Brief Report

N-Terminal Pro−B-Type Natriuretic Peptide (NT-proBNP) Measurements Until a 30% Reduction Is Attained During Acute Decompensated Heart Failure Admissions and Comparison With Discharge NT-proBNP Levels: Implications for In-Hospital Guidance of Treatment

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ABSTRACT

Background: A >30% N-terminal pro−B-type natriuretic peptide (NT-proBNP) reduction at discharge in acute decompensated heart failure (ADHF) predicts a favorable prognosis. To study the feasibility of guiding ADHF treatment by measuring NT-proBNP well before discharge, we assessed at which moment during hospitalization patients attain a NT-proBNP reduction of >30% (target) and whether this target is still attained at discharge.

Methods: Twenty-five consecutive ADHF patients with NT-proBNP >1,700 ng/L were included (original cohort). NT-proBNP was measured daily until the target was attained, at clinical stability, and at discharge and was analyzed as percentages of patients on target. For comparison purposes, the same analysis was performed in individual patient data from 2 other ADHF cohorts (42 and 111 patients, respectively), in which NT-proBNP was measured from admission to day 3 and at discharge.

Results: In the original cohort of 25 patients (median age 70 years, 40% male), the cumulative percentage of patients attaining the target increased gradually during admission to 22 patients (88%) in a median of 3 days (interquartile range 2−5). In the comparison cohorts, a similar course was observed in patients attaining the target before discharge. Compared with levels measured at days 2 and 3, rebound NT-proBNP increases to levels off-target at discharge were seen in up to 33% of patients in the original and comparison cohorts.

Conclusion: A target >30% NT-proBNP reduction is gradually attained before discharge, and rebound NT-proBNP increases to levels off-target occur in up to 33% of ADHF patients who initially attained target early during admission. (*J Cardiac Fail 2015;21:930−934*)

Key Words: NT-proBNP, relative reduction, serial, acute decompensated heart failure.

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Hospital admissions for acute decompensated heart failure (ADHF) are frequent and accompanied by high percentages of mortality and readmissions.[1] The best predictors of prognosis in ADHF patients appear to be plasma B-type natriuretic peptide (BNP) and the inactive N-terminal fragment of its precursor pro-BNP, NT-proBNP,[2–6] indicators of ventricular wall stretch.[7] Several studies have demonstrated that a relative NT-proBNP reduction of ≤30% at discharge for ADHF is a significant predictor of readmissions and mortality.[2,3,6,8] A role for NT-proBNP–guided ADHF treatment targeting a reduction of >30% is therefore suggested.[9] Whether an NT-proBNP target can be set at a time point well before discharge (at, eg, day 2 or 3) is unknown. The advantage of an early measurement would be to be able to adjust therapy within the usual time of admission. In contrast, an NT-proBNP measurement too early during admission may predate clinical circumstances that increase NT-proBNP levels again (such as worsening of heart failure [HF]). More NT-proBNP measurements are then warranted to ascertain that patients are discharged with a reduction of >30%.

To study the feasibility of performing an NT-proBNP measurement well before discharge with the future possibility to guide ADHF treatment targeting a >30% NT-proBNP reduction, we assessed the moment at which hospitalized patients attain this reduction and determined the percentage of patients who experienced rebound NT-proBNP increases to levels off-target at discharge.

Methods

Original Cohort

Daily NT-proBNP measurements were performed in 25 consecutive ADHF patients in a prospective substudy of the PRIMA II (hereafter named original cohort) enrolled from May 2012 to June 2013 in the Academic Medical Center in Amsterdam, The Netherlands. Rationale and design of the study have been previously reported.[9] This substudy was approved by the Medical Ethics Committee of the University of Amsterdam and Academic Medical Center, The Netherlands, and written informed consents were obtained from all patients.

From admission (day 0), daily NT-proBNP measurements were performed until a >30% reduction (target) was attained, at randomization, and at discharge. Patients were randomized on the day of clinical stability, a discharge criterion requiring the presence of 3 of 4 clinical variables.[9] No attempts were made to adjust therapy using these measurements before randomization. In patients subjected to conventional therapy, NT-proBNP measurements at randomization and discharge were blinded. In patients subjected to NT-proBNP–guided therapy, additional treatment options were reconsidered only after randomization and if applicable adjusted to attain target.

Analysis

In the original cohort, we evaluated—for each day of admission—the cumulative percentages of patients on target. Percentage of patients on target was also determined at the day of discharge. Percentages of patients that were on target at day 2 and 3 of admission but demonstrated a rebound NT-proBNP increase to levels off-target at discharge (hereafter named rebound NT-proBNP increase) were determined. Categoric variables are reported as frequencies and percentages; continuous variables are reported as mean ± SD or as median and interquartile range (IQR).

Comparison Cohorts

We analyzed individual data from 2 ADHF prospective registries for comparison of the results of the original cohort for the time-dependent course of patients attaining target during admission and rebound NT-proBNP increases between days 2 and 3 and discharge.[10,11] In the Rome cohort (n = 42), NT-proBNP was measured at admission, after 12, 24, 48, and 72 hours, and at discharge.[10] In the Brescia cohort (n = 121), NT-proBNP was measured at admission, after 6, 12, 24, and 48 hours, and at discharge.[11] We excluded 10 patients from the Brescia cohort for having a noncardiovascular cause of admission or for presence of multiple missing NT-proBNP values. Physicians in these cohorts were blinded for the NT-proBNP results.

Baseline characteristics and cumulative percentages of patients attaining target between cohorts were compared with the use of either Student *t* or Mann-Whitney *U* test where appropriate for continuous and chi-square test for categoric variables.

Results

Original Cohort

Baseline characteristics of the original cohort are listed in Table 1. None of the patients died during admission. The percentage of patients that attained the target during admission is depicted cumulatively in Figure 1. The target was gradually attained in 22 patients (88%) in a median of 3 days (IQR 2–5). Of the patients on target at days 2 and 3, 0% (0/9) and 8% (1/13), respectively, demonstrated a rebound NT-proBNP increase. In total, 4 of the patients that attained the target throughout the hospitalization demonstrated a rebound NT-proBNP increase. Clinical circumstances that could explain this NT-proBNP increase were development of a gastroenteritis (n = 1), atrial fibrillation (n = 1), cardiogenic shock after complete AV block (n = 1), and HF medication down-titration after experiencing lightheadedness (n = 1). Three patients did not attain the target during admission and discharge.

Thus, of 22 patients initially on target, 18 patients (72%) were discharged on target.

Comparison Cohorts

Baseline characteristics of the comparison cohorts are also listed in Table 1. The cohorts were heterogeneous, particularly regarding age, left ventricular ejection fraction, admission blood urea nitrogen and NT-proBNP levels, and intravenous furosemide starting doses.

Significant differences in percentages of patients attaining the target between the Rome and original cohort were observed at discharge (Fig. 2). The Brescia cohort showed significant differences in cumulative percentages of patients attaining the target at days 1 and 2 and discharge (Fig. 2). In patients that attained the target at day 2, a rebound

Table 1. Baseline Characteristics of Original and Comparison Cohorts

Variable	Original Cohort	Comparison Cohorts	
	Amsterdam (n = 25)	Brescia (n = 111)	Rome (n = 42)
Age, y, median (IQR)	70 (59−78)	68 (59−74)	78 (72−82)*
Age ≥75 y, n (%)	11 (44)	26 (23)	29 (69)
Male, n (%)	15 (60)	100 (90)***	28 (67)
History of DM, n (%)	9 (36)	39 (35)	12 (29)
History of hypertension, n (%)	14 (56)	47 (42)	29 (69)
History of CHF, n (%)	22 (88)	NA	31 (74)
Ischemic etiology, n (%)	10 (40)	57 (52)	21 (50)
LVEF, n (%)			
Preserved (≥45%)	1 (4)	14 (13)	15 (36)
Mild-moderate (25%−44%)	15 (60)	49 (46)	25 (60)***
Severe (<25%)	9 (36)	43 (41)	2 (5)
JVP distended at admission, n (%)	12 (52)	46 (41)	NA
Pulmonary rales at admission, n (%)	17 (68)	97 (87)*	31 (74)
Peripheral edema at admission, n (%)	18 (72)	59 (53)	34 (81)
SBP at admission, mm Hg, mean ± SD	127 ± 30	120 ± 30	136 ± 18
DBP at admission, mm Hg, mean ± SD	75 ± 20	75 ± 15	71 ± 11
Heart rate at admission, beats/min, mean ± SD	92 ± 28	87 ± 21	84 ± 23
Atrial fibrillation at admission, n (%)	10 (40)	42 (38)	20 (48)
NYHA functional class at admission, n (%)			
I	0 (0)	0 (0)	0 (0)
II	3 (13)	7 (7)	6 (14)
III	13 (54)	53 (49)	19 (45)
IV	8 (33)	48 (44)	17 (41)
Laboratory findings, mean ± SD			
Hemoglobin at admission, g/L	7.8 ± 1.5	8.1 ± 1.8	7.4 ± 1.3
Serum urea nitrogen at admission, mmol/L	15.6 ± 9.1	31.4 ± 20***	13 ± 7.1
Serum sodium at admission, mmol/L	136 ± 5	137 ± 4	138 ± 6
Serum potassium at admission, mmol/L	4.2 ± 0.6	4.3 ± 0.6	4.2 ± 0.7
eGFR at admission, mL min^{-1} 1.73 m^{-2}†	46 ± 25	57 ± 29	49 ± 27
NT-proBNP at admission, pg/mL, median (IQR)	7,491 (5,470−18,032)	4,740 (1,735−9,528)**	5,956 (2,285−13,723)
Duration admission, days, mean ± SD	19 ± 18	15 ± 11	NA
Medication at admission, n (%)			
Diuretics	23 (92)	95 (86)	34 (81)
Aldosterone antagonist	9 (36)	55 (50)	10 (24)
ACE-inhibitor	10 (40)	63 (57)	19 (45)
Angiotensin II receptor blocker	5 (20)	17 (16)	8 (19)
Beta blocker	20 (80)	71 (65)	16 (38)**
Furosemide starting dose at admission, mg, median (IQR)	160 (125−250)	250 (200−500)*	50 (20−174)***

IQR, interquartile range; SD, standard deviation; DM, diabetes mellitus; CHF, congestive heart failure; LVEF, left ventricle ejection fraction; JVP, jugular venous pressure; SBP, systolic blood pressure; DPB, diastolic blood pressure; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate.

*$P < .05$; **$P < .01$; ***$P < .001$ (comparison between comparison cohorts and original cohort).

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

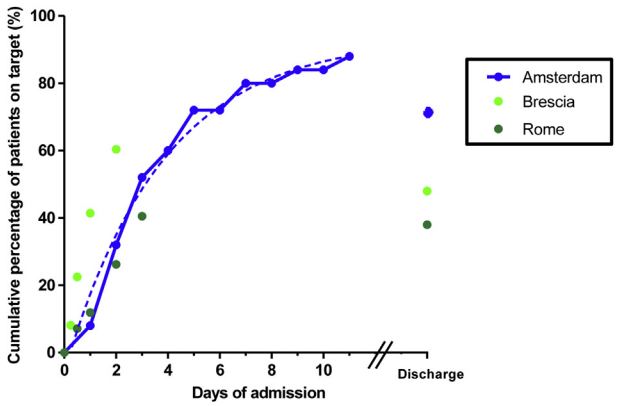

Fig. 1. Cumulative percentage of patients attaining a reduction of >30% in N-terminal pro−B-type natriuretic peptide levels during admission in the original (Amsterdam) and 2 comparison cohorts.

NT-proBNP increase was seen in 9% (1/11) and 33% (22/67) of patients in the Rome and Brescia cohorts, respectively. From day 3, 20% of patients (3/15) from the Rome cohort who attained the target demonstrated a rebound NT-proBNP increase.

Discussion

Our results suggest that 1) ADHF patients attain a target NT-proBNP reduction of >30% gradually during admission and 2) rebound NT-proBNP increases to levels off-target at discharge occur in patients who attained target early during admission (ie, day 2 or 3).

Gradual Increase in Patients Attaining Target

We observed a gradual increase in cumulative percentage of patients that attain target during admission in all 3 cohorts. The observed percentages of patients on target at

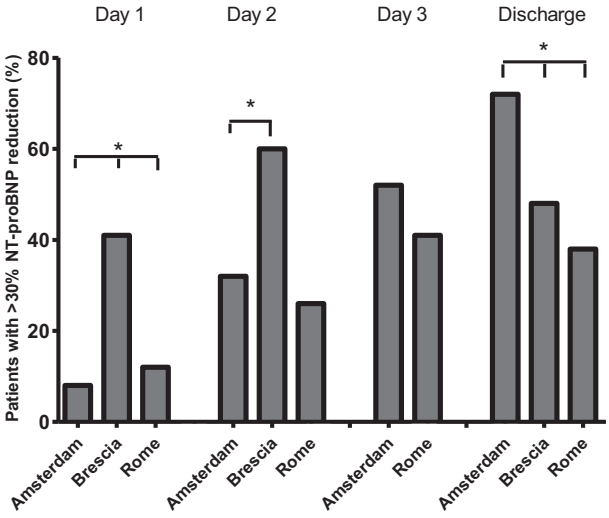

Fig. 2. Cumulative percentage of patients attaining a reduction of >30% in N-terminal pro−B-type natriuretic peptide (NT-proBNP) levels on days 1, 2, and 3 of admission and at discharge in different acute decompensated heart failure cohorts. *Statistically significant difference between the results from the original (Amsterdam) and comparison cohorts.

discharge (40%−70%) are similar to previous studies.[2,3,6,8] There are some interesting differences between cohorts: especially at day 1 and 2, significantly more patients attained the target in the Brescia cohort compared with the original cohort. One of the possible explanations is a higher dose of diuretics used in Brescia. The Diuretics Optimization Strategies Evaluation in ADHF (DOSE) trial demonstrated a trend for a greater absolute reduction in NT-proBNP with higher doses of furosemide during ADHF admissions compared with administration of low-dose diuretics.[12]

Rebound NT-proBNP Increases

In both the original and the comparison cohorts, up to 33% of patients experienced rebound NT-proBNP increases at discharge when they initially had attained the target at day 2 and 3 of admission. In the original cohort, there were 3 additional patients who demonstrated rebound NT-proBNP increases after day 3, suggesting that rebound increases may occur throughout the entire course of admission.

Various causes for reelevation of natriuretic peptide levels exist, such as cardiac arrhythmias, coronary ischemia, etc.[13] Searching for an explanation for this rebound NT-proBNP increase, we found that for each of these patients in the original cohort, it could potentially be attributed to cardiovascular deteriorating circumstances. Whether a rebound increase in NT-proBNP is always a surrogate marker of clinical deteriorating circumstances, or alternatively a recovery from underfilling, warrants further investigation.

Besides changes related to congestion, changes in NT-proBNP levels due to biologic variation should be considered. Studies on short-term biologic variation of NT-proBNP in chronic HF patients are limited and demonstrate variations up to 100% change, but these subclinical changes in NT-proBNP might have been caused by (subclinical) signs of worsening HF.[14] A >30% NT-proBNP reduction is near biologic variation levels, but has been found to be clinically meaningful in several end-point studies.[2,3,5,6,8]

Study Limitations

This study had a small sample size, and results should therefore be interpreted with caution. Some of this limitation was overcome by describing additional (unpublished) findings from 2 other ADHF cohorts. Another limitation is the heterogeneity of patients and treatments in the cohorts, as exemplified in the use of different furosemide starting doses, and any comparison between cohorts should be carefully interpreted. Additionally, NT-proBNP results in the original cohort were known to the treating physician (with the exception of levels at randomization and discharge for the conventional group), whereas they were not known in the comparison cohorts. However, after attaining target at day 2 or 3, NT-proBNP measurements were not performed until days of randomization and discharge. Of the 9 patients who were randomized to NT-proBNP−guided therapy, 2 patients were off-target at randomization and at discharge despite guidance, whereas the remaining 7 patients were on target at both moments. Therefore, guidance is not likely to have influenced the percentage of patients experiencing rebound NT-proBNP increases.

Conclusion

When the intention is to guide ADHF treatment with a target of >30% NT-proBNP reduction, one should be aware that the percentage of patients attaining target during admission is influenced both by a gradual increase in patients on target toward the end of admission and by occurrence of rebound NT-proBNP increases.

Disclosures

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References

1. Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. Am Heart J 1999;137:352−60.
2. Bayes-Genis A, Lopez L, Zapico E, Cotes C, Santalo M, Ordonez-Llanos J, et al. NT-proBNP reduction percentage during admission for acutely decompensated heart failure predicts long-term cardiovascular mortality. J Card Fail 2005;11(5 Suppl):S3−8.

3. Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. N-Terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 2004;110:2168−74.
4. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, 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.
5. Logeart D, Thabut G, Jourdain P, Chavelas C, Beyne P, Beauvais F, et al. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. J Am Coll Cardiol 2004;43:635−41.
6. Verdiani V, Ognibene A, Rutili MS, Lombardo C, Bacci F, Terreni A, et al. NT-proBNP reduction percentage during hospital stay predicts long-term mortality and readmission in heart failure patients. J Cardiovasc Med (Hagerstown) 2008;9:694−9.
7. Kinnunen P, Vuolteenaho O, Ruskoaho H. Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium: effect of stretching. Endocrinology 1993;132:1961−70.
8. Salah K, Kok WE, Eurlings LW, Bettencourt P, Pimenta JM, Metra M, et al. 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;100:115−25.
9. Stienen S, Salah K, Moons AH, Bakx AL, van Pol P, Schroeder-Tanka JM, et al. 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;168:30−6.
10. Disomma S, Magrini L, Pittoni V, Marino R, Peacock WF, Maisel A. Usefulness of serial assessment of natriuretic peptides in the emergency department for patients with acute decompensated heart failure. Congest Heart Fail 2008;14(4 Suppl 1):21−4.
11. Metra M, Nodari S, Parrinello G, Specchia C, Brentana L, Rocca P, et al. The role of plasma biomarkers in acute heart failure. Serial changes and independent prognostic value of NT-proBNP and cardiac troponin-T. Eur J Heart Fail 2007;9:776−86.
12. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797−805.
13. Mohammed AA, Januzzi JL Jr. Natriuretic peptide guided heart failure management. Curr Clin Pharmacol 2009;4:87−94.
14. Eurlings LW, Sanders-van WS, van Kraaij DJ, van Kimmenade R, Meeder JG, Kamp O, et al. 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;20:881−90.