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Effects of Sacubitril/Valsartan on N-Terminal Pro-B-Type Natriuretic Peptide in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

OBJECTIVES The authors sought to evaluate the prognostic significance of baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP), whether NT-proBNP modified the treatment response to sacubitril/valsartan, and the treatment effect of sacubitril/valsartan on NT-proBNP overall and in key subgroups.

BACKGROUND Sacubitril/valsartan reduces NT-proBNP in heart failure (HF) with both reduced and preserved ejection fraction (EF), but did not significantly reduce total HF hospitalizations and cardiovascular death compared with valsartan in patients with HF with preserved EF (HFpEF).

METHODS In the PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction) trial, 4,796 patients with HFpEF and elevated NT-proBNP were randomized to sacubitril/valsartan or valsartan. NT-proBNP was measured at screening in all patients and at 5 subsequent times in >2,700 patients: before, between, and after sequential valsartan and sacubitril/valsartan run-in periods, and 16 and 48 weeks post-randomization.

RESULTS Median NT-proBNP was 911 pg/ml (interquartile range: 464 to 1,613 pg/ml) at screening. Screening NT-proBNP was strongly associated with the primary endpoint, total HF hospitalizations and cardiovascular death (rate ratio [RR]: 1.68 per log increase in NT-proBNP, 95% confidence interval [CI]: 1.53 to 1.85; $p < 0.001$). This relationship was stronger in patients with atrial fibrillation (adjusted RR: 2.33 [95% CI: 1.89 to 2.87] vs. 1.58 [95% CI: 1.42 to 1.75] in patients without atrial fibrillation; p interaction <0.001) and weaker in obese patients (adjusted RR: 1.50 [95% CI: 1.31 to 1.71] vs. 1.92 [95% CI: 1.70 to 2.17] in nonobese patients; p interaction <0.001). Screening NT-proBNP did not modify the treatment effect of sacubitril/valsartan compared with valsartan (p interaction = 0.96). Sacubitril/valsartan reduced NT-proBNP by 19% (95% CI: 14% to 23%; $p < 0.001$) compared with valsartan 16 weeks post-randomization, with similar reductions in men (20%) and women (18%), and in patients with left ventricular EF ≤57% (20%) and >57% (18%). Decreases in NT-proBNP predicted lower subsequent risk of the primary endpoint.

CONCLUSIONS Baseline NT-proBNP predicted HF events but did not modify the sacubitril/valsartan treatment effect in patients with HFpEF. Sacubitril/valsartan reduced NT-proBNP consistently in men and women, and in patients with lower or higher EF. (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction [PARAGON-HF]; NCT01920711) (J Am Coll Cardiol HF 2020;8:372–81)

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Natriuretic peptides play key roles in the regulation of volume status and hemodynamics in patients with heart failure (HF) (1). Elevated plasma levels are useful for diagnosis and prognosis in HF (2,3). Sacubitril inhibits the endopeptidase neprilysin, which is responsible for degradation of vasoactive peptides including natriuretic

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peptides, thereby increasing their plasma levels (4,5). N-terminal pro-B-type natriuretic peptide (NT-proBNP), however, is not a substrate for neprilysin and thus reflects underlying hemodynamics and ventricular wall stress (6–8). In the PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction) trial, sacubitril/valsartan did not significantly reduce the primary endpoint of total HF hospitalizations and cardiovascular (CV) death, compared with valsartan (rate ratio [RR]: 0.87; p = 0.058) (9). Women and patients at the lower end of the included left ventricular ejection fraction (LVEF) spectrum appeared to benefit the most. We assessed the relationship between baseline NT-proBNP level and outcomes in patients with HF with preserved ejection fraction (HFpEF) enrolled in the PARAGON-HF trial and whether the baseline NT-proBNP level modified the effect of

ABBREVIATIONS AND ACRONYMS

adj. = adjusted

CI = confidence interval

CV = cardiovascular

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

RR = rate ratio

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sacubitril/valsartan on clinical outcomes. We also examined the effect of sacubitril/valsartan on NT-proBNP and the association between change in NT-proBNP and outcomes.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The PARAGON-HF trial was a multicenter, randomized, double-blind trial comparing sacubitril/valsartan with valsartan in patients with chronic HF, LVEF ≥45%, elevated NT-proBNP levels, and evidence of structural heart disease. The study design has been described in detail previously (10). Inclusion criteria included age ≥50 years, New York Heart Association (NYHA) functional class II to IV, either left ventricular hypertrophy or left atrial enlargement by echocardiogram, and diuretic use for at least 30 days. Screening visit NT-proBNP level >200 pg/ml for patients with HF hospitalization in the prior 9 months and >300 pg/ml for patients who had not been hospitalized was required; these thresholds were increased 3-fold for patients with atrial fibrillation on screening visit electrocardiogram.

Patients were exposed to sequential valsartan and sacubitril/valsartan run-in periods before randomization. During the 1- to 2-week valsartan run-in, valsartan 40 mg or 80 mg was administered twice daily; patients receiving the lower dose initially were increased to 80 mg twice daily. Patients tolerating valsartan were then exposed to a 2- to 4-week run-in period during which they received sacubitril/valsartan 49/51 mg twice daily. Only patients who tolerated both study drugs were eligible for randomization. During the double-blind follow-up period, doses were increased to sacubitril/valsartan 97/103 mg twice daily or valsartan 160 mg twice daily when possible.

CLINICAL ENDPOINTS. The primary efficacy endpoint was a composite of total (first and recurrent) HF hospitalizations and CV death. Key secondary endpoints included components of the primary outcome and all-cause mortality. A blinded clinical events committee at Brigham and Women's Hospital (Boston, Massachusetts) adjudicated these endpoints.

NT-proBNP MEASUREMENTS. Plasma NT-proBNP was measured in central laboratories from samples collected at individual sites. Screening visit samples (n = 4,757, 99% of patients) were analyzed to determine study eligibility at 9 regional laboratories owned by or affiliated with the central laboratory (Clinical Reference Laboratory, Lenexa, Kansas) with the Roche proBNP II (Roche Diagnostics, Penzberg, Germany) or the Siemens Immulite 1000 (Siemens, Munich, Germany) assays. Intraday and interday assay variation coefficients for all regional labs were ≤15%.

Measurements were made at 5 subsequent times in >2,700 patients: before the valsartan run-in period (n = 2,774), between the run-in periods (n = 3,247), randomization (n = 3,330), and 16 weeks (n = 1,651 in the sacubitril/valsartan arm and 1,593 in the valsartan arm) and 48 weeks (n=1,564 in sacubitril/valsartan arm and 1,494 in valsartan arm) after randomization. Samples from these 5 visits were analyzed in 2 fully harmonized central laboratories (Clinical Reference Laboratory, Lenexa, Kansas, and KingMed, Guangzhou, China) from plasma stored long-term at −80°C. Samples were analyzed in complete patient sets, in duplicate, with the Roche proBNP II assay. Intraday and interday assay variation coefficients were ≤2.5% and ≤3.2%, respectively. The analytic measurement range was 25 to 35,000 pg/ml.

STATISTICAL ANALYSIS. NT-proBNP levels were presented as median (interquartile range) or geometric mean (95% confidence interval [CI]). Changes in NT-proBNP were described using geometric mean and compared between the sacubitril/valsartan and valsartan arms overall and in key subgroups. NT-proBNP levels and changes were log-transformed due to right-skewed distributions. Baseline characteristics of patients in each of 4 quartiles of screening visit NT-proBNP and NT-proBNP change were described using proportions for categorical variables, mean and SD for normally distributed continuous variables, and median and interquartile range for skewed continuous variables, including NT-proBNP. These characteristics were compared by trend using parametric and nonparametric tests, as appropriate.

We evaluated the association between screening NT-proBNP level and the primary endpoint of total (first and recurrent) HF hospitalizations and CV death using the semiparametric proportional rates method of Lin et al. (11), adjusted for 21 relevant covariates: age; sex; race; region; history of diabetes, stroke, and myocardial infarction; ischemic cause of HF; NYHA functional class; prior HF hospitalization; medications (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, mineralocorticoid antagonist, diuretic agent, and beta-blocker); atrial fibrillation on screening electrocardiogram; body mass index; LVEF; systolic and diastolic blood pressure; serum potassium; and estimated glomerular filtration rate. Modification of the effect of sacubitril/valsartan on the primary endpoint by NT-proBNP was assessed by the interaction term between screening NT-proBNP and sacubitril/valsartan (vs. valsartan) treatment allocation, with and without adjustment

TABLE 1 Baseline Characteristics of Patients by Screening Visit NT-proBNP Quartile

	Quartile 1 (n = 1,190)	Quartile 2 (n = 1,189)	Quartile 3 (n = 1,189)	Quartile 4 (n = 1,189)	p Value
NT-proBNP, pg/ml	12.5–464	465–911	912–1,613	1,617–31,522	
Age, yrs	70.8 ± 8.4	72.6 ± 8.4	73.3 ± 8.2	74.4 ± 8.3	<0.001
Female	662 (55.6)	629 (52.9)	559 (47.0)	604 (50.8)	0.002
Race					0.85
White	964 (81.0)	955 (80.3)	995 (83.7)	958 (80.6)	
Asian	144 (12.1)	156 (13.1)	140 (11.8)	166 (14.0)	
Black	25 (2.1)	34 (2.9)	18 (1.5)	23 (1.9)	
Other	57 (4.8)	44 (3.7)	36 (3.0)	42 (3.5)	
Region					
Asia/Pacific and other	181 (15.2)	197 (16.6)	174 (14.6)	206 (17.3)	0.05
Central Europe	479 (40.3)	419 (35.2)	399 (33.6)	408 (34.3)	
Latin America	96 (8.1)	98 (8.2)	84 (7.1)	91 (7.7)	
North America	129 (10.8)	146 (12.3)	137 (11.5)	138 (11.6)	
Western Europe	305 (25.6)	329 (27.7)	395 (33.2)	346 (29.1)	
Diabetes	542 (45.5)	510 (42.9)	495 (41.6)	499 (42.0)	0.06
Stroke	98 (8.2)	99 (8.3)	142 (12.0)	167 (14.1)	<0.001
Hypertension	1,145 (96.2)	1,143 (96.1)	1,126 (94.7)	1,131 (95.1)	0.08
Prior myocardial infarction	267 (22.4)	340 (28.6)	217 (18.3)	252 (21.2)	0.01
Ischemic etiology of HF	453 (38.1)	454 (38.2)	380 (32.0)	426 (35.8)	0.036
New York heart association functional class					<0.001
I	45 (3.8)	36 (3.0)	29 (2.4)	26 (2.2)	
II	941 (79.1)	936 (78.7)	921 (77.5)	884 (74.4)	
III	199 (16.7)	215 (18.1)	234 (19.7)	271 (22.8)	
IV	4 (0.3)	2 (0.2)	5 (0.4)	7 (0.6)	
Prior HF hospitalization	626 (52.6)	542 (45.6)	489 (41.1)	632 (53.2)	0.66
Body mass index, kg/m^2	31.1 ± 5.1	30.4 ± 4.9	30.4 ± 5.0	29.0 ± 4.8	<0.001
Left ventricular ejection fraction, %	58.9 ± 7.9	57.8 ± 7.9	57.0 ± 7.6	56.3 ± 7.8	<0.001
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	1,072 (90.1)	1,014 (85.3)	1,013 (85.2)	1,006 (84.6)	<0.001
Mineralocorticoid receptor antagonist	264 (22.2)	301 (25.3)	312 (26.2)	353 (29.7)	<0.001
Diuretic agent	1,112 (93.4)	1,134 (95.4)	1,137 (95.6)	1,163 (97.8)	<0.001
Beta-blocker	926 (77.8)	920 (77.4)	971 (81.7)	976 (82.1)	0.001
Atrial fibrillation at screening visit	11 (0.9)	122 (10.3)	658 (55.4)	745 (63.0)	<0.001
Systolic blood pressure, mm Hg	132.1 ± 15.2	131.3 ± 15.3	128.7 ± 15.1	130.0 ± 16.0	<0.001
Diastolic blood pressure, mmHg	74.9 ± 9.9	73.8 ± 10.7	74.1 ± 10.5	74.4 ± 11.0	0.44
Potassium, mmol/l	4.5 ± 0.4	4.5 ± 0.4	4.5 ± 0.4	4.5 ± 0.5	0.11
Estimated glomerular filtration rate, ml/min/1.73 m^2	67.3 ± 19.8	63.0 ± 18.7	61.6 ± 18.1	58.1 ± 18.4	<0.001

Values are range, mean ± SD, or n (%).

HF = heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

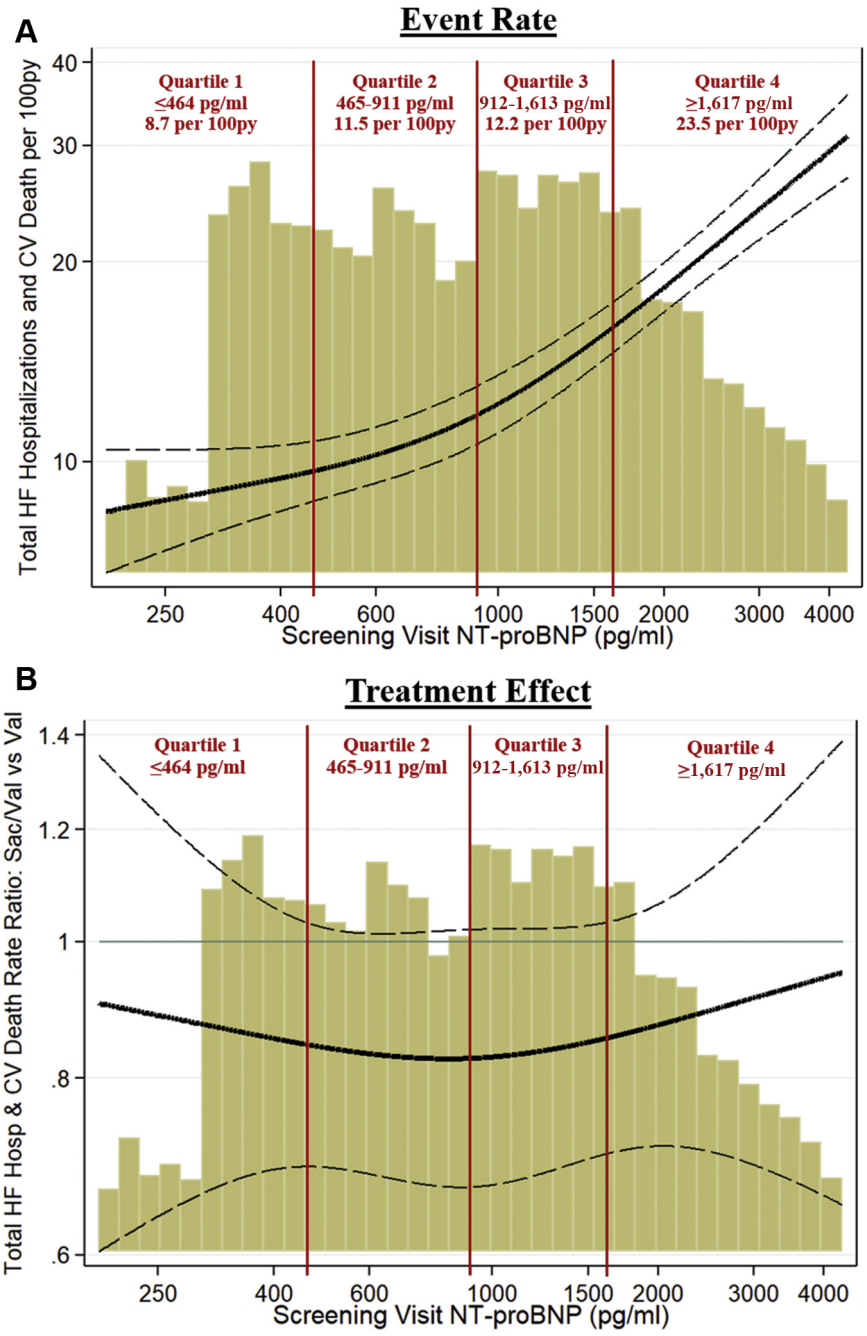
for known treatment interactions with LVEF, and sex. Cox proportional hazards regression models were constructed for CV and all-cause death endpoints. Continuous relationships between NT-proBNP level and the primary endpoint were assessed using restricted cubic splines. Using the same methods, we performed a landmark analysis to assess the association between change in NT-proBNP from before the run-in period to week 16 and subsequent events occurring after the week 16 visit. Changes in NT-proBNP levels were calculated relative to the pre-specified baseline measurement, which was collected after screening and before the start of the valsartan run-in period, in patients with available data at baseline and the subsequent time point only.

All patients in the PARAGON-HF trial provided written informed consent. Local ethics committees and institutional review boards at each participating site approved the study protocols. We performed statistical analysis using STATA software v14.1 (StataCorp, College Station, Texas). A 2-sided p value <0.05 was considered significant.

RESULTS

CLINICAL PROFILE AND OUTCOMES IN PATIENTS WITH HIGHER OR LOWER SCREENING VISIT NT-proBNP.

FIGURE 1 Variation in Primary Endpoint Event Rate and Sacubitril/Valsartan Treatment Effect by Screening Visit NT-proBNP



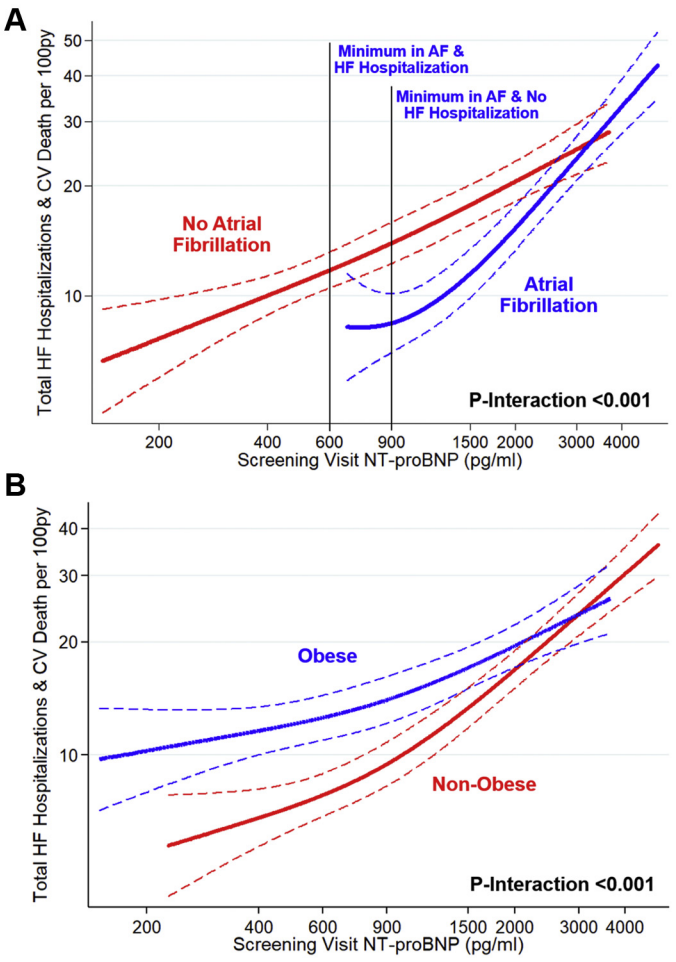
The histogram represents NT-proBNP at screening visit. The **solid line** represents the estimated primary endpoint incidence rate **(A)** and rate ratio for sacubitril/valsartan compared with valsartan **(B)** of the primary endpoint, total HF hospitalizations (Hosp) and CV death. The **dashed lines** represent the 95% confidence intervals for the estimated incidence rate or rate ratio. The highest and lowest 3% of NT-proBNP values are not shown. CV = cardiovascular; HF = heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; py = patient-years; Sac = sacubitril; Val = valsartan.

NT-proBNP concentrations at the screening visit were available in 4,757 (99.2%) of the 4,796 validly randomized patients. Median NT-proBNP was 911 pg/ml (25th to 75th percentiles: 464 to 1,613 pg/ml). The baseline characteristics of patients in each quartile of screening NT-proBNP are shown in Table 1. Patients with higher NT-proBNP were older and more likely male, with more prevalent atrial fibrillation and prior stroke, worse NYHA functional class, and lower body mass index, LVEF, and estimated glomerular filtration rate (all $p \leq 0.002$). Low atrial fibrillation prevalence in the lowest NT-proBNP quartile (1%) was due to the higher NT-proBNP inclusion threshold for patients with atrial fibrillation.

Screening visit NT-proBNP strongly predicted the primary endpoint, total HF hospitalizations and cardiovascular death. In a multivariable recurrent events regression model adjusted for 21 relevant covariates, higher NT-proBNP was associated with a greater risk of the primary endpoint (adjusted [adj.] RR: 1.68 per natural log increase in NT-proBNP, 95% CI: 1.53 to 1.85; $p < 0.001$) (Figure 1A). Similar elevations in risk were observed for secondary endpoints including all-cause death (adj. hazard ratio: 1.71, 95% CI: 1.55 to 1.89; $p < 0.001$), CV death (adj. hazard ratio: 1.93, 95% CI: 1.71 to 2.18; $p < 0.001$), and total HF hospitalizations (adj. RR: 1.61, 95% CI: 1.46 to 1.79; $p < 0.001$). The association between screening visit NT-proBNP and the primary endpoint was stronger in patients with atrial fibrillation (adj. RR: 2.33 [95% CI: 1.89 to 2.87] in atrial fibrillation vs. 1.58 [95% CI: 1.42 to 1.75] not in atrial fibrillation; p interaction <0.001) (Figure 2A). This interaction was maintained when the analysis was restricted to patients whose NT-proBNP levels met inclusion criteria regardless of atrial fibrillation status, and stratified by HF hospitalization in the previous 9 months (adj. RR: 2.39 [95% CI: 1.95 to 2.94] in atrial fibrillation vs. 1.50 [95% CI: 1.24 to 1.82] not in atrial fibrillation; p interaction <0.001). Conversely, the association between NT-proBNP and the primary endpoints was weaker in obese patients (adj. RR: 1.50 [95% CI: 1.31 to 1.71] in obese patients vs. 1.92 [95% CI: 1.70 to 2.17] in nonobese patients; p interaction <0.001) (Figure 2B). For a given NT-proBNP level, patients with atrial fibrillation had lower event rates, and obese patients had higher event rates, particularly at the lower end of the NT-proBNP range, compared with patients without atrial fibrillation and nonobese patients, respectively.

NT-proBNP level at screening did not modify the effect of sacubitril/valsartan compared with valsartan on the primary endpoint (p interaction = 0.96) (Figure 1B) alone or after adjustment for significant treatment interactions with LVEF and sex (p interaction = 0.82).

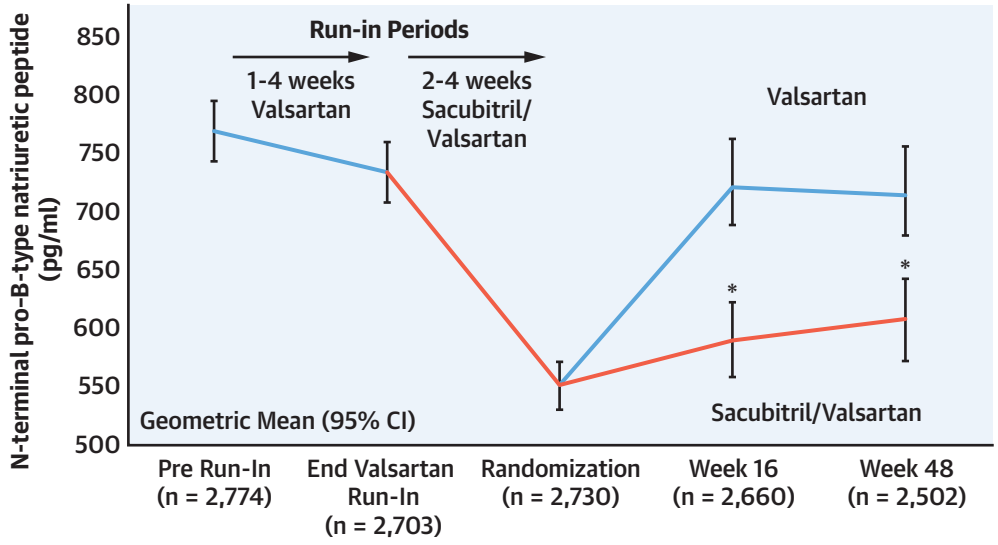
FIGURE 2 Association Between Screening Visit NT-proBNP and Primary Endpoint Event Rate in Patients With/Without AF and Obesity



(A) Relationship between screening NT-proBNP and the primary endpoint in patients with ad without atrial fibrillation. **(B)** Same relationship in obese and non-obese patients. The **solid lines** represent estimated continuous association of screening visit NT-proBNP with the incidence rate primary endpoint, without adjustment. **Dashed lines** represent the 95% confidence intervals. The highest and lowest 3% of NT-proBNP values in each subgroup are not shown. Atrial fibrillation was determined by the screening visit electrocardiogram. Patients in atrial fibrillation were only included in the PARAGON-HF trial if NT-proBNP was >600 pg/ml with recent HF hospitalization or >900 pg/ml without hospitalization. Obesity was defined by body mass index >30 kg/m^2. AF = atrial fibrillation; RR = rate ratio; other abbreviations as in Figure 1.

TRENDS IN NT-proBNP LEVELS DURING RUN-IN AND FOLLOW-UP PERIODS. Changes in NT-proBNP were assessed in the 2,774 patients (58% of validly randomized patients) with available data at the pre run-in visit, which was the pre-specified baseline visit. Clinical characteristics of these patients were

CENTRAL ILLUSTRATION **N-Terminal Pro-B-Type Natriuretic Peptide Trajectory in the PARAGON-HF Trial**



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Geometric mean NT-proBNP concentration with 95% confidence intervals are shown for patients with available NT-proBNP measurement at the pre run-in visit, which was the pre-specified baseline for biomarker comparisons over time. *Indicates statistically significant difference between treatment groups. CI = confidence interval; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PARAGON-HF = Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction trial.

similar to those without available data, except that they were more likely to be Asian, less likely to have been previously hospitalized or have atrial fibrillation, and had a higher screening visit NT-proBNP level (all $p < 0.01$) (Supplemental Table 1).

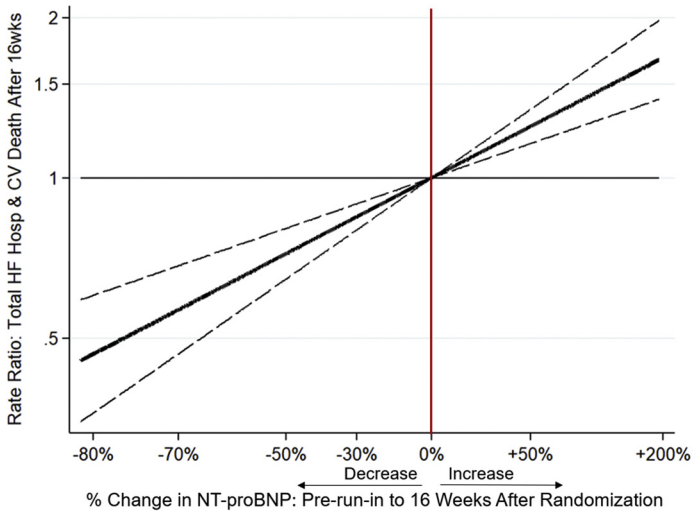
Sacubitril/valsartan rapidly and reversibly decreased NT-proBNP levels during the run-in and post-randomization follow-up periods (**Central Illustration**). Geometric mean NT-proBNP declined 5% during the valsartan run-in period, and a further 25% during the sacubitril/valsartan run-in period in patients with available data at both time points. In the first 16 weeks of treatment with study drug, NT-proBNP increased 7% in the sacubitril/valsartan group and 31% in the valsartan group. Compared with valsartan, sacubitril/valsartan decreased NT-proBNP by 19% (95% CI: 14% to 23%; $p < 0.001$) at 16 weeks, adjusted for the pre-run-in value, in patients with available data at both time points. At 48 weeks, sacubitril/valsartan decreased NT-proBNP by 17% (95% CI: 11% to 22%; $p < 0.001$) compared with valsartan, adjusted for the pre-run-in value. These trends were consistent when considering only patients with available data at all time points (Supplemental Figure 1).

NT-proBNP reductions with sacubitril/valsartan compared with valsartan at week 16 were similar in men and women (20% and 18%, respectively), patients with LVEF ≤ and > the median of 57% (20% and 18%, respectively), patients whose NT-proBNP at the start of run-in was < and > the median (20% and 18%, respectively), and obese and nonobese patients (20% and 18%, respectively). Patients with atrial fibrillation had smaller reductions in NT-proBNP levels with sacubitril/valsartan compared with valsartan (11% for patients in atrial fibrillation vs. 22% for patients not in atrial fibrillation; $p = 0.02$).

Patients whose NT-proBNP levels declined more were at lower risk for subsequent HF hospitalizations and CV death, regardless of treatment group. In a landmark analysis of primary endpoints occurring only after the week 16 visit, patients whose NT-proBNP decreased from pre-run-in baseline to 16 weeks post-randomization were at lower subsequent risk (RR: 0.62 per log decrease in NT-proBNP, 95% CI: 0.54 to 0.71; $p < 0.001$), adjusted for pre-run-in value and 21 clinical covariates (**Figure 3**). The primary endpoint rate was 11.2 (95% CI: 8.7 to 14.5) per 100 patient-years in the quartile of patients with greatest NT-proBNP decline (>38%), and 15.8 (95% CI:

13.1 to 19.1) per 100 patient-years in the quartile of patients who had NT-proBNP increased >25%. Adjusted reductions were similar for the components of the primary endpoint, CV death alone (RR: 0.62 per log decrease, 95% CI: 0.50 to 0.76; $p < 0.001$) and recurrent HF hospitalizations (RR: 0.62 per log decrease, 95% CI: 0.52 to 0.72; $p < 0.001$).

FIGURE 3 **Association Between NT-proBNP Change and Rate of Subsequent Total HF Hospitalizations and CV Death**



The **solid black line** represents estimated incidence rate ratio of the primary endpoint, total HF hospitalizations and CV death, occurring after 16 weeks, for patients at the given NT-proBNP change, compared with no change in NT-proBNP level. The **dashed lines** represent 95% confidence intervals for the estimated rate ratio. The highest and lowest 3% of NT-proBNP change values are not shown. Abbreviations as in Figure 1.

DISCUSSION

In contemporary patients with HFpEF enrolled in the PARAGON-HF trial, we found that NT-proBNP at screening strongly predicted risk of HF hospitalizations and CV death, but did not modify the treatment effect of sacubitril/valsartan. Sacubitril/valsartan consistently decreased NT-proBNP by 19% relative to valsartan in men and women and in patients with higher and lower LVEF. Patients who demonstrated the greatest reduction in NT-proBNP had the best subsequent outcomes. These data validate the prognostic importance of NT-proBNP in this contemporary HFpEF population and support consistent treatment effects of sacubitril/valsartan in reducing NT-proBNP levels overall and in key subgroups of patients with HFpEF.

Consistent with previous observational studies and clinical trials, we found that higher baseline NT-proBNP was strongly associated with greater risk for HF events (1,3). Event rates were lower in atrial fibrillation and higher in obesity for a given NT-proBNP level. Natriuretic peptide-based inclusion criteria are now commonly used in HF trials to confirm the diagnosis of HF and enrich for patients with higher expected event rates, and patients in the PARAGON-HF trial were required to have elevated NT-proBNP. Atrial fibrillation and obesity both confound the clinical diagnosis of HF (as alternative causes of exercise intolerance) and affect natriuretic peptide levels independently of risk (12–15). In the PARAGON-HF trial, the minimum NT-proBNP required for inclusion was 3 times higher in patients with atrial fibrillation. Our findings support this higher natriuretic peptide threshold. Indeed, an even higher minimum in atrial fibrillation may be optimal, as patients with atrial fibrillation and NT-proBNP just above the minimum had relatively low event rates. Conversely, a lower minimum NT-proBNP in obese patients could also be useful, because obese patients retained moderate risk even when NT-proBNP was just above the minimum level required. Obesity-related adjustment has been infrequently applied due to the challenges of confirming HF diagnosis in patients with low NT-proBNP but has been employed in select HF device trials (Reducing Lung Congestion Symptoms in Advanced Heart Failure [RELIEVE-HF]; NCT03499236; and Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation [COAPT]; NCT01626079).

Patients with HFpEF and low NT-proBNP levels are distinguished by a distinct clinical profile (younger age, obesity, black race, with lower rates of atrial fibrillation or chronic kidney disease). In prior post hoc analyses from the I-Preserve (Irbesartan in Heart Failure With Preserved Systolic Function) and TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) studies, the study drug benefit (of irbesartan or spironolactone, respectively) was greater in patients with lower natriuretic peptide levels at baseline (16,17). It was hypothesized that these patients may have less advanced disease, and their prognosis may be more readily modifiable by neurohormonal therapy. However, in the PARAGON-HF trial, we observed that the modest overall treatment effects of sacubitril/valsartan were consistent across the spectrum of baseline NT-proBNP. The present analysis included many more patients with available natriuretic peptide data, which improved the precision of treatment effect estimates. The efficacy of sacubitril/valsartan

in patients with a lower estimated glomerular filtration rate (who have higher NT-proBNP levels) and with recent HF hospitalization may explain consistent effects at higher natriuretic peptide ranges (18,19).

Sacubitril/valsartan reduced NT-proBNP by 19% compared with valsartan. This observation was consistent with the phase II PARAMOUNT (Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction) trial, which included ~10% the sample size of the PARAGON-HF trial and observed a 23% reduction in NT-proBNP after 12 weeks (20). Of note, entry criteria in the PARAMOUNT trial required higher baseline NT-proBNP levels. In the PARAGON-HF trial, NT-proBNP reduction occurred quickly and at submaximal doses during the 2- to 4-week run-in period. This change was reversible; after randomization, patients continuing sacubitril/valsartan retained the NT-proBNP improvement, whereas those randomized to valsartan returned to pre-sacubitril/valsartan levels. The magnitude of NT-proBNP reduction was lower than in HF with reduced ejection fraction studies, including the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) (28% at 8 to 10 weeks compared with enalapril), EVALUATE-HF (Study of Effects of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction) (33% at 12 weeks, compared with enalapril), and PROVE-HF (Effects of Sacubitril/Valsartan Therapy on Biomarkers, Myocardial Remodeling and Outcomes) (30% at 14 days and 35% at 6 months, compared with baseline values) trials (5–7).

Decreases in NT-proBNP in the early post-randomization period were associated with lower risk of the primary endpoint, consistent with prior work (21). Interestingly, the 2 subgroups with lower benefit for the primary outcome, men and patients with higher LVEF, nevertheless had reductions in NT-proBNP similar to women and patients with lower LVEF. Thus, apparent differences noted in the clinical effect of sacubitril/valsartan between sexes and across the LVEF spectrum cannot be explained by differences in effect on this natriuretic peptide. The relationship between NT-proBNP reduction and outcomes was not as strong as previously observed for patients with heart failure with reduced ejection fraction in the PARADIGM-HF trial. However, natriuretic peptide and clinical responses in individual subgroups may be underpowered and need to be considered in the context of a modest overall treatment benefit.

STUDY LIMITATIONS. First, screening visit NT-proBNP was measured at affiliated regional laboratories using 2 different assays. Screening visit NT-proBNP was used for risk modelling because all patients in the trial had available data. All assessments of NT-proBNP change compared post-screening visit samples that were analyzed in 2 fully harmonized central laboratories with a single assay. The definition of the pre-run-in period value as the baseline for comparisons was pre-specified in the statistical analysis plan. Second, we did not measure atrial natriuretic peptide and C-type natriuretic peptide, which are more direct substrates of neprilysin and whose levels are dramatically altered by sacubitril/valsartan in patients with HF with reduced ejection fraction (4). Third, only 2% of patients in the PARAGON-HF trial were black, so no conclusions about this group with lower NT-proBNP could be made.

CONCLUSIONS

Data from the PARAGON-HF trial affirm the strong prognostic significance of NT-proBNP in forecasting future risk of HF events in patients with HFpEF. Greater reduction in NT-proBNP from baseline to 16-week post-randomization was associated with a lower risk for adverse outcomes, regardless of treatment group. Baseline NT-proBNP levels did not significantly modify the effect of sacubitril/valsartan on HF events. Sacubitril/valsartan reduced NT-proBNP levels by 19%, and this reduction was consistently observed in men and women, and patients with lower and higher LVEF, despite differences in clinical response between these groups. The mechanisms by which neprilysin inhibition lowers NT-proBNP in HFpEF require further study and may be distinct from those that explain therapeutic benefits on clinical outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In the PARAGON-HF trial of sacubitril/valsartan compared with valsartan in HFpEF, baseline NT-proBNP and change in NT-proBNP over time strongly predicted HF events. The modest reduction in HF events with sacubitril/valsartan was similar in patients with higher and lower baseline NT-proBNP. Sacubitril/valsartan reduced NT-proBNP by 19% compared with valsartan.

TRANSLATIONAL OUTLOOK: Further studies are needed to identify patients with HFpEF who benefit most from sacubitril/valsartan and to investigate the mechanisms of NT-proBNP reduction with neprilysin inhibition.

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APPENDIX For a supplemental table and figure, please see the online version of this paper.