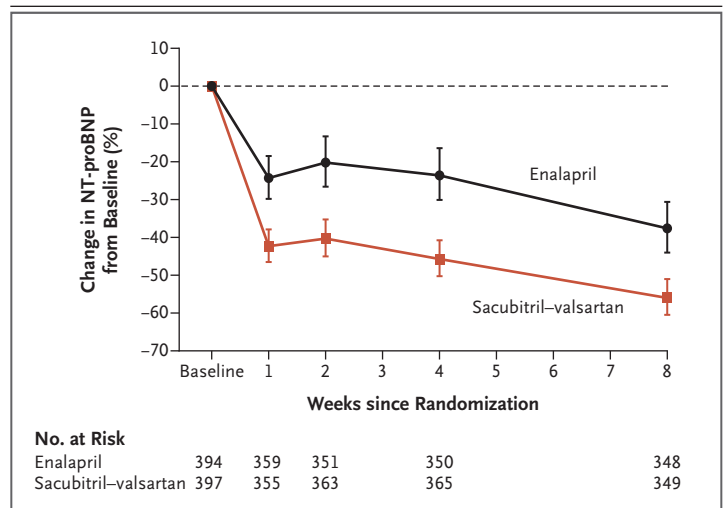


Figure 2. Change in the NT-proBNP Concentration.

The time-averaged reduction in the N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration was significantly greater in the sacubitril-valsartan group than in the enalapril group; the ratio of the geometric mean of values obtained at weeks 4 and 8 to the baseline value was 0.53 in the sacubitril-valsartan group as compared with 0.75 in the enalapril group (percent change, -46.7% vs. -25.3% ; ratio of change with sacubitril-valsartan vs. enalapril, 0.71; 95% CI, 0.63 to 0.81; $P < 0.001$).

initiation of treatment and continued to be present during the transition to home and throughout the subsequent “vulnerable period,” during which morbidity and mortality among patients with acute decompensated heart failure remain high.

The finding that the rates of renal dysfunction, hyperkalemia, and symptomatic hypotension did not differ significantly between the sacubitril-valsartan group and the enalapril group is reassuring, especially among patients with acute decompensated heart failure, who are at a high risk for hemodynamic instability. In addition, in the sacubitril-valsartan group, there was only one case of angioedema, with no cases among black patients. Results from previous trials of sacubitril-valsartan, most notably the PARADIGM-HF trial, were limited to ambulatory outpatients who had received established high doses of an ACE inhibitor or ARB, as well as the highest doses of enalapril and sacubitril-valsartan during sequential single-blind run-in periods before randomization. The PIONEER-HF trial made use of the lowest starting dose of sacubitril-valsartan (24 mg of sacubitril with 26 mg of valsartan), with which there was less experience.^{7,10}

The PIONEER-HF trial set specific requirements for the in-hospital initiation of sacubitril-valsartan therapy. Patients were required to have had a sys-

Table 2. Secondary Efficacy and Safety Outcomes.*

Outcome	Sacubitril–Valsartan (N = 440)	Enalapril (N = 441)	Sacubitril–Valsartan vs. Enalapril
Key safety outcomes — no. (%)			Relative risk (95% CI)
Worsening renal function†	60 (13.6)	65 (14.7)	0.93 (0.67 to 1.28)
Hyperkalemia	51 (11.6)	41 (9.3)	1.25 (0.84 to 1.84)
Symptomatic hypotension	66 (15.0)	56 (12.7)	1.18 (0.85 to 1.64)
Angioedema	1 (0.2)	6 (1.4)	0.17 (0.02 to 1.38)
Secondary biomarker outcomes — % (95% CI)‡			Ratio of change (95% CI)
Change in high-sensitivity troponin T concentration	−36.6 (−40.8 to −32.0)	−25.2 (−30.2 to −19.9)	0.85 (0.77 to 0.94)
Change in B-type natriuretic peptide concentration	−28.7 (−35.5 to −21.3)	−33.1 (−39.5 to −25.9)	1.07 (0.92 to 1.23)
Change in ratio of B-type natriuretic peptide to NT-proBNP	35.2 (28.8 to 42.0)	−8.3 (−3.6 to −12.7)	1.48 (1.38 to 1.58)
Exploratory clinical outcomes — no. (%)			Hazard ratio (95% CI)§
Composite of clinical events	249 (56.6)	264 (59.9)	0.93 (0.78 to 1.10)
Death	10 (2.3)	15 (3.4)	0.66 (0.30 to 1.48)
Rehospitalization for heart failure	35 (8.0)	61 (13.8)	0.56 (0.37 to 0.84)
Implantation of left ventricular assist device	1 (0.2)	1 (0.2)	0.99 (0.06 to 15.97)
Inclusion on list for heart transplantation	0	0	NA
Unplanned outpatient visit leading to use of intravenous diuretics	2 (0.5)	2 (0.5)	1.00 (0.14 to 7.07)
Use of additional drug for heart failure	78 (17.7)	84 (19.0)	0.92 (0.67 to 1.25)
Increase in dose of diuretics of >50%	218 (49.5)	222 (50.3)	0.98 (0.81 to 1.18)
Composite of serious clinical events¶	41 (9.3)	74 (16.8)	0.54 (0.37 to 0.79)

* NA denotes not available.

† Worsening renal function was defined by an increase in the serum creatinine concentration of 0.5 mg per deciliter or more ($\geq 44 \mu\text{mol}$ per liter) and a decrease in the estimated glomerular filtration rate of 25% or more.

‡ Shown are data on the time-averaged proportional change, from the baseline value to the geometric mean of values obtained at weeks 4 and 8.

§ Hazard ratios and associated 95% confidence intervals were calculated with a Cox proportional-hazards model. Confidence intervals have not been adjusted for multiple comparisons, and therefore, inferences drawn from these intervals may not be reproducible.

¶ The outcome of a composite of serious clinical events was added to the list of exploratory clinical outcomes in May 2018, before the database was locked and unblinding occurred. This end point included death, rehospitalization for heart failure, implantation of a left ventricular device, and inclusion on the list of patients eligible for heart transplantation.

tolic blood pressure of at least 100 mm Hg for the preceding 6 hours, with no increase in the dose of intravenous diuretics and no use of intravenous vasodilators during the preceding 6 hours and no use of intravenous inotropes during the preceding 24 hours. Sacubitril–valsartan therapy was initiated at a low dose among patients with lower systolic blood pressure, and the dose was adjusted according to a prespecified algorithm. A washout period of 36 hours was used to ensure that patients who had previously been taking an ACE inhibitor or ARB did not have any overlapping medication effects. Despite these precau-

tions, approximately 20% of the patients in each treatment group had discontinued treatment by 8 weeks, in most cases because of an adverse event. Taken together, these considerations suggest that the initiation of any neurohormonal agent in this population should be performed cautiously.

There are several limitations of our trial. The in-hospital initiation phase, which included the provision of placebo alone for the first two doses in the sacubitril–valsartan group and then mandatory observation for 6 hours after the third dose, may have prolonged the length of stay. These elements of the protocol were necessary to preserve

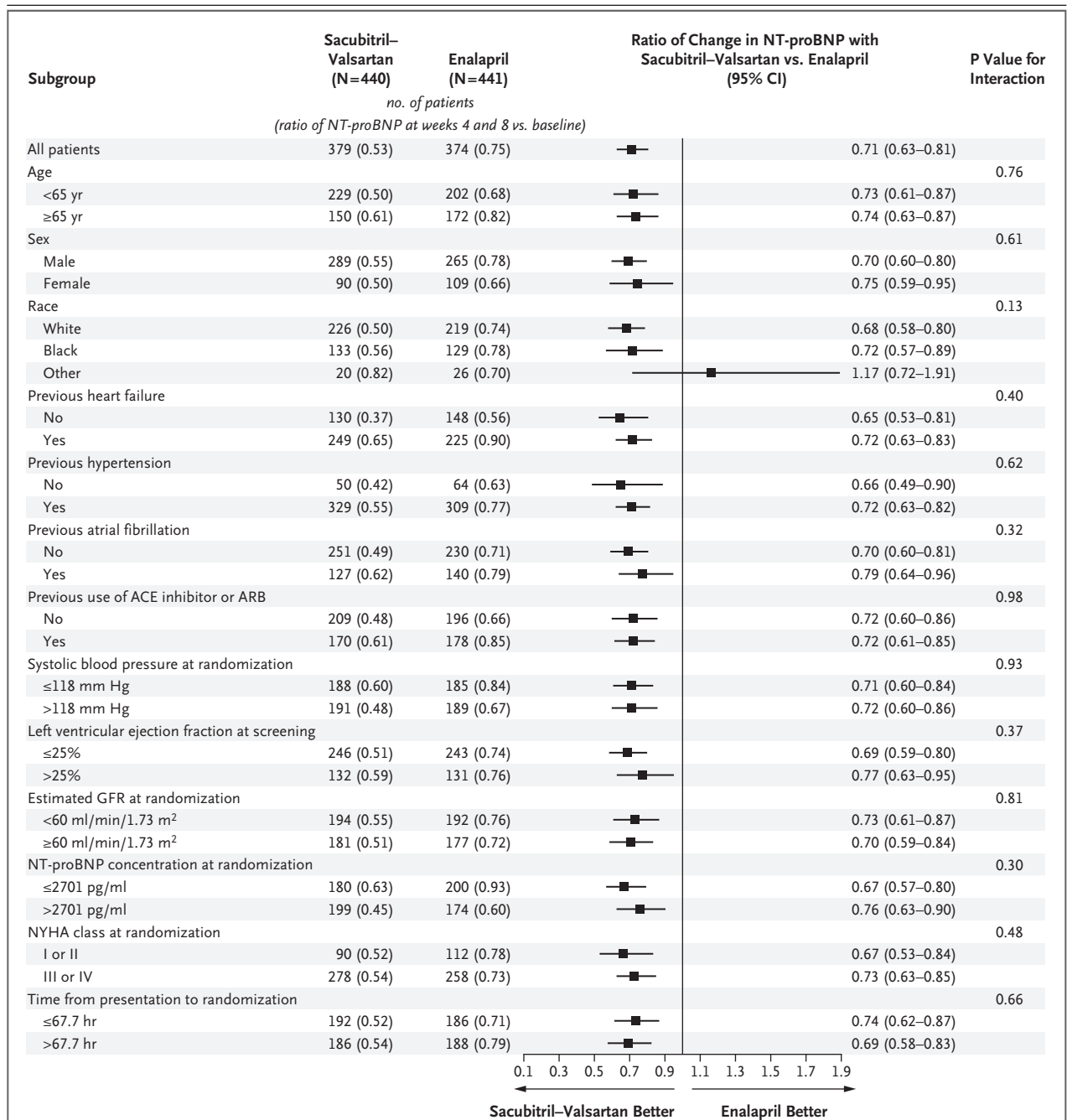


Figure 3. Subgroup Analyses of Change in the NT-proBNP Concentration.

Shown are data on the time-averaged proportional change in the NT-proBNP concentration, from the baseline value to the geometric mean of values obtained at weeks 4 and 8, with each treatment according to subgroup. Information on race was reported by the patient. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, GFR glomerular filtration rate, and NYHA New York Heart Association.

blinding, maintain protocol consistency, and ensure patient safety. In addition, approximately 0.5% of the patients were lost to follow-up and 15% had missing data on the NT-proBNP concentration, although the results for the primary efficacy outcome remained significant in an analysis with multiple imputation.

In conclusion, among patients who were hospitalized for acute decompensated heart failure, the initiation of sacubitril–valsartan therapy resulted in a significantly greater reduction in the NT-proBNP concentration than enalapril therapy. There were no significant differences between the sacubitril–val-

sartan group and the enalapril group with regard to the rates of renal insufficiency, hyperkalemia, symptomatic hypotension, and angioedema.

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

We thank Stacy Sabo, Eugene Patin, Lesley Schofield, and Amy Starinsky (Novartis), Layle Gurrieri (United BioSource Corporation), Mary Ann Sellers and Patricia Daraugh (Duke Clinical Research Institute), and Laura Grip (Thrombolysis in Myocardial Infarction Study Group) for assistance with trial operations; Elizabeth Cook (Duke Clinical Research Institute) for assistance with preparation of an earlier version of the manuscript; and the patients for their participation in the trial.

REFERENCES

1. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014; 63:1123-33.
2. Report to the Congress: Medicare and the health care delivery system — mandated report: the effects of the Hospital Readmissions Reduction Program. Washington, DC: Medicare Payment Advisory Commission, June 2018 (<http://www.medpac.gov/>).
3. Ramírez A, Abelman WH. Cardiac decompensation. *N Engl J Med* 1974;290: 499-501.
4. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017;136(6):e137-e161.
5. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37: 2129-200.
6. McMurray JJ, Packer M, Desai AS, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail* 2013; 15:1062-73.
7. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993-1004.
8. Ambrosy AP, Mentz RJ, Fiuzat M, et al. The role of angiotensin receptor-neprilysin inhibitors in cardiovascular disease-existing evidence, knowledge gaps, and future directions. *Eur J Heart Fail* 2018; 20:963-72.
9. Velazquez EJ, Morrow DA, DeVore AD, et al. Rationale and design of the comparison of sacubitril/valsartan versus Enalapril on Effect on nt-pro-bnp in patients stabilized from an acute Heart Failure episode (PIONEER-HF) trial. *Am Heart J* 2018;198:145-51.
10. Senni M, McMurray JJ, Wachter R, et al. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. *Eur J Heart Fail* 2016;18:1193-202.

Copyright © 2018 Massachusetts Medical Society.