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N-Terminal–Pro-Brain Natriuretic Peptide Predicts Outcome After Hospital Discharge in Heart Failure Patients

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Background—Heart failure (HF) is responsible for a huge burden in hospital care. Our goal was to evaluate the value of N-terminal–pro-brain natriuretic peptide (NT-proBNP) in predicting death or hospital readmission after discharge of HF patients.

Methods and Results—We included 182 patients consecutively admitted to hospital because of decompensated HF. Patients were followed up for 6 months. The primary end point was death or readmission. Twenty-six patients died in hospital. The median admission NT-proBNP level was 6778.5 pg/mL, and the median level at discharge was 4137.0 pg/mL ($P<0.001$). Patients were classified into 3 groups: (1) decreasing NT-proBNP levels by at least 30% (n=82), (2) no significant modifications on NT-proBNP levels (n=49), and (3) increasing NT-proBNP levels by at least 30% (n=25). The primary end point was observed in 42.9% patients. Variables associated with an increased hazard of death and/or hospital readmission in univariate analysis were length of hospitalization, heart rate, signs of volume overload, no use of ACE inhibitors, higher NYHA class at discharge, admission and discharge NT-proBNP, and the change in NT-proBNP levels. The variation in NT-proBNP was the strongest predictor of an adverse outcome. Independent variables associated with an increased risk of readmission or death were signs of volume overload and the change in NT-proBNP levels.

Conclusions—Variations in NT-proBNP levels are related to hospital readmission and death within 6 months. NT-proBNP levels are potentially useful in the evaluation of treatment efficacy and might help clinicians in planning discharge of HF patients. Whether therapeutic strategies aimed to lower NT-proBNP levels modify prognosis warrants future investigation. **(*Circulation*. 2004;110:2168-2174.)**

Key Words: heart failure ■ mortality ■ natriuretic peptides ■ prognosis

Heart failure (HF) is a disabling condition with high costs.[1,2] A huge burden of HF is related to hospital care. Prognosis after hospital discharge is poor, with high readmission rates and mortality.[3–5] It has been general practice to discharge patients according to improvement in symptoms. Some studies have tried to identify patients at higher risk of death and/or readmission who might benefit from more intensive therapy.[6]

B-type natriuretic peptide (BNP) is a hormone of predominantly ventricular origin, produced and released in response to increases in ventricular wall stress. BNP, the carboxyterminal portion of the preprohormone, is secreted into the peripheral blood in equimolar portions to the amino-terminal portion of the preprohormone (NT-proBNP).[7] The diagnostic value of BNP and NT-proBNP is well established in patients with suspected HF.[8–13] Because BNP and NT-proBNP levels can be manipulated by therapy, decrease in close correlation with falling wedge pressures, and correlate with functional capacity, we hypothesized that NT-proBNP levels might be useful in assessing response to therapy and defining a safe timing for discharge.

The aim of this study was to evaluate the value of NT-proBNP in predicting death or hospital readmission within 6 months of discharge in patients admitted with decompensated HF.

Methods

We studied all patients admitted between October 2002 and March 2003 to our Internal Medicine Department because of decompensated HF. Decompensated HF was defined as exacerbation of symptoms in patients with at least 1 NYHA class deterioration. The diagnosis of HF was based on the European Society of Cardiology criteria or, in patients without echocardiographic evaluation, the Framingham criteria. Patients with acute coronary syndromes were excluded.

Blood samples were collected within 24 hours after admission and before discharge in EDTA-containing tubes. NT-proBNP was measured with a chemiluminescent immunoassay kit (Roche Diagnostics) on an Elecsys 2010 analyzer (measuring range, 5 to 35 000 pg/mL. The intra-assay coefficient of variation is 0.9% at mean

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TABLE 1. Baseline Characteristics of Patients

	Admission	During Hospitalization	Discharge
Male, n (%)	73 (46.8)	...	...
Age, y	73.0±11.0	...	...
Ischemic etiology, n (%)	74 (47.4)	...	...
Atrial fibrillation, n (%)	72 (46.2)	...	...
Diabetes mellitus, n (%)	81 (51.9)	...	...
LV systolic function, n (%)*			
Preserved	...	31 (19.9)	...
Mild to moderately depressed	...	62 (39.7)	...
Severely depressed	...	36 (23.1)	...
Unknown	...	27 (17.3)	...
NYHA class, n (%)			
I	0	...	8 (5.1)
II	0	...	121 (77.6)
III	51 (32.7)	...	26 (16.7)
IV	105 (67.3)	...	1 (0.6)
Change in NYHA class, n (%)			
No change	...	...	4 (2.6)
Decrease by 1 class	...	...	67 (42.9)
Decrease by ≥2 classes	...	...	85 (54.5)
Volume overload, n (%)	153 (98.1)	...	92 (59.0)
Systolic blood pressure, mm Hg	129±28	...	111±18
Diastolic blood pressure, mm Hg	79±13	...	71±12
Heart rate, bpm	92±17	...	75±11
Serum urea, mg/L	82±45	...	89±45
Serum creatinine, mg/dL	1.4±0.9	...	1.4±0.9
Serum sodium, mEq/L	140.6±4.2	...	139.5±3.6
Plasma NT-proBNP, mean±SD (median), pg/mL	14 463±24 859 (6778.5)	...	10 405±21 199 (4137.0)
Furosemide, n (%)	133 (85.3)	153 (98.1)	153 (98.1)
Furosemide mean dose, mg/d	...	89.6±21.8	65.7±24.9
ACE inhibitor, n (%)	90 (57.7)	139 (89.1)	136 (87.2)
Lisinopril-equivalent dose, mg/d	...	8.7±5.3	10.0±5.9
β-Blocker, n (%)	31 (19.9)	62 (39.7)	61 (39.1)
Carvedilol-equivalent dose, mg/d	...	9.8±3.3	13.4±6.1
Spironolactone, n (%)	21 (13.5)	59 (37.8)	58 (37.2)
Spironolactone dose, mg/d	...	14.5±4.5	21.0±16.7
Inotropic support or intravenous vasodilators, n (%)	...	44 (28.2)	...

LV indicates left ventricular.

*Preserved systolic function, LV ejection fraction ≥45%; severely depressed, <25%.

values of 474 pg/mL, 1.1% at mean values of 8005 pg/mL, and 0.9% at mean values of 13 682 pg/mL. The normal ranges are <125 pg/mL for <75 years of age and <450 pg/mL in older people. In analyses of the change in NT-proBNP during hospitalization, patients were classified into 3 groups: (1) those whose NT-proBNP levels decreased with therapy (NT-proBNP decreased by at least 30% of the baseline level; n=82), (2) those with no significant modifications on NT-proBNP levels (NT-proBNP did not change by >30% of the baseline value; n=49), and (3) those with increasing NT-proBNP levels (NT-proBNP increased by at least 30% of the baseline value; n=25).

The presence of volume overload was evaluated at admission and discharge. Patients were considered to have volume overload in the presence of pulmonary rales, venous jugular distension, or peripheral edema.

Creatinine and sodium were measured at admission and before discharge. Biochemical analyses were made at the hospital laboratory with standard methods.

Patients received standard treatment with diuretics (furosemide with or without spironolactone), ACE inhibitors, and β-blockers according to attending physicians. Physicians were blinded to NT-proBNP levels.

Patients were followed up for 6 months. The primary end point was death or readmission. All-cause mortality was predefined as a secondary end point. Surveillance was made by telephone contact with patients or relatives by an investigator blinded to NT-proBNP levels. The occurrence and cause of readmissions or deaths were confirmed by consulting clinical records and death certificates.

TABLE 2. Determinants of Patterns of Change in NT-proBNP Levels

	Decrease ≥30%	Change <30%	Increase ≥30%	*P*
Male gender, n (%)	38 (46.3)	24 (49.0)	11 (44.0)	0.91
Age, y	72.3±12.2	73.4±8.6	74.4±11.2	0.67
Ischemic origin, n (%)	37 (45.1)	27 (55.1)	10 (40.0)	0.39
Diabetes mellitus, n (%)	41 (50.0)	30 (61.2)	10 (40.0)	0.20
Atrial fibrillation, n (%)	32 (39.0)	25 (51.0)	15 (60.0)	0.13
LV systolic function, n (%)				0.89
Preserved	19 (23.2)	7 (14.3)	5 (20.0)	
Mildly to moderately depressed	30 (36.6)	21 (42.9)	11 (44.0)	
Severely depressed	29 (24.4)	11 (22.4)	5 (20.0)	
Not assessed	13 (15.9)	10 (20.4)	4 (16.0)	
Systolic blood pressure at discharge, mm Hg	111±19	110±16	114±19	0.66
Diastolic blood pressure at discharge, mm Hg	72±12	71±13	70±12	0.75
Heart rate at discharge, bpm	74±9	74±11	80±14	0.32
Serum urea at discharge, mg/dL	87.0±43.5	84.3±37.8	103.3±59.5	0.63
Serum creatinine at discharge, mg/dL	1.26±0.71	1.35±0.94	1.71±1.14	0.39
Serum sodium at discharge, mEq/L	140±4	140±3	139±5	0.79
Length of stay, d	11.3±8.3	10.2±5.4	13.4±10.4	0.47
Diuretic, n (%)	82 (100)	46 (93.9)	25 (100)	0.03
ACE inhibitor, n (%)	74 (90.2)	46 (93.9)	16 (64.0)	0.003
β-Blocker, n (%)	34 (42.0)	19 (38.8)	8 (32.0)	0.66
Spironolactone, n (%)	31 (38.3)	23 (46.9)	4 (16.7)	0.03
NYHA class III/IV at discharge, n (%)	10 (12.2)	9 (18.4)	8 (32.0)	0.09
Hypervolemia at discharge, n (%)	44 (53.7)	32 (65.3)	16 (64.0)	0.36
Events, n (%)	22 (26.8)	24 (49.0)	21 (84.0)	<0.001

LV indicates left ventricular.

Statistical Analysis

We analyzed data using SPSS. Changes in continuous variables were compared by use of the Wilcoxon test. The χ^2 test was used to compare proportions between the 3 groups defined by the pattern of response of the natriuretic peptide system. Differences in continuous variables between these 3 classes of patients were tested through the use of ANOVA. Survival curves were estimated according to the Kaplan-Meier method and compared by the log-rank test. The association of independent variables with time to outcome was assessed by Cox regression and is expressed as hazard ratio (HR) and 95% CI. Unless otherwise noted, results are presented as mean±SD for numeric variables and as number (percent) for categorical variables. A significance level of 5% was used.

The local ethics committee approved the study. Patients gave informed consent.

Results

During the study period, 182 patients were admitted to hospital because of decompensated HF. Of these, 26 (14.3%) died in hospital. The results refer to the remaining 156 patients. Among these, 129 were diagnosed according to the European Society of Cardiology criteria, and 27 fulfilled the Framingham criteria for HF diagnosis. In Table 1, baseline characteristics of patients are described. NT-proBNP plasma levels decreased significantly during hospitalization ($P<0.001$). Table 2 shows the association between characteristics of patients and treatment variables and the patterns of NT-proBNP variation.

During the 6-month follow-up period, 28 patients (17.9%) died, all but 1 from cardiovascular causes. Fifty-eight patients (37.2%) were readmitted during this period, and in 43 of these, readmission was due to decompensated HF. The combined end point of death or readmission was observed in 67 patients (42.9%). Time to the first event was used as the dependent variable in survival analysis.

Univariate Cox regression analysis for the identification of predictors of adverse events after discharge from index hospitalization is shown in Table 3. The proportion of patients whose NT-proBNP levels decreased was higher among patients discharged in NYHA class I or II than among those in class III or IV; similarly, this proportion was larger among patients discharged without signs of volume overload, although these associations did not reach statistical significance. Among patients discharged in NYHA class I or II, there was still a strong and significant association between the pattern of change in NT-proBNP and time to readmission or death (HR, 1.93; 95% CI, 1.00 to 3.71 for change <30%; HR, 6.96, 95% CI, 3.44 to 14.1 for increase ≥30% compare with those with decreasing NT-proBNP by at least 30%). Among the 64 patients discharged without volume overload, a positive association between change in NT-proBNP and outcome was observed (HR, 2.66; 95% CI, 0.77 to 9.18 for change <30%; HR, 16.04; 95% CI, 9.49 to 52.02 for increase ≥30% compared with those with decreasing NT-proBNP by at least 30%).

TABLE 3. Univariate Cox Regression Analysis for the Identification of Predictors of Death and/or Hospital Readmission After Discharge From Index Hospitalization Resulting From HF

	HR	95% CI
Male gender (vs female)	0.69	0.42–1.12
Age	1.01	0.99–1.04
Ischemic origin (vs other origins)	1.06	0.66–1.72
Diabetes mellitus	0.76	0.47–1.22
Atrial fibrillation	1.38	0.86–2.24
LV systolic function (vs preserved)		
Mildly to moderately depressed	1.33	0.65–2.70
Severely depressed	1.42	0.67–3.03
Not assessed	1.76	0.80–3.88
Systolic blood pressure at discharge	0.995	0.981–1.009
Diastolic blood pressure at discharge	0.999	0.979–1.018
Heart rate at discharge	1.03	1.009–1.051
Serum urea at discharge	1.00	0.995–1.006
Serum creatinine at discharge	0.98	0.75–1.28
Serum sodium at discharge	1.005	0.937–1.077
Length of stay	1.02	1.00–1.05
Diuretic	1.16	0.16–8.35
ACE inhibitor	0.41	0.23–0.74
β-Blocker	0.86	0.52–1.42
Spironolactone	1.02	0.62–1.68
NYHA class at discharge III/IV (vs I/II)	2.14	1.23–3.71
Hypervolemic at discharge	2.23	1.29–3.82
Admission NT-proBNP (1000-pg/mL increase)	1.012	1.005–1.020
Discharge NT-proBNP (1000-pg/mL increase)	1.018	1.012–1.024
Change in NT-proBNP (vs decreased ≥30%)		
Changed <30% in either direction	2.19	1.23–3.91
Increased ≥30%	6.64	3.60–12.23

LV indicates left ventricular.

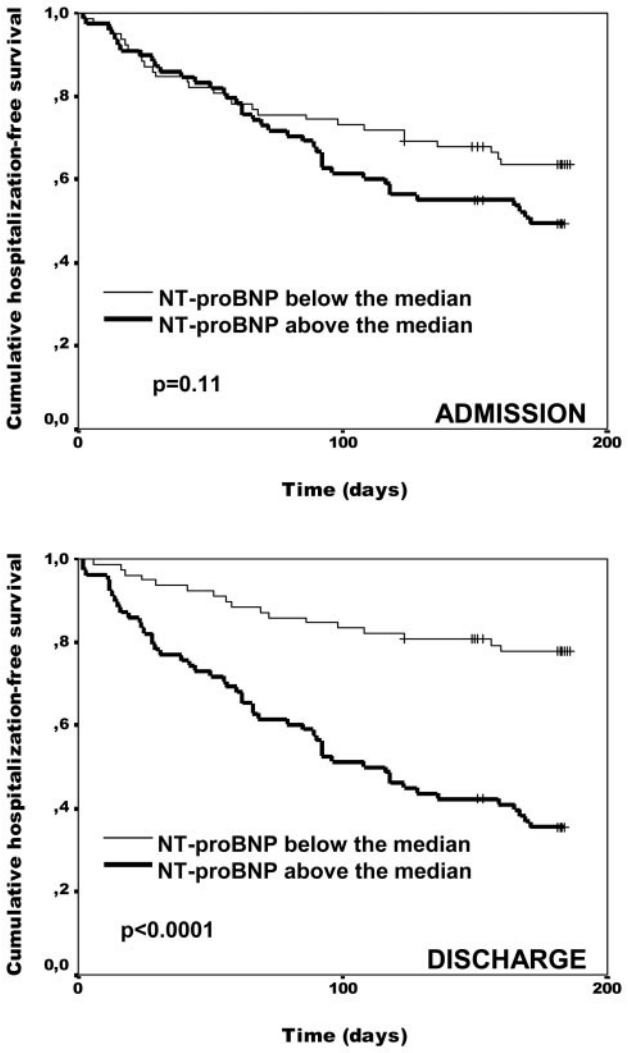

Figure 1. Cumulative hospitalization-free survival according to NT-proBNP plasma level at admission (median, 6778.5 pg/mL) and discharge (median, 4137.0 pg/mL).

The levels of NT-proBNP in plasma were measured in 25 of the 58 patients readmitted during follow-up. Readmission NT-proBNP in these patients was significantly higher than NT-proBNP at discharge from the index hospitalization (19 409.6±34 030.6 versus 13 004.7±32 789.7 pg/mL; $P<0.001$). On the other hand, NT-proBNP at the end of follow-up in 27 of the 89 patients without events was significantly lower than the discharge values (2720.7±384.3 versus 4643.0±3819.2 pg/mL; $P=0.001$).

Twenty-five patients had ≥2 hospitalizations during follow-up. The discharge NT-proBNP levels in these patients were higher than in patients with only 1 hospitalization during follow-up (27 477.3±44 617.2 versus 11 432.7± 11 847.9 pg/mL; $P=0.05$).

When admission and discharge NT-proBNP levels were dichotomized according to the median, only the discharge level was significantly associated with time to an adverse event (Figure 1). The variation of NT-proBNP levels, expressed by the change in levels during hospitalization, was the strongest predictor of death or readmission. Figure 2 presents the Kaplan-Meier cumulative hospitalization-free survival curve according to the change in NT-proBNP.

Table 4 shows the final multivariate Cox regression model performed by a stepwise method starting with all variables that in univariate analysis were significantly associated with a higher hazard of dying or being readmitted.

When death as the only end point was analyzed, the results were very similar, except that age and atrial fibrillation were significant predictors of death in univariate analysis. The multivariate model for the explanation of death is shown in Table 4.

Discussion

These results strongly suggest that variations in NT-proBNP levels during hospitalization and predischarge NT-proBNP levels are predictors of hospital readmission and death within 6 months of discharge of hospitalized HF patients. Thus, measurement of NT-proBNP is potentially

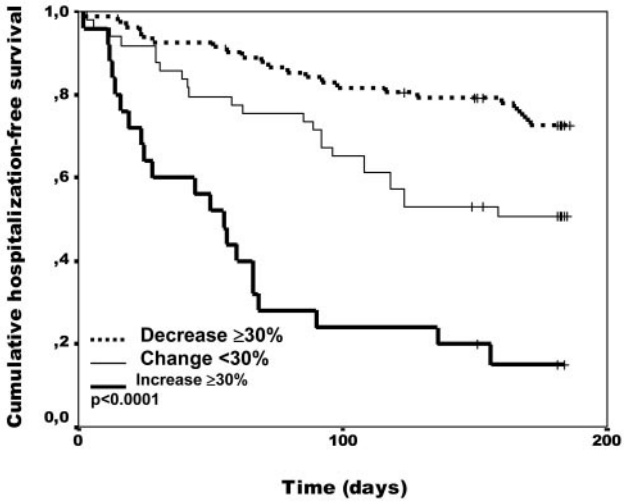

Figure 2. Cumulative hospitalization-free survival according to patterns of response of NT-proBNP (decreased by ≥30% of baseline value, changed by <30%, increased by ≥30%). Individual comparisons between pairs of the groups are as follows: decreased by ≥30% of baseline value vs changed by <30%, $P=0.006$; changed by <30% vs increased by ≥30%, $P=0.0002$; decreased by ≥30% of baseline value vs increased by ≥30%, $P<0.0001$.

useful in assisting clinicians in making the decision to discharge HF patients.

The decision of discharging patients with decompensated HF is determined by achievement of therapeutic adjustment and mainly by subjective evaluation (symptoms) and signs. This results in readmission rates between 20% and 50% at 6 months.[1–3,6] An approach to reduce this high rate of readmissions and related costs is necessary.

The prognostic value of BNP and NT-proBNP in HF and in acute coronary syndromes is well established.[10,14–17] We and others reported that high levels of BNP are related to 1- and 6-month rehospitalization and mortality in patients with decompensated HF.[18–20] In these studies, predischarge BNP levels and the direction of BNP changes were strongly associated with outcomes. In our study, prognosis of patients with a meaningful decrease in NT-proBNP levels (>30% of the baseline value) was significantly better than for patients with no significant change or increase in NT-proBNP levels, suggesting that these patients really improved during hospitalization. The identification of patients with successful hospital treatment (low-risk patients) can be the genesis for developing rules to hospital discharge strategies. In this context, it is particularly relevant that the variation in NT-proBNP levels added prognostic information to the clinical subjective impression of improvement, as shown by the positive association between the pattern of change in NT-proBNP and time to readmission or death among patients discharged in low NYHA class and without signs of volume overload.

Patients demonstrating a ≥30% increase in NT-proBNP levels during the course of their admission had the most adverse prognosis. In fact, these patients have been less aggressively treated. Significantly fewer received ACE inhibitors and spironolactone at discharge. This fact probably reflects the inability of this severely ill subgroup to tolerate the introduction of these medications. However, multivariate analysis showed that the inability to tolerate ACE inhibitors or spironolactone had no independent prognostic value, probably because of the small size of this subgroup.

These results provide evidence that changes in neurohumoral activation are associated with proportional changes in mortality and morbidity. In our sample, patients with a deactivation of the natriuretic system had a better outcome than those who maintained activation of the system. Our data suggest that NT-proBNP could be a guide of the efficacy of therapy because neurohormonal levels increase with the progression of HF and are correlated with the occurrence of adverse outcomes. The mechanism of sustained activation of the natriuretic peptide system has not been addressed in our study. However, previous data suggest that in severe HF there is an attenuation of the natriuretic response to endogenous and exogenous natriuretic peptides.[10] Whether interventions aimed to improve the effectiveness of the natriuretic system would be effective and modify prognosis warrants investigation.

The usefulness of serial evaluations of BNP has been previously evaluated in ambulatory HF patients.[21,22] Measurement of BNP 4 months apart in the Valsartan Heart Failure Trial (Val-HeFT) provided additional prognostic information. Patients with an increase in BNP levels

TABLE 4. Multivariate Cox Regression Analysis for the Identification of Predictors of Death and/or Hospital Readmission and Death Alone After Discharge From Index Hospitalization Resulting From HF

	Death or Readmission HR (95% CI)	Death HR (95% CI)
Age	...	1.08 (1.03–1.13)
NYHA class at discharge III/IV (vs I/II)	...	4.00 (1.90–8.44)
Volume overload at discharge	1.87 (1.08–3.23)	...
Change in NT-proBNP (vs decrease ≥30%)		
Change <30%	2.03 (1.14–3.64)	2.59 (0.98–6.87)
Increase ≥30%	5.96 (3.23–11.01)	3.67 (1.36–9.87)

HR indicates hazard ratio; NYHA, New York Heart Association.

>30% had an almost double mortality. Patients with >45% decrease in BNP levels had a significantly lower mortality than those with an increase in BNP of >30%. We previously found that patients with high baseline and increasing BNP levels during an 8- to 12-month period had an ominous outcome, whereas patients with low baseline BNP levels that decreased during follow-up had an excellent outcome with a 3-year mortality of <10%. Our results extend these data from ambulatory patients to hospitalized HF patients.

It was not the purpose of our study to evaluate the effect of therapy in NT-proBNP. Previous reports have shown that BNP levels can be manipulated by therapy and decrease in close relation to the falling of wedge pressures in patients with severe HF under invasive hemodynamic monitoring.[23–26] In ambulatory patients, there is now a considerable body of evidence showing that ACE inhibitors, angiotensin II receptor 1 antagonists, and spironolactone decrease BNP levels.[21,23–26] The decrease of BNP in response to β-blockers is observed after 6 to 12 months of therapy.[27] A pilot study reported that HF therapy guided to decrease NT-proBNP levels is associated with improved prognosis compared with therapy according to clinical status.[28] However, it is unclear whether all patients with severe HF necessarily respond to therapy with decreasing BNP.

Our study is a single-center study, and its reproduction in other centers or by multicenter studies would argue for its validity. However, these results are in accordance with previous observations.[18–20] Moreover, in different topics such as the differential diagnosis of patients with acute dyspnea, observations from single centers have later been validated in multicenter studies.[12,29] Our sample included very old patients, >50% women, and ≈20% with preserved systolic function, representing a real-world hospitalized HF population.

It is known that BNP levels can rapidly fall on treatment by up to 50% between visits in ambulatory patients.[30] Patients with clinical improvement during a 6- to 12-month follow-up have a 45% decrease in BNP levels.[31] We arbitrarily defined 30% variation of NT-proBNP levels as the threshold for meaningful variation because length of hospital stay was much shorter than time between ambulatory visits and because the biological variability is lower in NT-proBNP determination than in BNP.[32] Moreover, in a previous small study, patients with the worst prognosis had a 15% decrease in NT-proBNP levels, whereas patients who did not suffer the adverse outcome had a decrease >30%.[33] Because this was a single-center study, our cutoff cannot be extrapolated, and more studies are needed to identify the best cutoff and percent variations that may be extrapolated to any group of hospitalized HF patients.

Our results are in concordance with our hypothesis and suggest another possible use for NT-proBNP, which is a cheap, potentially widely available marker of neurohumoral activation in HF. Objective data yielded by NT-proBNP might be useful in reducing the current arbitrariness of the discharge decision and in the selection of patients who need more intensive intervention.

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