

Prognostic Implications of Changes in N-Terminal Pro-B-Type Natriuretic Peptide in Patients With Heart Failure



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ABSTRACT

BACKGROUND Natriuretic peptides (NP) have prognostic value in heart failure (HF), although the clinical importance of changes in NP from baseline is unclear.

OBJECTIVES The authors assessed whether a reduction in N-terminal pro-B-type NP (NT-proBNP) was associated with a decrease in HF hospitalization and cardiovascular mortality (primary endpoint) in patients with HF and reduced ejection fraction, whether treatment with sacubitril/valsartan reduced NT-proBNP below specific partition values more than enalapril, and whether the relationship between changes in NT-proBNP and changes in the primary endpoint were dependent on assigned treatment.

METHODS In PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial), baseline NT-proBNP was measured in 2,080 patients; 1,292 had baseline values >1,000 pg/ml and were reassessed at 1 and 8 months. We related change in NT-proBNP to outcomes.

RESULTS One month after randomization, 24% of the baseline NT-proBNP levels >1,000 pg/ml had fallen to ≤1,000 pg/ml. Risk of the primary endpoint was 59% lower in patients with a fall in NT-proBNP to ≤1,000 pg/ml than in those without such a fall. In sacubitril/valsartan-treated patients, median NT-proBNP was significantly lower 1 month after randomization than in enalapril-treated patients, and it fell to ≤1,000 pg/ml in 31% versus 17% of patients treated with sacubitril/valsartan and enalapril, respectively. There was no significant interaction between treatment and the relationship between change in NT-proBNP and the subsequent risk of the primary endpoint.

CONCLUSIONS Patients who attained a significant reduction in NT-proBNP had a lower subsequent rate of cardiovascular death or HF hospitalization independent of the treatment group. Treatment with sacubitril/valsartan was nearly twice as likely as enalapril to reduce NT-proBNP to values ≤1,000 pg/ml. (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial) [PARADIGM-HF]; [NCT01035255](https://doi.org/10.1035/255).) (J Am Coll Cardiol 2016;68:2425–36) © 2016 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



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**ABBREVIATIONS
AND ACRONYMS**

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blocker

BNP = B-type natriuretic peptide

CHF = congestive heart failure

CI = confidence interval

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

IQR = interquartile range

NP = natriuretic peptide

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

PARADIGM-HF = Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure

Natriuretic peptides (NPs), specifically B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), have diagnostic and prognostic value in patients with heart failure (HF) (1-6). Decreases in NP during follow-up are associated with reduced morbidity and mortality outcomes, whereas increasing NP portends poor patient outcomes (5-22). Clinical trials assessing whether changes in NP from baseline could be useful in evaluating treatment success have yielded mixed results (23-31) and were limited by small size, low event rates, effectiveness of treatment strategies, frequency of NP measurement, length of follow-up, and NP partition values (32,33).

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Although the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial was not designed to address the prognostic value of changes in NPs, the large sample size, significant event rate, effectiveness of treatment strategy, frequency of NP measurements, and length of follow-up of PARADIGM-HF provide an opportunity to address issues that limited earlier reports (34,35). We analyzed data from PARADIGM-HF to determine: 1) whether and to what degree a

change in NT-proBNP was associated with a change in morbidity and mortality rates in patients with HF with reduced ejection fraction (HFrEF); 2) whether treatment of HFrEF patients with sacubitril/valsartan lowered NT-proBNP below specific partition values more often than enalapril; and 3) whether the relationship between change in NT-proBNP and change in morbidity and mortality event rates was influenced by treatment.

METHODS

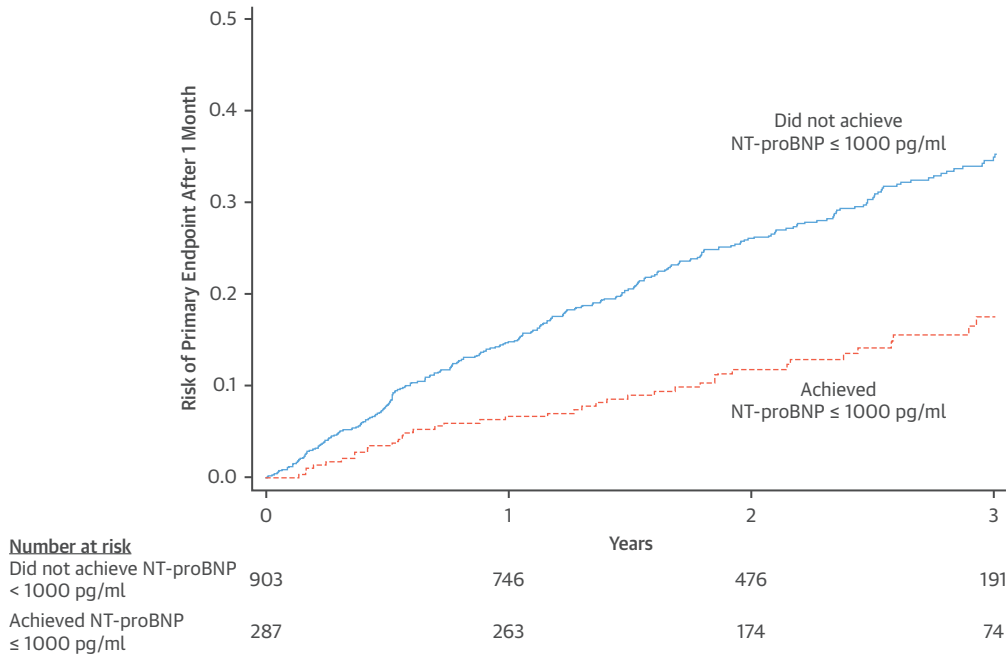
STUDY PATIENTS. The design and primary results of PARADIGM-HF were described previously (12). The institutional review boards of 1,043 participating institutions (in 47 countries) approved the protocol, and all patients gave written informed consent. Patients had New York Heart Association functional class II to IV symptoms, an ejection fraction of $\leq 35\%$, and a BNP ≥ 150 pg/ml (or NT-proBNP ≥ 600 pg/ml), or if they had been hospitalized for HF within the previous 12 months, a BNP ≥ 100 pg/ml (or an NT-proBNP ≥ 400 pg/ml) (12). Patients taking any dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and able to tolerate the equivalent of enalapril 10 mg daily for ≥ 4 weeks before screening, along with stable doses of a β -blocker (unless contraindicated or not tolerated) and a mineralocorticoid antagonist (if indicated), were included. Patients were excluded for a history of intolerance to ACE inhibitors or ARBs (12).

TABLE 1 Change in NT-proBNP From Baseline (V2/V2a) to 1 Month After Randomization (V7)

Change in NT-proBNP at 1 Month	All Patients (N = 1,942)	Sacubitril/Valsartan (n = 971)	Enalapril (n = 971)	Between Treatment		
				Odds Ratio	95% CI	p Value
Among patients with NT-proBNP (of any value) at baseline						
Any reduction	1,262 (65.0)	729 (75.1)	533 (54.9)	2.48	2.04-3.00	<0.001
Reduction >10%	1,106 (57.0)	667 (68.7)	439 (45.2)	2.66	2.21-3.20	<0.001
Reduction >20%	910 (46.9)	562 (57.9)	348 (35.8)	2.46	2.05-2.95	<0.001
Reduction >30%	709 (36.5)	461 (47.5)	248 (25.5)	2.64	2.18-3.19	<0.001
Reduction >40%	523 (26.9)	358 (36.9)	165 (17.0)	2.85	2.31-3.53	<0.001
Reduction >50%	357 (18.4)	256 (26.4)	101 (10.4)	3.08	2.40-3.96	<0.001
Change $\leq 10\%$	293 (15.1)	114 (11.7)	179 (18.4)	0.59	0.46-0.76	<0.001
Increase 10%-50%	315 (16.2)	120 (12.4)	195 (20.1)	0.56	0.44-0.72	<0.001
Increase >50%	228 (11.7)	70 (7.2)	158 (16.3)	0.40	0.30-0.54	<0.001
Among patients with NT-proBNP >1,000 mg/dl at baseline						
NT-proBNP $\leq 1,000$ pg/ml	288 (23.9)	187 (30.6)	101 (17.0)	2.15	1.63-2.83	<0.001
NT-proBNP ≤ 750 pg/ml	154 (12.8)	108 (17.6)	46 (7.7)	2.55	1.77-3.68	<0.001
NT-proBNP ≤ 500 pg/ml	67 (5.6)	52 (8.5)	15 (2.5)	3.58	1.99-6.44	<0.001

Values are n (%).
NT-proBNP = N-terminal pro-B-type natriuretic peptide.

FIGURE 1 Effects on Risk of Primary Endpoint if NT-proBNP Achieved or Did Not Achieve a Value of <1,000 pg/ml 1 Month After Randomization



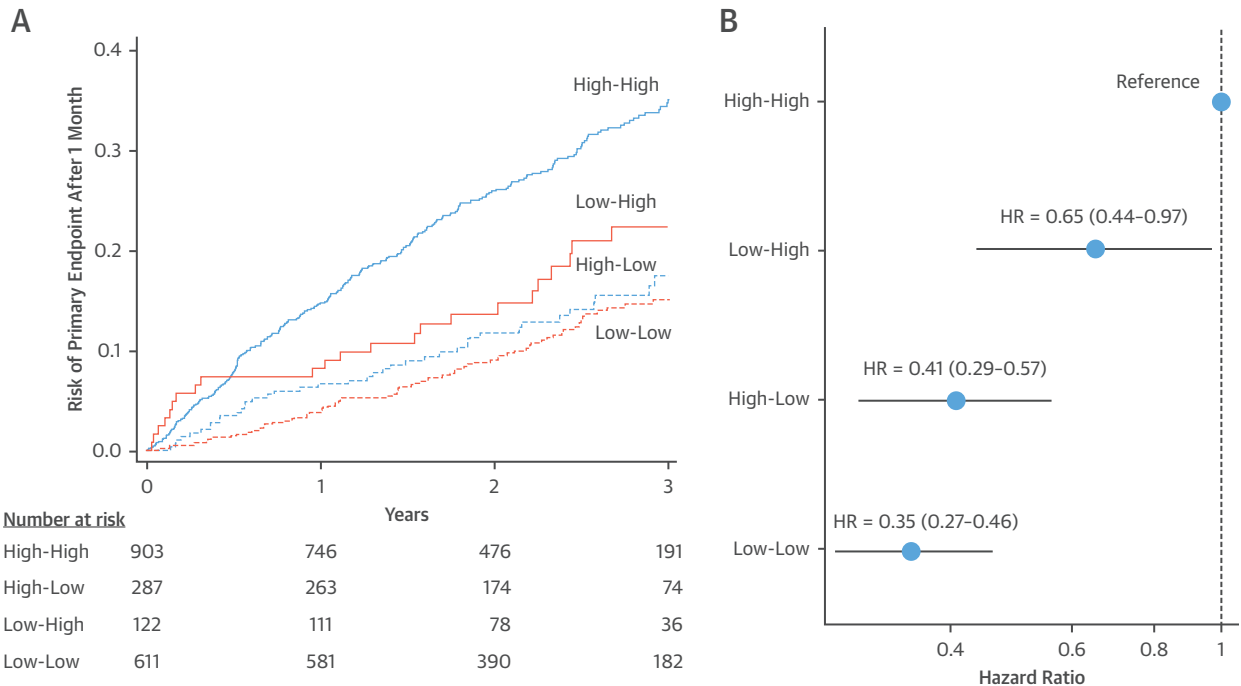
Risk of primary endpoint after 1 month of randomization in patients with a baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) (V2/V2a) >1,000 pg/ml who had a reduction in NT-proBNP at 1 month after randomization (V7) versus those patients who did not achieve a reduction in NT-proBNP at 1 month after randomization. The risk at 3 yrs of follow-up was ≈50% less in those who achieved a NT-proBNP ≤1,000 pg/ml than in those who did not.

TABLE 2 Effect on Primary Event Rate of a Change in NT-proBNP From Baseline (V2/V2a) to 1 Month After Randomization (V7)

Change in NT-proBNP at 1 Month	All Patients (N = 1,942)				Sacubitril/Valsartan (n = 971)				Enalapril (n = 971)			
	n	HR	95% CI	p Value	n	HR	95% CI	p Value	n	HR	95% CI	p Value
Among patients with NT-proBNP (of any value) at baseline												
Any reduction	1,262	0.76	0.63-0.93	0.007	729	0.71	0.52-0.96	0.028	533	0.84	0.65-1.10	0.205
Reduction >10%	1,106	0.78	0.64-0.94	0.010	667	0.79	0.59-1.07	0.129	439	0.80	0.61-1.05	0.108
Reduction >20%	910	0.77	0.64-0.94	0.011	562	0.79	0.59-1.05	0.104	348	0.81	0.61-1.07	0.137
Reduction >30%	709	0.78	0.63-0.96	0.017	461	0.85	0.64-1.13	0.258	248	0.75	0.54-1.03	0.078
Reduction >40%	523	0.79	0.62-0.99	0.040	358	0.84	0.62-1.13	0.248	165	0.78	0.53-1.14	0.202
Reduction >50%	357	0.75	0.57-0.99	0.041	256	0.79	0.56-1.11	0.169	101	0.77	0.48-1.25	0.295
Among patients with NT-proBNP (of any value) at baseline (adjusted for baseline NT-proBNP)												
Any reduction	1,262	0.62	0.50-0.75	<0.001	729	0.56	0.41-0.77	<0.001	533	0.69	0.52-0.90	0.007
Reduction >10%	1,106	0.63	0.52-0.77	<0.001	667	0.63	0.47-0.85	0.003	439	0.66	0.50-0.87	0.003
Reduction >20%	910	0.63	0.51-0.77	<0.001	562	0.62	0.46-0.83	0.001	348	0.66	0.49-0.88	0.005
Reduction >30%	709	0.63	0.51-0.78	<0.001	461	0.68	0.51-0.92	0.011	248	0.60	0.43-0.84	0.003
Reduction >40%	523	0.61	0.48-0.77	<0.001	358	0.65	0.47-0.88	0.006	165	0.58	0.39-0.86	0.007
Reduction >50%	357	0.57	0.43-0.76	<0.001	256	0.58	0.41-0.82	0.002	101	0.59	0.36-0.97	0.036
All Patients (N = 1,207) Sacubitril/Valsartan (n = 612) Enalapril (n = 595)												
Among patients with NT-proBNP >1,000 pg/ml at baseline												
NT-proBNP ≤1,000 pg/ml	288	0.41	0.29-0.58	<0.001	187	0.44	0.29-0.68	<0.001	101	0.38	0.21-0.67	0.001
NT-proBNP ≤750 pg/ml	154	0.46	0.29-0.71	0.001	108	0.49	0.29-0.83	0.009	46	0.43	0.19-0.97	0.041
NT-proBNP ≤500 pg/ml	67	0.64	0.36-1.14	0.129	52	0.58	0.28-1.18	0.134	15	0.92	0.34-2.49	0.875

CI = confidence interval; HR = hazard ratio; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

FIGURE 2 Effects on Risk of Primary Endpoint if N-Terminal Pro-B-Type Natriuretic Peptide Changed From Baseline to 1 Month After Randomization: High-High, High-Low, Low-High Analysis



Categorical analysis. Patients were divided into 4 categorical groups described in the Methods. (A) The lowest primary event rate occurred in the Low-Low group; the highest primary event rate occurred in the High-High group; the High-Low and Low-High groups had intermediate primary event rates. (B) Hazard ratio (HR) and 95% confidence intervals for each category, with High-High serving as a reference.

TABLE 3 Change in NT-proBNP From Baseline (V2/V2a) to 1 Month After Randomization (V7): Categorical Analysis

Change in NT-proBNP at 1 Month	All Patients (N = 1,942)	Sacubitril/Valsartan (n = 971)	Enalapril (n = 971)	Between Treatments		
				OR†	95% CI	p Value
Among patients with NT-proBNP >1,000 pg/ml at baseline (N = 1,206) (n = 612) (n = 594)						
High-High*	918 (76.1)	425 (69.4)	493 (83.0)			
High-Low	288 (23.9)	187 (30.6)	101 (17.0)	2.15	1.63-2.83	<0.001
Among patients with NT-proBNP ≤ 1,000 pg/ml at baseline (N = 736) (n = 359) (n = 377)						
Low-High	124 (16.8)	38 (10.6)	86 (22.8)			
Low-Low	612 (83.2)	321 (89.4)	291 (77.2)	2.5	1.62-3.88	<0.001

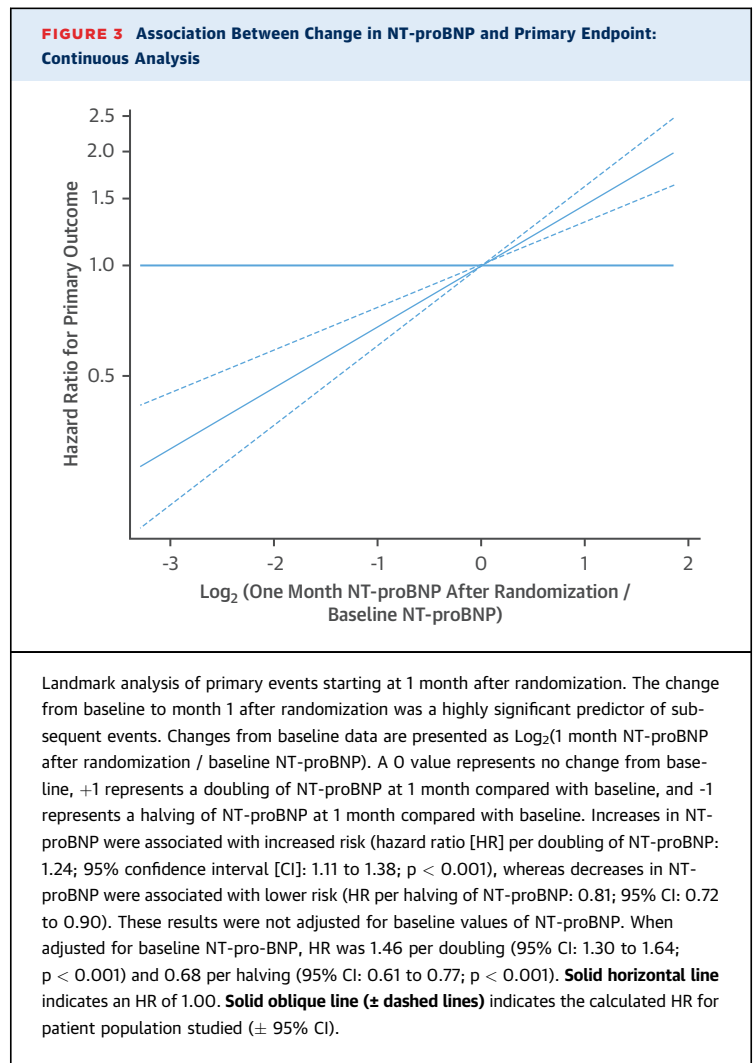
Values are n (%). *High = NT-proBNP > 1,000 pg/ml; Low = NT-proBNP ≤ 1,000 pg/ml. †OR for patients in the High-High group having a reduction of NT-proBNP that converted them to the High-Low group was twice as likely in those treated with sacubitril/valsartan versus those treated with enalapril (OR: 2.15); the OR of patients in the Low-Low group maintaining this low value of NT-proBNP and remaining in the Low-Low group was twice as likely in those treated with sacubitril/valsartan versus those treated with enalapril (OR: 2.50). NT-proBNP = N-terminal pro-B-type natriuretic peptide; OR = odds ratio.

STUDY PROCEDURES. At trial entry, all ACE inhibitors or ARBs were stopped, but other HF treatments were continued. Patients then received enalapril 10 mg twice daily for 2 weeks (single blind) followed by sacubitril/valsartan (single blind) for 4 to 6 weeks, initially at 49 mg/51 mg (100 mg of LCZ696) twice daily and then 97 mg/103 mg (200 mg of LCZ696) twice daily. Patients tolerating both drugs at target doses were randomized in a 1:1 ratio to double-blind treatment with either enalapril 10 mg twice daily or sacubitril/valsartan 97 mg/103 mg twice daily. The enalapril dose was selected on the basis of its effect in reducing mortality in the Studies of Left Ventricular Dysfunction Treatment Trial (36); higher doses have not been more effective or well tolerated long-term (36-38). After randomization, patients were maintained on the highest tolerated doses of the study medication. Worsening HF was treated by adjusting the doses of any concomitant drug and using any interventions that were clinically indicated. Mean follow-up was 2.4 years.

NT-proBNP ASSAY. The principal analysis was change in plasma NT-proBNP. NT-proBNP was measured at 5 time points: baseline before run-in (V2/V2a, n = 2,080 [1,051 subsequently treated with sacubitril/valsartan, 1,029 with enalapril]), after enalapril run-in (V3, n = 875 [440 treated with sacubitril/valsartan, 435 with enalapril]), at randomization (V5, n = 2,015 [1,018 treated with sacubitril/valsartan, 997 with enalapril]), at 1 month (V7, n = 1,942 [971 treated with sacubitril/valsartan, 971 with enalapril]), and at 8 months (V10, n = 1,759 [885 treated with sacubitril/valsartan, 874 with enalapril]) after randomization (Online Figure 1). Plasma NT-proBNP was measured with the Roche Elecsys proBNP assay (Roche Diagnostics GmbH, Mannheim, Germany). The coefficient of variation for NT-proBNP determined with the Roche Elecsys proBNP assay (Roche Diagnostics) was <2.5% at all levels tested between 47 pg/ml and 34,160 pg/ml. All available data at each time point were used to examine the change in NT-proBNP over time and the effect of treatment on NT-proBNP. All analyses were performed only in those patients who had both a baseline and a post-randomization measurement at the specified time point.

STATISTICAL ANALYSIS. Only the primary study endpoint (the first occurrence of cardiovascular death or HF hospitalization) was examined. To assess the relationship between change in NT-proBNP from baseline and subsequent risk of a primary endpoint, we performed several landmark analyses, starting with the 1-month post-randomization visit. First, among patients with elevated NT-proBNP values at baseline (>1,000 pg/ml), the hazard ratios (HRs) associated with attaining or not attaining post-baseline NT-proBNP values below specific thresholds were estimated. An initial threshold of ≤1,000 pg/ml was chosen on the basis of previous and ongoing studies (34-44), but analyses were also performed using thresholds of ≤750 pg/ml and ≤500 pg/ml. For each of these analyses, only those patients with a baseline NT-proBNP >1,000 pg/ml were examined. However, all patients with paired samples at baseline and 1 month were used for the landmark analysis of threshold changes of 10%, 20%, 30%, 40%, and 50% reduction from baseline.

Next, based on NT-proBNP values at baseline and at 1 month, patients were grouped into 4 categories: NT-proBNP ≤1,000 pg/ml at both baseline and 1 month (Low-Low group); NT-proBNP >1,000 pg/ml at baseline and 1 month (High-High group); NT-proBNP >1,000 pg/ml at baseline and ≤1,000 pg/ml at 1 month (High-Low group); and NT-proBNP



≤1,000 pg/ml at baseline and >1,000 pg/ml at 1 month (Low-High group). Kaplan-Meier curves and Cox proportional hazards models were used to characterize risk of subsequent events in each group. In addition, among all patients, the HRs associated with attaining or not attaining specific relative reductions in NT-proBNP were estimated, with and without adjustment for the log-transformed baseline NT-proBNP value. We created mutually exclusive categories of relative NT-proBNP reduction and reported event rates for each group, in all patients, and then for each treatment group. Between-group comparisons were made with respect to randomized treatment and interactions between treatment and changes in NT-proBNP.

The association between relative changes in NT-proBNP from baseline (using log_2 -transformed values) and differences in risk of subsequent events was assessed with Cox proportional hazards models,

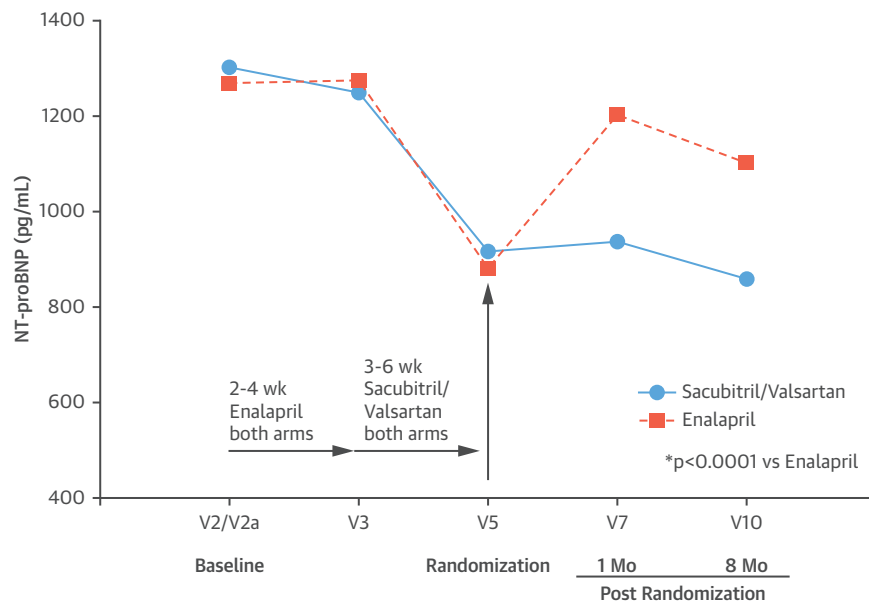
with and without adjustment for baseline NT-proBNP. The impact of randomized therapy on post-baseline NT-proBNP values was compared using the median (interquartile range [IQR]) for each treatment arm at each time point, with differences assessed for significance by Wilcoxon rank sum test. Proportions of patients experiencing the specific reductions described previously were compared with odds ratios describing the relative increase or decrease in frequency associated with study medication. Whether baseline NT-proBNP (based on a quartile analysis) modified the treatment effect of sacubitril/valsartan compared with enalapril on the primary event rate was assessed by 2 analyses. We tested for interaction between randomized therapy and quartiles of baseline NT-proBNP values (V2/V2a, n = 2,080) and estimated subgroup-specific treatment effects. To

increase power to detect meaningful differences in treatment effect, we repeated this analysis using NT-proBNP values obtained at screening (average 13 days before baseline, n = 8,348) and analyzed at local study sites (not at a central core laboratory). p Values <0.05 were considered statistically significant. No adjustments of the type I error were made for multiple testing. All analyses were conducted with STATA version 14.1 (Stata Corp., College Station, Texas).

RESULTS

CHANGE IN NT-proBNP AND CHANGE IN PRIMARY EVENT RATE. Overall, 2,080 patients had NT-proBNP measured at baseline, of whom 1,292 patients (62%) had values >1,000 pg/ml. Baseline characteristics

FIGURE 4 NT-proBNP Values in Patients Treated With Sacubitril/Valsartan Versus Enalapril at Each Study Time Point



NT-proBNP (pg/mL) Median (Q1;Q3)					
	V2/V2a	V3	V5	V7	V10
Sacubitril/Valsartan n	1303 (781;2371) 1051	1251 (653;2208) 440	917 (526;1653) 1018	938 (511;1595) 971	859 (450;1708) 885
Enalapril n	1269 (762;2184) 1029	1276 (698;2186) 435	882 (517;1692) 997	1203 (711;2061) 971	1102 (610;2073) 874

Median N-terminal pro-B-type natriuretic peptide (NT-proBNP) values in the sacubitril/valsartan-treated patients (blue circles, blue solid line) versus enalapril-treated patients (orange squares, orange dashed line) at each measurement time point are shown. Numeric values for median (interquartile range: Q1;Q3) in patients with values available at each time point are presented in the table below the figure. NT-proBNP was significantly lower in the sacubitril/valsartan-treated patients than in the enalapril-treated patients at 1 and 8 months after randomization. *p < 0.05. V2/V2a = baseline before run-in; V3 = after enalapril run-in; V5 = at randomization; V7 = 1 month after randomization; and V10 = 8 months after randomization.

for patients with baseline NT-proBNP >1,000 versus ≤1,000 pg/ml are presented in [Online Table 1](#). One month after randomization, 24% of the baseline elevated NT-proBNP levels had fallen to ≤1,000 pg/ml ([Table 1](#)); in those patients, risk of a subsequent primary endpoint was 59% lower (HR: 0.41; 95% confidence interval [CI]: 0.29 to 0.58; p < 0.0001) than in patients without a fall in NT-proBNP to ≤1,000 pg/ml at 1 month ([Figure 1, Table 2](#)). Similar lower rates of the primary event rate were seen in patients with NT-proBNP >1,000 pg/ml at baseline when the 1-month partition value was set to a reduction in NT-proBNP of ≤750 and ≤500 pg/ml ([Table 2](#)). In addition, the risk of a primary event was significantly lower when the decrease in NT-proBNP from baseline to 1 month after randomization was measured as a percent change; this analysis included all patients with a measured NT-proBNP at baseline and 1 month ([Table 1](#)).

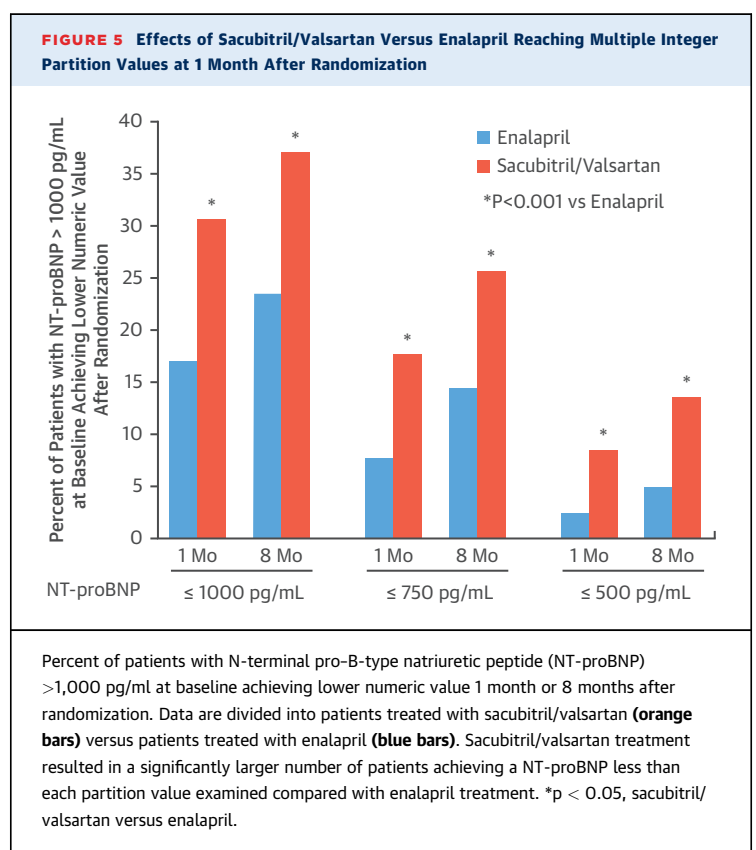
Using a categorical analysis ([Figure 2, Table 3](#)), the lowest primary event rate occurred in patients in the Low-Low group, and the highest primary event rate was seen in patients in the High-High group. Patients in the High-Low group and Low-High group had intermediate rates of the primary event. Baseline characteristics for patients in each group are presented in [Online Table 2](#).

Using a continuous analysis ([Figure 3, Online Table 3](#)), the change from baseline to month 1 was a highly significant predictor of subsequent events; the primary event rate increased as the value of NT-proBNP increased at 1 month, and the primary event rate decreased as the value of NT-proBNP decreased at 1 month. After adjustment for baseline NT-proBNP, the HR per doubling of NT-proBNP at 1 month was 1.46 (95% CI: 1.30 to 1.64), whereas the HR per halving of NT-proBNP at 1 month was 0.68 (95% CI: 0.61 to 0.77).

TREATMENT WITH SACUBITRIL/VALSARTAN VERSUS ENALAPRIL. Median NT-proBNP at baseline was 1,269 (IQR: 762 to 2,184) pg/ml for enalapril-treated patients and 1,303 (IQR: 781 to 2,371) pg/ml for sacubitril/valsartan treated patients ([Figure 4](#)). The median NT-proBNP did not change significantly during the enalapril run-in but decreased significantly during the sacubitril/valsartan run-in. One month after randomization, NT-proBNP was significantly lower in the sacubitril/valsartan-treated patients (938 [IQR: 511 to 1,595] pg/ml) compared with enalapril-treated patients (1,203 [IQR: 711 to 2,061] pg/ml; p < 0.001) for the difference between groups. At this time, NT-proBNP fell to ≤1,000 pg/ml in 31% of sacubitril/valsartan-treated patients versus 17% of

enalapril-treated patients (odds ratio: 2.15; 95% CI: 1.63 to 2.83; p < 0.0001) ([Table 1, Figure 5](#)). Among patients with NT-proBNP reduction to ≤1,000 pg/ml at 1 month and available NT-proBNP data at 8 months, NT-proBNP remained ≤1,000 pg/ml in 74% of those treated with sacubitril/valsartan versus 59% of those treated with enalapril treated (p = 0.011). Similar results were seen when the partition value was set at a reduction in NT-proBNP ≤750 and ≤500 pg/ml ([Table 1, Figure 5](#)); a larger proportion of patients treated with sacubitril/valsartan achieved these reductions than enalapril-treated patients. A similar differential treatment effect on the changes in NT-proBNP, measured as a percent reduction from baseline to 1 month after randomization ([Table 1](#)) and using the categorical analysis ([Table 3](#)), was seen with sacubitril/valsartan versus enalapril. In each analysis, a reduction in NT-proBNP or maintenance of a low NT-proBNP occurred more frequently in patients treated with sacubitril/valsartan than enalapril.

EFFECT OF BASELINE AND CHANGE IN NT-proBNP LEVELS ON TREATMENT EFFECT OF SACUBITRIL/VALSARTAN VERSUS ENALAPRIL AND THE PRIMARY EVENT RATE. Although baseline NT-proBNP was predictive of subsequent events in both treatment arms,



baseline NT-proBNP did not modify the treatment effect of sacubitril/valsartan versus enalapril (p for interaction = 0.35) (Figure 6). In each quartile of baseline NT-proBNP, treatment with sacubitril/valsartan decreased the primary event rate compared with treatment with valsartan (Figure 6). This result was consistent using both the baseline (V2/V2a, pre-run in patient group $n = 2,018$) and screening (patient group $n = 8,348$) NT-proBNP data.

There was no significant interaction between treatment and the relationship between change in NT-proBNP from baseline and the subsequent risk of the primary endpoint ($p = 0.67$ for interaction). In patients treated with sacubitril/valsartan, risk of a subsequent primary endpoint was 56% lower (HR: 0.44; 95% CI: 0.29 to 0.68; $p < 0.001$) in patients with a fall in NT-proBNP to $\leq 1,000$ pg/ml at 1 month than in patients without such a fall. In patients treated with enalapril, the risk of a subsequent primary endpoint was 62% lower (HR: 0.38; 95% CI: 0.21 to 0.66; $p = 0.001$) in patients with a fall in NT-proBNP to $\leq 1,000$ pg/ml at 1 month than in patients without such a fall (Table 2, Online Figure 2). Similar results were obtained when the partition value was set at a reduction in NT-proBNP ≤ 750 pg/ml and ≤ 500 pg/ml and when a percent reduction in NT-proBNP from baseline to 1 month after randomization was

examined (Table 2, Online Figure 3). There were no significant interactions between treatment and the relationship between change in NT-proBNP and the subsequent risk of the primary endpoint for any of these analyses (all $p > 0.40$) (Table 3, Online Figure 4).

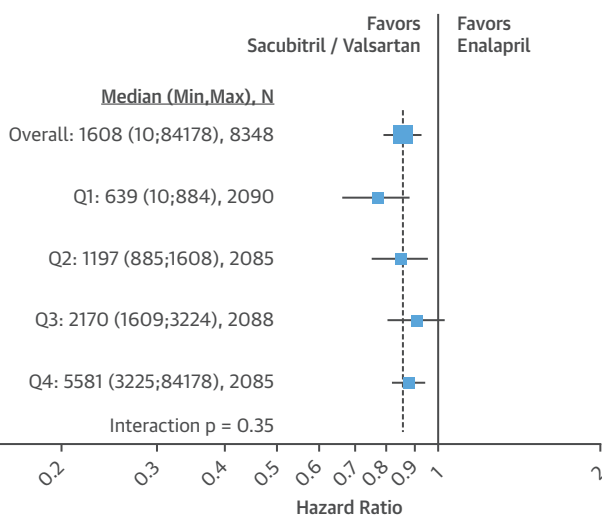
The differences in effects of enalapril versus sacubitril/valsartan on the relationship between change in NT-proBNP and a change in the primary event rate were examined by use of a continuous analysis, unadjusted and adjusted for baseline NT-proBNP values. NT-proBNP changes from baseline to month 1 were a highly significant predictor of subsequent primary events for patients in both treatment groups; adjusted for baseline NT-proBNP, the HR per doubling for enalapril patients was 1.38 (95% CI: 1.16 to 1.63; $p < 0.001$) and the HR per doubling for patients assigned to sacubitril/valsartan was 1.54 (95% CI: 1.30 to 1.82; $p < 0.001$; p for interaction = 0.54) (Online Figure 5).

DISCUSSION

In this study, a change in plasma NT-proBNP was associated with a change in cardiovascular mortality and HF hospitalization rate in patients with HFrEF. Whether NT-proBNP fell to less than a specific numeric value, decreased by a specific percentage from baseline, or changed from a higher to a lower value, these reductions were associated with a significantly lower rate of morbidity and mortality. Sacubitril/valsartan was nearly twice (≈ 1.8 times) as likely to cause a meaningful reduction in NT-proBNP as enalapril. Furthermore, the relationship between changes in NT-proBNP and changes in subsequent risk of a primary endpoint event was independent of treatment group assignment.

Sacubitril/valsartan reduces degradation of several endogenous compensatory vasoactive peptides, including BNP (35), by inhibiting neprilysin (Central Illustration). These actions can produce both hemodynamic and biological benefits that reduce the stimulus for NP synthesis, leading to the observed decrease in NT-proBNP, which is not a substrate for neprilysin and thus remains a good marker of the severity of HF even in the setting of neprilysin inhibition. Therefore, treatment with sacubitril/valsartan would be expected to both increase BNP and decrease NT-proBNP. Hemodynamic benefits produced by other treatments for HF could also lead to a reduction in NT-proBNP. ACE inhibitors and ARBs, by causing vasodilation, afterload reduction, reverse remodeling, and perhaps other effects, and cardiac resynchronization therapy, by causing reverse remodeling,

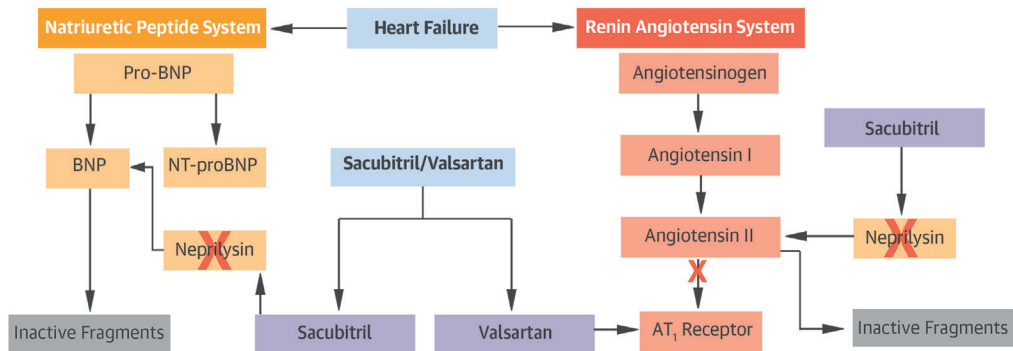
FIGURE 6 Effect of Randomized Therapy on Relationship Between Baseline NT-proBNP and Primary Event Rate



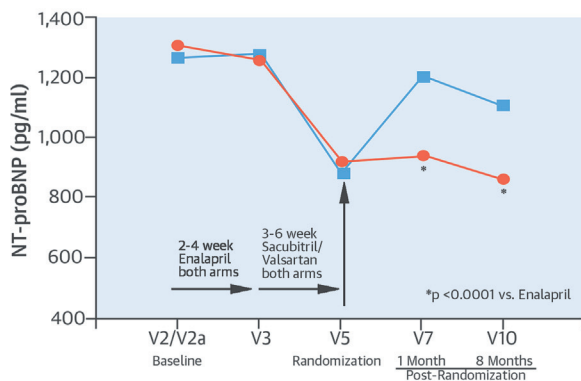
There was a significant impact of randomized therapy on the relationship between baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the primary event rate. In each quartile of baseline NT-proBNP, treatment with sacubitril/valsartan decreased the primary event rate compared with treatment with valsartan.

CENTRAL ILLUSTRATION NT-proBNP in Patients With Heart Failure: Prognostic Implications of Changes

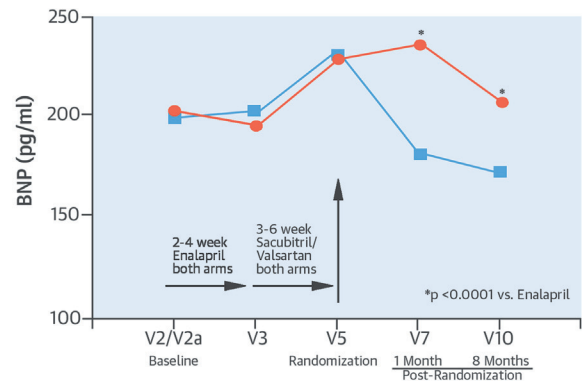
A. Sacubitril/Valsartan



B. Change in NT-proBNP: Effects of Treatment



C. Change in BNP: Effects of Treatment



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Sacubitril/Valsartan is a first-in-class neprilysin, angiotensin receptor inhibitor that promotes vasodilation and reduces vasoconstriction (A). Effects of sacubitril/valsartan could be due to direct biochemical inhibition of neprilysin and the resultant biological effect on the determinants of natriuretic synthesis. By inhibiting neprilysin, sacubitril/valsartan reduces degradation of B-type natriuretic peptide (BNP), resulting in an increase in BNP (C) and other vasoactive peptides. This might decrease both preload and afterload through diuretic and cell signaling effects. Increases in BNP and other vasoactive peptides could reduce the stimulus for natriuretic peptide synthesis by acting on the determinants of its synthesis; this conclusion is supported by the observed decrease in NT-proBNP (B). Treatment with sacubitril/valsartan would be expected to both increase BNP and decrease NT-proBNP.

also reduce NP levels, and changes in NP associated with these therapies have been related to changes in clinical outcomes.

In this analysis, changes in NT-proBNP had prognostic significance, but the relationship between change in NP and clinical outcomes has not been consistent in other studies. In 1 meta-analysis of 21 trials using study-level data (5), change in BNP and NT-proBNP was not correlated with drug- or device-induced change in mortality. However, another

meta-analysis that used individual patient data and focused on hospitalization for HF as the primary outcome (6) concluded that changes in BNP and NT-proBNP were significantly associated with the treatment-related changes in outcome.

Our analysis has a number of novel features. No previous study examined the number and variety of specific changes in NT-proBNP partition values and related these changes to morbid and mortal outcomes. We demonstrated the predictive value of

multiple partition values for absolute change, percent change, categorical change, and continuous change from baseline. The lack of interaction between NT-proBNP reduction and treatment group with respect to outcomes suggests that the prognostic value of a change in NT-proBNP is similar in patients taking sacubitril/valsartan and enalapril. However, the current data should not be interpreted as having utility in choosing which patients should receive continued long-term treatment with sacubitril/valsartan versus enalapril or when and if treatment should be terminated. At all values of baseline NT-proBNP, sacubitril/valsartan reduced the primary event rate compared with enalapril. A sustained reduction in NT-proBNP was significantly more likely with sacubitril/valsartan than with enalapril.

One ongoing prospective study, GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure; [NCT01685840](#)) is designed to evaluate the efficacy of a biomarker-guided HF treatment strategy compared with optimized medical therapy alone in a cohort of high-risk patients with HFrEF (44). However, GUIDE-IT will use a single NP partition value; the effects on outcomes will be examined in patients with a baseline >1,000 pg/ml who will be treated to target the decrease in NT-proBNP to ≤1,000 pg/ml.

STUDY LIMITATIONS. The accuracy of the predictive value of a change in any biomarker is in part dependent on at least 2 factors that influence variability in that biomarker. These include analytic variability (imprecision of the test) and biological variability (expected variability within the subject over time). Although data evaluating the percent change in NT-proBNP required to reflect a real change are limited, 1 study of 43 patients with congestive HF (CHF) (45) and another of 23 CHF patients (46) estimated the reference change value could range from 50% to 80%. In the current study, the change from baseline data in particular should therefore be interpreted in light of

the influence of the biological variability known to be present in CHF patients.

CONCLUSIONS

We demonstrated that a change in NT-proBNP, independent of the treatment group, was associated with a change in the subsequent risk of cardiovascular mortality and HF hospitalization and that sacubitril/valsartan was twice as likely to cause a prognostically meaningful reduction in NT-proBNP as enalapril.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: Patients with heart failure and reduced left ventricular ejection fraction treated with sacubitril plus valsartan are nearly twice as likely to exhibit reductions in NT-proBNP values to ≤1,000 pg/ml as those treated with enalapril, and this is associated with a lower subsequent rate of heart failure hospitalization or cardiovascular death.

TRANSLATIONAL OUTLOOK: Further studies are needed to elucidate the pathophysiological mechanisms linking biomarkers to clinical outcomes in patients with heart failure and to compare outcomes achieved with biomarker-guided therapy with those based on conventional clinical parameters alone.

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KEY WORDS biomarker, chronic heart failure, natriuretic peptide, reduced ejection fraction

APPENDIX For supplemental figures and tables, please see the online version of this article.