Circulation

ORIGINAL RESEARCH ARTICLE

NT-proBNP (N-Terminal pro-B-Type Natriuretic Peptide)-Guided Therapy in Acute Decompensated Heart Failure

PRIMA II Randomized Controlled Trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?)

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BACKGROUND: The concept of natriuretic peptide guidance has been extensively studied in patients with chronic heart failure (HF), with only limited success. The effect of NT-proBNP (N-terminal probrain natriuretic peptide)-guided therapy in patients with acute decompensated HF using a relative NT-proBNP target has not been investigated. This study aimed to assess whether NT-proBNP-guided therapy of patients with acute decompensated HF using a relative NT-proBNP target would lead to improved outcomes compared with conventional therapy.

METHODS: We conducted a prospective randomized controlled trial to study the impact of in-hospital guidance for acute decompensated HF treatment by a predefined NT-proBNP target (>30% reduction from admission to discharge) versus conventional treatment. Patients with acute decompensated HF with NT-proBNP levels >1700 ng/L were eligible. After achieving clinical stability, 405 patients were randomized to either NT-proBNP-guided or conventional treatment (1:1). The primary end point was dual: a composite of all-cause mortality and HF readmissions in 180 days and the number of days alive out of the hospital in 180 days. Secondary end points were all-cause mortality within 180 days, HF readmissions within 180 days, and a composite of all-cause mortality and HF readmissions within 90 days.

RESULTS: Significantly more patients in the NT-proBNP-guided therapy group were discharged with an NT-proBNP reduction of >30% (80% versus 64%, *P*=0.001). Nonetheless, NT-proBNP-guided therapy did not significantly improve the combined event rate for all-cause mortality and HF readmissions (hazard ratio, 0.96; 95% confidence interval, 0.72–1.37; *P*=0.99) or the median number of days alive outside of the hospital (178 versus 179 days for NT-proBNP versus conventional patients, *P*=0.39). Guided therapy also did not significantly improve any of the secondary end points.

CONCLUSIONS: The PRIMA II trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?) demonstrates that the guidance of HF therapy to reach an NT-proBNP reduction of >30% after clinical stabilization did not improve 6-month outcomes.

CLINICAL TRIAL REGISTRATION: URL: http://www.trialregister.nl. Unique identifier: NTR3279.

Key Words: biomarkers ■ heart failure ■ hospitalization ■ mortality ■ natriuretic peptide, brain ■ patient readmission ■ randomized controlled trial

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Clinical Perspective

What Is New?

- Although several studies have investigated the use of NT-proBNP (N-terminal probrain natriuretic peptide)-guided therapy in patients with chronic heart failure, guidance of therapy in patients with acute heart failure using a relative NT-proBNP target has never been investigated.
- We demonstrate that NT-proBNP-guided therapy targeting an NT-proBNP reduction of >30% did not improve clinical outcomes.

What Are the Clinical Implications?

- Our study does not support the use of serial NT-proBNP measurements for the guidance of therapy during admission for acute heart failure.

The prognosis of patients admitted for and discharged after acute decompensated heart failure (ADHF) is poor, with ≥50% of patients being readmitted or deceased within 6 months.[1–4] The immediate goal of treatment in patients with ADHF is to relieve congestion, for which several measures of effect are available.[5–7] As the main mechanism of congestion, elevated filling pressures at discharge have been related to a poor prognosis.[8] A subsequent effort to guide therapy in patients with ADHF with systolic HF toward lower filling pressures before discharge was successful in reducing filling pressures but did not improve prognosis after discharge.[9] Noninvasive assessment of preload and afterload by brain natriuretic peptide (BNP) or NT-proBNP (N-terminal probrain natriuretic peptide) may extend these earlier studies by showing that higher absolute levels and a lack of decrease of these BNPs are associated with worse outcomes in patients with ADHF.[4,10–12] The studies provide a new impetus for these biomarkers as attractive targets to guide in-hospital therapy because they reflect decongestion (preload reduction) and also mirror other mechanisms of heart failure in the measurable response of the biomarkers to several HF therapies that improve prognosis.[13–15] Current guidelines state that the usefulness of NT-proBNP-guided HF therapy to reduce hospitalization or mortality in patients with chronic HF is not well established.[16,17] For ADHF, a first attempt was made to use an absolute NT-proBNP cut-off level (>3000 ng/L predischarge) to randomize 280 patients to further optimization of HF medication (but without a prespecified NT-proBNP target) versus to proceed to discharge without any adjustments to therapy.[18] This study was unable to demonstrate a difference in 6-month outcomes between groups.

The PRIMA II trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?) is the first prospectively randomized study on in-hospital guidance of ADHF treatment by targeting an NT-proBNP reduction of ≥30% at discharge, with the aim to decrease event rates 6 months after discharge.[19] Previous studies demonstrated that the target of a >30% decrease in NT-proBNP during admission for ADHF would be a robust predictor of prognosis[4,10,11]

METHODS

Study Design and Oversight

The study design has been reported previously.[19] Briefly, this investigator-initiated, multicenter, international, randomized controlled, prospective open 2-arm trial aimed to study the effect of in-hospital guidance of ADHF treatment by a predefined NT-proBNP target of >30% reduction from admission to discharge on the reduction of readmission and mortality rates in ≤180 days. Patients were included from 9 Dutch participating hospitals, 1 Portuguese hospital, and 1 Spanish hospital. The trial was approved by the Medical Ethics Committee of the University of Amsterdam and Academic Medical Center, The Netherlands, and registered in The Netherlands Trial Register (NTR3279). All patients provided written informed consent. The steering committee consisting of S.S., K.S., J.T., Y.P., and W.K. was responsible for the design, execution, and data analysis of the study. The trial was reviewed by an independent data and safety monitoring board. The first and subsequent drafts of the manuscript were prepared by the first and last authors. All authors approved the manuscript for publication and confirm that its contents adhere to the specifications in the protocol. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Patients, Group Assignments, and Interventions

Inclusion and exclusion criteria for participation in PRIMA II are listed in Table 1.

From the day of admission, HF treatment was started or continued at the discretion of the treating physician until clinical stability was achieved. Patients were defined clinically stable when they were admitted for ≥3 days and when a minimum of 3 out of 4 of the following criteria were present: target weight was reached, stable levels of serum creatinine (<25% increase from baseline) were obtained, improved symptoms and mobilization was possible, or adequate discharge medication was prescribed. When clinically stable, patients were randomized to either NT-proBNP-guided or conventional treatment (1:1). Although patients were included shortly after admission, they were randomized only after clinical stabilization. As described in our trial design,[19] the rationale for randomizing after clinical stabilization is as follows. First, the NT-proBNP target aimed at in our trial is derived from a discharge prediction model, not accounting for in-hospital mortality. By randomizing at the moment of clinical stability, we assumed that we could use the predictive value of the NT-proBNP discharge target taken from our

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Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
Admission for acute decompensated heart failure
NT-proBNP levels of >1700 ng/L (>200 pmol/L) within 24 h of hospital admission
Exclusion criteria
Severe chronic obstructive pulmonary disease with forced expiratory volume in 1 s of <1 L
Pulmonary embolism within 1 mo before admission and pulmonary hypertension not caused by left ventricle dysfunction
Patients undergoing continuous ambulant peritoneal dialysis/patients on hemodialysis
Patients with planned coronary artery bypass grafting, percutaneous coronary intervention, cardiac resynchronization therapy, or valvular surgery before admission (until 1 day before admission)
Patients with planned coronary artery bypass grafting, percutaneous coronary intervention, cardiac resynchronization therapy, or valvular surgery during admission until the moment of randomization
Patients in cardiogenic shock at admission requiring invasive treatment
Patients with a history of ST-segment elevated myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, cardiac resynchronization therapy, or valvular surgery within 1 mo before admission
Signed informed consent for any current interventional study
Presence of severe noncardiac related life-threatening disease before inclusion with an expected survival of <6 mo after inclusion
Unwillingness to give or mental or physical status not allowing written informed consent
Circumstances that prevent follow-up (no permanent home address, transient, etc)

NT-proBNP indicates N-terminal pro-B-type natriuretic peptide.

previous study, and thus we did not randomize patients who died shortly after admission before randomization. Second, randomization at admission might introduce a bias by either undertreatment or intensified treatment of the conventional therapy group, whereas in the present study randomization was followed by either discharge or extra therapy. Third, some of the patients admitted for acute decompensated HF receive interventions (eg, percutaneous coronary intervention, coronary artery bypass graft, valvular surgery, etc) immediately or within a few days after admission. We decided to exclude these patients from our study if these interventions were planned before randomization in either an NT-proBNP-guided or a conventional treatment group. In this way, procedures would not influence results unless such interventions were intended to improve NT-proBNP levels after randomization. Randomizing patients predischarge (in a clinically stable state) avoids inclusion of these patients in the study. Randomization was stratified per center and HF severity (mild or severe HF).

After clinical stabilization, at the day of randomization, NT-proBNP levels were determined for all study patients. Levels were revealed to the treating physicians for patients in the NT-proBNP-guided group, and it was possible to plan discharge and follow-up when NT-proBNP had decreased >30% already at the day of randomization. Patients in the NT-proBNP group in whom NT-proBNP had not decreased ≥30% from the admission value entered a predefined algorithm consisting of several steps, including additional NT-proBNP measurements and suggested interventions to try to attain the desired >30% reduction in NT-proBNP levels. Briefly, suggested interventions were titration of HF medication (angiotensin converting enzyme [ACE]-inhibitors, β-blockers, and mineralocorticoid receptor antagonists [MRAs]) in eligible patients,[20] invasive therapies such as implantation of cardiac resynchronization therapy if indicated,[20] diagnostic coronary angiography when there was a suspicion of coronary ischemia, and electric cardioversion for patients with new-onset atrial fibrillation (see separately published design paper for details on the algorithm[19]). Further therapy adjustments were left at the discretion of the treating physician (ie, diuretics when it was felt that the patient was still or again became congested). When patients were randomized to NT-proBNP-guided therapy and had a reduction of <30% in NT-proBNP at randomization, the study coordinator contacted the site for therapy advice. In addition, reasons for not initiating or titrating HF medication had to be reported by the treating physician. For patients in the conventional therapy group, NT-proBNP levels determined at the day of randomization and discharge were blinded to the treating physicians. This was in contrast to NT-proBNP-guided patients, in whom discharge was further guided by NT-proBNP levels. Discharge and follow-up of conventionally treated patients were planned at the discretion of the treating physician. Discharge NT-proBNP measurements were reported as missing values when they were not determined ≤48 hours of discharge. In addition to NT-proBNP data, laboratory values on renal function and hemoglobin were collected. Hemoglobin levels at admission and discharge were used to determine the number of patients with hemoconcentration, which was defined as an absolute increase in hemoglobin levels and may serve as a measure of effective diuresis.[7] There was no predefined postdischarge program for follow-up, but patients who were included in The Netherlands were seen on a regular basis in dedicated HF outpatient clinics, similar to the previous outpatient study (PRIMA).[21]

Study Outcomes

The first primary end point was a composite end point of readmission for HF and all-cause mortality in 180 days after randomization, and the second primary end point was the number of days alive out of the hospital in 180 days after discharge. The secondary end points were readmissions for HF in 180 days, all-cause mortality in 180 days, and HF readmissions and mortality in the first 90 days. Adjudication of these end points was carried out in a blinded fashion by an independent committee of 2 cardiologists.

Statistical Analysis

The expected hazard ratio (HR) of experimental subjects relative to control subjects was 0.70 (ie, a reduction in the composite end point from 50% to 35%). Therefore, we estimated that we would need to randomize 340 patients (170 in each group) to provide the study with a power of 80% to detect a relative risk reduction of 30% in the first primary end point at an overall 2-sided α level of 0.05.

During the course of the study, we noticed that it was not possible to lower NT-proBNP levels to the target in ≈10% of patients in the NT-proBNP-guided group despite intensified therapy. To avoid a potential type 2 error, we increased our

sample size to 400 patients (2 x 200) to be able to detect an adapted relative risk reduction of 27% (ie, a reduction in primary end point from 50% to 36.5%).

Demographic characteristics are presented as frequencies and percentages when it concerns categorical data, and the Fisher exact test was used to make a comparison. Normally distributed, continuous variables are reported as mean±SD and were compared using Student *t* test. Other continuous data, expressed as median with interquartile range (IQR), were compared using the Mann–Whitney *U* test.

According to the intention-to-treat principle, we analyzed data of all patients who were randomized. Because this study had 2 primary end points, the Hochberg extension of the Bonferroni method for multiple comparisons was used to test for statistical significance.[22] Both end points are statistically significant if *P* of both end points is <0.05. If *P* is <0.05 for only 1 end point, then the *P* of this end point should be <0.025 to be declared statistically significant. Time-to-event data were evaluated with the use of Kaplan–Meier estimates and Cox proportional hazards models. HRs, 95% confidence intervals (CI), and 2-sided *P* values were calculated with the Cox models. We assessed the consistency of the treatment effect among 7 prespecified subgroups.

RESULTS

Study Population

From November 2011 through September 2015, 431 patients were included. Ten patients did not fulfill the criteria for randomization, 9 patients were discharged or deceased before randomization, 1 patient withdrew consent, and 6 patients were not randomized for other reasons. As a result, 405 patients were randomized to receive NT-proBNP-guided or conventional therapy (Figure 1). After randomization, 1 patient in the NT-proBNP-guided group withdrew informed consent and refused further data collection. Intention-to-treat analyses were hence performed in 404 patients. Baseline characteristics of these patients according to their study groups are displayed in Table 2.

Effect of Randomized Assignment on NT-proBNP

NT-proBNP levels at different time points during admission for patients in the NT-proBNP-guided and conventional therapy group are listed in Table 3. From admission to randomization, similar percentages of patients in the NT-proBNP-guided and conventional therapy groups attained the desired NT-proBNP reduction of ≥30% (64% versus 63%, *P*=0.75). Of the 71 patients who had not yet attained >30% NT-proBNP reduction at randomization, 3 patients did not have a discharge NT-proBNP measurement. From the remaining patients, 52% (35/68) of patients in the NT-proBNP-guided group eventually attained >30% NT-proBNP reduction at discharge, whereas in the group of conventional patients, only 14% (9/63) eventually attained >30% NT-proBNP reduction at discharge (*P*<0.001). At discharge, significantly more patients in the NT-proBNP-guided group attained a reduction of >30% in NT-proBNP (from admission to discharge) compared with patients in the conventional therapy group (80% [144/179] versus 64% [113/177], *P*<0.001). The number of patients attaining and not attaining the NT-proBNP target at randomization and discharge and missing NT-proBNP levels is depicted in Table I in the online-only Data Supplement.

In line with this, patients in the NT-proBNP-guided therapy group attained a significantly larger relative and absolute reduction in NT-proBNP from admission to discharge compared with patients in the conventional therapy group, although no significant difference in absolute NT-proBNP levels at discharge was observed (Table 3).

Effect of Randomization Assignment on HF Therapy

Seventy-one patients in the NT-proBNP-guided group had an NT-proBNP reduction of ≤30% at randomization and therefore were subjected to the study algorithm to increase guideline-based directives for the management of HF. In 48 of these patients (68%), ≥1 subset of the algorithm was followed (start or titration of ACE inhibitor or angiotensin II receptor blocker (ARB), β-blocker or MRA, and an intervention planned or performed). In 4 patients (6%), attempts were made to start or titrate HF medication but were stopped because of side effects. In 13 patients (18%), physicians documented that they were not able to titrate or start HF medication because of severe renal insufficiency, hypotension, bradycardia, or simply because patients had a left ventricular ejection fraction >40%, and HF medication was not indicated in these patients. In 6 patients (8%), the algorithm was not followed adequately, although diuretics were uptitrated in 4 of these patients.

Changes in HF medication in patients in both NT-proBNP-guided and conventional groups between randomization and discharge are listed in Table 4. Attempts to adjust HF medication in the NT-proBNP-guided group were also scored. ACE inhibitors or ARBs and diuretics were initiated significantly more often or increased in dosages in patients in the NT-proBNP-guided group compared with those in the conventional group (25% versus 16%, *P*=0.04 for ACE inhibitors and ARBs; 29% versus 19%, *P*=0.03 for diuretics). Therapy changes in β-blockers and MRAs did not significantly differ between patients in NT-proBNP-guided and conventional groups (Table 4). In selected patients with a left ventricular ejection fraction <40%, there were no significant differences in ACE inhibitors or ARBs, MRAs, and diuretics between treatment groups. β-blockers in

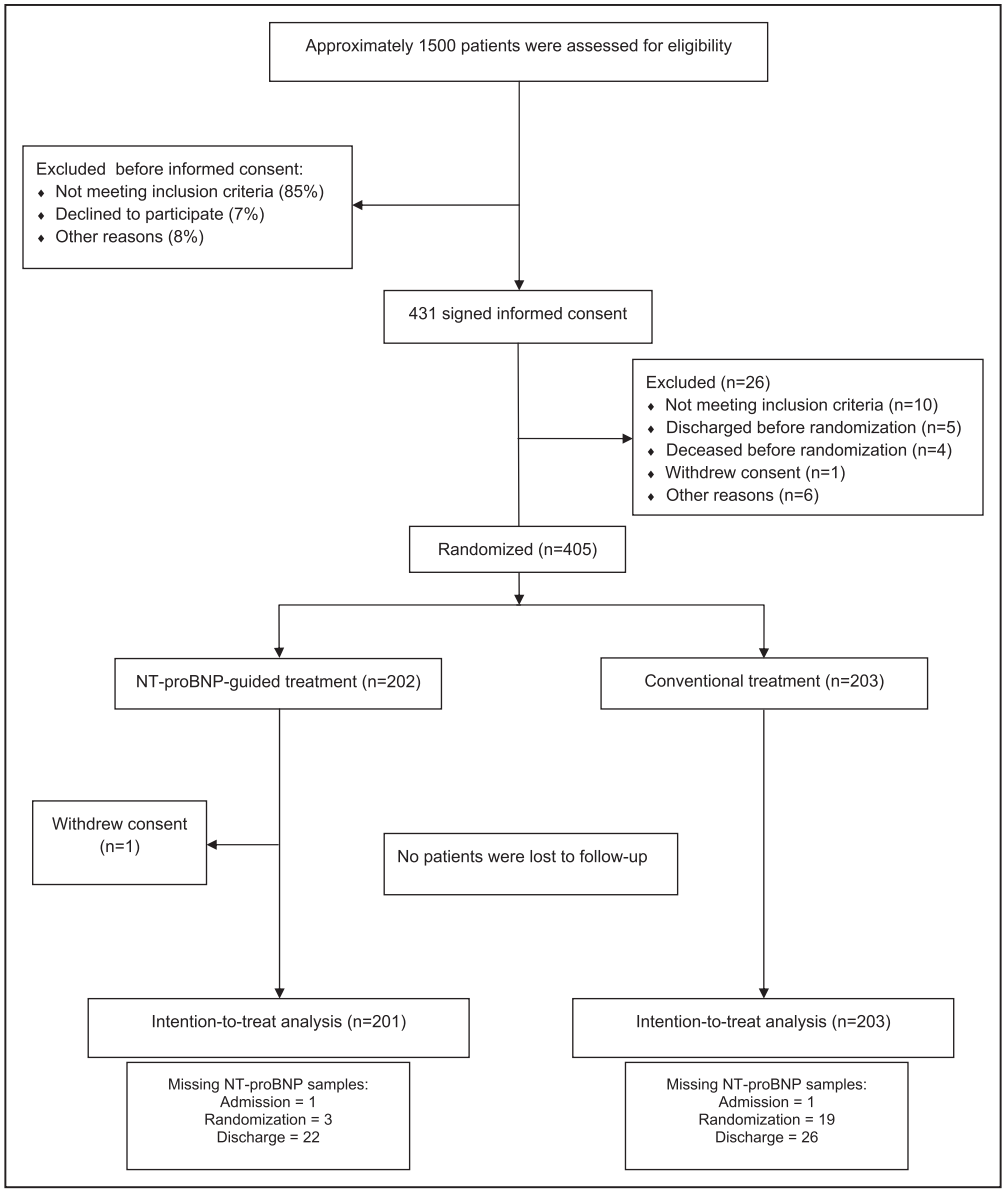

Figure 1. Outline of the PRIMA II trial.
NT-proBNP indicates N-terminal pro-B-type natriuretic peptide; and PRIMA II, Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?

patients with a left ventricular ejection fraction <40% were more often stopped or downtitrated in patients in the NT-proBNP-guided group compared with those in the conventional therapy group. Dosages of ACE inhibitors or ARBS, β-blockers, MRAs, and diuretics were similar at randomization and at discharge.

At discharge, no significant differences between patients in the NT-proBNP-guided and conventional groups were observed for the prescription rates and dosages of ACE inhibitors or ARBs, β-blockers, MRAs, and diuretics. This finding was not different between patients in the complete cohort and in selected patients with a left ventricular ejection fraction <40% (Table II in the online-only Data Supplement). There were no differences in discharge laboratory values, especially not in renal function (Table III in the online-only Data Supplement). The percentages of patients with hemoconcentration did not differ between the NT-proBNP-guided and conventional groups between admission and randomization (62% versus 55%, P=0.33), between randomization and discharge (32% versus 30%, P=0.77), and between admission and discharge (58% versus 58%, P=1.0).

Rates of electric cardioversion, coronary angiography, and cardiac resynchronization therapy ≤4 weeks after randomization were infrequent and did not differ between patients in the NT-proBNP-guided and conventional therapy groups (Table 4).

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Table 2. Baseline Characteristics

Variable	NT-proBNP-Guided Therapy (n=201)	Conventional Therapy (n=203)	*P* Value
Age, y, median (IQR)	78 (69–85)	77 (68–84)	0.4
Male sex, n (%)	92 (47)	106 (54)	0.2
History of diabetes mellitus, n (%)	71 (35)	67 (33)	0.7
History of hypertension, n (%)	128 (65)	126 (62)	0.7
History of chronic obstructive pulmonary disease, n (%)	33 (17)	46 (23)	0.1
History of atrial fibrillation, n (%)	96 (48)	100 (50)	0.8
History of congestive heart failure, n (%)	120 (60)	126 (62)	0.7
Ischemic etiology, n (%)	53 (46)	49 (41)	0.4
Previous heart failure admission in the past 12 mo, n (%)	54 (45)	56 (44)	1.0
History of coronary artery disease, n (%)	75 (39)	69 (36)	0.5
History of cerebrovascular accident/transient ischemic attack, n (%)	35 (18)	33 (16)	0.8
LVEF, %, mean±SD	36±15	38±15	0.7
Preserved LVEF (>45%), n (%)	47 (27)	49 (30)	0.7
Mild-moderate reduced LVEF (25% to 45%), n (%)	89 (51)	78 (47)	
Severely reduced LVEF (<25%), n (%)	37 (21)	39 (24)	
Jugular venous pressure distended at admission, n (%)	68 (54)	74 (60)	0.4
Pulmonary rales at admission, n (%)	156 (79)	146 (76)	0.6
Peripheral edema at admission, n (%)	145 (74)	140 (72)	0.7
Systolic blood pressure at admission, mm Hg, median (IQR)	134 (115–158)	130 (116–156)	0.9
Diastolic blood pressure at admission, mm Hg, median (IQR)	78 (65–91)	79 (65–96)	0.6
Heart rate at admission, bpm, median (IQR)	86 (72–110)	90 (74–112)	0.3
Atrial fibrillation at admission, n (%)	71 (36)	83 (41)	0.3
New York Heart Association class at admission, n (%)			
I	3 (2)	3 (2)	0.7
II	34 (17)	41 (21)	
III	102 (52)	104 (53)	
IV	57 (29)	47 (24)	
Laboratory findings			
Hemoglobin at admission, mmol/L	7.6±1.2	7.8±1.2	0.2
Serum urea nitrogen at admission, mmol/l	9.5 (7.2–13.7)	9.5 (6.5–14.8)	0.7
Serum sodium at admission, mmol/l	139 (136–141)	139 (136–141)	0.6
Serum potassium at admission, mmol/L	4.2 (3.8–4.6)	4.3 (3.9–4.6)	0.3
Creatinine at admission, µmol/L	112 (87–157)	109 (82–150)	0.4
Estimated glomerular filtration rate at admission, ml/min/1.73m²*	46 (33–60)	52 (35–67)	0.2
High-sensitivity cardiac troponin T at admission, µg/L	0.04 (0.02–0.07)	0.04 (0.03–0.09)	0.3
NT-proBNP at admission, ng/L	6293 (3949–11 438)	6122 (3252–11 371)	0.3
Medication at admission, n (%)			
Diuretics	136 (68)	136 (67)	0.9
Angiotensin-converting enzyme inhibitors or angiotensin receptor blocker	105 (52)	116 (57)	0.4
β-Blocker	125 (62)	135 (67)	0.4
Mineralocorticoid receptor antagonist	45 (22)	48 (24)	0.8
Triple heart failure medication (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, BB, and mineralocorticoid receptor antagonist)	19 (10)	27 (13)	0.3
No heart failure medication	23 (11)	26 (13)	0.8

Values indicate n (%) or mean (IQR). Missing values (in NT-proBNP vs conventional patient, respectively): history of diabetes mellitus (0 vs 1), history of heart failure (3 vs 1), history of chronic obstructive pulmonary disease (2 vs 0), history of atrial fibrillation (1 vs 2), ischemic etiology of heart failure (87 vs 83), previous hospitalization for heart failure (81 vs 77), history of coronary artery disease (10 vs 9), history of cerebrovascular accident/transient ischemic attack (1 vs 0), jugular venous pressure at admission (75 vs 79), rales at admission (3 vs 11), peripheral edema at admission (6 vs 8), systolic blood pressure at admission (0 vs 3), diastolic blood pressure at admission (0 vs 3), HR at admission (2 vs 2), New York Heart Association class (5 vs 8), hemoglobin levels (4 vs 2), serum urea nitrogen levels (45 vs 43), sodium levels (1 vs 2), potassium levels (2 vs 2), hsTnT levels (80 vs 73), NT-proBNP levels (1 vs 1). BB indicates beta-blocker; IQR, interquartile range; LVEF, left ventricle ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Calculated as 186.3 × (creatinine mg/dL)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.210 if black).

Effect of Randomization Assignment on Duration of Admission

Between patients in the NT-proBNP and conventional groups, the number of days from admission to randomization (both median 5 days [IQR, 3–8], *P*=0.31) and

Table 3. NT-proBNP Levels at Different Time Points and Changes in NT-proBNP Throughout Hospital Admission for Different Study Groups

	Admission (ng/L)	Randomization (ng/L)	Discharge (ng/L)	Reduction at Randomization		Reduction at Discharge	
				Percentage	Absolute (ng/L)	Percentage	Absolute (ng/L)
NT-proBNP median (IQR)	6350 (4152–11 327)	3498 (1833–5818)	2909 (1568–5340)	45 (16–64)	2411 (773–5414)	50 (34–67)*	2872 (1444–6687)†
Conventional median (IQR)	6013 (3711–11 113)	3286 (1922–7463)	3036 (1679–7092)	43 (8–63)	2130 (650–3963)	45 (9–66)*	2100 (651–5003)†

IQR indicates interquartile range; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.
*Statistical significant difference with $P<0.05$.
†Difference with $P<0.01$.

from randomization to discharge (both median 3 days [IQR, 1–7], $P=0.11$) was similar. Total duration of admission did not differ between patients in the NT-proBNP-guided compared to the conventional therapy group (both groups a median of 9 days [IQR, 6–15], $P=0.84$; and both groups a mean of 12 days±10, $P=0.9$).

Patients in the NT-proBNP-guided therapy group who failed to attain 30% NT-proBNP reduction at randomization had a significantly longer duration of admission (median of 11 days [IQR, 8–17 days]) compared with patients in the NT-proBNP-guided group who attained that target at randomization (median of 8 [IQR, 6–13] days, $P<0.001$) and compared with patients in the conventional therapy group (median of 9 [IQR, 6–15] days, $P=0.01$). There was no significant difference in duration of admission between conventionally treated patients who failed to attain an NT-proBNP reduction of 30% compared to those attaining a reduction >30% at randomization (respectively, 9 days [IQR, 6–14] versus 9 days [IQR, 6–15], $P=0.74$).

In patients in the NT-proBNP-guided group, we observed that a longer hospital stay after randomization (≥3 days after admission) was associated with a larger NT-proBNP reduction after randomization. This relationship was not present in patients in the conventional therapy group (Table IV in the online-only Data Supplement).

Outcomes

All-cause mortality or readmission for HF ≤180 days after randomization occurred in 72 patients (36%) in the NT-proBNP-guided group and in 73 patients (36%) in the conventional therapy group (HR for NT-proBNP-guided therapy, 0.96; 95% CI, 0.72–1.37; $P=0.99$) (Figure 2). Patients in the NT-proBNP-guided and conventional therapy groups were alive outside of the hospital a median of 178 (IQR, 153–180 and 179 (IQR, 160–180) days, respectively ($P=0.39$).

For the secondary end points, readmission for HF ≤180 days occurred in 49 patients (24%) in the NT-proBNP-guided therapy group and in 53 patients (26%) in the conventional therapy group (HR for NT-proBNP-guided therapy, 0.93; 95% CI, 0.63–1.38; $P=0.73$) (Figure IA in the online-only Data Supplement). All-cause mortality ≤180 days after randomization occurred in 39 (19%) and 35 (17%) of patients, respectively (HR for NT-proBNP-guided therapy, 1.12; 95% CI, 0.71–1.77; $P=0.63$) (Figure IB in the online-only Data Supplement).

Across all predefined subgroups, a consistently neutral treatment effect was observed for the first primary end point, except for sex, which showed a significant interaction (Figure 3).

Post Hoc Analyses

In the patients assigned to NT-proBNP-guided therapy, we analyzed event rates and NT-proBNP reduction percentages in subgroups of patients who were (1) successfully guided (from a reduction of ≤30% at randomization to >30% at discharge), (2) unsuccessfully guided (still ≤30% reduction at discharge), and (3) nonguided (including those patients randomized to NT-proBNP-guided therapy who attained >30% NT-proBNP reduction at randomization and remained at this level at discharge) (Figure 4). Event rates were significantly lower in nonguided patients compared with patients who needed guidance, and successfully guided patients had lower (although not statistically significant) event rates compared with unsuccessfully guided patients. Differences in event rates were reflected by differences in NT-proBNP reduction percentages: nonguided patients had a significantly larger reduction in NT-proBNP levels (from admission to discharge) compared with successfully and unsuccessfully guided patients (Figure 4).

In patients with an NT-proBNP reduction of ≤30% at randomization, there was no significant difference in event rate between patients randomized to the NT-proBNP-guided compared to the conventional therapy group (49% versus 55%, $P=0.5$; HR, 0.8, 95% CI, 0.5–1.3; $P=0.3$).

DISCUSSION

In our study involving patients with both de novo and acute-on-chronic ADHF, NT-proBNP-guided therapy

Table 4. Prescription of Heart Failure Therapy From Randomization to Discharge in Different Study Groups

	NT-proBNP (All LVEF %)	Conventional (All LVEF %)	*P* Value	NT-proBNP (LVEF <40%)	Conventional (LVEF <40%)	*P* Value
ACE inhibitor or ARB						
Proportion of target dose, median (IQR)						
Admission	0.5 (0.3–0.7)	0.5 (0.3–0.7)	0.5	0.4 (0.3–0.7)	0.5 (0.3–0.7)	0.8
Randomization	0.3 (0.3–0.5)	0.5 (0.3–0.5)	0.2	0.3 (0.3–0.5)	0.5 (0.3–0.7)	0.08
Discharge	0.3 (0.3–0.5)	0.5 (0.3–0.5)	0.2	0.3 (0.3–0.5)	0.5 (0.3–0.6)	0.6
Therapy changes between randomization and discharge, n (%)						
Initiation or uptitration	50 (25)	33 (16)	0.04	28 (26)	19 (21)	0.5
Stop or downtitration	30 (15)	37 (18)	0.4	15 (14)	20 (22)	0.2
No change in dosages	80 (40)	88 (44)	0.5	48 (44)	41 (45)	1.0
No ACE inhibitor/ARB at randomization and discharge	38 (19)	43 (21)	0.6	18 (17)	12 (13)	0.6
β-Blocker						
Proportion of target dose, median (IQR)						
Admission	0.5 (0.3–0.5)	0.4 (0.3–0.5)	0.3	0.4 (0.3–0.5)	0.3 (0.3–0.5)	0.2
Randomization	0.4 (0.3–0.5)	0.3 (0.3–0.5)	0.3	0.3 (0.3–0.5)	0.3 (0.1–0.5)	0.3
Discharge	0.5 (0.3–0.5)	0.4 (0.3–0.5)	0.3	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.5
Therapy changes between randomization and discharge, n (%)						
Initiation or uptitration	47 (24)	50 (25)	0.8	31 (28)	31 (34)	0.4
Stop or downtitration	33 (17)	26 (13)	0.3	18 (17)	6 (7)	0.03
No change in dosages	78 (39)	97 (48)	0.09	42 (39)	42 (46)	0.3
No ACE inhibitor/ARB at randomization and discharge	40 (20)	28 (14)	0.1	18 (17)	13 (14)	0.7
Mineralocorticoid receptor antagonist						
Proportion of target dose, median (IQR)						
Admission	0.5 (0.5–0.5)	0.5 (0.3–0.5)	0.3	0.5 (0.5–0.5)	0.5 (0.4–0.5)	0.7
Randomization	0.5 (0.5–0.5)	0.5 (0.5–0.5)	0.9	0.5 (0.5–0.5)	0.5 (0.4–0.5)	0.9
Discharge	0.5 (0.3–0.5)	0.5 (0.3–0.5)	0.8	0.5 (0.3–0.5)	0.5 (0.5–0.5)	0.4
Therapy changes between randomization and discharge, n (%)						
Initiation or uptitration	26 (13)	32 (16)	0.5	14 (13)	16 (17)	0.4
Stop or downtitration	28 (14)	20 (10)	0.2	18 (17)	12 (13)	0.6
No change in dosages	71 (36)	80 (40)	0.5	43 (39)	41 (45)	0.5
No ACE inhibitor/ARB at randomization and discharge	72 (36)	69 (34)	0.7	33 (30)	23 (25)	0.4
Diuretics						
Proportion of target dose, median (IQR)						
Admission	40 (0–80)	40 (0–80)	0.8	40 (0–80)	40 (0–80)	0.8
Randomization	80 (40–143)	80 (40–125)	1.0	80 (40–160)	80 (40–125)	0.4
Discharge	80 (40–120)	80 (40–120)	1.0	80 (40–160)	80 (40–120)	0.5
Therapy changes between randomization and discharge, n (%)						
Initiation or uptitration	57 (29)	38 (19)	0.03	29 (27)	17 (19)	0.2
Stop or downtitration	48 (24)	58 (29)	0.3	23 (21)	28 (31)	0.1
No change in dosages	91 (46)	93 (47)	0.9	57 (52)	42 (46)	0.4
No ACE inhibitor/ARB at randomization and discharge	2 (1)	12 (6)	0.5	0 (0)	5 (5)	0.6
Coronary angiography, n (%)	21 (11)	24 (12)	0.8	NA	NA	NA
Electric cardioversion, n (%)	11 (6)	6 (3)	0.2	NA	NA	NA
Cardiac resynchronization therapy, n (%)	1 (1)	1 (1)	1.0	NA	NA	NA
ACE inhibitor/ARB, BB, and MRA initiated/uptitrated and intervention planned, n (%)	110 (56)	100 (50)	0.3	66 (61)	50 (54)	0.4
ACE inhibitor/ARB, BB, MRA, and diuretic initiated/uptitrated and intervention planned, n (%)	138 (70)	120 (60)	0.04	81 (74)	58 (63)	0.08

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, beta-blocker; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NA, not available; and NT-proBNP, N-terminal pro-B-type natriuretic peptide. In-hospital deaths between randomization and discharge were excluded from these analyses (n=5). Proportion of target dose was calculated according to target doses in the ESC guidelines.[20]

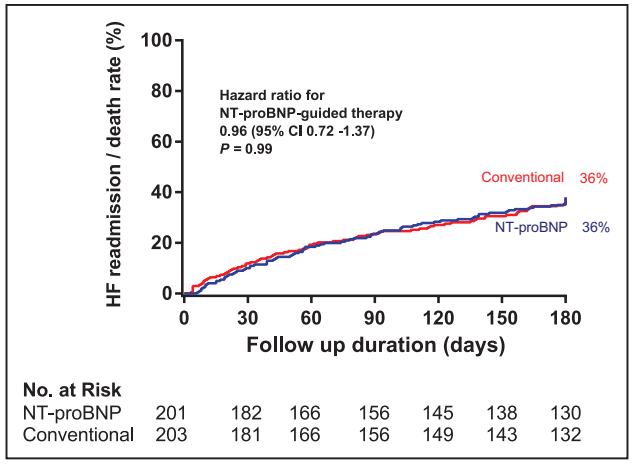

Figure 2. Kaplan–Meier curve for cumulative survival according to study group.
CI indicates confidence interval; HF, heart failure; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

(targeting a reduction of >30% in NT-proBNP levels from admission to discharge) and conventional therapy demonstrated similar event rates for all-cause mortality and readmissions for HF within 180 days after randomization and a comparable number of days alive outside of the hospital within 180 days after discharge. This finding was despite a significantly higher percentage of patients achieving NT-proBNP target in the NT-proBNP-guided compared with the conventional group (80% versus 62%, *P*=0.001) and despite similar baseline NT-proBNP levels in both groups. The strength of our study is the focus on target NT-proBNP levels as discharge targets, in addition to using NT-proBNP levels as a selection criterion for patients at higher risk before guidance of therapy. Several explanations can be given for an apparent lack of benefit of guidance in our study.

First, the primary composite event rate of patients in the conventional therapy group was 36% and was much lower than the expected 50% event rate.[1–4] This finding was not caused by a difference in mortality rates between our and previous studies (18% versus 18%)[4] and therefore may be attributed to lower readmission rates in PRIMA II. A reduction in HF readmission rates by improvements in HF care may only partly explain the lower than expected readmission rates because mortality rates would also be expected to decrease with these efforts.[23] Another explanation for lower readmission rates may be the switch from readmission for cardiovascular reason as an end point in our preliminary calculations[4] to readmission for HF (in our trial).

Second, to explain why a demonstrable further reduction in NT-proBNP does not translate into a better outcome, one may argue that a longer duration of admission in the patients in the NT-proBNP-guided therapy group led to the desired drop in NT-proBNP, and it was not (solely) achieved by intensification of therapy. However, in contrast to patients in the NT-proBNP-guided therapy group selected to be guided from randomization (ie, with an NT-proBNP reduction of <30%

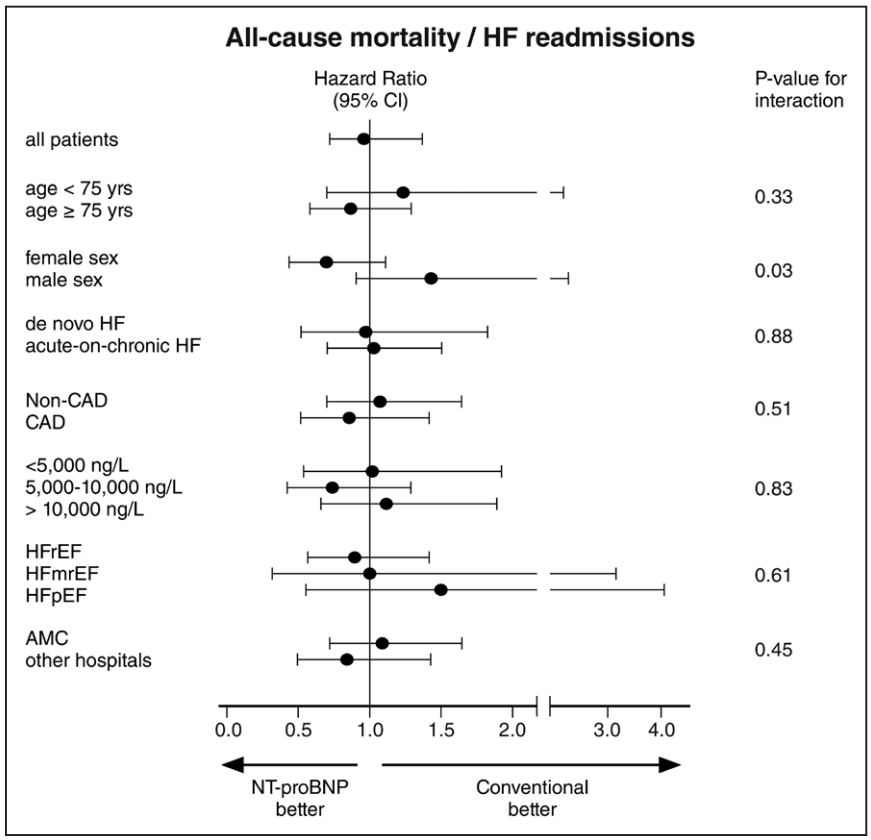

Figure 3. Subgroup analyses of primary end point.
AMC indicates Academic Medical Center; CAD, coronary artery disease; CI, confidence interval; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

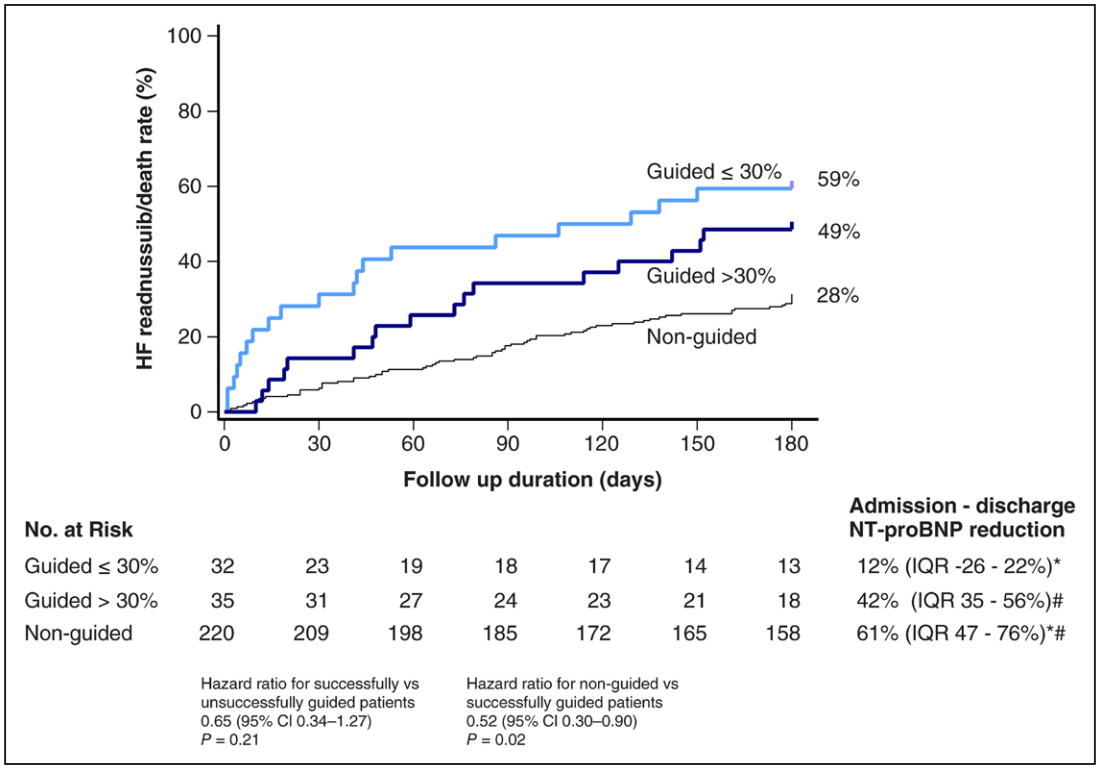

Figure 4. Kaplan–Meier curve for the primary end point for nonguided >30% NT-proBNP reduction, successfully guided, and unsuccessfully guided patients.

CI indicates confidence interval; HF, heart failure; IQR, interquartile range; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.*Statistically significant difference with *P*<0.001 between nonguided and unsuccessfully guided patients. #Statistical significant difference with *P*<0.001 between nonguided and successfully guided patients.

at randomization), we did not observe a significantly greater percentage NT-proBNP reduction in conventional patients who also had a longer length of stay after randomization. Neither was this found in patients in the NT-proBNP-guided therapy group who already had a reduction of >30% at randomization and had a longer hospital stay. If a longer hospital stay would cause more patients to attain the NT-proBNP target of >30%, then we should have seen a relationship between length of stay and percentage NT-proBNP reduction in patients in nonguided NT-proBNP-guided and conventional therapy groups as well.

Third, although we accounted for an attainability of the NT-proBNP target of 90%, the attainability of 80% in the NT-proBNP-guided therapy group was still less than expected. Further study is needed to investigate why it was not possible to lower NT-proBNP levels in 20% of patients. When we correct the sample size to adjust for an attainability of 80%, we would have had to enroll 536 patients (2 x 268) to be able to detect an adapted relative risk reduction of 24% (ie, a reduction in primary end point from 50% to 38%). However, increasing the sample size to these numbers probably would not have led to a significant difference in outcome between patients in the NT-proBNP-guided versus conventionally treated groups because there were still other factors influencing the study outcome. One is the lower than expected primary event rate in the conventional therapy group (as mentioned earlier), and the other is our finding that a significantly smaller reduction in NT-proBNP was obtained in patients in the NT-proBNP-guided group who needed guidance compared with patients who achieved a >30% NT-proBNP reduction without guidance (Figure II in the online-only Data Supplement; respectively, a median NT-proBNP reduction from admission to discharge of 42% versus 61%). However, the latter were findings from our post hoc analyses and remain hypothesis-generating.

Implications for Future Research

In this study, we suggest that the outcome of patients who are successfully guided toward an NT-proBNP target of >30% reduction needs to be differentiated from the outcome of patients who attain an NT-proBNP reduction of >30% without guiding. Larger studies in selected high-risk patients (ie, with an NT-proBNP reduction of <30% at clinical stability) with sample sizes based on adapted event rates for patients in the intervention group are mandatory before we dismiss the idea of NT-proBNP guidance of therapy in patients with acute HF.

Limitations

Some limitations to this study should be noted.

First, the criteria that we used for the definition of clinical stability are not evidence-based. To date, no clear, validated guidelines exist for what metrics should be used for adequate discharge of patients with ADHF. If by any rule, such a definition should be a composite of measures as previously suggested in the MEASURE-AHF study (An International, Prospective Registry to Evaluate the Evolution of Measures of Disease Severity in Acute Heart Failure).[24] Because our definition of clinical stability is not validated, it is possible that the moment of randomization slightly differed among patients, physicians, and hospitals.

Our criteria for clinical stability consisted of several measures reflecting (to some extent) clinical status and vital signs, but after this moment predischarge we did not collect data regarding clinical status, vital signs, or weight. As a measure of decongestion, we analyzed percentages of patients with hemoconcentration in both study groups at clinical stability and at discharge.[7,25] There was no difference in the percentage of patients with hemoconcentration, and percentages were comparable to percentages mentioned in previous publications.[7,25] Therefore, we believe that patients were equally decongested at clinical stability (randomization) and at discharge. However, it is possible that the continuing assessment of clinical signs of congestion after initial clinical stability would have helped physicians to make appropriate choices from the protocol. The possibility remains that patients again become congested between randomization and discharge.[26]

Second, although the study sites were contacted for therapy advice and physicians had to report reasons for not initiating or titrating HF medication for patients in the NT-proBNP-guided group who had an NT-proBNP reduction of <30% at randomization, the choice of which HF therapy to use was left to the treating physician. In addition, although ACE inhibitors, ARBs, and diuretics were more frequently initiated or titrated in patients in the NT-proBNP-guided therapy group, there were no differences in prescription rates and dosages at discharge between study groups. We cannot exclude the possibility that fewer than possible adjustments in therapy were made and that the changes in HF medication that were made during hospitalization were too small to result in significantly higher prescription rates and dosages at discharge.

Last, the relatively small number and exclusively European centers limit generalizability, and therefore the results of this study may not apply to countries with different healthcare systems. For example, it must be taken into account that the median length of stay in our study was 9 days, which differs from the length of stay in, for example, the United States (≈6 days).[27] In addition, because there is no evidence for NT-proBNP guidance after discharge, there were no study requirements for care after discharge (ie, care in all Dutch centers was delivered by a multidisciplinary HF team). Different care systems among countries may have resulted in different clinical outcomes among countries. However, differences in outcome were not detectable for patients in Dutch centers versus other European centers.

CONCLUSIONS

To our knowledge, this study is the first to evaluate the prognostic impact of NT-proBNP-guided therapy using an individualized selection target and discharge target in patients with ADHF. The PRIMA II demonstrates that guidance of HF therapy after clinical stability to increase the number of patients with an NT-proBNP target of >30% reduction in the present study did not improve outcomes.

ARTICLE INFORMATION

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Dr Ferreira reports receiving modest board fees from Novartis and modest speaker fees from Roche. Dr Marques reports receiving modest honoraria and

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REFERENCES

1. Fonarow GC. Epidemiology and risk stratification in acute heart failure. *Am Heart J*. 2008;155:200–207. doi: 10.1016/j.ahj.2006.10.043.
2. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA*. 2003;290:2581–2587. doi: 10.1001/jama.290.19.2581.
3. O'Connor CM, Hasselblad V, Mehta RH, Tasissa G, Califf RM, Fiuzat M, Rogers JG, Leier CV, Stevenson LW. Triage after hospitalization with advanced heart failure: the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) risk model and discharge score. *J Am Coll Cardiol*. 2010;55:872–878. doi: 10.1016/j.jacc.2009.08.083.
4. Salah K, Kok WE, Eurlings LW, Bettencourt P, Pimenta JM, Metra M, Bayes-Genis A, Verdiani V, Bettari L, Lazzarini V, Damman P, Tijssen JG, Pinto YM. A novel discharge risk model for patients hospitalised for acute decompensated heart failure incorporating N-terminal pro-B-type natriuretic peptide levels: a European Collaboration on Acute Decompensated Heart Failure: ELAN-HF Score. *Heart*. 2014;100:115–125. doi: 10.1136/heartjnl-2013-303632.
5. Kociol RD, McNulty SE, Hernandez AF, Lee KL, Redfield MM, Tracy RP, Braunwald E, O'Connor CM, Felker GM; NHLBI Heart Failure Network Steering Committee and Investigators. Markers of decongestion, dyspnea relief, and clinical outcomes among patients hospitalized with acute heart failure. *Circ Heart Fail*. 2013;6:240–245. doi: 10.1161/CIRCHEARTFAILURE.112.969246.
6. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, Piovanelli B, Carubelli V, Bugatti S, Lombardi C, Cotter G, Dei Cas L. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail*. 2012;5:54–62. doi: 10.1161/CIRCHEARTFAILURE.111.963413.
7. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation*. 2010;122:265–272. doi: 10.1161/CIRCULATIONAHA.109.933275.
8. Stevenson LW, Tillisch JH, Hamilton M, Luu M, Chelimsky-Fallick C, Moriguchi J, Kobashigawa J, Walden J. Importance of hemodynamic response to therapy in predicting survival with ejection fraction less than or equal to 20% secondary to ischemic or nonischemic dilated cardiomyopathy. *Am J Cardiol*. 1990;66:1348–1354.
9. Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, Stevenson LW, Francis GS, Leier CV, Miller LW; ESCAPE Investigators and ESCAPE Study Coordinators. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA*. 2005;294:1625–1633. doi: 10.1001/jama.294.13.1625.
10. Bayés-Genís A, Lopez L, Zapico E, Cotes C, Santaló M, Ordonez-Llanos J, Cinca J. NT-ProBNP reduction percentage during admission for acutely decompensated heart failure predicts long-term cardiovascular mortality. *J Card Fail*. 2005;11(5 suppl):S3–S8.
11. Bettencourt P, Azevedo A, Pimenta J, Friões F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation*. 2004;110:2168–2174. doi: 10.1161/01.CIR.0000144310.04433.BE.
12. Verdiani V, Ognibene A, Rutili MS, Lombardo C, Bacci F, Terreni A, Nozzoli C. NT-ProBNP reduction percentage during hospital stay predicts long-term mortality and readmission in heart failure patients. *J Cardiovasc Med (Hagerstown)*. 2008;9:694–699. doi: 10.2459/JCM.0b013e3282f447ae.
13. Rosenberg J, Gustafsson F, Remme WJ, Riegger GA, Hildebrandt PR. Effect of beta-blockade and ACE inhibition on B-type natriuretic peptides in stable patients with systolic heart failure. *Cardiovasc Drugs Ther*. 2008;22:305–311. doi: 10.1007/s10557-008-6099-6.
14. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539–1549. doi: 10.1056/NEJMoa050496.
15. Sargento L, Satendra M, Longo S, Lousada N, Palma dos Reis R. Early NT-proBNP decrease with ivabradine in ambulatory patients with systolic heart failure. *Clin Cardiol*. 2013;36:677–682. doi: 10.1002/clc.22183.
16. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–e161. doi: 10.1161/CIR.0000000000000509.
17. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129–2200. doi: 10.1093/eurheartj/ehw128.
18. Carubelli V, Lombardi C, Lazzarini V, Bonadei I, Castrini AI, Gorga E, Richards AM, Metra M. N-terminal pro-B-type natriuretic peptide-guided therapy in patients hospitalized for acute heart failure. *J Cardiovasc Med (Hagerstown)*. 2016;17:828–839. doi: 10.2459/JCM.0000000000000419.
19. Stienen S, Salah K, Moons AH, Bakx AL, van Pol PE, Schroeder-Tanka JM, Voogel AJ, Keijer JT, Kortz RA, Dickhoff C, Meregalli PG, Tijssen JG, Pinto YM, Kok WE. Rationale and design of PRIMA II: a multicenter, randomized clinical trial to study the impact of in-hospital guidance for acute decompensated heart failure treatment by a predefined NT-PRoBNP target on the reduction of readmIssion and Mortality rAtes. *Am Heart J*. 2014;168:30–36. doi: 10.1016/j.ahj.2014.04.008.
20. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2012;14:803–869. doi: 10.1093/eurjhf/hfs105.
21. Eurlings LW, van Pol PE, Kok WE, van Wijk S, Lodewijks-van der Bolt C, Balk AH, Lok DJ, Crijns HJ, van Kraaij DJ, de Jonge N, Meeder JG, Prins M, Pinto YM. Management of chronic heart failure guided by individual N-terminal pro-B-type natriuretic peptide targets: results of the PRIMA (Can Pro-Brain-Natriuretic Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Morbidity and Mortality?) study. *J Am Coll Cardiol*. 2010;56:2090–2100. doi: 10.1016/j.jacc.2010.07.030.
22. Benjamini Y, Hochberg Y. Controlling the false dscovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol*. 1995;57:289–300.
23. Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG, Laroche C, Seferovic PM, Anker SD, Ferrari R, Ruschitzka F, Lopez-Fernandez S, Miani D, Filippatos G, Maggioni AP; ESC Heart Failure Long-Term Registry Investigators. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017;19:1242–1254. doi: 10.1002/ejhf.890.
24. Allen LA, Metra M, Milo-Cotter O, Filippatos G, Reisin LH, Bensimhon DR, Gronda EG, Colombo P, Felker GM, Cas LD, Kremastinos DT, O'Connor CM, Cotter G, Davison BA, Dittrich HC, Velazquez EJ. Improvements in signs and symptoms during hospitalization for acute heart failure follow different patterns and depend on the measurement scales used: an in-

ternational, prospective registry to evaluate the evolution of measures of disease severity in acute heart failure (MEASURE-AHF). *J Card Fail*. 2008;14:777–784. doi: 10.1016/j.cardfail.2008.07.188.
25. van der Meer P, Postmus D, Ponikowski P, Cleland JG, O'Connor CM, Cotter G, Metra M, Davison BA, Givertz MM, Mansoor GA, Teerlink JR, Massie BM, Hillege HL, Voors AA. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. *J Am Coll Cardiol*. 2013;61:1973–1981. doi: 10.1016/j.jacc.2012.12.050.
26. Eurlings LW, Sanders-van Wijk S, van Kraaij DJ, van Kimmenade R, Meeder JG, Kamp O, van Dieijen-Visser MP, Tijssen JG, Brunner-La Rocca HP, Pinto YM. Risk stratification with the use of serial N-terminal pro-B-type natriuretic peptide measurements during admission and early after discharge in heart failure patients: post hoc analysis of the PRIMA study. *J Card Fail*. 2014;20:881–890. doi: 10.1016/j.cardfail.2014.08.014.
27. Fonarow GC, Heywood JT, Heidenreich PA, Lopatin M, Yancy CW; ADHERE Scientific Advisory Committee and Investigators. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J*. 2007;153:1021–1028. doi: 10.1016/j.ahj.2007.03.012.

Henry Ford Hospital

To serve the rapidly growing workforce and population in booming Detroit during the early 1900s, Henry Ford spearheaded the creation of a hospital, which first opened on October 1, 1915. From its inception, the mission of Henry Ford Hospital was to provide the best patient care, foster innovation through clinical research, and be a pillar in the community. This foundation was established by Drs Frank Sladen and Roy McClure, pupils of Sir William Osler and Dr William Halsted, respectively.

The hospital has provided innumerable contributions to the field of medicine and surgery, particularly in cardiovascular and cerebrovascular care. Dr Conrad Lam was the first physician to administer heparin to treat blood clots and also pioneered the creation of the heart-lung machine. In the 1990s, led by Drs KMA Welch and Barbara Tilley, the hospital was the lead coordinating center for the NINDS tPA trial. Most recently, Drs William O'Neill and Adam Greenbaum have pioneered techniques advancing the field of interventional cardiology. Currently, the hospital houses nearly 900 beds and boasts the largest number of intensive care unit beds in the state of Michigan.

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