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# Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

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## ABSTRACT

### BACKGROUND

The angiotensin receptor–neprilysin inhibitor sacubitril–valsartan led to a reduced risk of hospitalization for heart failure or death from cardiovascular causes among patients with heart failure and reduced ejection fraction. The effect of angiotensin receptor–neprilysin inhibition in patients with heart failure with preserved ejection fraction is unclear.

### METHODS

We randomly assigned 4822 patients with New York Heart Association (NYHA) class II to IV heart failure, ejection fraction of 45% or higher, elevated level of natriuretic peptides, and structural heart disease to receive sacubitril–valsartan (target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily) or valsartan (target dose, 160 mg twice daily). The primary outcome was a composite of total hospitalizations for heart failure and death from cardiovascular causes. Primary outcome components, secondary outcomes (including NYHA class change, worsening renal function, and change in Kansas City Cardiomyopathy Questionnaire [KCCQ] clinical summary score [scale, 0 to 100, with higher scores indicating fewer symptoms and physical limitations]), and safety were also assessed.

### RESULTS

There were 894 primary events in 526 patients in the sacubitril–valsartan group and 1009 primary events in 557 patients in the valsartan group (rate ratio, 0.87; 95% confidence interval [CI], 0.75 to 1.01; P=0.06). The incidence of death from cardiovascular causes was 8.5% in the sacubitril–valsartan group and 8.9% in the valsartan group (hazard ratio, 0.95; 95% CI, 0.79 to 1.16); there were 690 and 797 total hospitalizations for heart failure, respectively (rate ratio, 0.85; 95% CI, 0.72 to 1.00). NYHA class improved in 15.0% of the patients in the sacubitril–valsartan group and in 12.6% of those in the valsartan group (odds ratio, 1.45; 95% CI, 1.13 to 1.86); renal function worsened in 1.4% and 2.7%, respectively (hazard ratio, 0.50; 95% CI, 0.33 to 0.77). The mean change in the KCCQ clinical summary score at 8 months was 1.0 point (95% CI, 0.0 to 2.1) higher in the sacubitril–valsartan group. Patients in the sacubitril–valsartan group had a higher incidence of hypotension and angioedema and a lower incidence of hyperkalemia. Among 12 prespecified subgroups, there was suggestion of heterogeneity with possible benefit with sacubitril–valsartan in patients with lower ejection fraction and in women.

### CONCLUSIONS

Sacubitril–valsartan did not result in a significantly lower rate of total hospitalizations for heart failure and death from cardiovascular causes among patients with heart failure and an ejection fraction of 45% or higher. (Funded by Novartis; PARAGON-HF ClinicalTrials.gov number, NCT01920711.)

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*Lists of the PARAGON-HF investigators and committee members are provided in the Supplementary Appendix, available at NEJM.org.

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Heart failure with preserved ejection fraction is common and is associated with substantial morbidity and mortality.[1] Several physiological mechanisms have been postulated, including myocardial hypertrophy and fibrosis,[2] impaired diastolic compliance and relaxation,[3] subclinical systolic dysfunction,[4] and renal dysfunction leading to elevated intracardiac filling pressures, fluid retention, and exercise intolerance. No therapy has convincingly reduced morbidity or mortality.[5-8]

The angiotensin receptor–neprilysin inhibitor sacubitril–valsartan resulted in a lower rate of hospitalization for heart failure or death from cardiovascular causes than enalapril among patients with heart failure and reduced ejection fraction (≤40%).[9] In patients with heart failure and preserved left ventricular ejection fraction, sacubitril–valsartan resulted in a lower level of N-terminal pro–B-type natriuretic peptide (NT-proBNP), a larger reduction in left atrial size, and greater improvement in the New York Heart Association (NYHA) functional class than valsartan.[10] We tested whether sacubitril–valsartan would result in a lower rate of a composite outcome of total hospitalizations for heart failure and death from cardiovascular causes than valsartan.

## Methods

### Trial Design and Oversight

The Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial was a randomized, double-blind, active-comparator trial.[11] The steering committee designed and oversaw the conduct of the trial and data analysis, in collaboration with the sponsor, Novartis. Ethics committee approval was provided at each trial center. An independent data and safety monitoring committee monitored trial conduct and patient safety. 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 author, who had complete access to the data. All 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, available with the full text of this article at NEJM.org.

### Trial Patients

Eligibility requirements at screening included an age of 50 years or older, signs and symptoms of heart failure, NYHA class II to IV, an ejection fraction of 45% or higher within the previous 6 months, elevated level of natriuretic peptides (with different cutoffs depending on the occurrence of recent hospitalization for heart failure and the presence of atrial fibrillation or flutter), evidence of structural heart disease, and diuretic therapy. Detailed inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org. All the patients provided written informed consent.

### Trial Procedures

The trial consisted of a screening period, a single-blind run-in period, and a double-blind treatment period (see the Supplementary Appendix). During the run-in period, all patients first received valsartan at half the target dose, followed by sacubitril–valsartan at half the target dose. Participants who had no unacceptable side effects in both run-in phases and whose laboratory values remained within prespecified safety criteria were randomly assigned in a 1:1 ratio to receive double-blind treatment with either sacubitril–valsartan (target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily) or valsartan (target dose, 160 mg twice daily). Patients were evaluated at trial visits every 4 to 16 weeks. Renin–angiotensin system inhibitors other than mineralocorticoid-receptor antagonists were discontinued before the run-in period, but all other background medications were continued. The dose of the trial drugs could be adjusted down if the target dose led to unacceptable side effects.

### Trial Outcomes

The primary outcome was a composite of total (first and recurrent) hospitalizations for heart failure and death from cardiovascular causes. Secondary outcomes were the change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ)[12] (scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations); the change from baseline to 8 months in NYHA class; the first occurrence of a decline in renal function (decrease in the estimated glomerular filtration rate of ≥50%, development of end-stage renal disease, or death due to renal failure) in a time-to-event analysis; and death from



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any cause in a time-to-first-event analysis. All the outcomes except KCCQ score and NYHA class were blindly adjudicated according to prespecified criteria (Section 5 in the Supplementary Appendix). Hypotension, renal dysfunction, hyperkalemia, and angioedema were prespecified adverse events of interest; angioedema was adjudicated by a separate committee.

### STATISTICAL ANALYSIS

We determined that 1847 primary events would provide the trial with 95% power to detect an overall 22% lower rate in the sacubitril–valsartan group (corresponding to a 30% lower risk of hospitalization for heart failure and a 10% lower risk of death from cardiovascular causes) and at least 80% power to detect an overall 19% lower rate (corresponding to a 25% lower risk of hospitalization for heart failure and a 10% lower risk of death from cardiovascular causes). We estimated that the target number of events would be obtained by enrolling 4600 patients over a period of 29 months with a minimum follow-up of 26 months, on the basis of an anticipated time-to-first-primary-event rate of 9 events per 100 patient-years.

The primary efficacy outcome was evaluated with the use of the semiparametric proportional rates method of Lin et al.[13] and a joint gamma frailty model[14] stratified according to geographic region. Ghosh–Lin and Kaplan–Meier curves were used to show the cumulative recurrent and first events, respectively. There was one interim analysis, with an adjusted alpha level of 0.048 for the final analysis. Several prespecified sensitivity analyses of the primary outcome were also conducted, including other methods to analyze recurrent events, the addition of urgent heart-failure episodes that resulted in treatment but not hospitalization to the primary composite outcome, investigator-reported outcomes, and conventional time-to-first-event outcomes. We assessed the consistency of the treatment effect among 12 prespecified subgroups that were analyzed individually and then in a multivariable model.

Analyses of the primary and secondary outcomes were conducted according to the intention-to-treat principle. If the primary outcome reached significance, a hierarchical, sequentially rejective procedure was planned for the analysis of secondary efficacy outcomes, with the alpha level split equally between KCCQ score and NYHA class, followed by the renal composite outcome. Confidence intervals for the secondary and exploratory efficacy outcomes have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible. Additional information regarding the statistical analysis is provided in the Supplementary Appendix.

## RESULTS

### ENROLLMENT, RANDOMIZATION, AND FOLLOW-UP

From July 18, 2014, through December 16, 2016, we screened 10,359 patients at 848 centers in 43 countries (Fig. 1). A total of 4822 patients were randomly assigned to receive either sacubitril–valsartan or valsartan. A total of 26 patients were excluded from all efficacy analyses because they had been enrolled at a site that was closed for major violations of Good Clinical Practice, so 4796 patients were included in the efficacy analysis. At the end of the trial (April 30, 2019), fatal and nonfatal outcomes were known for all but 7 patients who had withdrawn consent and 2 patients who were lost to follow-up.

The characteristics of the patients at baseline were balanced between the two treatment groups, except for small differences in ischemic cause of heart failure and mineralocorticoid-receptor antagonist use (Table 1). The median duration of follow-up was 35 months (interquartile range, 30 to 41) in each group.

### OUTCOMES

There were 894 primary events (690 hospitalizations for heart failure and 204 deaths from cardiovascular causes) in 526 patients in the sacubitril–valsartan group and 1009 primary events (797 hospitalizations for heart failure and 212 deaths from cardiovascular causes) in 557 patients in the valsartan group (rate ratio, 0.87; 95% confidence interval [CI], 0.75 to 1.01; P=0.06) (Table 2 and Fig. 2). Because this difference did not meet the predetermined level of statistical significance, subsequent analyses were considered to be exploratory. Components of the primary outcome are shown in Table 2. The prespecified sensitivity analyses of the primary outcome are shown in Tables S2 and S3 in the Supplementary Appendix.

The primary outcome in the 12 prespecified subgroups is shown in Figure 3. In a multivariable model that accounted for all potential interactions and that used continuous measures when



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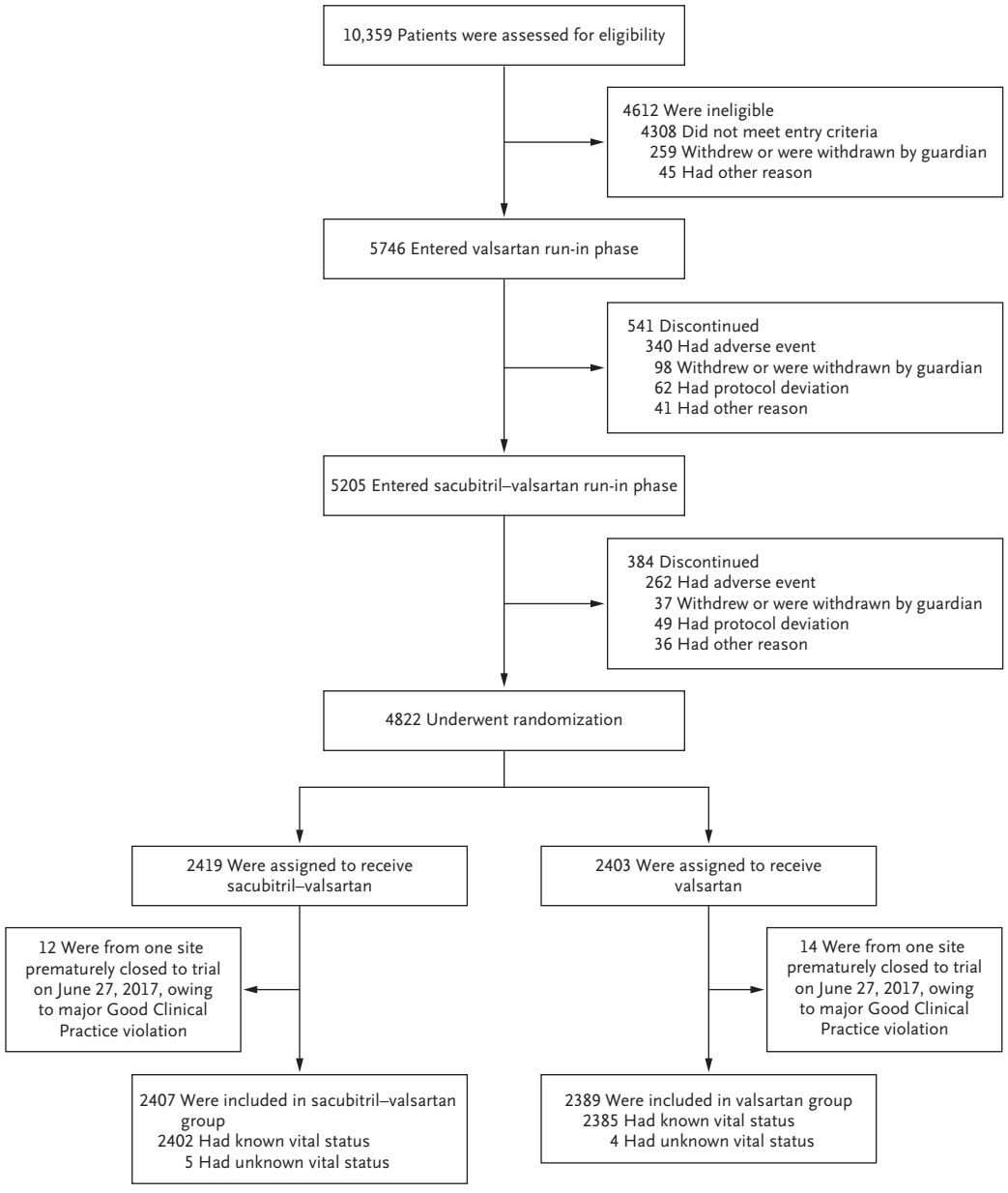


**Figure 1. Screening, Randomization, and Follow-up.**

The median duration of the valsartan run-in phase was 15 days (interquartile range, 12 to 22). One patient completed the valsartan run-in phase and underwent randomization without entering the sacubitril–valsartan run-in phase. The median duration of the sacubitril–valsartan run-in phase was 19 days (interquartile range, 15 to 23). One patient completed screening and entered the sacubitril–valsartan run-in phase without having entered the valsartan run-in phase.

appropriate, there was suggestion of heterogeneity of treatment effect with possible benefit in patients with lower ejection fraction and in women (Table S4 in the Supplementary Appendix).

Between baseline and month 8, there was a mean decrease in the KCCQ clinical summary score of 1.6 points in the sacubitril–valsartan group and 2.6 points in the valsartan group



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(between-group difference, 1.0 point; 95% CI, 0.0 to 2.1). A higher percentage of patients in the sacubitril–valsartan group than in the valsartan group had an improvement of 5 or more points in the KCCQ clinical summary score (33.0% vs. 29.6%; odds ratio, 1.30; 95% CI, 1.04 to 1.61). In the sacubitril–valsartan group, 15.0% of the patients had an improvement in NYHA class at 8 months, 76.3% had no change, and 8.7% had a worse NYHA class, as compared with 12.6%, 77.8%, and 9.6%, respectively, in the valsartan group (odds ratio for improvement, 1.45; 95% CI, 1.13 to 1.86). Worsening renal function occurred in 33 patients (1.4%) in the sacubitril–valsartan group and in 64 patients (2.7%) in the valsartan group (hazard ratio, 0.50; 95% CI, 0.33 to 0.77). Death from any cause occurred in 342 patients (14.2%) in the sacubitril–valsartan group and in 349 patients (14.6%) in the valsartan group (hazard ratio, 0.97; 95% CI, 0.84 to 1.13).

### SAFETY

After randomization, 610 patients (25.3%) in the sacubitril–valsartan group and 638 (26.7%) in the valsartan group discontinued the trial drug for reasons other than death, and 370 patients (15.4%) in the sacubitril–valsartan group and 387 (16.2%) in the valsartan group discontinued the trial drug because of an adverse event. At the final visit, among the patients who were continuing therapy, 82.0% in sacubitril–valsartan group were taking the target dose, as compared with 85.1% in the valsartan group.

Patients in the sacubitril–valsartan group were more likely to have hypotension but less likely to have increases in the creatinine and potassium levels than those in the valsartan group (Table 3). The mean systolic blood pressure at 8 months was 4.5 mm Hg (95% CI, 3.6 to 5.4) lower in the sacubitril–valsartan group than in the valsartan group, but this difference was not correlated with the potential treatment effect (Fig. S1 and Table S2 in the Supplementary Appendix). Confirmed angioedema after randomization occurred in 14 patients in the sacubitril–valsartan group and in 4 patients in the valsartan group; no patients had airway compromise. The most frequent serious adverse events and adverse events are summarized in Tables S5 and S6, respectively, in the Supplementary Appendix.

## DISCUSSION

In this trial involving patients with heart failure and preserved left ventricular ejection fraction, we compared treatment with sacubitril–valsartan with treatment with valsartan alone. The primary composite outcome of total hospitalizations for heart failure and death from cardiovascular causes did not differ significantly between the two groups. The findings from nine prespecified supportive and sensitivity analyses were consistent with those from the primary analysis.

There were fewer primary outcome events with sacubitril–valsartan than with valsartan, and an analysis of investigator-reported primary outcomes suggested a benefit of this therapy. There was a modest, although statistically nonsignificant, lower rate of hospitalizations for heart failure with sacubitril–valsartan than with valsartan and no significant difference in the risk of death from cardiovascular causes. Of four prespecified secondary outcomes, which were considered to be exploratory, the change in the NYHA class from baseline to month 8 and the occurrence of a decline in renal function favored sacubitril–valsartan over valsartan. Sacubitril–valsartan was associated with a higher incidence of hypotension and angioedema but a lower incidence of elevated serum creatinine or potassium levels than valsartan.

Patients with heart failure and preserved ejection fraction are phenotypically heterogeneous,[15] and our data raise the possibility of a differential treatment effect in the broad population studied. Of the 12 prespecified subgroups, 2 showed possible heterogeneity of treatment effect, with a suggestion of benefit in patients with an ejection fraction in the lower part (45 to 57%) of the range studied and in women, who represent a high proportion of patients with heart failure with preserved ejection fraction and who were well represented in this trial. The potential benefit of sacubitril–valsartan in patients with an ejection fraction at or below the median has biologic plausibility. Several post hoc analyses of previous trials have shown that other treatments that were efficacious in patients with heart failure and reduced ejection fraction may also benefit patients with left ventricular ejection fraction in the range of 40 to 55%, who often have subtle systolic dysfunction and are at higher risk for hospitalization for heart failure.[16-20] Our findings should also be considered in the context of the



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positive PARADIGM-HF trial,[9] which had nearly identical entry criteria apart from a lower ejection fraction. Other diseases, such as amyloid cardiomyopathy, may account for the reduced responsiveness with higher ejection fraction.[21] The present data suggest that patients with a mildly reduced ejection fraction may have a response to sacubitril–valsartan and possibly other therapies that improve outcomes in patients with heart failure and a more markedly reduced ejection fraction (≤40%).

We tested sacubitril–valsartan against an ac-

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Sacubitril–Valsartan (N=2407) | Valsartan (N=2389) |
|---|---|---|
| Age — yr | 72.7±8.3 | 72.8±8.5 |
| Female sex — no. (%) | 1241 (51.6) | 1238 (51.8) |
| Race — no. (%)† | | |
| White | 1963 (81.6) | 1944 (81.4) |
| Black | 52 (2.2) | 50 (2.1) |
| Asian | 297 (12.3) | 310 (13.0) |
| Other | 95 (4.0) | 85 (3.6) |
| Geographic region — no. (%) | | |
| North America | 288 (12.0) | 271 (11.3) |
| Latin America | 191 (7.9) | 179 (7.5) |
| Western Europe | 699 (29.0) | 691 (28.9) |
| Central Europe | 856 (35.6) | 859 (36.0) |
| Asia–Pacific or other | 373 (15.5) | 389 (16.3) |
| Systolic blood pressure — mm Hg‡ | 130.5±15.6 | 130.6±15.3 |
| Heart rate — beats/min‡ | 70.6±12.3 | 70.3±12.2 |
| Body-mass index§ | 30.2±4.9 | 30.3±5.1 |
| Serum creatinine — mg/dl‡ | 1.1±0.3 | 1.1±0.3 |
| Estimated GFR — ml/min/1.73 $m^2$ | 63±19 | 62±19 |
| Clinical features of heart failure | | |
| Ischemic cause — no. (%) | 899 (37.4) | 824 (34.5) |
| Left ventricular ejection fraction — % | 57.6±7.8 | 57.5±8.0 |
| Median NT-proBNP (interquartile range) — pg/ml | 904 (475–1596) | 915 (453–1625) |
| NYHA functional class at randomization — no. (%)‡ | | |
| I | 73 (3.0) | 64 (2.7) |
| II | 1866 (77.5) | 1840 (77.0) |
| III | 458 (19.0) | 474 (19.8) |
| IV | 8 (0.3) | 11 (0.5) |
| Missing data | 2 (0.1) | 0 |
| Medical history — no. (%) | | |
| Hypertension | 2304 (95.7) | 2280 (95.4) |
| Diabetes | 1046 (43.5) | 1016 (42.5) |
| Atrial fibrillation or flutter | 775 (32.2) | 777 (32.5) |
| Stroke | 266 (11.1) | 242 (10.1) |
| Hospitalization for heart failure | 1135 (47.2) | 1171 (49.0) |
| Myocardial infarction | 561 (23.3) | 522 (21.9) |



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**Table 1. (Continued.)**

| Characteristic | Sacubitril–Valsartan (N=2407) | Valsartan (N=2389) |
|---|---|---|
| Treatment — no. (%) | | |
| Diuretic agent at randomization | 2294 (95.3) | 2291 (95.9) |
| ACE inhibitor or ARB at screening | 2074 (86.2) | 2065 (86.4) |
| Mineralocorticoid-receptor antagonist at randomization | 592 (24.6) | 647 (27.1) |
| Beta-blocker at randomization | 1922 (79.9) | 1899 (79.5) |

* Plus–minus values are means ±SD. The characteristics of the patients at baseline were balanced between the two treatment groups, except for small differences in ischemic cause of heart failure and mineralocorticoid-receptor antagonist use. Data were missing for the following characteristics: systolic blood pressure (for 1 patient in the valsartan group), heart rate (for 1 in the valsartan group), body-mass index (for 1 in the sacubitril–valsartan group), creatinine level (for 1 in the valsartan group), ischemic cause of heart failure (for 1 patient in the sacubitril–valsartan group), N-terminal pro–B-type natriuretic peptide (NT-proBNP) level (for 19 patients in the sacubitril–valsartan group and 20 in the valsartan group), and atrial fibrillation or flutter status (for 6 and 10, respectively). All other baseline data are complete unless otherwise noted. Percentages may not total 100 because of rounding. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, GFR glomerular filtration rate, and NYHA New York Heart Association.
† Race was reported by the patient.
‡ This characteristic was measured at the randomization visit instead of at the screening visit.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

**Table 2. Primary and Secondary Outcomes.***

| Outcome | Sacubitril–Valsartan (N=2407) | Valsartan (N=2389) | Ratio or Difference (95% CI) |
|---|---|---|---|
| **Primary composite outcome and components** | | | |
| Total hospitalizations for heart failure and death from cardiovascular causes† | | | RR, 0.87 (0.75–1.01) |
| Total no. of events | 894 | 1009 | |
| Rate per 100 patient-yr | 12.8 | 14.6 | |
| Total no. of hospitalizations for heart failure | 690 | 797 | RR, 0.85 (0.72–1.00) |
| Death from cardiovascular causes — no. (%) | 204 (8.5) | 212 (8.9) | HR, 0.95 (0.79–1.16) |
| **Secondary outcomes** | | | |
| Change in NYHA class from baseline to 8 mo — no./total no. (%) | | | OR, 1.45 (1.13–1.86) |
| Improved | 347/2316 (15.0) | 289/2302 (12.6) | |
| Unchanged | 1767/2316 (76.3) | 1792/2302 (77.8) | |
| Worsened | 202/2316 (8.7) | 221/2302 (9.6) | |
| Change in KCCQ clinical summary score at 8 mo‡ | –1.6±0.4 | –2.6±0.4 | Difference, 1.0 (0.0–2.1) |
| Renal composite outcome — no. (%)§ | 33 (1.4) | 64 (2.7) | HR, 0.50 (0.33–0.77) |
| Death from any cause — no. (%) | 342 (14.2) | 349 (14.6) | HR, 0.97 (0.84–1.13) |

* Plus–minus values are means ±SD. Confidence intervals for secondary and exploratory efficacy outcomes have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible. HR denotes hazard ratio, OR odds ratio, and RR rate ratio.
† Total hospitalizations for heart failure included first and recurrent events. The primary analysis was based on the model of Lin et al.,[13] and the composite outcome was adjudicated.
‡ Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations.
§ The renal composite outcome was defined as death from renal failure, end-stage renal disease, or a decrease in the estimated glomerular filtration rate of 50% or more from baseline.



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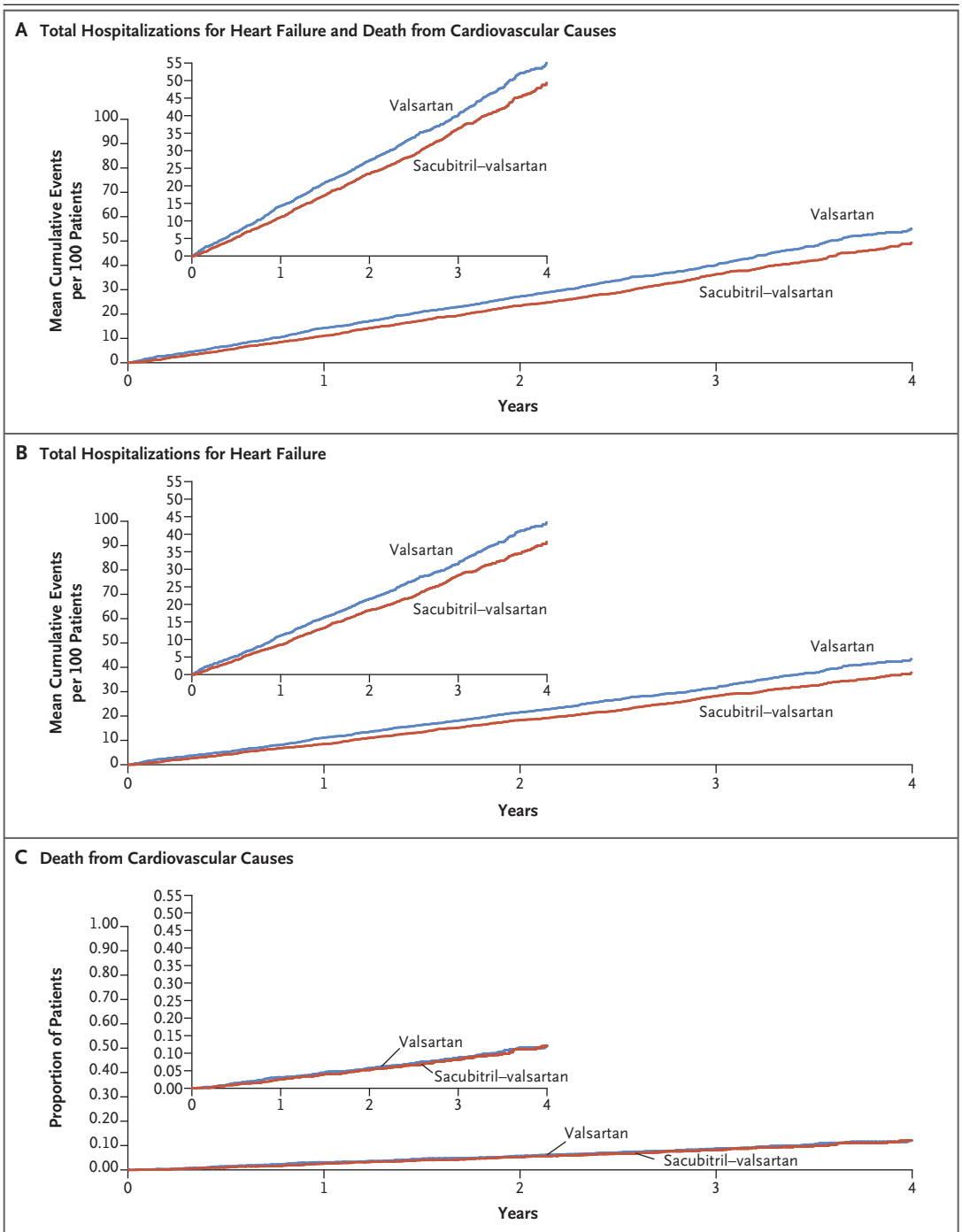


**Figure 2. Time-to-Event Curves for Primary Composite Outcome and Its Components.**

Panel A shows Ghosh–Lin curves for the primary composite outcome of total hospitalizations for heart failure and death from cardiovascular causes, Panel B Ghosh–Lin curves for total hospitalizations for heart failure, and Panel C Kaplan–Meier curves for death from cardiovascular causes. Insets show the same data on an enlarged y axis.



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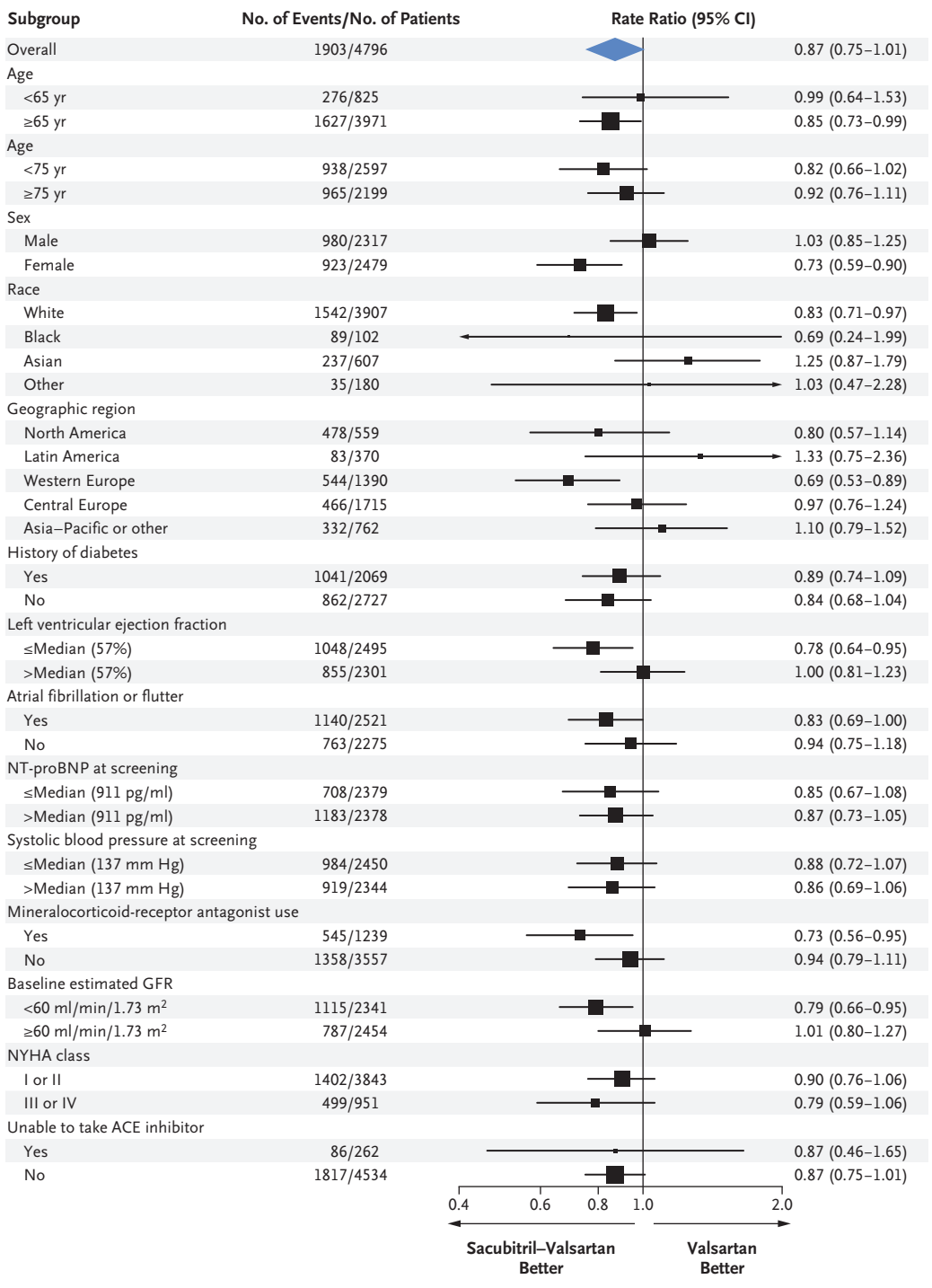


**Figure 3. Primary Outcome in Prespecified Subgroups.**

The primary outcome was a composite of total hospitalizations for heart failure and death from cardiovascular causes. Race was reported by the patient. New York Heart Association (NYHA) class may have changed between screening and randomization. Additional information is provided in Table S4 in the Supplementary Appendix. The diamond indicates the overall effect, the size of the boxes is proportional to the number of patients in the subgroup, and arrows indicate that the upper or lower boundary of the confidence interval is off the scale. ACE denotes angiotensin-converting enzyme, GFR glomerular filtration rate, and NT-proBNP N-terminal pro–B-type natriuretic peptide.



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**Table 3. Adverse Events during Randomized Treatment.**

| Event | Sacubitril–Valsartan (N=2407) | Valsartan (N=2389) | P Value |
|---|---|---|---|
| Hypotension with systolic blood pressure <100 mm Hg — no. (%) | 380 (15.8) | 257 (10.8) | <0.001 |
| Elevated serum creatinine — no. (%) | | | |
| ≥2.0 mg/dl | 261 (10.8) | 328 (13.7) | 0.002 |
| ≥2.5 mg/dl | 97 (4.0) | 109 (4.6) | 0.36 |
| ≥3.0 mg/dl | 38 (1.6) | 40 (1.7) | 0.79 |
| Elevated serum potassium — no./total no. (%) | | | |
| >5.5 mmol/liter | 316/2386 (13.2) | 361/2367 (15.3) | 0.048 |
| >6.0 mmol/liter | 75/2386 (3.1) | 101/2367 (4.3) | 0.04 |
| Angioedema — no. (%) | 14 (0.6) | 4 (0.2) | 0.02 |
| Liver-related adverse event — no. (%) | 151 (6.3) | 178 (7.5) | 0.11 |

tive comparator, valsartan, because most patients were receiving a renin–angiotensin system inhibitor before enrollment, which made a placebo-controlled trial impractical. Nevertheless, the potential benefit of angiotensin-receptor blockers in patients with heart failure with preserved ejection fraction (suggested in trials such as the Candesartan in Heart Failure — Assessment of Reduction in Mortality and Morbidity [CHARM-Preserved] trial[5]) may have contributed to the smaller-than-anticipated treatment difference between groups.[17] We cannot rule out the possibility that the run-in period may have influenced our results by excluding higher-risk patients and patients who could not take the trial drugs because of side effects.

We did not find a significant benefit of sacubitril–valsartan in patients with heart failure with preserved ejection fraction with respect to the primary composite outcome of total hospitalizations for heart failure and death from cardiovascular causes. In the context of known benefit of this treatment in patients with heart failure and left ventricular systolic dysfunction, and with the suggestion of a differential effect of sacubitril–valsartan in our trial in relation to left ventricular ejection fraction, future research should focus on the potential role of angiotensin receptor–neprilysin inhibition in patients with heart failure and ejection fraction that is below normal but not frankly reduced.[22,23]

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## APPENDIX

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