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CME

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

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Results of the PRIMA (Can PRo-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) Study

Objectives The purpose of this study was to assess whether management of heart failure (HF) guided by an individualized N-terminal pro–B-type natriuretic peptide (NT-proBNP) target would lead to improved outcome compared with HF management guided by clinical assessment alone.

Background Natriuretic peptides may be attractive biomarkers to guide management of heart failure (HF) and help select patients in need of more aggressive therapy. The PRIMA (Can PRo-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) study is, to our knowledge, the first large, prospective randomized study to address whether management of HF guided by an individualized target NT-proBNP level improves outcome.

Methods A total of 345 patients hospitalized for decompensated, symptomatic HF with elevated NT-proBNP levels at admission were included. After discharge, patients were randomized to either clinically-guided outpatient management ($n = 171$), or management guided by an individually set NT-proBNP ($n = 174$) defined by the lowest level at discharge or 2 weeks thereafter. The primary end point was defined as number of days alive outside the hospital after index admission.

Results HF management guided by this individualized NT-proBNP target increased the use of HF medication ($p = 0.006$), and 64% of HF-related events were preceded by an increase in NT-proBNP. Nevertheless, HF management guided by this individualized NT-proBNP target did not significantly improve the primary end point (685 vs. 664 days, $p = 0.49$), nor did it significantly improve any of the secondary end points. In the NT-proBNP–guided group mortality was lower, as 46 patients died (26.5%) versus 57 (33.3%) in the clinically-guided group, but this was not statistically significant ($p = 0.206$).

Conclusions Serial NT-proBNP measurement and targeting to an individual NT-proBNP value did result in advanced detection of HF-related events and importantly influenced HF-therapy, but failed to provide significant clinical improvement in terms of mortality and morbidity. (Effect of NT-proBNP Guided Treatment of Chronic Heart Failure [PRIMA]; NCT00149422) (J Am Coll Cardiol 2010;56:2090–100) © 2010 by the American College of Cardiology Foundation

Current management of patients with heart failure (HF) is mainly based on clinical signs and symptoms. This approach allows clinicians to respond to worsening HF once it is recognized, but does not allow selection of individuals who are most likely to progress to increased morbidity and mortality and are thus in need of more intensive treatment. Plasma levels of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) are established indicators of decompensated HF (1,2) and predictors of HF morbidity and mortality (3,4). Natriuretic peptides may therefore be attractive biomarkers to guide management of HF and help select patients in need of more aggressive therapy.

See page 2101

Troughton et al. (5) were the first to suggest in a small pilot study that guiding HF management by aiming for a target NT-proBNP level may improve outcome. In this study, the investigators aimed to achieve NT-proBNP levels of 200 pmol/l (1,700 pg/ml) or lower, a goal that is difficult to achieve in many patients with established HF. The clinical value of such stringent (NT-pro)BNP levels has recently been addressed in several other clinical outcome studies (6–8). These studies failed to show an overall reduction in mortality, but did suggest improved outcome in HF patients under the age of 75 years. Also, the (NT-pro)BNP target value was achieved only in a minority of patients. In the STARS-BNP (Systolic Heart Failure Treatment Supported by BNP) Multicenter study, only 33% reached the BNP target (8), whereas in TIME-CHF (Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure) and the BATTLESCARRED (NT-proBNP-Assisted Treatment to Lessen Se-

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
BNP = B-type natriuretic peptide
ESC = European Society of Cardiology
HF = heart failure
IQR = interquartile range
LVEF = left ventricular ejection fraction
NT-proBNP = N-terminal pro–B-type natriuretic peptide
QOL = quality of life

rial Cardiac Readmissions and Death) trial, at least 50% of the subjects had not achieved the desired target at the end of the study. At the same time, the TIME-CHF investigators speculated that intensification of therapy might be harmful in the elderly (7).

As the target NT-proBNP level in the aforementioned studies was not achieved in the majority of HF patients randomized to (NT-pro)BNP–guided therapy, most subjects randomized to the (NT-pro)BNP–guided arms received intensified treatment. These studies therefore show that a more generalized intensification of HF therapy may be beneficial in specific subgroups. However, it was not addressed whether serial assessment of NT-proBNP enables to select patients at risk of increased morbidity and mortality. Therefore, the question remains whether it is beneficial to intensify HF therapy only in those patients most likely to progress towards events.

It is well known that in many HF patients, NT-proBNP levels never normalize, whereas these patients still remain clinically stable over years. This suggests that patients with stable NT-proBNP levels (even when clearly elevated) may have an acceptable prognosis. We hypothesized that elevation of outpatient NT-proBNP levels as compared with the patient's individualized target level, allows selection of those HF patients most likely to progress towards events. The individualized target level was defined as the lowest level at discharge or at 2 weeks follow-up after admission because of HF. We further hypothesized that restricting treatment intensification to these selected patients would be beneficial without additional risk of adverse effects. We therefore performed a prospective randomized study to address whether treatment of HF, guided by an individualized target NT-proBNP level, improves outcome in HF patients.

Methods

Study design and study population. To be included, patients had to be hospitalized for decompensated, symptomatic HF, fulfilling the European Society of Cardiology (ESC) diagnostic guideline criteria for acute HF (9). In addition, NT-proBNP levels at admission were required to be at least 1,700 pg/ml, as additional objective evidence of HF (1).

Exclusion criteria were: life-threatening cardiac arrhythmias during the index hospitalization, urgent invasive or surgical intervention performed or planned during the index hospital admission, severe chronic obstructive pulmonary disease with a forced expiratory volume in 1 s (FEV1) of <1 l/s, pulmonary embolism less than 3 months prior to admission, pulmonary hypertension not caused by left ventricular systolic dysfunction, a non–HF-related expected survival of less than 1 year, and patients undergoing hemodialysis or continuous ambulant peritoneal dialysis. A lesser degree of renal dysfunction was not an exclusion criterion. Patients were screened and included during the index admission because of acute HF (Fig. 1). Informed consent was obtained and NT-proBNP levels were measured at hospital discharge. Patients demonstrating a significant decrease in NT-proBNP levels during hospitalization, defined as a decrease of more than 10%, with a drop in NT-proBNP levels of at least 850 pg/ml, were randomized to treatment that was either NT-proBNP guided or clinically guided. Patients in whom NT-proBNP levels decreased <10% during admission were considered not to modulate their NT-proBNP levels enough to allow NT-proBNP–guided treatment. Therefore, these patients were not included. Regular follow-up visits were scheduled at 2 weeks and 1 month, and then every 3 months until the follow-up period of 2 years was completed. Follow-up visits were performed by dedicated HF cardiologists and nurses. The institutional review board or ethics committee at each site approved the protocol, and all patients provided written informed consent before enrollment.

Treatment in the NT-proBNP–guided group was guided by the combination of clinical assessment and NT-proBNP levels. The individual NT-proBNP target value was set at the lowest level at discharge or at 2 weeks follow-up. If at subsequent outpatient visits, NT-proBNP levels were more than 10% with a minimum of 850 pg/ml above this individual target level, NT-proBNP level was considered "off-target," and therapy was intensified according to the ESC HF treatment guidelines (10). In this treatment group, an electronic case record form indicated at each visit whether NT-proBNP levels were off-target and indicated whether intensification was necessary. Therapy in the clinically-guided treatment group was determined by clinical assessment alone. A therapy advisor, incorporated in the electronic case record form, was designed to give individual treatment advice, depending on several individual variables including the cause of HF (ischemic vs. nonischemic), left ventricular ejection fraction (LVEF), clinical signs of HF, and creatinine clearance. Also, titration schemes for diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, angiotensin receptor blockers, and aldosterone receptor blockers were provided. In the clinically-guided treatment group, all cardiologists were blinded to the NT-proBNP levels of the patients during follow-up. At every outpatient visit, vital status was assessed. Quality of life (QOL) was assessed at 3-month intervals by the Minnesota Living with Heart Failure Questionnaire (11). NT-proBNP levels were measured on a Roche Diagnostics Elecsys platform (Roche Diagnostics Ltd., Rotkreuz, Switzerland) at every participating site, except for 1 center where the NT-proBNP levels of patients randomized to the NT-proBNP guided group were measured within 24 h in a participating university hospital nearby.

Definition of study end points. The primary end point of the PRIMA (Can PRo-brain-natriuretic peptide guided

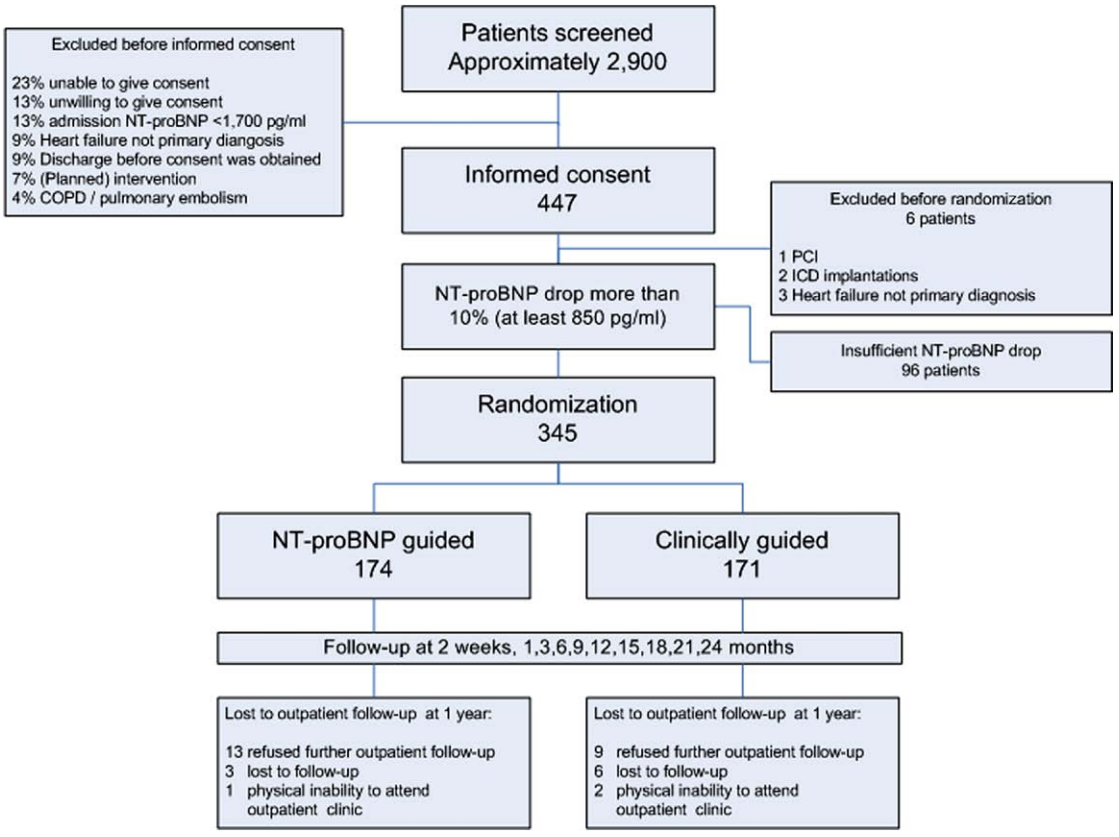


Figure 1 **Trial Outline**

Overview of patients screened, reasons for exclusion, and the total number of patients randomized into the NT-proBNP–guided and the clinically-guided groups. Furthermore, insight is given into patients lost to follow-up after 1 year of randomization. COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PCI = percutaneous coronary intervention.

therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) study was defined as the difference in total number of days alive and outside the hospital between the NT-proBNP–guided and the clinically-guided group. This primary end point replaced the initial end point of reduction in number of events, as the end point of number of days alive outside the hospital included hospital admission as mortality. The primary end point was changed before any patient had been included, in the start-up phase of the study. Major secondary end points encompassed total and cardiovascular mortality, total and cardiovascular hospitalization, and the combined end points of total and cardiovascular morbidity and mortality. Furthermore, renal function, left ventricular systolic function, and age subgroups were analyzed. Additionally, analysis of the use of evidence-based HF medication was performed. Evidence-based HF medication target dose was defined as the recommended maintenance dose approved for the treatment of HF in Europe (10). Finally, it was predefined to analyze the prognostic impact of NT-proBNP levels above the individually set target level at outpatient visits. All events were adjudicated by a blinded event committee, consisting of medical specialists in cardiology, nephrology, vascular medicine, pulmonology, and neurology. Serious adverse events included admissions to the emergency room, hospital admissions, and death.

Treatment in the NT-proBNP group was considered to be protocol adherent when 1 of the following actions was undertaken upon an elevated outpatient NT-proBNP level: starting or intensifying HF medication according to the ESC guidelines, all therapeutic and diagnostic actions searching for underlying causes of HF such as hypertension, ischemic heart disease, valvular heart disease, anemia, and cardiac arrhythmias; hospital admission (for decompensated HF); or registering for heart transplantation.

Statistical analysis. Based on previous studies and observations, it was estimated that, with an event rate of 20%, 480 patients would be needed to reach a relative risk reduction in number of events of 50% in the NT-proBNP–guided group compared with the clinically-guided group at an α level of 0.05 and a power level of 0.80. Although the primary end point changed during the start-up phase of the study, power analysis remained the same. One year after the first patient being included, a pre-specified interim analysis was performed, with a difference in events ($p < 0.01$) as criterion to preliminary stop

Table 1 Baseline Characteristics

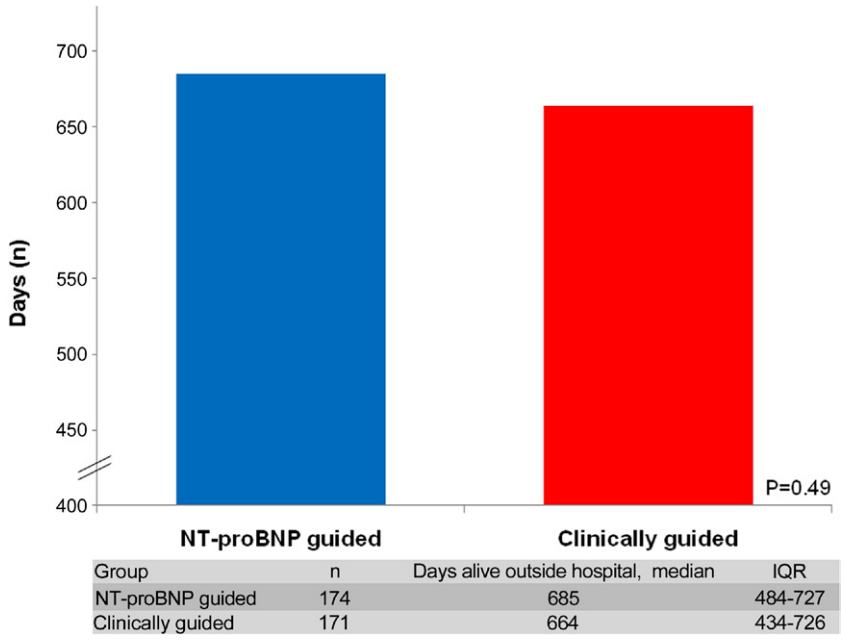
Characteristics	NT-proBNP–Guided (n = 174)	Clinically-Guided (n = 171)	p Value
Baseline			
Age, yrs	71.6 ± 12.0	72.8 (11.7)	NS
Female	79 (45.4)	69 (40.3)	NS
Hypertension	83 (47.7)	84 (49.1)	NS
Diabetes mellitus	44 (25.3)	47 (27.5)	NS
Transient ischemic attack	8 (4.6)	25 (14.6)	0.002
Stroke	17 (9.8)	18 (10.5)	NS
COPD	29 (16.7)	30 (17.5)	NS
Smoking			
Current	37 (21.3)	37 (21.6)	NS
History	56 (32.2)	49 (28.7)	NS
Atrial fibrillation			
Chronic	29 (16.7)	29 (17.0)	NS
Paroxysmal	28 (16.1)	26 (15.2)	NS
Coronary artery disease	97 (55.7)	109 (63.7)	NS
Myocardial infarction	65 (37.4)	74 (43.3)	NS
PCI	20 (11.5)	24 (14.0)	NS
CABG	32 (18.4)	29 (17.0)	NS
Valve replacement	11 (6.3)	9 (5.3)	NS
Pacemaker	11 (6.3)	21 (12.3)	NS
ICD	13 (7.5)	10 (5.8)	NS
History of heart failure			
Ischemic	40 (23.0)	33 (19.3)	
Nonischemic	26 (14.9)	26 (15.2)	
Cause unknown	1 (0.6)	0	NS
Discharge			
NYHA functional class			
I	20 (11.5)	17 (9.9)	
II	113 (64.9)	121 (70.8)	
III	41 (23.6)	33 (19.3)	NS
LVEF, %	34.9 ± 13.7	36.7 ± 14.8	NS
LVEDD, %	57.5 ± 9.6	58.5 ± 9.4	NS
Mitral regurgitation grade ≥II	84 (48.3)	63 (36.8)	NS
Systolic BP, mm Hg	116.8 ± 18.5	119.4 ± 22.4	NS
Diastolic BP, mm Hg	68.7 ± 11.3	69.2 ± 11.6	NS
Pulse, beats/min	72.1 ± 11.4	74.5 (16.1)	NS
QRS duration	116.0	108.0	NS
Sodium, mmol/l	139.5 ± 3.2	139.1 ± 3.8	NS
Potassium, mmol/l	4.27 ± 0.46	4.27 ± 0.46	NS
Urea, U/l	11.5 (8.2–16.2)	11.9 (9.0–16.0)	NS
Creatinine, U/l	121 (97.8–157.3)	126 (104.0–166.3)	NS
Hemoglobin, mmol/l	8.5 ± 1.2	8.4 ± 1.3	NS
NT-proBNP, pg/ml			
Admission	8,034 (4,210–13,831)	8,168 (4,288–14,051)	NS
Discharge	2,961 (1,383–5,144)	2,936 (1,291–5,525)	NS
Target	2,491 (1,109–4,435)		
Follow-up, days	720 (492–730)	699 (464–730)	NS

Values are expressed as mean (SD), n (%), or median (interquartile range).

BP = blood pressure; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NS = not significant; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

according to lan-DeMets alpha spending rule. The interim analysis demonstrated a pooled event rate of 65%. Thereupon the power analysis was re-evaluated. It was calculated that 364 patients were needed to demonstrate a minimum reduction in pooled events of 30%.

Results are presented as frequencies, mean (SD), or median (interquartile range [IQR]), where appropriate. Between-group comparisons were performed using the *t* test, Mann-Whitney U test, or chi-square test where appropriate. Event rates for all-cause mortality were estimated by the Kaplan-



Group	n	Days alive outside hospital, median	IQR
NT-proBNP guided	174	685	484-727
Clinically guided	171	664	434-726

Figure 2 **Primary End Point: Number of Days Alive Outside the Hospital**

No significant difference was seen in the primary end point. NT-proBNP = N-terminal pro–B-type natriuretic peptide.

Meier method. Hazard ratios were calculated using Cox regression analysis. Time-dependent Cox regression analysis was performed to analyze the prognostic impact of elevated NT-proBNP levels above target value at the outpatient clinic. All calculations were performed with the use of the SPSS statistical package version 15.0 (SPSS Inc., Chicago, Illinois).

Results

PRIMA is a prospective, randomized, single-blind study executed in 12 Dutch university and large general hospitals. Patients were recruited between June 2004 and September 2007. In total, 345 patients were randomized: 174 patients to the NT-proBNP–guided treatment group and 171 patients to the clinically-guided group.

Baseline characteristics are shown in Table 1, which did not reveal significant differences between the 2 study groups except for the number of transient ischemic attacks (4.6% in the NT-proBNP–guided vs. 14.6% in the clinically-guided group, $p = 0.002$). Patients were elderly with a mean age of 72 years, more than 40% were female, and a large proportion had cardiovascular risk factors such as hypertension and diabetes mellitus. History of HF was present in 37% of subjects, and almost a quarter had a LVEF above 45%. After the index admission, most patients were in New York Heart Association functional class II at discharge. The median NT-proBNP target value in the NT-proBNP–guided treatment group was 2,491 pg/ml. The median follow-up was 702 days (IQR: 488 to 730 days). In 34 patients (17 in both randomization groups, see Fig. 1), outpatient follow-up visits after 1-year follow-up were not completed.

End points. Management guided by an individualized NT-proBNP target did not significantly improve the primary end point, the number of days alive outside the hospital: median number of days alive outside the hospital was 685 versus 664 days, $p = 0.49$ (Fig. 2). In the NT-proBNP–guided group, mortality was lower, as 46 patients died (26.5%), versus 57 (33.3%) in the clinically-guided group (Fig. 3), but this was not statistically significant. The number of scheduled visits did not differ between the NT-proBNP–guided and the clinically-guided group (mean 7.1 ± 3.1 vs. 6.9 ± 3.0, $p = 0.424$). However, there was a trend towards an increase in unscheduled visits in the NT-proBNP–guided group (mean 1.4 ± 1.9 vs. 1.1 ± 1.7, $p = 0.063$). The total number of cardiovascular and HF-related admissions between the NT-proBNP–guided and the clinically-guided groups were not different (mean 1.11 ± 2.20 vs. 1.05 ± 1.47, $p = 0.552$, and 0.70 ± 1.89 vs. 0.60 ± 1.25, $p = 0.989$). In addition, none of the other prespecified end points was statistically significantly different between the groups (Table 2).

In the subset of patients with left ventricular systolic dysfunction (ejection fraction below 45%), total mortality tended to be lower in the NT-proBNP–guided group, which however did not attain statistical significance (mortality: 25% in NT-proBNP–guided vs. 33% in usual care, $p = 0.164$). In contrast, in patients with preserved left ventricular systolic function, mortality was identical in both groups (31%). Furthermore, in patients under 75 years of age, a

JACC Vol. 56, No. 25, 2010
December 14/21, 2010:2090–100

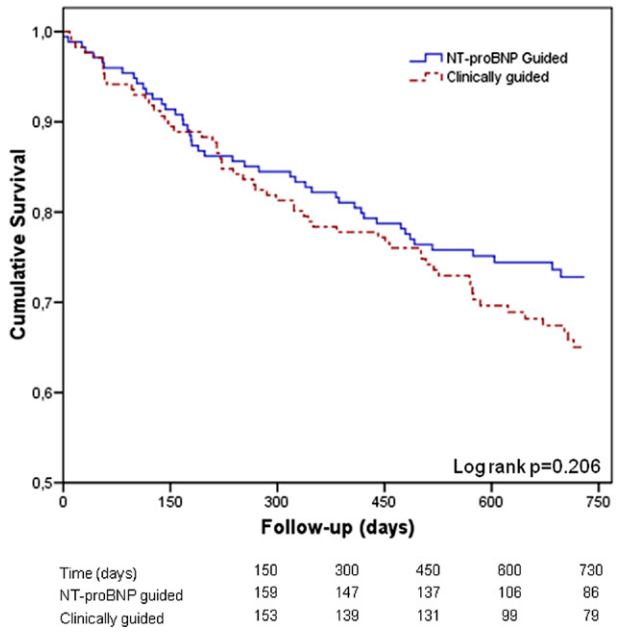


Figure 3 **Survival in the NT-proBNP–Guided and the Clinically-Guided Groups**

Survival of patients with heart failure receiving treatment guided by an individualized NT-proBNP target level **(blue line)** or treatment guided by clinical assessment alone **(red line)**. NT-proBNP = N-terminal pro–B-type natriuretic peptide.

trend was seen towards improved outcome in the NT-proBNP–guided treatment arm (number of days alive outside hospital as percentage of total follow-up: 87.4% vs. 82.8%, p = 0.114). Therapy guided by NT-proBNP levels also tended to be favorable in patients with lower discharge creatinine levels, but again these differences did not attain statistical significance (number of days alive outside hospital as percentage of total follow-up: 92.7% vs. 87.9%, p = 0.076).

NT-proBNP levels and use of medication. After 1-year follow-up, 80% of patients were at or below their individual target level. In 23% of all outpatient visits, NT-proBNP levels were above the individualized target level. In 79% of all outpatient visits with an off-target NT-proBNP level, protocol adherent action was undertaken (Table 3). Evidence-based medication for HF was extensively used in both groups (Table 4). Renin-angiotensin inhibition was used significantly more frequently after 1 year in the NT-proBNP–guided group. Management guided by an individualized NT-proBNP target also led to an overall increased use of HF medication (Table 5). An increased NT-proBNP value most often prompted physicians to intensify diuretic therapy. The lack of significant beneficial outcomes suggests that intensifying diuretic therapy may not be adequate to prevent events. We therefore compared the effects of intensifying evidence-based HF medication (i.e., increase renin-angiotensin system blockade, beta-blockade, and spironolactone) to the effect of intensifying diuretics in response to an increased NT-proBNP level. However, no differences were found between the 2 types of treatment in ability to increase the number of patients on or below target level at the next outpatient follow-up (40% vs. 33%, p = 0.369). Moreover, in general, intensifying HF medication (evidence-based HF medication or diuretics) compared with no pharmacological HF intervention was not associated with a significantly higher number of patients who reached their NT-proBNP target (47% vs. 36%, p = 0.117).

During follow-up, NT-proBNP levels and levels of urea and creatinine did not significantly differ between both treatment groups, although there was a trend for increased creatinine in the NT-proBNP–guided group (Table 6). Also, no difference was seen in QOL between the NT-proBNP–guided and the clinically-guided groups: median QOL at discharge: 47 (IQR: 34 to 62) versus 48 (IQR: 36 to 60), p = 0.95, at 6-month follow-up: 23 (IQR: 10 to 39) versus 25 (IQR: 11 to 42), p = 0.64, and at 12-month follow-up: 20 (IQR: 6 to 36) versus 23 (IQR: 10 to 38), p = 0.6.

The individualized NT-proBNP target value appeared to be of prognostic importance. Most HF-related events (64%) were preceded by off-target NT-proBNP levels at previous outpatient follow-up. Outpatient elevation of NT-proBNP levels above this individualized target value indicated an increased risk for major end points such as total mortality (hazard ratio [HR]: 1.84, p = 0.007), cardiovascular mortality (HR: 2.53, p < 0.001), and HF-related mortality (HR: 3.69, p < 0.001) (Table 7).

Discussion

The PRIMA study is a prospective randomized study to address whether HF therapy, guided by an individualized NT-proBNP level, improves outcome in HF patients.

The PRIMA study randomized 345 patients to HF therapy guided by an individually set NT-proBNP target level in addition to clinical signs, or by clinical signs only. It addressed the benefit of selective intensification of therapy only when NT-proBNP increases beyond the individually defined "optimal" NT-proBNP level. Assessing the optimum natriuretic peptide target level is most challenging (12). As such, the PRIMA study complements the recent studies on the benefits of a more general intensification of therapy by aiming for absolute NT-proBNP targets (6,7).

PRIMA showed that selective intensification by an individualized NT-proBNP target did not significantly improve any of the pre-specified primary or secondary outcome measures. Although treatment guided by an individualized NT-proBNP target slightly improved the number of days alive outside the hospital, and improved overall mortality, these changes were not statistically significant.

Individualized NT-proBNP–guided therapy resulted in significantly intensified pharmacological HF therapy reflected by an increased use of diuretics and ACE inhibitors or angiotensin II receptor antagonists in the NT-proBNP–guided group.

We hypothesized that individualized NT-proBNP–guided treatment would improve outcome. Our first as-

Table 2 Secondary Outcome Measures

	Days Alive Outside the Hospital*				Mortality		CV Mortality		Days Admitted to the Hospital†		
	n	Mean, % (±SD)	Median, % (IQR)	p Value	n (%)	Log-Rank p Value	n (%)	Log-Rank p Value	Mean, % (±SD)	Median, % (IQR)	p Value
Total group											
NT-proBNP–guided	174	81.3 (31.6)	99.0 (74.4–100.0)	0.174	46 (26)	0.206	34 (20)	0.705	5.09 (9.94)	0.68 (0.00–4.56)	0.490
Clinically-guided	171	79.2 (32.0)	98.5 (64.4–99.9)		57 (33)		36 (21)		4.46 (8.67)	0.93 (0.14–4.62)	
LVEF ≤45%											
NT-proBNP–guided	112	83.5 (29.1)	99.2 (82.2–100.0)	0.140	28 (25)	0.164	20 (18)	0.439	5.26 (10.8)	0.48 (0.00–4.42)	0.334
Clinically-guided	117	78.2 (31.1)	98.6 (57.3–99.9)		39 (33)		25 (21)		5.13 (9.93)	0.93 (0.07–0.51)	
LVEF >45%											
NT-proBNP–guided	42	75.2 (36.6)	97.3 (42.8–99.7)	0.946	13 (31)	0.861	12 (29)	0.421	5.92 (9.35)	1.67 (0.16–8.52)	0.760
Clinically-guided	42	82.1 (29.8)	98.0 (82.3–99.6)		13 (31)		9 (21)		3.32 (5.00)	1.04 (0.30–4.73)	
Discharge NT-proBNP >2,950 pg/ml											
NT-proBNP–guided	87	74.7 (34.6)	97.5 (43.8–99.7)	0.325	31 (36)	0.139	21 (24)	0.504	6.61 (10.51)	2.19 (0.17–8.47)	0.897
Clinically-guided	85	69.1 (35.6)	92.9 (33.6–99.5)		41 (48)		24 (28)		6.28 (10.57)	1.23 (0.16–7.91)	
Discharge NT-proBNP ≤2,950 pg/ml											
NT-proBNP–guided	87	88.0 (26.9)	99.7 (96.8–100.0)	0.248	15 (17)	0.845	13 (15)	0.853	3.58 (9.15)	0.24 (0.00–2.05)	0.196
Clinically-guided	86	89.2 (24.4)	99.2 (95.4–99.9)		16 (19)		12 (14)		2.66 (5.75)	0.55 (0.00–3.16)	
Age ≤ median 74 yrs											
NT-proBNP–guided	92	87.4 (26.4)	99.5 (95.4–100.0)	0.114	17 (18)	0.225	13 (14)	0.653	4.40 (10.08)	0.37 (0.00–2.71)	0.138
Clinically-guided	81	82.8 (30.9)	98.7 (88.6–99.9)		21 (26)		13 (16)		3.85 (7.79)	0.93 (0.14–3.83)	
Age > median 74 yrs											
NT-proBNP–guided	82	74.5 (35.6)	97.9 (42.2–99.9)	0.908	29 (35)	0.745	21 (26)	0.874	5.88 (9.79)	1.23 (0.10–7.83)	0.587
Clinically-guided	90	76,0 (32.8)	96.6 (50.6–99.8)		36 (40)		23 (26)		5.00 (9.40)	0.88 (0.10–4.96)	
Discharge creatinine ≤123 U/l											
NT-proBNP–guided	85	92.7 (19.4)	99.7 (97.8–100.0)	0.076	11 (13)	0.198	7 (8)	0.157	2.33 (6.77)	0.27 (0.00–1.39)	0.116
Clinically-guided	80	87.9 (25.9)	99.4 (96.4–100.0)		16 (20)		12 (15)		2.49 (5.92)	0.55 (0.00–2.71)	
Discharge creatinine >123 U/l											
NT-proBNP–guided	81	71.3 (35.8)	95.4 (37.0–99.6)	0.742	32 (40)	0.656	24 (30)	0.561	6.92 (10.2)	2.33 (0.16–9.82)	0.804
Clinically-guided	82	71.0 (35.3)	93.0 (33.8–99.3)		37 (45)		21 (26)		6.54 (10.6)	1.85 (0.17–8.41)	

All reported data demonstrate no significant differences in outcome between the NT-proBNP–guided group and the clinically-guided group. *The number of days alive outside the hospital as a percentage of total days of follow-up; †days admitted to the hospital as a percentage of total days alive.

Abbreviations as in Table 1.

JACC Vol. 56, No. 25, 2010
December 14/21, 2010:2090–100

Table 3 Response to Elevated NT-proBNP Levels During Follow-Up

Drug intervention*	
Diuretics	109 (40.5)
ACE inhibitors	17 (6.3)
Beta-blockers	30 (11.2)
Digoxin	9 (3.3)
Aldosteron antagonists	11 (4.1)
AT_2 antagonists	11 (4.1)
Nitrates	10 (3.7)
Alpha-blocker	1 (0.4)
Anti-arrythmic agent	1 (0.4)
Hydralazine	1 (0.4)
Decrease calcium-channel blocker	2 (0.7)
Total change medication	202 (75.1)
Diagnostics	
Echocardiogram	8 (3.0)
Ischemia†	6 (2.2)
Holter monitoring	7 (2.6)
Consultation‡	5 (1.9)
Chest X-ray	2 (0.7)
Total diagnostics	28 (10.4)
Other interventions	
Admission because of heart failure	18 (6.7)
Admission emergency department	1 (0.4)
Pacemaker implantation	1 (0.4)
ICD implantation	2 (0.7)
Admission other	2 (0.7)
Heart revalidation	1 (0.4)
Analysis/treatment anemia	3 (1.1)
Information way of life	2 (0.7)
Electro cardioversion	4 (1.5)
Total other interventions	34 (12.6)
Total interventions	234
No intervention	
No treatment options	5 (1.9)
Patient on dialysis	2 (0.7)
Severe hypotension	1 (0.4)
No valid reason given	46 (17.1)
No NT-proBNP at disposal	1 (0.4)
Intervention refused by patient	1 (0.4)
Total no intervention	56 (20.8)
Total elevated NT-proBNP levels	269 (100.0)

Values are n (%). *Except for calcium-channel blockers, drug intervention concerns the start or increase of medication, or change in type of medication. †MIBI stress test, coronary angiography, or exercise test. ‡Specialized cardiologist/internal medicine/other.

ACE = angiotensin-converting enzyme; AT_2 = angiotensin II; NT-proBNP = N-terminal pro–B-type natriuretic peptide.

sumption was that stability of NT-proBNP would portend an improved prognosis, even when the stable NT-proBNP level is well above normal. This first assumption was confirmed in this study. Patients who maintained their individual NT-proBNP target level indeed had a highly significantly better outcome. Most events occur in patients with an unstable NT-proBNP. Indeed, increases of NT-proBNP level above each individual optimum was a strong predictor of HF-related events with hazard ratios up to 4.17, $p < 0.001$. Our second assumption was that treatment of HF guided by an individualized target NT-proBNP level could

Table 4 Use of Evidence-Based HF Medication at the Index Admission, Discharge, and During Follow-Up

Medication Used in the PRIMA Study	Admission		Discharge		6-Month Follow-Up		12-Month Follow-Up	
	NT-proBNP–Guided	Clinically-Guided	NT-proBNP–Guided	Clinically-Guided	NT-proBNP–Guided	Clinically-Guided	NT-proBNP–Guided	Clinically-Guided
Loop diuretics	104 (60)	111 (65)	169 (97)	162 (95)	131 (93)	128 (93)	119 (91)	110 (92)
ACE inhibitors	71 (41)	75 (44)	112 (64)	111 (65)	90 (64)	82 (59)	84 (66)*	66 (55)*
Target dose	60 (45)	51 (38)	60 (45)	57 (61)	71 (91)	64 (59)	76 (95)	69 (55)
ARB	28 (16)	31 (18)	31 (18)	34 (20)	30 (21)	29 (21)	35 (28)	35 (29)
Target dose	82 (63)	93 (63)	98 (91)	92 (64)	71 (65)	85 (88)	66 (62)	88 (87)
Beta-blockers	96 (55)	97 (57)	139 (80)	126 (74)	120 (85)	110 (80)	111 (87)*	95 (79)*
Target dose	45 (28)	51 (34)	47 (49)	49 (56)	47 (32)	58 (43)	53 (36)	58 (39)
Aldosterone antagonist	28 (16)	36 (21)	92 (53)	95 (56)	62 (44)	69 (50)	59 (47)	62 (52)
Target dose	98 (35)	125 (81)	99 (45)	109 (48)	86 (31)	93 (44)	92 (41)	97 (41)
ACE inhibitor or ARB	94 (54)	101 (59)	138 (79)	134 (78)	115 (82)	107 (78)	111 (87)†	93 (78)†
≥50% target dose	60 (35)	68 (40)	104 (60)	90 (53)	84 (60)*	67 (49)*	79 (62)	66 (55)
ACE inhibitor/ARB and beta-blocker	69 (40)	67 (39)	117 (67)*	98 (57)*	99 (70)	88 (64)	98 (77)†	76 (63)†
≥50% target dose	21 (12)	26 (15)	37 (21)	30 (18)	39 (28)	33 (24)	38 (30)	33 (28)

Values for medication are expressed as n (%). For ACE inhibitors, ARBs, and beta-blockers the used dosage was expressed as percentage of the target dose for that specific drug. The table depicts the mean percentage of the target dose (±SD), and the number of patients receiving at least 50% of the target dose of ACE inhibitor or ARB and ACE inhibitor or ARB in combination with a beta-blocker, n (%). *$p < 0.1$; †$p < 0.05$.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; HF = heart failure.

Table 5 Number of Increases of HF Medication During Follow-Up

	NT-proBNP–Guided (n = 174)	Clinically-Guided (n = 171)	p Value
Diuretics	168	120	0.02
Beta-blockers	105	95	0.35
ACE inhibitors	77	55	0.1
AT_2 antagonists	41	22	0.39
Aldosterone antagonists	19	15	0.86
Digoxin	14	19	0.63
Total	424	326	0.006

Abbreviations as in Tables 3 and 4.

avert HF events. Despite the ability to detect 64% of the imminent events, and despite the subsequent intensification of HF medication, events were not significantly averted. This suggests that although NT-proBNP measurement can help detect worsening HF, current standard-of-care HF therapy is unable to avert subsequent events. NT-proBNP levels react upon ventricular wall stretch (13). Therefore, deterioration of HF is needed before levels rise. Elevated marker levels before an increase in cardiac pressures takes place might help us identify patients at risk for events; in such an early phase, medical intervention can still avert worse outcome. NT-proBNP appears to be a "passenger-seat" marker: you can see which direction your car is heading, but you are not in control of the steering wheel. In order to reduce morbidity and mortality, a "driver-seat" marker is urgently needed.

A number of reasons may account for this lack of significant improvement. First, not enough events during follow-up may have been detected, as 36% of events were undetected by measurement of NT-proBNP at 3-month intervals. Second, intensification of treatment against a background of high use of evidence-based HF therapy may not suffice to avert an imminent event. Third, current "gold-standard" HF therapy may altogether be inadequate in preventing HF-related events in patients with deterioration of HF.

Subgroups analyzed. The effects of NT-proBNP guidance seemed mitigated in patients with preserved systolic function, although differences did not reach statistical significance. The lack of well-established medical or other intervention measures for patients with preserved ejection fraction HF may limit the success of interventions prompted by off-target NT-proBNP in this group.

The effects of NT-proBNP guidance seemed more favorable in younger patients (age under 75 years) and those with better renal function, although these differences also did not reach statistical significance. Both younger patients and patients with preserved renal function have less comorbidity, and are expected to better tolerate intensification of therapy. It is these type of patients that have been included in most landmark trials that yielded the evidence for HF therapy. Elderly patients with severe renal dysfunction and patients with preserved left ventricular systolic function HF form the majority of HF patients, but they are underrepresented in landmark trials (14). Therefore, speculatively, it seems that the intensified use of evidence-based HF therapy is mainly effective in the subgroups where this evidence was obtained.

Table 7 Time-Dependent HR if the Outpatient NT-proBNP Level Is Above the Individually Set Target Value

	n (%)	HR	95% CI	p Value
Total mortality	103 (29.9)	1.84	1.18–2.85	0.007
CV mortality	70 (20.3)	2.53	1.52–4.21	<0.001
HF mortality	45 (13.0)	3.69	2.02–6.72	<0.001
First CV admission	193 (55.9)	2.70	1.96–3.73	<0.001
First HF admission	115 (33.3)	4.17	2.84–6.13	<0.001

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; NT-proBNP = N-terminal pro–B-type natriuretic peptide.

Previous studies have demonstrated that NT-proBNP levels fall in response to optimizing HF therapy (15–17). In PRIMA, intensifying HF therapy in patients with rising NT-proBNP levels failed to lower these levels.

The lack of benefit seen in our study is in line with the overall lack of benefit seen with studies of NT-proBNP–guided therapy by an absolute NT-proBNP target (6,7). PRIMA shows that treatment of HF guided by an individualized NT-proBNP target against a background of optimal HF therapy does not have additional beneficial effects.

Study limitations. As opposed to what could be expected from large HF surveys (18), only a minority of patients included in our study had a history of HF. NT-proBNP levels might decrease more in response to HF treatment in patients with de novo HF compared with patients with a history of HF and background therapy before admission. Because we excluded patients if NT-proBNP levels decreased <10%, with a minimum of 850 pg/ml, more patients with a history of HF and prolonged exposure to therapy might be excluded than patients with de novo HF.

Power analysis was based on the initial primary end point of reduction in events. Sample size was calculated to demonstrate a minimum reduction in pooled events of 30%.

Table 6 Changes in NT-proBNP, Urea, and Creatinine Levels During Follow-Up

Dynamic Changes During Follow-Up	6-Month Follow-Up			12-Month Follow-Up		
	NT-proBNP–Guided	Clinically-Guided	p Value	NT-proBNP–Guided	Clinically-Guided	p Value
NT-proBNP, pg/ml	−254 (−1,415 to 530)	−287 (−1,186 to 688)	0.60	−432 (−1,392 to 297)	−572 (−1,329 to 434)	0.99
Urea, mmol/l	−0.5 (−3.8 to 2.6)	−0.8 (−3.3 to 1.2)	0.41	0.0 (−3.8 to 2.2)	−1.0 (−4.1 to 1.7)	0.16
Creatinine, μmol/l	7.00 (−12.0 to 32.0)	2.0 (−15 to 19)	0.06	8.0 (−10.3 to 31.8)	3.0 (−14.0 to 22.0)	0.07

Values are expressed as median (interquartile range).
NT-proBNP = N-terminal pro–B-type natriuretic peptide.

A post hoc power analysis indicated that a difference of 4% in percentage of time (approximately 28 days) alive outside the hospital could have been detected.

One may surmise that choosing an individual (often elevated) NT-proBNP target is not accurate enough, and that more stringent targets should be aimed for in all subjects. However, the prognostic impact we observed of NT-proBNP levels above the individual target, even when the target is clearly elevated, argues against this notion. Furthermore, the most common reaction to an elevated NT-proBNP level was to increase dosage of diuretics. We have not been able to demonstrate the ability of any subtype of intervention (evidence-based medication, diuretics, or nonpharmacologic) to be more effective in lowering off-target NT-proBNP levels. The use of our electronic therapy advisor might have lead to more intensified treatment in the clinically-guided group than would occur in daily practice where such advices are not generated.

Previous studies have demonstrated that discharge NT-proBNP levels, decrease in NT-proBNP levels during admission because of HF, and outpatient NT-proBNP levels in patients with stable, chronic HF were of prognostic importance (4,19,20). The possible additive value of a combination of static and dynamic NT-proBNP levels for determining individual prognosis still remains to be assessed.

Conclusions

This is the first study to our knowledge that evaluated whether HF therapy guided by an individualized NT-proBNP target level improves outcome. PRIMA shows that unstable NT-proBNP levels indeed indicate imminent events, but that intensification of currently used medication in patients on optimal HF therapy does not prevent further deterioration.

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REFERENCES

1. Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 2006;27:330–7.
2. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161–7.
3. Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. BMJ 2005;330:625.
4. Hartmann F, Packer M, Coats AJ, et al. Prognostic impact of plasma N-terminal pro-brain natriuretic peptide in severe chronic congestive heart failure: a substudy of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial. Circulation 2004;110:1780–6.
5. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000;355:1126–30.
6. Lainchbury JG, Troughton RW, Strangman KM, et al. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. J Am Coll Cardiol 2009;55:53–60.
7. Pfisterer M, Buser P, Rickli H, et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. JAMA 2009;301:383–92.
8. Jourdain P, Jondeau G, Funck F, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. J Am Coll Cardiol 2007;49:1733–9.
9. Nieminen MS, Bohm M, Cowie MR, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:384–416.
10. Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:1115–40.
11. Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. Am J Cardiol 1993;71:1106–7.
12. Maisel A. Natriuretic peptide-guided therapy for heart failure: ready for "battle" or too "scarred" by the challenges of trial design? J Am Coll Cardiol 2009;55:61–4.
13. McCullough PA, Sandberg KR. Sorting out the evidence on natriuretic peptides. Rev Cardiovasc Med 2003;4 Suppl 4:S13–9.
14. Lenzen MJ, Boersma E, Reimer WJ, et al. Under-utilization of evidence-based drug treatment in patients with heart failure is only partially explained by dissimilarity to patients enrolled in landmark trials: a report from the Euro Heart Survey on Heart Failure. Eur Heart J 2005;26:2706–13.
15. Murdoch DR, McDonagh TA, Byrne J, et al. Titration of vasodilator therapy in chronic heart failure according to plasma brain natriuretic peptide concentration: randomized comparison of the hemodynamic and neuroendocrine effects of tailored versus empirical therapy. Am Heart J 1999;138:1126–32.
16. Yoshimura M, Mizuno Y, Nakayama M, et al. B-type natriuretic peptide as a marker of the effects of enalapril in patients with heart failure. Am J Med 2002;112:716–20.
17. Zugck C, Haunstetter A, Kruger C, et al. Impact of beta-blocker treatment on the prognostic value of currently used risk predictors in congestive heart failure. J Am Coll Cardiol 2002;39:1615–22.
18. Nieminen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006;27:2725–36.
19. Bayes-Genis A, Pascual-Figal D, Fabregat J, et al. Serial NT-proBNP monitoring and outcomes in outpatients with decompensation of heart failure. Int J Cardiol 2007;120:338–43.
20. O'Brien RJ, Squire IB, Demme B, Davies JE, Ng LL. Pre-discharge, but not admission, levels of NT-proBNP predict adverse prognosis following acute LVF. Eur J Heart Fail 2003;5:499–506.

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