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NT-proBNP Response to Sacubitril/Valsartan in Hospitalized Heart Failure Patients With Reduced Ejection Fraction

TRANSITION Study

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ABSTRACT

OBJECTIVES This study examined the effects of sacubitril/valsartan on N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and determined patient characteristics associated with favorable NT-proBNP reduction response.

BACKGROUND NT-proBNP levels reflect cardiac wall stress and predict event risk in patients with acute decompensated heart failure (ADHF).

METHODS Post-hoc analysis of the TRANSITION (Comparison of Pre- and Post-discharge Initiation of Sacubitril/Valsartan Therapy in HFrEF Patients After an Acute Decompensation Event) study, including stabilized ADHF patients with reduced ejection fraction, randomized to open-label sacubitril/valsartan initiation in-hospital (pre-discharge) versus post-discharge. NT-proBNP was measured at randomization (baseline), discharge, and 4 and 10 weeks post-randomization. A favorable NT-proBNP response was defined as reduction to ≤1,000 pg/ml or >30% from baseline.

RESULTS In patients receiving sacubitril/valsartan in-hospital, NT-proBNP was reduced by 28% at discharge, with 46% of patients obtaining favorable NT-proBNP reduction response compared with a 4% reduction and 18% favorable response rate in patients initiated post-discharge ($p < 0.001$). NT-proBNP was reduced similarly in patients initiating sacubitril/valsartan pre- and post-discharge (reduction at 4 weeks: 25%/22%; 10 weeks: 38%/34%) with comparable favorable response rates (46%/42% and 51%/48% at 4 and 10 weeks, respectively). NT-proBNP favorable response at 4 weeks was associated with lower risk of first heart failure (HF) rehospitalization or cardiovascular death through 26 weeks (hazard ratio: 0.57; 95% confidence interval [CI]: 0.38 to 0.86; $p = 0.007$). Predictors of a favorable response at 4 weeks were starting dose ≥49/51 mg twice daily, higher baseline NT-proBNP, lower baseline serum creatinine, de novo HF, no atrial fibrillation, angiotensin-converting enzyme inhibitor–naive or angiotensin receptor blocker–naive, and no prior myocardial infarction.

CONCLUSIONS In-hospital initiation of sacubitril/valsartan produced rapid reductions in NT-proBNP, statistically significant at discharge. A favorable NT-proBNP response over time was associated with a better prognosis and predicted by higher starting dose and predisposing clinical profile. (Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event [TRANSITION]; NCT02661217)
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Concentrations of cardiac natriuretic peptides are independent prognostic markers in patients with heart failure (HF), irrespective of the setting (1,2). The prognostic utility of natriuretic peptides is recognized in current clinical guidelines as a Class I recommendation (1). In patients with HF and reduced ejection fraction (HFrEF), a greater N-terminal pro-B-type natriuretic peptide (NT-proBNP) reduction in response to sacubitril/valsartan administration than to enalapril has been observed in ambulatory patients (PARADIGM-HF [Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure] trial) (3) and patients hospitalized for acute decompensated HF (ADHF) (PIONEER-HF [Comparison of Sacubitril/Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode] trial) (4). In the PARADIGM-HF trial, sacubitril/valsartan was associated with a significantly lower median NT-proBNP compared with enalapril at 4 weeks after randomization (5), with nearly twice as many patients on sacubitril/valsartan achieving a NT-proBNP value <1,000 pg/ml at 4 weeks (6). Patients who attained this magnitude of reduction in NT-proBNP had a lower subsequent rate of cardiovascular (CV) death or HF hospitalization during the follow-up (6). In the PROVE-HF (Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure) trial, significant reductions in NT-proBNP were observed as early as 2 weeks and were sustained throughout the treatment period (7). Further, in the EVALUATE-HF (Effects of Sacubitril/Valsartan versus Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction) trial at 3 months and in the PROVE-HF trial at both 6 and 12 months after sacubitril/valsartan initiation, NT-proBNP reductions correlated significantly with improvements in measures of cardiac remodeling and function (7–9). The PIONEER-HF trial demonstrated a statistically significant reduction in NT-proBNP with sacubitril/valsartan versus enalapril, with differences observed as early as 1 week following initiation of in-hospital therapy (4). In that study, sacubitril/valsartan treatment was associated with a lower HF rehospitalization rate at 8 weeks compared with enalapril.

Although the PIONEER-HF trial demonstrated that in-hospital initiation of sacubitril/valsartan reduced the time-averaged NT-proBNP concentration compared with enalapril in patients with ADHF, it did not provide data on discharge NT-proBNP levels (4). In hospitalized patients with ADHF, NT-proBNP levels at discharge are a relevant and guideline-recommended measure for risk stratification (1,2). It has also been demonstrated that patients with ADHF who attain values of NT-proBNP either equal to or lower than 1,000 pg/ml (≤1,000 pg/ml), or a reduction >30% from baseline, have more favorable outcomes (10–13). In addition, identification of clinical predictors of NT-proBNP reduction response could aid prognosis in-hospital and for the vulnerable period following hospitalization.

The TRANSITION (Comparison of Pre- and Post-discharge Initiation of Sacubitril/Valsartan Therapy in HFrEF Patients After an Acute Decompensation Event) study included patients with reduced left ventricular ejection fraction (≤40%) hospitalized for ADHF and demonstrated that initiation of sacubitril/valsartan in-hospital, or shortly after discharge, was feasible and well tolerated (14,15). NT-proBNP was measured at discharge and during the vulnerable phase after hospitalization. The current study aimed to describe the pattern and clinical predictors of NT-proBNP response to sacubitril/valsartan when initiated either in-hospital or shortly after discharge.

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ADHF = acute decompensated heart failure

AF = atrial fibrillation

ARB = angiotensin receptor blocker

CI = confidence interval

CV = cardiovascular

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

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

METHODS

STUDY POPULATION AND DESIGN. TRANSITION (NCT02661217) was a randomized, multicenter, open-label study performed in 19 countries and 156 hospitals that compared the tolerability of initiating sacubitril/valsartan in-hospital versus early after discharge in patients with ADHF and HFrEF. The study design and rationale and a detailed description of population characteristics and primary results have

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Heart Failure* author instructions page.

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TABLE 1 Baseline Characteristics

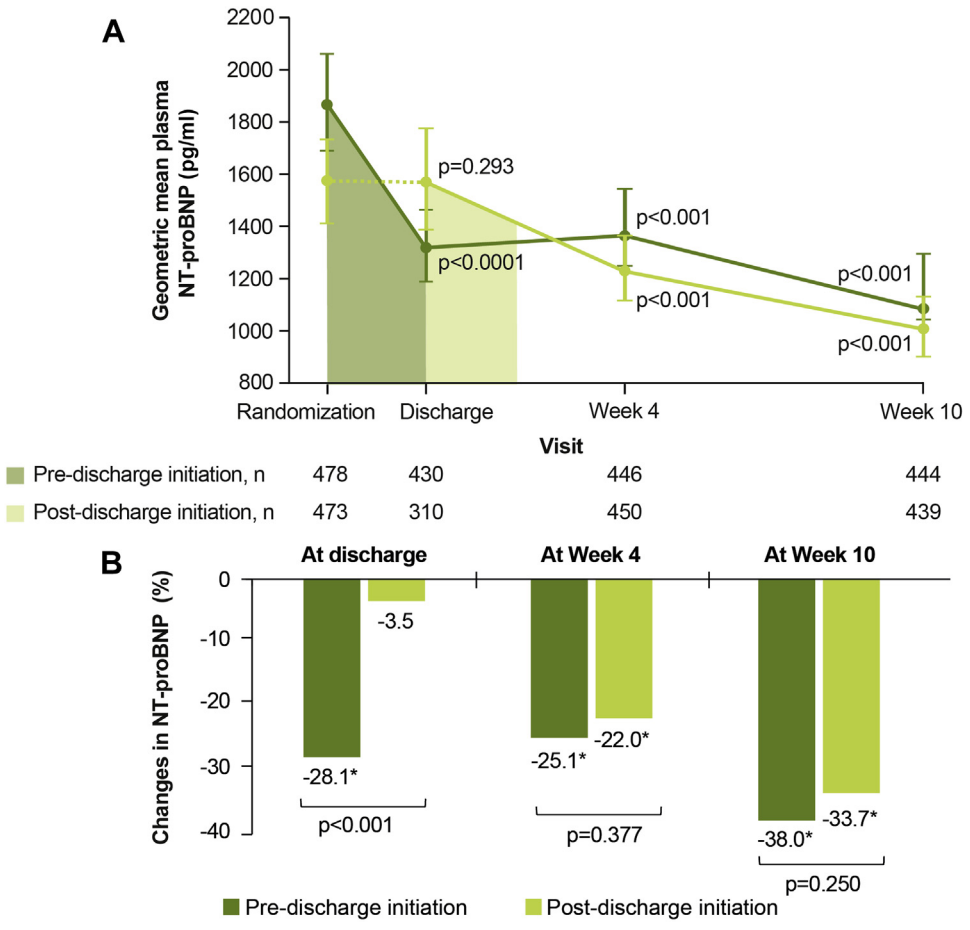
	Pre-Discharge Initiation (n = 495)	Post-Discharge Initiation (n = 496)	Total Population (N = 991)
Mean age, yrs	66.7	66.9	66.8
Male	371 (74.9)	373 (75.2)	744 (75.1)
Caucasian	483 (97.6)	480 (96.8)	963 (97.2)
BMI, kg/m^2*	27.9 (17.6–58.8)	28.8 (17.1–53.8)	28.4 (17.1–58.8)
LVEF, %	28.6 ± 7.5	29.0 ± 7.6	28.8 ± 7.6
NYHA functional class*			
I	0 (0.0)	3 (0.6)	3 (0.3)
II	320 (64.6)	315 (63.5)	635 (64.1)
III	166 (33.5)	173 (34.9)	339 (34.2)
IV	7 (1.4)	4 (0.8)	11 (1.1)
SBP, mm Hg	124.0 ± 13.8	124.0 ± 14.1	124.0 ± 14.0
Pulse, beats/min	73.8 ± 13.6	74.9 ± 12.2	74.4 ± 12.9
eGFR, ml/min/1.73 m^2*	61.6 ± 20.5	62.5 ± 19.4	62.0 ± 20.0
Ischemic HF etiology	218 (44.0)	239 (48.2)	457 (46.1)
De novo HF	148 (29.9)	138 (27.8)	286 (28.9)
Prior hospitalization for HF	236 (47.7)	249 (50.2)	485 (48.9)
NT-proBNP, pg/ml*	1,902 (945–3,847)	1,669 (706–3,599)	1,744 (846–3,719)
hs-TnT, ng/l*	29 (18–45)	28 (17–44)	29 (18–44)
Starting dose of sacubitril/valsartan†			
24/26 mg twice daily	436 (88.4)	413 (84.5)	849 (86.5)
49/51 mg twice daily	57 (11.6)	76 (15.5)	133 (13.5)
97/103 mg twice daily	0	0	0
Medical history			
Hypertension	372 (75.2)	375 (75.6)	747 (75.4)
Diabetes	226 (45.7)	234 (47.2)	460 (46.4)
AF	243 (49.1)	237 (47.8)	480 (48.4)
Myocardial infarction	168 (33.9)	171 (34.5)	339 (34.2)
Stroke	51 (10.3)	46 (9.3)	97 (9.8)
CRT	38 (7.7)	50 (10.1)	88 (8.9)
Implantable cardioverter-defibrillator insertion	73 (14.7)	79 (15.9)	152 (15.3)
Stratification at screenings			
ACE inhibitor	250 (50.5)	253 (51.0)	503 (50.8)
ARB	123 (24.8)	124 (25.0)	247 (24.9)
ACE inhibitor/ARB-naive	122 (24.6)	119 (24.0)	241 (24.3)
Other HF- and CV-related medications prior to admission			
Beta-blocker	213 (43.0)	233 (47.0)	446 (45.0)
MRA	169 (34.1)	181 (36.5)	350 (35.3)
Diuretic	248 (50.1)	261 (52.6)	509 (51.4)
Loop diuretics	238 (48.1)	245 (49.4)	483 (48.7)
Thiazide diuretics	15 (3.0)	13 (2.6)	28 (2.8)
Cardiac glycosides	63 (12.7)	45 (9.1)	108 (10.9)
Nitrates	31 (6.3)	45 (9.1)	76 (7.7)

Values are mean, n (%), median (interquartile range), or mean ± SD. Parameters were assessed at screening except, with some exceptions. Modified with permission from Wachter et al. (15). *Assessed at randomization. †Assessed from safety set.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; CRT = cardiac resynchronization therapy; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; hs-TnT = high-sensitivity troponin T; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure.

been previously published (14,15). In brief, the study included male or female subjects ≥18 years of age who were hospitalized for an episode of ADHF (de novo HF or deterioration in chronic HF), with left ventricular ejection fraction ≤40%, New York Heart Association functional class II to IV, and blood pressure ≥100 mm Hg at screening. Prior to randomization, patients were stratified based on their pre-admission use of renin-angiotensin-aldosterone system inhibitor therapy: angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or ACE inhibitor or ARB treatment naive. Within each stratum and 24 h after hemodynamic stabilization (defined as no need for intravenous diuretic agents in

FIGURE 1 NT-proBNP Response Following Sacubitril/Valsartan Initiation at Pre-Discharge Versus Post-Discharge

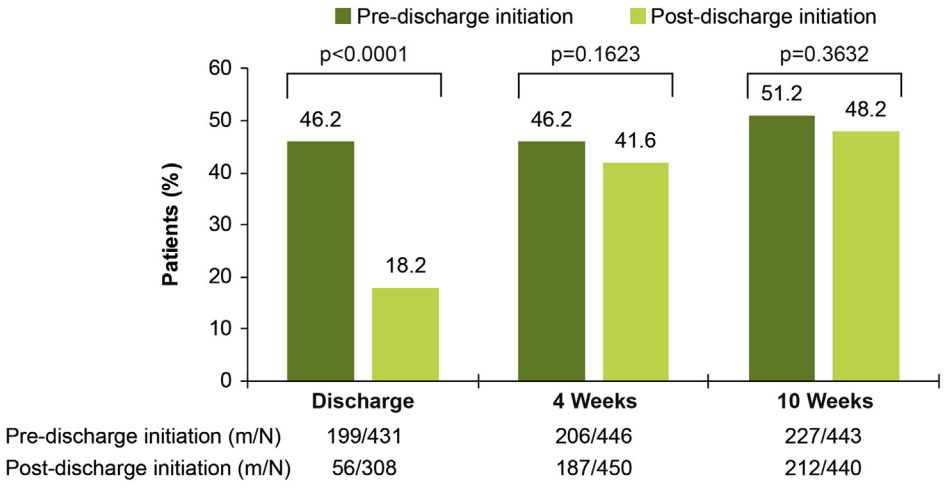


(A) N-terminal pro-B-type natriuretic peptide (NT-proBNP) (pg/ml) geometric mean by visit and treatment. **Dotted line** represents time of optimized heart failure treatment without sacubitril/valsartan in post-discharge group. **(B)** Change from baseline (randomization visit) in NT-proBNP. *Change from baseline is $p < 0.05$; mixed model with repeated measures. Total safety set was n = 493 pre-discharge and n = 489 post-discharge. **Numbers in the figure** reflect the numbers of patient samples measured at each time point.

the 24 h prior to signing informed consent, and systolic blood pressure ≥110 mm Hg for at least 6 h prior to randomization), patients were randomized 1:1 to start sacubitril/valsartan either in-hospital (pre-discharge) or post-discharge. Patients in the pre-discharge group received the first dose of sacubitril/valsartan no later than 12 h before discharge and ≤7 days after randomization. Patients in the post-discharge group received the first dose of sacubitril/valsartan at any time between days 1 and 14 post-discharge. Investigators were encouraged to up-titrate sacubitril/valsartan in order to achieve and maintain the target dose (97/103 mg twice daily) along with optimization of other HFrEF therapies. Down-titration or temporary discontinuation of sacubitril/valsartan was allowed in both groups at any time in line with label recommendations.

In total, 1,002 patients were randomized, and the full analysis set comprised 991 patients (n = 495 and n = 496 for the pre-and post-discharge groups, respectively). Of these, 982 patients received at least 1 dose of sacubitril/valsartan (safety analysis set) and were included in the analysis (15). The mean time from index admission to randomization was 7.1 ± 4.0 days (Supplemental Table 1). The study was conducted in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice and with the ethical principles laid down in the Declaration of Helsinki (16). Trial protocol was approved by ethics committees at participating centers. All subjects provided written informed consent.

FIGURE 2 Proportion of Patients Achieving a Favorable NT-proBNP Reduction Response to Sacubitril/Valsartan Treatment Initiation



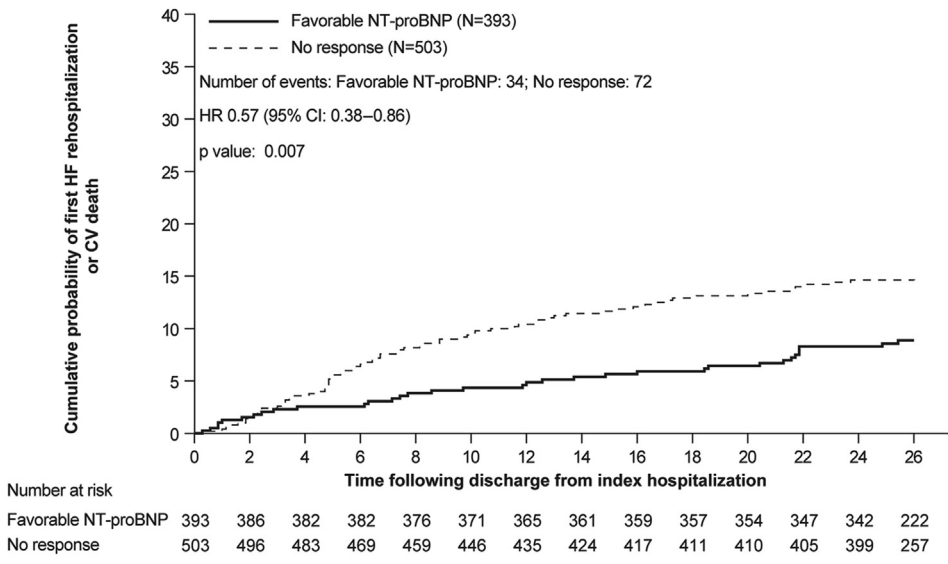
Favorable reduction response is defined as achievement of either N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels ≤1,000 pg/ml or >30% reduction vs. baseline. Note that at discharge patients who were randomized to the post-discharge initiation group had not received sacubitril/valsartan, and values presented are reflective of condition of the patients under optimized standard of care heart failure therapies. m = number of patients with NT-proBNP assessments ≤1,000 pg/ml or >30% reduction from baseline; N = number of patients with nonmissing NT-proBNP assessments at both baseline and corresponding post-baseline time point.

NT-proBNP ANALYSIS. NT-proBNP was measured at randomization (following hemodynamic stabilization), discharge, 4 weeks, and 10 weeks post-randomization in a centralized core lab. Personnel measuring NT-proBNP were blinded to clinical data pertaining to study participants. Plasma NT-proBNP analysis employed a chemiluminescent immunoassay (proBNP II, Roche Diagnostics GmbH, Mannheim, Germany) with a reporting range of 5 to 35,000 pg/ml. Patterns of NT-proBNP response at discharge and 4 and 10 weeks post-randomization were assessed as a predefined exploratory endpoint. Based on previous findings that NT-proBNP reduction is a strong predictor of outcome in both ADHF and stabilized HF patients (6,10–13,17), a post hoc subanalysis of data obtained during the TRANSITION study was conducted in which we defined a favorable NT-proBNP response to sacubitril/valsartan therapy as the achievement of either levels ≤1,000 pg/ml or >30% reduction versus baseline.

STATISTICAL ANALYSIS. A repeated-measurement model was performed on change from baseline log-transformed biomarker data. Least square means, treatment differences, and 95% confidence intervals (CIs) were back-transformed to provide geometric least square means (as a ratio to baseline) for each time point. A nominal p value <0.05 was considered statistically significant without adjusting for multiplicity.

A multivariate logistic regression model analysis was performed to identify baseline predictors of achieving a favorable NT-proBNP response at each of the 3 time points—discharge, week 4, and week 10. Odds ratios and 95% CI were obtained to identify factors with a high likelihood of achieving a favorable response. Candidate predictors were identified from baseline and medical history variables and filtered in a univariate analysis at a level of $p < 0.20$. In the final multivariate analysis models, only predictors with $p < 0.05$, baseline NT-proBNP level, and treatment group were maintained. The full set of predictors included in the univariate analysis and corresponding p values are included in Supplemental Table 2. We also evaluated the cumulative incidence of the composite of first rehospitalization for HF or CV death. Cumulative event rates were calculated according to the Kaplan-Meier method and compared between early favorable NT-proBNP reduction response versus no favorable NT-proBNP reduction response groups at 4 weeks. Hazard ratios (HRs) with associated 95% CIs were calculated using a Cox proportional hazards model. Tests for proportional hazards were performed. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina) based on the safety population set that consisted of all randomized patients who received at least 1 dose of the study drug (14).

FIGURE 3 Effect of Favorable NT-proBNP Reduction Response to Sacubitril/Valsartan at Week 4 on Clinical Outcomes From Discharge Through 26 Weeks



Kaplan-Meier plot depicting cumulative probability of the clinical composite outcome of first heart failure (HF) rehospitalization or cardiovascular (CV) death by early favorable N-terminal pro–B-type natriuretic peptide (NT-proBNP) reduction response at week 4. Favorable NT-proBNP reduction response = achievement of either NT-proBNP levels ≤1,000 pg/ml or >30% reduction from baseline at week 4. No favorable NT-proBNP reduction response = patients who did not meet the criteria for a NT-proBNP favorable response at week 4. The p value was obtained from Cox proportional hazards regression analysis model, with NT-proBNP response at week 4 and treatment initiation group in the model. Data represent patients in the safety analysis set. CI = confidence interval; HR = hazard ratio.

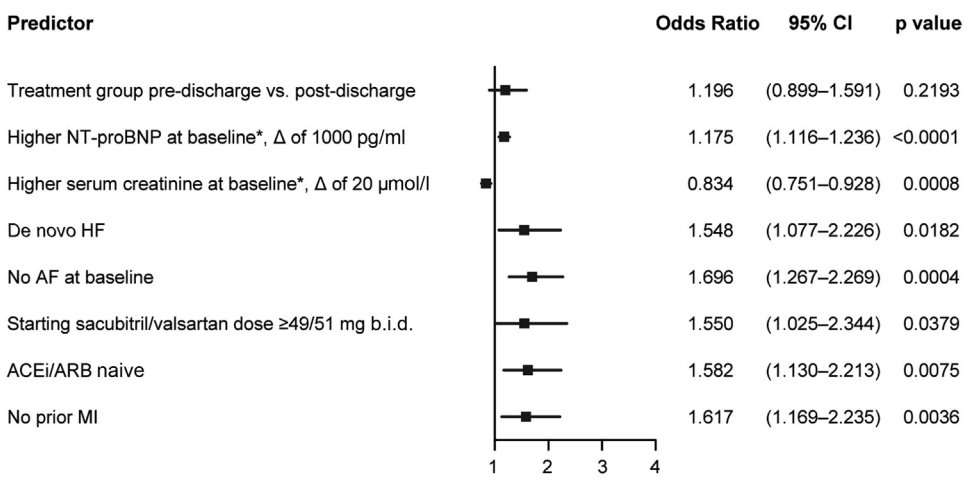
RESULTS

STUDY POPULATION. In total, 982 patients received at least 1 dose of sacubitril/valsartan (safety analysis set) and were included in the analysis. Baseline characteristics for pre- and post-discharge initiation groups are shown in **Table 1**. Median NT-proBNP level at randomization (baseline) was 1,902 (interquartile range: 945 to 3,847) pg/ml in the pre-discharge initiation group (n = 495) pg/ml and 1,669 (interquartile range: 706 to 3,599) pg/ml in the post-discharge initiation group (n = 496), with no statistically significant difference between groups (p = 0.236). The timing of initiation of sacubitril/valsartan with respect to study visits, and the duration of index hospitalization are shown in Supplemental Table 1.

NT-proBNP RESPONSE. The time course of changes in NT-proBNP levels is depicted in **Figure 1**. The mean time from randomization (baseline) to discharge was 2.4 days and 1.5 days for the pre- and post-discharge initiation groups, respectively (Supplemental Table 1). In the pre-discharge initiation patients, NT-proBNP was reduced by 28% at discharge ($p < 0.0001$), compared with a 4% reduction ($p = 0.293$) achieved in the patients who received optimized standard of care at the time of discharge and who started sacubitril/valsartan only post-discharge (between group $p < 0.001$) (**Figure 1**). Similarily, a favorable NT-proBNP response to sacubitril/valsartan at discharge was achieved in 46% of patients in the pre-discharge initiation group versus 18% of the post-discharge initiation group (**Figure 2**). At week 4 after randomization, when patients in both groups were receiving sacubitril/valsartan, the NT-proBNP reduction from baseline became significant in both groups: 25% in the pre-discharge initiation group ($p < 0.001$) and 22% in post-discharge initiation group ($p < 0.001$), with no statistically significant differences between groups (p = 0.377) (**Figure 1**). At week 10, a further reduction in NT-proBNP was observed, resulting in reductions from baseline of 38% and 34% in the pre- and post-discharge initiation groups respectively (both $p < 0.001$), with no statistically significant differences between groups (p = 0.250) (**Figure 1**). As shown in **Figure 2**, the corresponding rates of a favorable NT-proBNP response were 46% and 42% at 4 weeks, and 51% and 48% at 10 weeks, without differences between the pre- and post-discharge groups.

NT-proBNP RESPONSE AND RISK OF ADVERSE EVENTS. A total of 118 (12%) patients presented with

FIGURE 4 Predictor Analyses for Attaining a Favorable NT-proBNP Reduction Response From Baseline (Either NT-proBNP Levels ≤1,000 pg/ml or >30% Reduction From Baseline) at 4 Weeks



Multivariate logistic regression was used for the analyses. Only predictors with p values <0.05 were kept in the final model. Treatment group and baseline NT-proBNP, Δ of 1,000 pg/ml was included as a covariate in the model regardless of the p value. For NT-proBNP and serum creatinine, the baseline assessment was taken at randomization visit. Data represent patients in the safety analysis set. ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; b.i.d. = twice daily; MI = myocardial infarction; other abbreviations as in Figure 3.

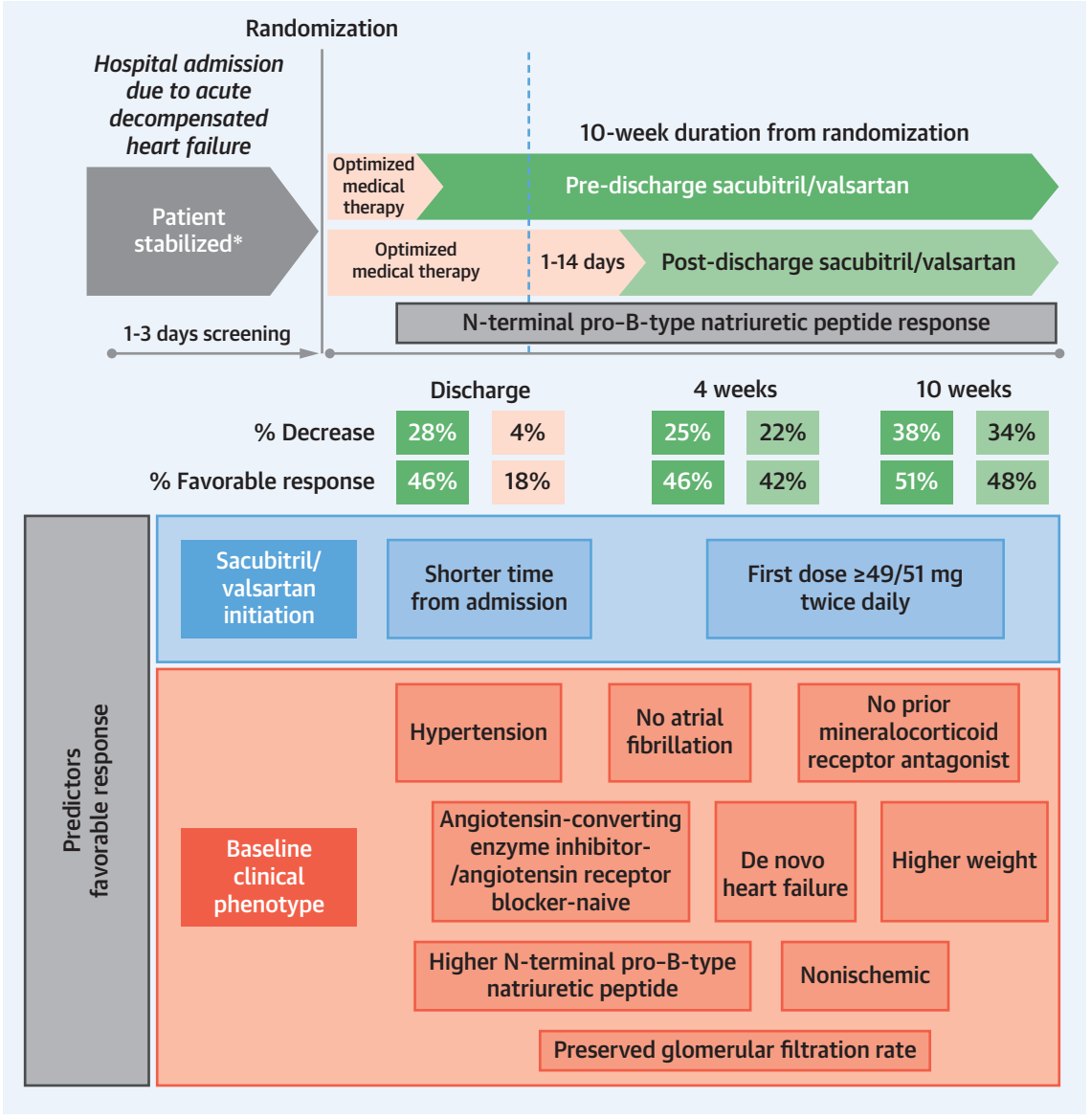
a first HF rehospitalization and 19 (1.9%) CV deaths were reported over the 6-month period of follow-up. Those patients above the median of NT-proBNP at baseline elicited a higher risk of first HF readmission or CV death (HR: 0.27; 95% CI: 0.18 to 0.42; $p < 0.001$) (Supplemental Figure 1). The risk of events did not differ between the treatment initiation groups, pre-discharge versus post-discharge (HR: 0.99; 95% CI: 0.70 to 1.41; $p = 0.957$) (Supplemental Figure 2), but considering the NT-proBNP response to sacubitril/valsartan, those patients with a favorable NT-proBNP response at 4 weeks elicited a significant lower risk of the composite clinical outcome of first HF rehospitalization or CV death (HR: 0.57; 95% CI: 0.38 to 0.86; $p = 0.007$) (Figure 3).

CLINICAL PREDICTORS OF NT-proBNP RESPONSE. We explored clinical predictors of achieving a favorable NT-proBNP response at discharge, 4 weeks, and 10 weeks (Supplemental Table 2). After multivariate logistic regression, the only significant ($p < 0.05$) predictors of attaining a favorable NT-proBNP response at discharge were history of hypertension and shorter time from admission to first sacubitril/valsartan dose (Supplemental Table 3). Predictors of favorable NT-proBNP response at 4 weeks were higher NT-proBNP at baseline, lower serum creatinine at baseline, de novo HF, no atrial fibrillation (AF) at baseline, higher initial dose of sacubitril/valsartan (≥49/51 mg twice daily), ACE inhibitor- or ARB-naive, and no prior myocardial infarction (Figure 4 and Supplemental Table 4). At 10 weeks, the predictors were similar to week 4, and included higher NT-proBNP at baseline, lower serum creatinine at baseline, de novo HF, no AF at baseline, higher initial dose of sacubitril/valsartan (≥49/51 mg twice daily), ACE inhibitor- or ARB-naive, no mineralocorticoid receptor antagonist at baseline, nonischemic etiology, and higher weight (Supplemental Table 5).

DISCUSSION

This analysis of the TRANSITION study expands the knowledge about the NT-proBNP response to sacubitril/valsartan initiation in patients with HFrEF provided by the PARADIGM-HF and PIONEER-HF trials (4-6). The data presented show rapid NT-proBNP reduction after in-hospital initiation of sacubitril/valsartan therapy, which was significant at the time of discharge, (i.e., within 2 to 3 days). Notably, a sustained favorable NT-proBNP response at 4 weeks was predictive of better clinical outcomes through 26 weeks. In addition, we identified clinical predictors associated with a favorable NT-proBNP response up to 10 weeks post-randomization. All of these findings support the close relationship between

CENTRAL ILLUSTRATION **TRANSITION Study: NT-proBNP Response to Sacubitril/Valsartan and Patient Characteristics Associated With a Favorable Reduction Response**



Pascual-Figal, D. et al. J Am Coll Cardiol HF. 2020;8(10):822-33.

ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; GFR = glomerular filtration rate; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OMT = optimized medical therapy; sac/val = sacubitril/valsartan.

NT-proBNP response and sacubitril/valsartan therapy (Central Illustration).

Within a few days after in-hospital initiation of sacubitril/valsartan in the pre-discharge group, NT-proBNP levels declined by a statistically significant 28% at discharge, in contrast to the nonsignificant 4% decrease in patients treated in-hospital with optimized standard of care therapies for HFrEF. As per the study design, the first biomarker samples to assess the effect of sacubitril/valsartan post-discharge were

TABLE 2 NT-proBNP Response to Sacubitril/Valsartan and Relationship With Clinical Events Across a Range of Studies

	PARADIGM-HF Trial	PROVE-HF Trial	PIONEER-HF Trial	TRANSITION Study
Total number of sacubitril/valsartan treated patients	4,187	794	440	982
Baseline setting	Out of hospital, CHF	Out of hospital, CHF	In hospital, 2.0–3.0 days after admission due to ADHF event	In hospital, 7–7.3 days after admission due to ADHF event
First significant NT-proBNP reduction				
Time	End of sacubitril/valsartan run-in period (4–6 weeks)	2 weeks	1 week	Discharge (mean 2.4 days)
Reduction from baseline	30%	30%	43%	28%
Last reported sustained NT-proBNP reduction				
Time	8 months	12 months	12 weeks	10 weeks
Reduction from baseline	34%	37%	65%	38%
Association with composite clinical outcome (HFH or CV death)				
Reference	Decrease from >1,000 pg/ml to ≤1,000 pg/ml	Not reported	Not reported	Decrease of >30% from baseline or from >1,000 pg/ml to ≤1,000 pg/ml
Time	Baseline to 4 weeks	Not reported	Not reported	Baseline to 4 weeks
Risk reduction	50% at 3 yrs	Not reported	Not reported	43% at 26 weeks

ADHF = acute decompensated heart failure; CHF = chronic heart failure; HFH = heart failure hospitalization; PARADIGM-HF = Prospective comparison of angiotensin receptor neprilysin inhibitor with angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure; PIONEER-HF = Comparison of Sacubitril/Valsartan Versus Enalapril on Effect on NTproBNP in Patients Stabilized From an Acute Heart Failure Episode; PROVE-HF = Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure; TRANSITION = Comparison of Pre- and Post-discharge Initiation of Sacubitril/Valsartan Therapy in HFrEF Patients After an Acute Decompensation Event; other abbreviations as in Table 1.

taken at 4 weeks post-randomization in both initiation groups. At this time point, a similar NT-proBNP reduction of 25% and 22% was observed in both groups. This pattern was even more pronounced in terms of the proportion of patients achieving a favorable NT-proBNP response. By discharge, 46% of patients who initiated sacubitril/valsartan in-hospital had already reached a favorable NT-proBNP response, which remained unchanged at week 4 (46%). In contrast, in the post-discharge initiation group, the proportion of patients achieving a favorable NT-proBNP response at discharge and at week 4 were 18% and 42%, respectively. This rapid reduction of NT-proBNP in response to sacubitril/valsartan was also observed in the PIONEER-HF trial, in which a reduction of approximately 43% was observed at 1 week from randomization in the sacubitril/valsartan group (4). Rapid reductions in NT-proBNP following initiation of sacubitril/valsartan were also observed in the outpatient setting. Recently, the PROVE-HF trial reported a 30% NT-proBNP reduction 2 weeks after sacubitril/valsartan initiation (7). In the PARADIGM-HF trial, NT-proBNP did not change significantly during the enalapril run-in period, but an approximate 30% decrease was observed during the sacubitril/valsartan run-in (6). In the extension phase of the PIONEER-HF trial, a 37% reduction in NT-proBNP was observed at week 4 after the group on enalapril had been switched to sacubitril/valsartan (18). Therefore, the TRANSITION study data provide supporting evidence for the rapid effect of sacubitril/valsartan initiation on NT-proBNP reduction that is apparent within a few days, suggesting a fast improvement in cardiac wall stress (19,20). This rapid reduction in NT-proBNP is relevant given the association of NT-proBNP concentrations at discharge, with adverse clinical outcomes during the vulnerable phase after ADHF event (21). Notably, this reduction was attained despite the lower starting dose of sacubitril/valsartan (24/26 mg twice daily) being selected by the investigators for most patients (88%) in the pre-discharge initiation group (15).

After the initial rapid decrease of NT-proBNP concentrations, the relative reduction from baseline and the proportion of patients achieving a favorable response remained constant for the next 10 weeks. This pattern of a rapid NT-proBNP decrease with sacubitril/valsartan followed by sustained reduction has been also observed in other studies, after in-hospital or ambulatory initiation (4,5,7). In the PROVE-HF trial, the magnitude of the NT-proBNP reduction remained similar after the first measurement at 2 weeks: -30% (day 14), -31% (day 30), -35% (6 months), and -37% (12 months) (7). This sustained

reduction in NT-proBNP after the initiation of sacubitril/valsartan may be associated with a cardioprotective effect.

Trajectories of NT-proBNP change after discharge are more predictive than changes measured during hospitalization, and are associated with risk of rehospitalization and CV death (ASTRONAUT [Aliskiren Trial on Acute Heart Failure Outcomes] trial) (22). As expected, we found an association of baseline NT-proBNP levels with outcomes. The lack of differences in terms of events between treatment initiation groups in the TRANSITION study may be explained by the fact that patients in the post-discharge group received the first dose of sacubitril/valsartan relatively soon—at a mean of 3.3 days after discharge. However, when all patients were on therapy, we found that a favorable NT-proBNP response at 4 weeks was associated with a decreased risk of clinical outcomes. This association is in line with previous evidence showing that NT-proBNP response to sacubitril/valsartan predicts clinical outcomes (PARADIGM-HF [Prospective comparison of angiotensin receptor neprilysin inhibitor with angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure] and PIONEER-HF [Comparison of Sacubitril/Valsartan Versus Enalapril on Effect on NTproBNP in Patients Stabilized From an Acute Heart Failure Episode] trials) (6,23) and a sustained decrease of NT-proBNP over time correlates more closely with clinical prognosis than single measures (PARADIGM-HF trial; Val-HeFT [Valsartan Heart Failure Trial]; meta-analysis in patients with chronic HF) (6,20,24). **Table 2** summarizes the comparative findings from the TRANSITION study and other randomized trials, regarding the earliest time point of NT-proBNP response to sacubitril/valsartan initiation and the relationship with reduced risk of HF rehospitalizations and CV death events.

To date, no data on predictors of a persistent NT-proBNP reduction response over time after initiating sacubitril/valsartan have been published. In this context, the identification of predictors of either a favorable or unfavorable response could assist the clinician. The new evidence from the TRANSITION study allows, for the first time, an analysis of predictors for maintaining a favorable NT-proBNP response to sacubitril/valsartan at discharge and at 4 and 10 weeks during the vulnerable post-ADHF phase. A history of hypertension and a shorter time from admission to sacubitril/valsartan initiation were the identified predictors of a rapid and favorable NT-proBNP reduction response at discharge. The latter could explain the greater ratio of the geometric mean of NT-proBNP reduction obtained at weeks 4 and 8 relative to the baseline value (-47%) observed in the PIONEER-HF trial, in which patients initiated sacubitril/valsartan earlier—at a median of 68 h after admission, in contrast to the median of 7 days in TRANSITION. The set of predictors was quite similar for 4 weeks and 10 weeks, reflecting the existence of a clinical profile predisposed to attaining and retaining a favorable NT-proBNP response over time. De novo HF patients, absence of AF, better renal function, higher NT-proBNP concentration at randomization, and a nonischemic HF etiology were associated with a favorable NT-proBNP response, as well as being naive to ACE inhibitor, ARB, or mineralocorticoid receptor antagonist treatment. Notably, a higher probability of NT-proBNP reduction response over time was associated with a higher starting dose of sacubitril/valsartan (49/51 mg twice daily), which could be explained by a greater exposure to the medication or, alternatively, reflect a more selected clinical profile. In the PIONEER-HF trial, NT-proBNP improvement at 8 weeks was achieved irrespective of dose level of sacubitril/valsartan in treated patients (23,25).

The new evidence from the TRANSITION study indicates that early initiation of sacubitril/valsartan induces a rapid lowering in the level of NT-proBNP that is already detectable at discharge. Although, the initiation after discharge resulted in a similar magnitude of reduction in NT-proBNP after a few weeks, delayed initiation may result in patients with ADHF missing important clinical benefits during the vulnerable phase and beyond. The PIONEER-HF trial provided the first evidence of the superiority of in-hospital initiation shortly after ADHF of sacubitril/valsartan over the ACE inhibitor enalapril, with a comparable tolerability profile. The difference in clinical outcomes persisted in the extension phase, when all patients were on sacubitril/valsartan and differences in NT-proBNP were no longer evident at 12 weeks (18). The results of the TRANSITION study described here further support the earliest possible initiation of sacubitril/valsartan in patients stabilized after ADHF (26).

STUDY LIMITATIONS. Limitations of the analysis are the lack of NT-proBNP concentration at admission and the definition of favorable reduction response, based on data from previous trials that included mainly ambulatory HF populations. The baseline measure of NT-proBNP was obtained ~7 days following admission, 24 h after discontinuation of intravenous diuretics, still in the transition phase but not fully encompassing the decompensated phase.

Despite the current consensus of 24 h on oral diuretic therapy prior to discharge (27), variability in clinical practice between health systems could not be accounted for. Nevertheless, randomization ensured NT-proBNP values at baseline did not differ between treatment initiation groups, and the definition of NT-proBNP favorable reduction response is well supported in the literature as a clinically meaningful response (10–13).

CONCLUSIONS

This analysis from TRANSITION shows a rapid decrease of NT-proBNP concentrations at discharge, within a few days of sacubitril/valsartan in-hospital initiation. A favorable response to sacubitril/valsartan at 4 weeks was associated with a better prognosis and was predicted by higher starting dose and a predisposing clinical profile. These findings, along with current clinical evidence, provide support for early in-hospital initiation of sacubitril/valsartan in patients hospitalized with ADHF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The results presented here expand current knowledge by showing rapid and significant NT-proBNP reduction after initiating sacubitril/valsartan in-hospital, which was already significant at discharge. In addition, this study supports that a sustained favorable NT-proBNP response to sacubitril/valsartan is clinically meaningful after discharge and provides clinical predictors of that NT-proBNP response over time, which could assist the clinician during hospitalization and the vulnerable phase after discharge.

TRANSLATIONAL OUTLOOK: This work provides new insights into the rapid mechanistic effects of sacubitril/valsartan initiation in hospitalized patients with HFrEF, and identifies clinical predictors of a maintained favorable response of NT-proBNP over time.

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APPENDIX For an expanded Methods section and supplemental tables and figures, please see the online version of this paper.