

## Accepted Manuscript

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PII: S1071-9164(18)30979-5  
DOI: <https://doi.org/10.1016/j.cardfail.2019.04.002>  
Reference: YJCAF 4313

To appear in: *Journal of Cardiac Failure*

Please cite this article as: Justin L. Grodin MD MPH , Max J. Liebo MD , Javed Butler MD , Marco Metra MD , G. Michael Felker MD , Adrian F. Hernandez , Adriaan A. Voors MD , John J. McMurray MD , Paul W. Armstrong MD , Christopher O'Connor MD , Randall C. Starling MD MPH , Richard W. Troughton MD PhD , W.H. Wilson Tang MD , Prognostic Implications of Changes in Amino-Terminal Pro-B-Type Natriuretic Peptide in Acute Decompensated Heart Failure: Insights from ASCEND-HF, *Journal of Cardiac Failure* (2019), doi: <https://doi.org/10.1016/j.cardfail.2019.04.002>

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**Prognostic Implications of Changes in Amino-Terminal Pro-B-Type Natriuretic Peptide in Acute Decompensated Heart Failure: Insights from ASCEND-HF**

**Short title:** Changes in NTproBNP in Acute HF

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**Date:** March 25, 2019

**Word Count:** 3,181

**Page count:** 28

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**ABSTRACT**

**BACKGROUND.** Amino terminal pro-B-type natriuretic peptide (NTproBNP) is closely associated with prognosis in acute decompensated heart failure (ADHF). As a result, there has been great interest measuring it during the course of treatment. The prognostic implications in both short-term and follow-up changes in NTproBNP need further clarification.

**METHODS.** Baseline, 48-72 hour, and 30-day NTproBNP levels were measured in 795 subjects in the ASCEND-HF trial. Multivariable logistic and Cox-proportional hazards models were used to test the association between static, relative, and absolute changes in NTproBNP with outcomes during and after ADHF.

**RESULTS.** The median NTproBNP at baseline was 5,773 (2,981-11,579) pg/ml; at 48-72 hours was 3,036 (1,191-6,479) pg/ml; and at 30 days was 2,914 (1,364-6,667) pg/ml. Absolute changes in NTproBNP by 48-72 hours were not associated with 30-day heart failure rehospitalization or mortality ( $P=0.065$ ), relative changes in NTproBNP were nominally associated ( $P=0.046$ ). In contrast, both absolute and relative changes in NTproBNP from baseline to 48-72 hours and to 30 days were closely associated with 180-day mortality ( $P<0.02$  for all) with increased discrimination in comparison to the multivariable models with baseline NTproBNP ( $P<0.05$  for models with relative and absolute change at both time points).

**CONCLUSIONS.** Although the degree of absolute change in NTproBNP was dependent on baseline levels, both short-term absolute and relative changes in NTproBNP were independently and incrementally associated with long-term clinical outcomes. Changes

in NTproBNP levels at 30-days were particularly well associated with long-term clinical outcomes.

**KEYWORDS.** Natriuretic peptide; Nesiritide; Acute heart failure

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## INTRODUCTION

The majority of the morbidity, mortality, and socioeconomic cost of heart failure (HF) is attributable to hospitalizations for acute decompensated heart failure (ADHF) and poor post-discharge outcomes.(1-3) A number of time- and resource-intensive interventions have been shown to improve outcomes in those at highest risk for subsequent events;(4-6) however, identifying risk in this heterogeneous population remains a challenge. Natriuretic peptides, namely B-type natriuretic peptide and its amino-terminal cleavage equivalent (NTproBNP), have a wealth of evidence supporting their use as powerful noninvasive prognostic markers when measured at baseline or during the course of treatment for ADHF.(7-14) As a result, changes in NTproBNP levels are commonly used to monitor clinical improvement and are used as endpoints in ADHF clinical trials.(15,16) However, more clarity is needed regarding 3 important key topics pertaining to NTproBNP change: (1) the dependency of absolute or relative NTproBNP change on baseline levels; (2) the prognostic impact of absolute or relative NTproBNP change; and (3) whether baseline NTproBNP levels influence the risk associated with NTproBNP change.

In order to address these questions, we analyzed data from a pre-specified biomarker substudy of Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) using a clinically available assay for NTproBNP.(17)

## METHODS

**Study Population.** The ASCEND-HF trial was a multicenter, randomized, double-blind placebo-controlled trial that sought to determine the effects of nesiritide, a recombinant B-type natriuretic peptide with vasodilating properties, in patients hospitalized with ADHF. Participants with clinical evidence for an acute coronary syndrome or baseline cardiac troponin  $>5x$  the upper reference limit, as measured by the local clinical laboratory, were excluded. The design and primary results of ASCEND-HF were previously reported.(17,18) Of the 7,411 patients randomized, 904 were enrolled into a pre-specified biomarker sub-study. These patients had serial venous blood sampling at baseline, 48–72 hours after therapy initiation, and at a 30-day follow-up visit.(19-22) Blood samples were collected in ethylenediaminetetraacetic acid–plasma, immediately centrifuged and stored at  $-80^{\circ}\text{F}$  for analysis at a core laboratory blinded to all clinical data.

**NT-proBNP Measurement.** Circulating NTproBNP levels were determined with a clinically available NTproBNP assay (VITROS NTproBNP, Ortho Clinical Diagnostics, Raritan, NJ, USA). Briefly, the linear range of the assay is 2.29 to 44,700 pg/mL with a limit of detection calculated at 4.29 pg/mL and a 20% coefficient of variation at 9.4 pg/mL.(23)

**Clinical Endpoints.** The co-primary endpoints from the ASCEND-HF trial were dyspnea improvement (via 7-point Likert scale) at 6 to 24 hours and the composite endpoint of death or recurrent heart failure hospitalization within 30 days of randomization. Death and worsening heart failure were assessed together as a composite secondary endpoint and all events were adjudicated through 180 days.

**Statistical Analyses.** Absolute change in NTproBNP from baseline to 48-72 hours was calculated as: 48-72 hour NTproBNP - baseline NTproBNP. Relative change in NTproBNP from baseline to 48-72 hours was calculated as:  $100 \times (48-72 \text{ hour NTproBNP} - \text{baseline NTproBNP}) / (\text{baseline NTproBNP})$ . The same method was used to determine absolute and relative changes in NTproBNP from baseline to 30 days. Baseline characteristics were presented as median (interquartile range) for continuous variables and as percentage for categorical variables. Right-skewed variables were transformed via log-base-2 to represent the doubling of the variable values. Variables were transformed as linear splines where appropriate. Scatterplots were generated to show the relationship between static and changes in NTproBNP levels. The Jonckheere-Terpstra and Cochran-Armitage trend tests were used to test trend across tertiles of absolute change in NTproBNP and relative change in NTproBNP from baseline to 48-72 hours for continuous and categorical variables, respectively. Spearman correlation coefficients were generated to determine correlates between both static and changes in NTproBNP levels. The Kaplan-Meier method was used to plot cumulative 180-day mortality stratified by tertiles of absolute and relative change in NTproBNP and differences in curves were compared via the log-rank test. The associations of the static and changes in NTproBNP levels and 30-day clinical outcomes and 180-day mortality were performed via logistic regression and Cox-proportional hazards models, respectively. The proportional hazards assumption was verified by determining if there were trends with time for the Schoenfeld residuals. For multivariable analyses, we adjusted for covariates identified for the overall ASCEND-HF study population which were previously described (Supplement 1).(19-22) All models

incorporating either absolute or relative changes in NTproBNP were additionally adjusted for the static baseline NTproBNP level and were landmark analyses from the time of the follow-up measurement. Harrell's concordance statistics (C-statistic) were determined to describe the additive discrimination impact of static or changes in NTproBNP levels on 180-day mortality to the ASCEND-HF models.<sup>(24)</sup> Continuous by continuous interactions to determine the prognostic effect of NTproBNP level changes given baseline NTproBNP levels were also tested. Margins plots were generated to display the continuous relationship between changes in NTproBNP levels across a spectrum of baseline levels. Mixed effects models with unstructured variance tested the association between study treatment assignment and serial NTproBNP levels. Two-sided p-values <0.05 were considered statistically significant. All statistical analyses were performed using Stata software, version 13.1 (StataCorp LP, College Station, TX).

## RESULTS

**Study Population.** Of the 795 patients with baseline NTproBNP levels (Supplement 2), 746 had NTproBNP levels drawn at 48-72 hours, and 659 had NTproBNP levels drawn at 30 days. The median NTproBNP at baseline was 5,773 (2,981-11,579) pg/ml; at 48-72 hours was 3,036 (1,191-6,479) pg/ml; and at 30 days was 2,914 (1,364-6,667) pg/ml. Figure 1a and 1b illustrates the relationship between baseline NTproBNP levels and either absolute and relative change in NTproBNP from baseline to 48-72 hours, respectively. Figure 1a qualitatively highlights the dependency of the magnitude of absolute NTproBNP changes on the baseline NTproBNP level. This



is in contrast to Figure 1b which suggests no such dependency between relative changes in NTproBNP on the baseline NTproBNP level.

Baseline characteristics across increasing tertiles in magnitude of absolute NTproBNP change from baseline to 48-72 hours are shown in Table 1. Increasing tertiles in magnitude of absolute NTproBNP change (more NTproBNP decrease) were associated with older age, less prevalent male sex and diabetes; but were not associated with race, ischemic heart failure, or ejection fraction. Although increasing magnitude absolute NTproBNP change was significantly associated with higher sodium and Cystatin C levels, the trend in these lower levels was only modest and there were no complimentary associations between increasing tertiles in magnitude of absolute NTproBNP change and other cardiorenal markers of neurohormonal activation such as BUN or creatinine.

This is in contrast to the baseline characteristics across increasing tertiles in magnitude of relative NTproBNP change from baseline to 48-72 hours, which are shown in Table 2. These highlight the differential relationships between the type of NTproBNP change and demographics and clinical characteristics. Increasing tertiles in magnitude of relative NTproBNP change (more relative NTproBNP decrease) were not associated with age or diabetes, but were closely associated with less prevalent male sex and ischemic heart failure. Relative NTproBNP change from baseline to 48-72 hours was more closely associated with classic clinical markers of heart failure severity including ejection fraction, total bilirubin and cardiorenal neurohormonal activation: sodium, BUN, creatinine, and cystatin C.

Along similar lines to the relationships in Figures 1a and 1b, absolute changes in NTproBNP from baseline to 48-72 hours were closely related to baseline levels of commonly used prognostic biomarkers in heart failure: cardiac troponin I, NTproBNP, and sST2 (Table 1). On the other hand, relative changes in NTproBNP from baseline to 48-72 hours were not associated with these biomarkers (Table 2).

**Correlation between Static and Changes in NT-proBNP Levels.** Spearman correlation coefficients were generated to determine the monotonic relationships between the static NTproBNP levels measured at baseline, 48-72 hours, and 30 days to both absolute and relative changes between baseline NTproBNP levels at the two follow-up time points and are shown in Table 3. Static NTproBNP levels at all 3 time points were all highly correlated. However, there was a contrasting relationship between baseline and follow-up NTproBNP levels according to the type of change. Absolute changes in NTproBNP were modestly correlated with their baseline levels, where relative changes in NTproBNP were modestly correlated with their follow-up levels.

**Changes in NT-proBNP and Clinical Outcomes.** There were  $n/N=95/782$  and  $83/667$  HF hospitalizations or deaths by 30 days from baseline and 48-72 hours, respectively. Logistic regression models with adjusted odds ratios are shown in Table 4. Baseline NTproBNP was not associated with 30-day HF hospitalization or death ( $P=0.18$ ). However, follow-up NTproBNP measured at 48-72 hours was significantly associated with 30-day HF hospitalization or death ( $P=0.013$ ), and is likely more closely representative of relative NTproBNP change ( $P=0.046$ ) in comparison to absolute NTproBNP change ( $P=0.065$ ). There was no improvement in discrimination when either

the static or changes by 48-72 hours in NTproBNP were added to the ASCEND-HF model (Table 4,  $P>0.05$  for all).

There were  $n/N=96/795$ ,  $82/746$ , and  $52/659$  deaths by 180 days from baseline, 48-72 hours, and 30 days, respectively. For patients with available NTproBNP change data, there were  $n/N=78/677$  and  $46/582$  deaths by 180-days for 48-72 hour and 30 days, respectively. Kaplan-Meier estimates of cumulative mortality are shown in Figures 2a and 2b for tertiles of NTproBNP absolute change and relative change in levels from baseline to 48-72 hours, respectively.

Cox-proportional hazards models with the adjusted hazards ratios are shown in Table 4. Not surprisingly, all static NTproBNP levels measured at each of the three time points were significantly associated with 180-day mortality risk. Every doubling in static NTproBNP levels had an approximate 37%, 50%, and 76% increased risk of 180-day mortality for NTproBNP checked at baseline, 48-72 hours, and 30 days; respectively. Both absolute and relative change in NTproBNP from baseline to 48-72 hours and from baseline to 30 days were significantly associated with 180-day mortality. An absolute 500 pg/mL increase in NTproBNP from baseline to either follow-up time point was associated with an approximate 2% increased risk of 180-day mortality. A relative 20% increase in NTproBNP from baseline to 48-72 hours and from baseline to 30 days was associated with a significant 15% and 18% increased risk in 180-day mortality, respectively. With the exception of baseline NTproBNP which showed a trend towards improved discrimination versus the baseline ASCEND-HF model ( $C=0.74$  vs.  $C=0.71$ , respectively,  $P=0.06$ ) for 180-day mortality; all models with follow-up static NTproBNP

levels or changes in NTproBNP had improved discrimination than the baseline ASCEND-HF model ( $P < 0.05$  for all).

First order and second order Interactions were tested between baseline NTproBNP levels and both types of NTproBNP changes to each time point and were non-significant ( $P > 0.05$  for all). Therefore, despite the differential dependency of absolute or relative NTproBNP change on either baseline or follow-up levels, the risk attributed to NTproBNP change was statistically associated with the baseline level. The graphical risk-relationship between absolute and relative changes according to various baseline NTproBNP levels are shown in Supplement 3. Although the modelled risk-relationship for different levels of absolute change and relative change in NTproBNP differed in shape (linear vs. curvilinear; respectively), both show relatively parallel increments or decrements in risk attributable to NTproBNP change given baseline NTproBNP levels.

## DISCUSSION

This analysis from the ASCEND-HF biomarker substudy highlights important concepts adding to our understanding of changes in NTproBNP in patients with ADHF. The primary finding was that both absolute and relative change in NTproBNP were highly independently and incrementally prognostic to static baseline NTproBNP levels. Furthermore, although absolute NTproBNP changes from baseline were highly dependent on baseline NTproBNP levels, baseline NTproBNP levels had no impact on either NTproBNP change (absolute or relative) risk-relationship. These findings underscore what has become a solid body of evidence supporting the prognostic value

natriuretic peptides in heart failure and enlighten the interpretation of natriuretic peptide changes during ADHF.

Since their association with heart failure was first described,(25) B-type natriuretic peptide (BNP, and its biologically inert split-product NTproBNP) have been of great interest for their clinical use in managing heart failure(26) and in clinical research where their values inform patient selection and yield important mechanistic insights to therapeutic responses. Serum natriuretic peptide levels fluctuate in parallel with intracardiac hemodynamics during both decompensation and clinical improvement.(27-30). Not surprisingly, these fluctuations during the treatment of ADHF also prognosticate the likelihood of rehospitalization and death after discharge.(7-14,31,32) Therefore, our finding that static NTproBNP is associated with both 30-day and 180-day adverse clinical outcomes underscores the clinical importance of this biomarker and continues to emphasize its prognostic role in ADHF.

When checked at different time points during the course of treatment for ADHF, natriuretic peptide measurements might confer different prognostic information. In particular, both BNP and NTproBNP levels measured at hospital discharge are likely more reflective of both heart failure rehospitalization and mortality.(8,10-12,14,33) Reasons for this are perhaps reflective of the achievement of a more stable hemodynamic and cardiorenal state following treatment for ADHF. Our finding that both types of NTproBNP change whether in the short-term (48-72 hours) or mid-term (30 days) were independently and incrementally prognostic to their static baseline counterparts (in addition to factors derived by the ASCEND-HF model) supports prior these findings. However, they also suggest that changes in NTproBNP levels when

checked early, during the course of treatment for ADHF, stratify risk (likely representing treatment response), and identify long-term prognosis, thus obviating the need to check discharge NTproBNP.

Indeed, prior cohorts have placed emphasis on the relative reduction in NTproBNP from baseline to discharge and its impact on heart failure readmission; (9,13,31,34) and, not surprisingly, relative changes have been considered as surrogate endpoints for treatment efficacy in ADHF.(15) The distinction between absolute and relative changes extends beyond mathematical concepts. As shown in Table 2 and Figure 1a absolute changes in NTproBNP may be dependent on their baseline levels whereas relative changes in NTproBNP may be dependent on their follow-up levels and therefore likely more reflective of treatment. Given their different associations with baseline clinical and metabolic characteristics, the degree of relative changes in NTproBNP are likely more reflective of the degree of cardiorenal neurohormonal activation at baseline (i.e. serum sodium, BUN, and creatinine/cystatin C – well-known parameters associated treatment response (35) - not captured by the baseline NTproBNP levels alone.

A prior compilation of seven ADHF cohorts has also emphasized the differences between absolute and relative targets in NTproBNP levels from baseline to discharge.(32) Thematically similar to our findings, they found that absolute and relative NTproBNP targets pre-discharge were prognostic and that relative NTproBNP targets offered more consistent prognostic information. However, our analysis adds a more robust understanding of NTproBNP changes in 3 ways: 1) there is valuable prognostic information in short term absolute or relative changes in NTproBNP; 2) although

independent of, the prognostic modification of risk is related to the baseline NTproBNP risk-relationship for both absolute and relative changes; but 3) the trajectory of risk was not modified by baseline NTproBNP levels. It is also worth noting, that short-term changes in NTproBNP might be more reflective of risk for long-term outcomes in comparison to shorter-term clinical outcomes such as 30-day heart failure readmissions.

The results of this study must be interpreted in light of various limitations inherent to its design. First, we cannot exclude selection bias for patients whom agreed to participate in the ASCEND-HF trial. Although, the baseline characteristics of this cohort (Table 1) are representative of contemporary ADHF populations. Second, there was a paucity of data to assess the contribution of other heart failure pharmacotherapies to changes in NTproBNP levels during treatment that might have a deferential impact on clinical events. Worth noting however, there was no association with those randomized to nesiritide and serial NTproBNP levels (Supplement 4) and it did not modify the risk-relationship of NTproBNP on 30-day and 180-day clinical outcomes ( $P$ -interaction $>0.1$  for both, respectively). Regardless, our analysis suggests that both absolute and relative changes in NTproBNP are prognostically informative and provides insight into early and follow-up natriuretic peptide measurements in heart failure.

## CONCLUSIONS

Although the degree of absolute change in NTproBNP was dependent on baseline levels, both short-term absolute and relative changes in NTproBNP were independently and incrementally associated with long-term clinical outcomes. NTproBNP levels at follow-up were particularly well associated with long-term clinical outcomes. These

findings support the hypothesis that short-term changes in NTproBNP, soon after the initiation of therapy and before discharge, can identify high-risk ADHF patients.

## **FUNDING**

The ASCEND-HF study, including the biomarker substudy, was funded by Scios Inc.; Janssen Research & Development LLC retains operational responsibility for the ASCEND-HF study. Ortho Clinical Diagnostics performed all NT-proBNP assays, and was blinded from the trial database or analyses. Statistical analyses, and manuscript preparation were conducted independent of the sponsors, and the authors have access to all the data in its entirety and approved the final manuscript.

## **DISCLOSURE**

J. Grodin: None. M. Liebo: None. J. Butler: Consultant/Advisory Board; Modest; Johnson&Johnson. M. Metra: Consultant/Advisory Board; Modest; Corthera, Daiichi, Novartis, Serrvier. G. Felker: Research Grant; Significant; Johnson&Johnson, Roche Diagnostics, Critical Diagnostics, BG Medicine. A.A. Voors: Consultant/Advisory Board; Modest; Johnson&Johnson, Alere, Bayer, Boehringer Ingelheim, Cardio3Biosciences, Celladon, Merck/MSD, Novartis, Servier, Trevena, Vifor Pharma. J.J. McMurray: Research Grant; Significant; Johnson&Johnson. P.W. Armstrong: Research Grant; Significant; Johnson&Johnson, Ortho Biotech. A.F. Hernandez: Research Grant; Significant; Johnson&Johnson. C.M. O'Connor: Research Grant; Significant; Johnson&Johnson. R.C. Starling: Other Research Support; Modest; Johnson&Johnson. Consultant/Advisory Board; Modest; Johnson&Johnson. W. Tang: MyoKardia Inc, Sequanal Medical Inc.



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**Table 1.** Baseline Characteristics Across Tertiles of Absolute Change in NTproBNP from Baseline to 48-72 hours

Characteristic	Absolute Change in NTproBNP [pg/mL]			P-Trend
	> -1,280 (N=224)	-1,280 to -3,850 (N=227)	< -3,850 (N=226)	
Age [y]	65 [52-77]	65 [54-76]	71 [59-80]	<0.001
Male	172 (76.8)	173 (76.1)	136 (60.2)	<0.001
White	149 (66.5)	153 (67.4)	163 (72.1)	0.20
Black	68 (30.4)	70 (30.8)	53 (23.4)	0.10
Diabetes	123 (54.9)	103 (45.4)	101 (44.7)	0.03
Ischemic Heart Failure	140 (62.5)	129 (56.8)	148 (65.5)	0.52
NYHA Class 3 or 4	117 (69.6)	118 (73.3)	114 (72.2)	0.61
Elevated JVP	152 (67.9)	151 (66.5)	133 (58.9)	0.046
BMI [kg/m <sup>2</sup> ]	31.7 [26.3-39.4]	31.1 [26.7-36.6]	28.0 [24.4-32.7]	<0.001
Heart rate [bpm]	77 [68-88]	80 [70-92]	77 [70-86]	0.95
SBP [mm Hg]	120 [108-135]	128 [114-141]	128 [114-142]	<0.001
Ejection Fraction [%]	30 [18-40]	26 [20-40]	25 [20-40]	0.91
Albumin [g/dL]	3.5 [3.2-4.0]	3.6 [3.3-3.9]	3.5 [3.2-3.9]	0.64
ALT [U/L]	26 [17-38]	29 [19-42]	25 [16-46]	0.049
AST [U/L]	27 [21-39]	28 [20-41]	26 [21-37]	0.63
Total Bilirubin [μmol/L]	15.4 [10.1-25.7]	15.4 [10.3-20.5]	13.7 [9.0-20.5]	0.12
Sodium [mmol/L]	138 [135-141]	140 [137-141]	139 [137-141]	0.002
BUN [mg/dL]	24 [17-40]	21 [16-31]	28 [21-37]	0.051
Creatinine [mg/dL]	1.3 [1.1-1.8]	1.2 [1.0-1.5]	1.4 [1.1-1.9]	0.11
Cystatin C [g/dL]	1.5 [1.2-2.1]	1.4 [1.1-1.7]	1.7 [1.3-2.1]	0.005

Troponin I [pg/mL]	13.5 [7.9-26.5]	15.6 [8.5-31.5]	20.2 [12.6-43.0]	<0.001
NTproBNP [pg/mL]	2,898 [1,405- 6,334]	4,354 [3,037- 6,296]	13,653 [9,631- 22,427]	<0.001
sST2 [ng/mL]	65.8 [44.0-100.4]	69.2 [49.2-103.5]	93.9 [63.9-134.8]	<0.001
Beta-Blocker	160 (71.4)	176 (77.5)	182 (80.5)	0.023
MRA	60 (26.8)	55 (24.2)	48 (21.2)	0.17
RAS-Blocker	143 (63.8)	150 (66.1)	136 (60.2)	0.42
Abbreviations: NYHA, New York Heart Association; JVP, jugular venous pressure; BMI, body mass index; SBP, systolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; NTproBNP; N-terminal pro-B-type natriuretic peptide; sST2, soluble ST2; MRA, mineralocorticoid antagonist; and RAS, renin-angiotensin system.				

**Table 2.** Baseline Characteristics Across Tertiles of Relative Change in NTproBNP from Baseline to 48-72 hours

Characteristic	Relative Change in NTproBNP [%]			P-Value
	> -30% (N=225)	-30% to -61% (N=226)	< -61% (N=226)	
Age [y]	68 (56-79)	67 (56-78)	64 (54-77)	0.12
Male	174 (77.3)	164 (72.6)	143 (63.3)	0.001
White	153 (68.0)	165 (73.0)	147 (65.0)	0.50
Black	60 (26.7)	57 (25.2)	74 (32.7)	0.15
Diabetes	124 (55.1)	99 (43.8)	104 (46.0)	0.054
Ischemic Heart Failure	159 (70.7)	136 (60.2)	122 (54.0)	<0.001
NYHA Class 3 or 4	125 (71.8)	116 (78.4)	108 (68.4)	0.50
Elevated JVP	161 (71.6)	139 (61.5)	136 (60.2)	0.01
BMI [kg/m <sup>2</sup> ]	29.6 (25.0-36.0)	29.7 (25.3-35.4)	31.0 (26.3-37.1)	0.14
Heart rate [bpm]	77 (68-87)	79 (69-88)	80 (70-90)	0.09
SBP [mm Hg]	119 (108-133)	126 (113-139)	131 (116-145)	<0.001
Ejection Fraction [%]	25 (18-35)	25 (20-40)	30 (20-45)	0.009
Albumin [g/dL]	3.5 (3.1-3.9)	3.6 (3.2-3.9)	3.6 (3.3-4.0)	0.06
ALT [U/L]	24 (17-36)	25 (17-40)	26 (17-46)	0.13
AST [U/L]	28 (21-37)	28 (21-40)	25 (20-35)	0.13
Total Bilirubin [μmol/L]	17.1 (11.0-25.8)	15.4 (10.3-20.5)	13.3 (8.6-20.5)	0.001
Sodium [mmol/L]	139 (135-141)	139 (136-141)	140 (138-141)	0.002
BUN [mg/dL]	29 (21-44)	24 (18-34)	22 (16-30)	<0.001
Creatinine [mg/dL]	1.4 (1.2-2.0)	1.3 (1.0-1.7)	1.2 (1.0-1.5)	<0.001
Cystatin C [g/dL]	1.6 (1.3-2.5)	1.5 (1.2-1.9)	1.4 (1.2-1.8)	<0.001



Troponin I [pg/mL]	17.7 (10.2-32.0)	14.3 (8.5-29.7)	17.6 (9.8-35.1)	0.79
NTproBNP [pg/mL]	6,018 (2,982- 12,084)	6,037 (3,029- 12,936)	5,693 (3,032- 11,294)	0.68
sST2 [ng/mL]	80.4 (52.0- 116.0)	73.2 (48.8- 118.5)	71.5 (49.4- 110.8)	0.51
Beta-Blocker	169 (75.1)	180 (80.0)	169 (74.8)	0.93
MRA	61 (27.1)	58 (25.7)	44 (19.5)	0.06
RAS-Blocker	135 (60.0)	147 (65.0)	147 (65.0)	0.27
Abbreviations: NYHA, New York Heart Association; JVP, jugular venous pressure; BMI, body mass index; SBP, systolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; NTproBNP; N-terminal pro-B-type natriuretic peptide; sST2, soluble ST2; MRA, mineralocorticoid antagonist; and RAS, renin-angiotensin system.				

**Table 3.** Spearman Correlates Between Static and Changes in NTproBNP Levels\*

	Baseline NTproBNP †	48-72 Hour NTproBNP †	30 Day NTproBNP †	Absolute $\Delta$ in NTproBNP to 48-72 Hours	Absolute $\Delta$ in NTproBNP to 30 Days	Relative $\Delta$ in NTproBNP to 48-72 Hours	Relative $\Delta$ in NTproBNP to 30 Days
Baseline NTproBNP†	--	0.82	0.71	-0.68	-0.62	0.02**	-0.19
48-72 Hour NTproBNP†	0.82	--	0.77	-0.25	-0.35	0.54	0.08**
30 Day NTproBNP†	0.71	0.77	--	-0.30	-0.02**	0.30	0.49
Absolute $\Delta$ in NTproBNP to 48-72 Hours	-0.68	-0.25	-0.30	--	0.68	0.59	0.41
Absolute $\Delta$ in NTproBNP to 30 Days	-0.62	-0.35	-0.02**	0.68	--	0.28	0.78
Relative $\Delta$ in NTproBNP to 48-72 Hours	0.02**	0.54	0.30	0.59	0.28	--	0.44
Relative $\Delta$ in NTproBNP to 30 Days	-0.19	0.08**	0.49	0.41	0.78	0.44	--

\*Units of NTproBNP and Absolute  $\Delta$  in NTproBNP are pg/mL and for Relative  $\Delta$  in NTproBNP are %.  
\*\*P>0.05 otherwise all P<0.001  
†log-base-2 transformed

**Table 4.** Association of Static NTproBNP and Changes in NTproBNP Levels and 30-Day and 180-Day Clinical Outcomes Added to the ASCEND-HF Model.

Variable	Outcome	HR/OR †	95% CI for HR/OR	P-Value	C-statistic*	95% CI for C-Statistic
Baseline NTproBNP	30-Day HF Hosp. or Mortality	1.13	0.94-1.36	0.184	0.72	0.66-0.77
	180-Day Mortality	1.37	1.17-1.60	<0.001	0.74	0.69-0.79
48-72 Hour NTproBNP	30-Day HF Hosp. or Mortality	1.23	1.04-1.44	0.013	0.73	0.68-0.79
	180-Day Mortality	1.50	1.29-1.74	<0.001	0.76‡§	0.71-0.82
Abs. $\Delta$ in NTproBNP to 48-72 Hours	30-Day HF Hosp. or Mortality	1.02	0.99-1.02	0.065	0.73	0.68-0.79
	180-Day Mortality	1.02	1.003-1.03	0.014	0.76‡§	0.70-0.81
% $\Delta$ in NTproBNP to 48-72 Hours	30-Day HF Hosp. or Mortality	1.12	1.002-1.25	0.046	0.73	0.68-0.78
	180-Day Mortality	1.15	1.04-1.27	0.005	0.75‡	0.70-0.81
30 Day NTproBNP	180-Day Mortality	1.76	1.43-2.16	<0.001	0.78‡§	0.71-0.84
Abs. $\Delta$ in NTproBNP to 30 Days	180-Day Mortality	1.02	1.01-1.03	0.003	0.77‡§	0.70-0.84

% $\Delta$ in NTproBNP to 30 Days	180-Day Mortality	1.18	1.09-1.27	<0.001	0.77†§	0.70-0.84
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\*C-Statistics represent the discrimination of the exposures of interest (static NTproBNP or  $\Delta$  NTproBNP) with variables from the ASCEND-HF model for 30-day HF hosp. or mortality and 180-day mortality. C-statistics for the variables in the baseline ASCEND-HF model are 0.71 (95% CI 0.66-0.77) and 0.71 (95% CI 0.66-0.77) for 30-day HF hosp. and 180-day mortality, respectively.

†For static NTproBNP, HR/OR represent every log-base-2 change; for Abs.  $\Delta$  in NTproBNP, HR represent per 500 pg/mL change; and for %  $\Delta$  in NTproBNP, HR represent per 20% change. All point-estimates are multivariable adjusted for baseline variables in the ASCEND-HF model.

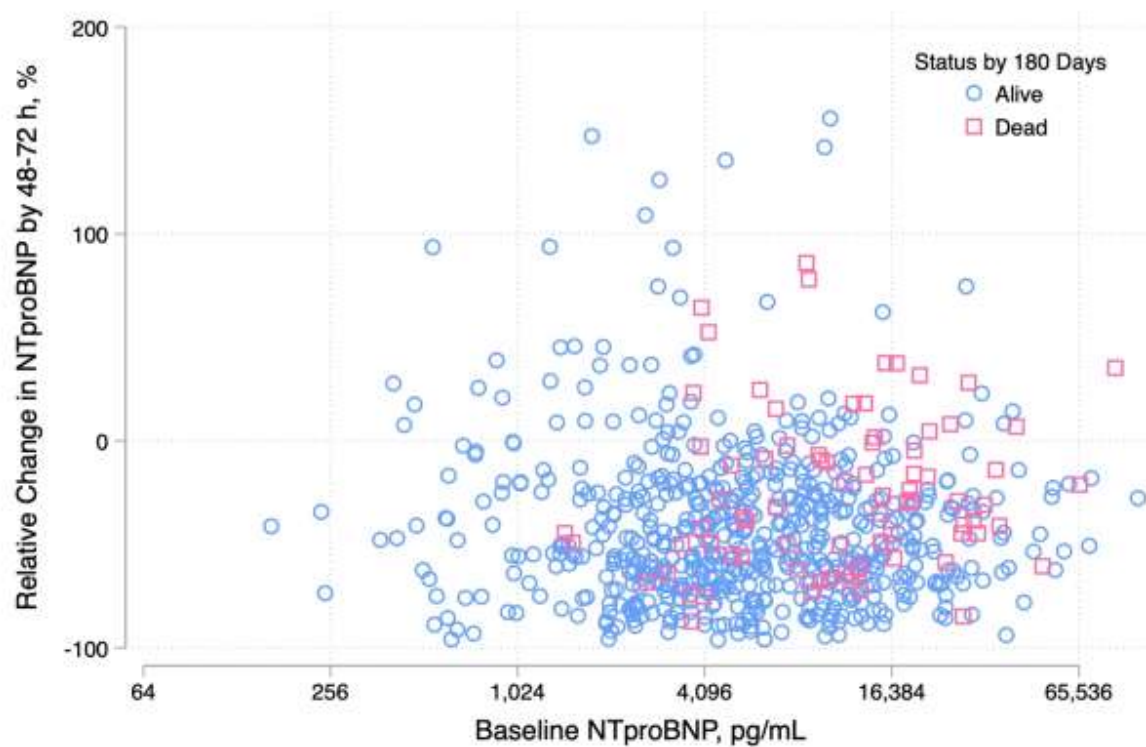
‡For C-statistic comparison to baseline ASCEND-HF model  $P < 0.05$ .

§For C-statistic comparison to the model with baseline ASCEND-HF variables and NTproBNP levels,  $P < 0.05$ .

||P-value for HR/OR.



Figure 1b.



## FIGURE LEGENDS

## Figure 1.

**Title.** Scatterplots of 48-72 hour Changes in NTproBNP Levels by Baseline NTproBNP Levels

**Caption.** The plots represent both (a) absolute change and (b) relative change. The horizontal axes on a log-base-2 transformed scale.

Figure 2a.

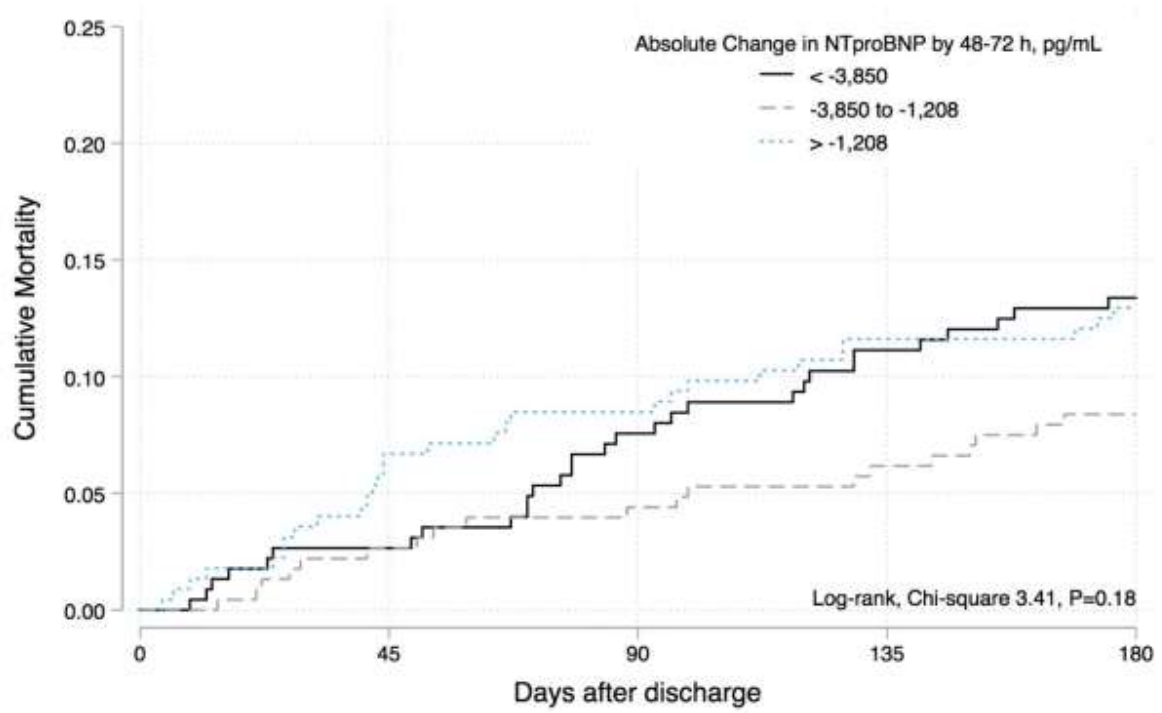


Figure 2b.

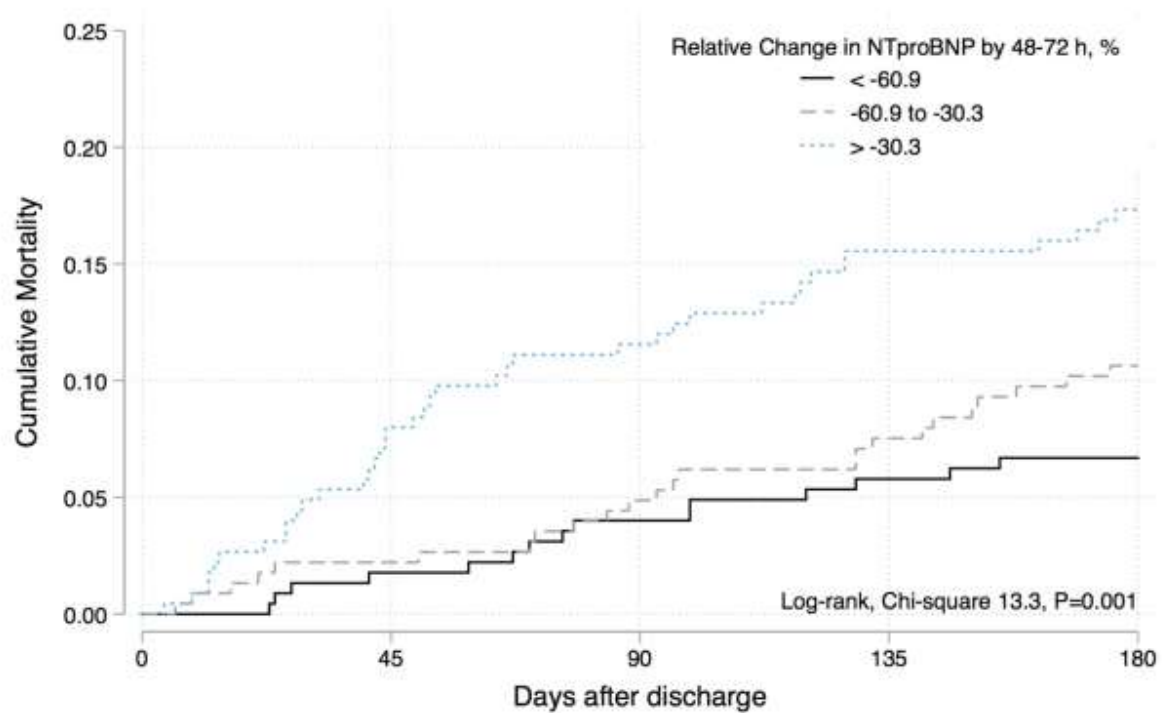


Figure 2.

**Title.** Kaplan-Meier Estimates of 180-Day Mortality Across 48-72 hour Changes in NTproBNP Levels

**Caption.** The plots represent tertiles of (a) absolute change and (b) relative change.