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How often we need to measure brain natriuretic peptide (BNP) blood levels in patients admitted to the hospital for acute severe heart failure? Role of serial measurements to improve short-term prognostic stratification

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Abstract

Background: Brain natriuretic peptide (BNP) is increasingly used in the management of patients with heart failure (HF). It is still unclear how to use serial BNP measurement in HF.
Aim: To evaluate the usefulness of three consecutive measurements of BNP in patients (pts) hospitalized for acute HF.
Methods: Clinical evaluation, BNP levels and echocardiography were assessed in 150 pts (67% males, age: 69±12 years; left ventricular ejection fraction: 34±14%) admitted for severe HF (NYHA class III–IV: 146/150). BNP measurements were obtained: at admission (basal, T0), at discharge (T1) and at first ambulatory control (T2), after optimization of medical therapy in those with discharge BNP level >250 pg/mL. End-points were death and hospital readmission during 6-month follow-up.
Results: According to BNP levels 3 groups of patients were identified: Group 1 (62 pts, 41%), in whom discharge (T1) BNP was high and persisted elevated at T2 despite aggressive medical therapy; at 6-month follow-up 72% died or were hospitalized for HF. Group 2 (36 pts, 24%), in whom discharge (T1) BNP was high but decreased after medical therapy (T2); death and HF-readmission were observed in 8 pts (26%). Group 3 (52 pts, 35%), in whom discharge (T1) BNP levels were <250 pg/mL and persisted below this value at T2; death and HF-hospital readmission were observed in 6 pts (12%). Event rate differences among groups were statistically significant ($p<0.001$). At Cox-analysis discharge BNP cutoff of 250 pg/mL was the only parameter predictive of a worse outcome.
Conclusion: These data suggest that 3 BNP measurements, at admission, at discharge and few weeks later can allow to identify HF pts whom, despite a further potentiation of medical therapy, will present a worsening or even will die during short-term follow-up.

Keywords: Heart failure; Brain natriuretic peptide; Left ventricular dysfunction; Prognosis

1. Introduction

Despite recent advances in medical treatment, mortality and morbidity of patients (pts) admitted to the hospital for worsening heart failure (HF) remains high (50% mortality

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and 30% hospital readmission at 1-year, respectively, for severe HF pts) [1].

B-type natriuretic peptide (BNP) is a cardiac hormone secreted mainly from left ventricle as a consequence of ventricular volume and pressure overload. There is large interest on the role of BNP for the differential diagnosis of dyspnoea [2], and as prognostic marker in several clinical conditions, such as pulmonary embolism [3], acute myocardial infarction [4] and, specially, HF [5–16].

Furthermore, it has been demonstrated that lower BNP levels in HF pts usually reflect improved neurohormonal modulation and a better hemodynamic profile, which may be associated with better short- and long-term outcome [5,6]. Recently, several reports have focused on the prognostic role of *serial* measurements of natriuretic peptide serum levels in HF pts, evaluating the role of admission and discharge BNP and BNP changes after therapy [8–13]. However, the number and the time interval of BNP measurements which best predict short-term prognosis after discharge have not been defined.

Thus, the aim of this study was to [1] assess the role of changes in BNP levels for short-term prognostic stratification and [2] their potential additive role to clinical assessment for medical therapy and discharge optimization. Accordingly, we evaluated the usefulness of three consecutive measurements of BNP serum levels (at the time of admission, at the time of discharge and at the first ambulatory visit) in pts hospitalized for acute severe HF and discharged after clinical improvement, as assessed by symptoms and physical signs evaluation only.

2. Methods

2.1. Study population

We studied prospectively 150 pts (100 males, 67%) admitted in a 4-month period to Cardiology Department in four Hospitals for acute worsening of chronic HF secondary to left ventricular (LV) systolic and/or diastolic dysfunction and discharged alive after clinical improvement as a consequence of intensive medical treatment. All participating Investigators had expertise in HF management. All pts were in New York Heart Association functional class III and IV at admission, indicating acute severe HF. Pts with HF due to acute coronary syndrome, severe valve disease, pulmonary embolism, and those with clinical conditions requiring surgical or percutaneous myocardial revascularization within the next six months were excluded; other exclusion criteria were advanced chronic renal disease (plasma creatinine > 3 mg%), documented hepatic cirrhosis and chronic obstructive pulmonary disease. Regarding the causes of HF, a documented previous myocardial infarction or angiographic evidence of > 70% stenosis of at least one epicardial coronary artery was necessary to identify an ischemic aetiology; a long term history of systemic hypertension and no evidence of coronary artery disease identified an hypertensive cardiopathy as probable aetiology of clinical picture; an idiopathic dilated cardiomyopathy was considered present when a left ventricular systolic dysfunction unrelated to coronary artery disease or systemic hypertension was found. The 150 pts enrolled into the study correspond to 28% of all patients ($n = 527$) screened during the same period. Each patient gave written informed consent.

Clinical information such as prior medical history and pharmacological therapy before admission, New York Heart Association (NYHA) functional class and biochemical parameters were collected. All patients underwent chest X-ray and Doppler-ecocardiographic evaluation at the time of hospital admission and at discharge.

2.2. Echocardiographic-Doppler examination

On the two-dimensional echo tracings, the LV ejection fraction (LVEF) was measured using the Simpson method; a LVEF ≤ 50% was considered to identify LV systolic dysfunction as pathophysiological mechanism of HF. The severity of functional atrio-ventricular valve regurgitation was assessed semiquantitatively (scale 0–4/4) on Doppler color flow images. The right ventricle to right atrial pressure gradient on continuous wave Doppler of tricuspid regurgitation was used for the indirect estimation of systolic pulmonary artery pressure. Furthermore, the Doppler tracings of transmitral and pulmonary venous flow were evaluated according to a standard approach. The following parameters were assessed: on transmitral flow, the peak velocity of early filling (E) and atrial systole (A), their ratio (E/A) and the deceleration time of early filling (DT); on pulmonary venous flow (PV), the peak velocity of systolic (S) and diastolic (D) wave and their ratio (S/D), the peak velocity of reverse A wave during atrial systole (AR). The classification of diastolic (dys)function was a predefined modification of classifications used in prior studies [17–19]: 1) impaired relaxation pattern: E/A velocity ratio < 0.8 (in subjects aged > 55 years) or E/A < 1 (in subjects aged < 55 years) and DT > 220 ms, PV S/D ratio > 1, and atrial reversal wave (AR) < 35 cm/s); 2) pseudonormal pattern: E/A 1 to 2, DT 150 to 220 ms, S/D ratio < 1 on PV, and AR > 35 cm/s; 3) restrictive pattern: E/A > 2, DT < 150 ms, PV S/D ratio < 1, and AR > 35 cm/s. The presence of one of these patterns, in the presence of a normal LVEF (> 50%), was defined as isolated diastolic dysfunction. In patients suffering from atrial fibrillation at the time of the echocardiogram, diastolic function was classified as: 1) restrictive pattern (DT < 150 ms) or 2) indeterminate (DT > 150 ms).

2.3. BNP measurements

Blood samples were taken after 30 min of supine rest and were collected in tubes containing potassium ethylenediaminetetraacetic. B-type natriuretic peptide serum levels were obtained using a commercially available kit (Triage Biosite B-Type natriuretic peptide point of care test, Biosite Diagnostics Inc., San Diego, California).

In all pts, blood samples for BNP levels were obtained at the time of hospital admission (time 0, T0), at the time of hospital discharge (time 1, T1) and at the first ambulatory visit (time 2, T2).

2.4. Study design

Immediately after the initial clinical evaluation, medical therapy optimization was started using intravenous loop diuretics, vasodilators (such as sodium nitroprusside or nitrate) and/or inotropic agents (such as dobutamine or enoximone) infusion; this treatment overlapped with oral administration of furosemide (at dosages required to obtain and maintain resolution of pulmonary and systemic congestion), digoxin, oral nitrates, ACE-inhibitors or angiotensin 2-receptor blockers, beta-blockers and aldosterone antagonists, according to the European Society of Cardiology (ESC) Guidelines [20] and until a stable clinical improvement was observed.

Hospital discharge took place when patients had no symptoms at rest and during in-hospital mobilization and physical examination showed persistent reduction of pulmonary ("rales") and systemic (hepatic enlargement, jugular venous distention, leg edema) congestion. In order to obtain uniformity among centers for discharge, six criteria had to be simultaneously met, according to a previously validated approach [21]: a) subjective improvement on the basis of NYHA class; b) 90 < systolic blood pressure < 120 mm Hg; c) heart rate < 100 bpm; d) pulse oxymetry in ambient air > 90%; e) diuresis > 1000 mL/day; f) improvement in fluid overload.

Decision to discharge by physician responsible for patient care was not influenced by BNP serum levels. However, to those pts with BNP plasma levels at discharge > 250 pg/mL (see below) a medical therapy adjustment at home (such as a further increase of dosages of loop diuretics, beta-blockers, ace-inhibitors and other vasodilator drugs) was prescribed. The first ambulatory visit was scheduled 2–3 weeks after hospital discharge. Then, six-month follow-up for death and hospital readmission for HF was obtained by ambulatory control or telephone contact with patients or relatives. New hospitalizations for worsening HF and deaths were confirmed evaluating medical records. The institutional ethical committee at all participating centers approved the study.

2.5. Study groups

We found three distinct patterns of BNP behaviour and classified patients accordingly:

Group I: 62 pts (41%) with high levels of BNP at admission (T0) showing no relevant changes after in-hospital therapy (<30% reduction from T0 at T1) and discharge (T1) BNP levels >250 pg/mL, persisting also at the first ambulatory control (T2), despite further medical therapy optimization (see study design).

Group II: 36 pts (24%) with high levels of BNP at admission (T0) showing a large change after in-hospital therapy (>30% reduction from T0 at T1), and persisting high BNP values (>250 pg/mL) at discharge (T1), but with a decrease at <250 pg/mL at the first ambulatory control (T2), after further medical therapy optimization (see study design).

Group III: 52 pts (35%) with high levels of BNP at admission (T0) showing a large (>30%) BNP reduction at discharge (T1) with resulting values below 250 pg/mL, also persisting at the first ambulatory visit (T2), in absence of further medical therapy optimization (according to the protocol).

A discharge cut-off value of 250 pg/mL or more of BNP serum levels to identify patients requiring further medical therapy optimization was selected in view of recent data showing that discharge BNP levels above values ranging from 200 to 350 pg/mL allow for the identification of HF patients with high risk of hospital re-admission and death in a short and medium term follow-up [6,9,21].

2.6. Statistical analysis

Categorical data are presented as numbers (percent), and continuous data as means ± standard deviation. A value of $p < 0.05$ was considered significant. Parametric and non parametric tests were used, according to the model of data distribution. We used the Mann–Whitney *U*-test and the Wilcoxon test for the comparisons between samples, while the association between variables was verified with Fisher's exact test. Cox proportional hazards regression models were used to examine the relation of clinical variables, BNP levels, and echocardiographic parameters with the incidence of the combined endpoint during the six months after discharge. BNP levels were evaluated both as a continuous variable and as a categorical variables (based on cut-off values). To compare the occurrence of events in relation to BNP levels Kaplan–Meier curves were traced. A receiver operating characteristics (ROC) curve was also used to test whether BNP values obtained at different times could be utilized as prognostic markers. Analyses were performed using SPSS software per Windows, release 11.0 (SPSS Inc., Chicago, USA).

3. Results

3.1. Baseline data

Aetiology of heart failure was ischemic dilated cardiomyopathy in 77 patients (51%), idiopathic dilated cardiomyopathy in 36 patients (24%), and hypertensive cardiopathy in 37 patients (25%). Before hospital admission 87% of patients were already treated with an ACE inhibitor or Angiotensin II-receptor blocker, 90% with loop diuretics, 50% with beta blockers.

Table 1
Demographic, clinical, Doppler-echocardiographic and biochemical characteristics of patients at admission to the hospital for acute severe HF.

	All patients (n=150)	Group 1 (n=62)	Group 2 (n=36)	Group 3 (n=52)
Age (years)	69±12	73±12	68±14	64±10[a]
Men (%)	100(67%)	44(71%)	23(64%)	33(64%)
Admission NYHA class III or IV	146/150	67/67	33/33	46/50
Systolic arterial pressure (mm Hg)	105±8	104±10	106±12	105±10
LV ejection fraction (%)	34±14	37±15	33±14	30±10[a]
Isolated LV diastolic dysfunction (%)	13	19[#]	15[#]	2[#]
LV end-diastolic diameter (mm)	64±9	63±8	63±9	64±9
Mitral regurgitation (scale 0–4/4)	3±0.5	2.7±0.8	2.8±0.7	2.8±0.6
Tricuspid regurgitation (scale 0–4/4)	3.0±0.5	2.2±0.8	2.5±0.8	2.8±.09
Restrictive filling pattern (%)	61	63	58	62
Admission systolic pulmonary arterial pressure (mm Hg)	50±10	52±9	51±10	48±11
Serum creatinine (mg/dL)	1.5±0.9	1.8±1.3	1.6±0.5	1.2±0.3[a]
BNP at admission — T0 (pg/mL)	1000±684	1302±894	882±353[a]	720±353[a]

[a] $p<0.05$ *vs* Group 1, Oneway ANOVA and post-hoc Tukey test.
[#] $p<0.001$, Pearson Chi Square test.
See text for details.

Clinical, echocardiographic and laboratory data assessed at the time of hospital admission are presented in Table 1 for the study population considered as a whole and for the three groups of pts identified according to pattern of BNP behaviour (see Methods section). In general, the patients had severe HF, characterized by severe LV systolic dysfunction (prevalence of isolated diastolic dysfunction was only 13%), an at least moderate degree of functional mitral and tricuspid regurgitation, a frequent restrictive pattern of LV filling on pulsed Doppler flow, indicating an elevated left atrial pressure, and indirect sign of moderate to severe pulmonary hypertension

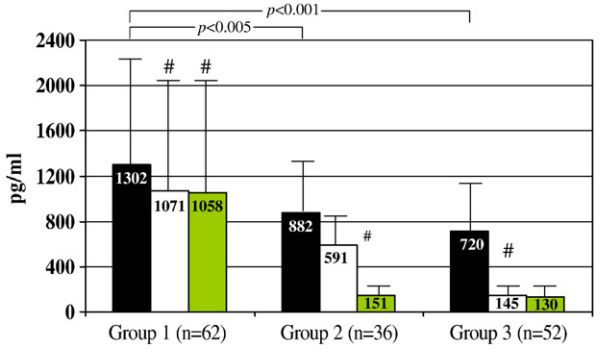

Fig. 1. Behaviour of BNP serum levels at hospital admission (T0), hospital discharge (T1) and first ambulatory visit (T2) in the three groups. p refers to Oneway ANOVA and post-hoc Tukey test. #$p<0.001$ Kruskall–Wallis ANOVA for repeated measures. See text for details.

Table 2
Six-month outcome in the three groups of patients identified according to the behaviour of serum BNP levels.

	Hospitalization	Mortality
Group 1 (n=62)	15 (24%)*	30 (48%)*
Group 2 (n=36)	3 (8%)	5 (18%)
Group 3 (n=52)	1 (2%)	5 (10%)

*$p<0.001$ versus Group 2 and Group 3. Pearson Chi Square test.
See text for details.

(Table 1). Furthermore, a marked increase of admission (T0) BNP blood levels was observed (1000±684 pg/mL). No patient had a BNP values at T0<250 pg/mL.

Group 1 pts were, compared to the other groups, slightly older (difference statistically significant only versus Group 3), and showed a larger prevalence of isolated diastolic dysfunction; accordingly, LVEF was slightly higher compared with that measured in the other groups (difference statistically significant only versus Group 3). Also, serum creatinine was higher in Group 1, compared to the other groups (difference statistically significant only versus Group 3), reflecting a worse baseline renal function. BNP levels at admission were significantly higher in Group1 compared to Groups 2 and 3 (Table 1).

3.2. Clinical and BNP changes

After in-hospital intensive medical therapy optimization (minimum 7 days) some degree of clinical improvement, as documented by at least 1 NYHA class decrease, or absence of resting symptoms (at least for pts with refractory IV class HF) and of pulmonary and systemic congestion present at admission, was observed in all pts.

In the study population considered as a whole BNP levels significantly decreased from admission (T0) at the end of intensive medical treatment (coincident with the time of hospital discharge, T1), from 1000±684 to 635±722 pg/mL ($p<0.05$, average reduction 36%). The behaviour of BNP changes in the three groups was different and is presented in Fig. 1. Average BNP reduction from T0 to T1 was minimal in Group 1 (17%, $p<0.05$), moderate in Group 2 (33%, $p<0.05$) and large in Group 3 (80%, $p<0.05$); by study design, all Group 3 pts had BNP values at T1<250 pg/mL.

Table 3
Predictors of events on multivariate Cox regression according to discharge (T1) BNP cutoff levels of 250 pg/mL.

Variable	HR	CI	p value
BNP≥250 pg/mL	4.5	2.0–10.3	0.0003
NYHA class	1.8	1.0–3.2	0.0402
Restrictive pattern	1.1	0.6–2.0	0.8083
Age (yrs)	1.0	1.0–1.0	0.7356
LV ejection fraction (%)	1.0	1.0–1.0	0.9823
Creatinine (mg/dL)	1.1	0.8–1.3	0.6722

CI=confidence interval; HR=hazard ratio: LV=left ventricular.
See text for details.

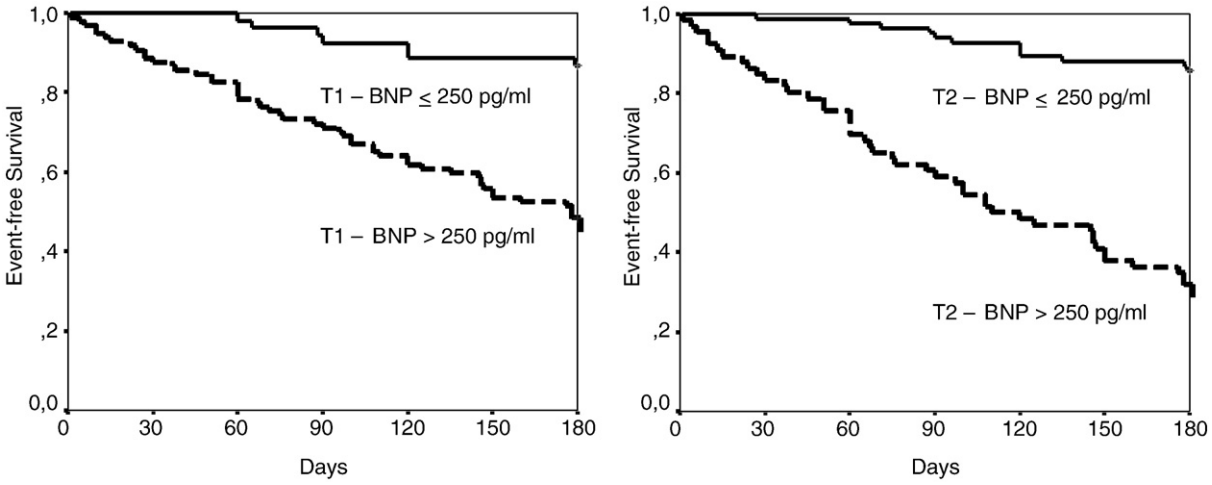

Fig. 2. Kaplan–Meier curves showing the cumulative incidence of death and readmission according to BNP levels in the study population. *Left*, BNP values obtained at discharge (T1); *right*, BNP values obtained at the first ambulatory control (T2). Tarone–Ware's test <0.001 for all the comparisons. See text for details.

Patients were discharged after a mean length of stay 10±2 days. There were no significant differences in the duration of hospital stay and in the time interval between BNP measurement at admission (T0) and at discharge (T1) among the three groups. At discharge 97% of pts received an ACE-inhibitor or an angiotensin II-receptor blocker at 85% of the ESC guidelines recommended doses [20], 82% of pts received a beta-blocker at 54% of the recommended dosage [2], all pts received furosemide and 54% of pts received a low-dose of aldosterone antagonists; mean daily dosage of furosemide at discharge was significantly higher in Group 1 (92±87 mg), versus Group 2 and Group 3 (68±72 mg and 63±94 mg, respectively, $p<0.05$). By study design, only to Group 1 and Group 2 pts (BNP values at discharge, T1, >250 pg/mL) a further increase of diuretic and vasodilator dosages was prescribed at home, even though they appeared clinically free of oedema at discharge.

The first post-discharge BNP measurement (T2) was performed a mean of 20±5 days after hospital discharge, and this time interval was similar among the three groups. During this time interval, the average increase in furosemide and ace-inhibitor (enalapril-equivalent) dosage was 47 mg/day and 4 mg/day, respectively (only in Groups 1 and 2). The BNP levels assessed at the first ambulatory visit (T2) are presented in Fig. 1: Group 2 pts showed a marked change in BNP at T2 compared to predischarge (T1) values (from 591±212 to 151±61 pg/mL, $p<0.05$, average 74% reduction) and Group 3 pts showed persistently low BNP values (from 145±57 to 130±55 pg/mL, difference not significant, average 10% reduction). Six out of 52 pts of Group 3 showed a slight increase in BNP levels at T2, compared with T1 values, always below 250 pg/mL. On the other hand, Group 1 pts still had markedly elevated BNP values at T2, similar to those observed at T1 (from 1071±920 to 1059±971 pg/mL, difference not significant, average 1.2% reduction). A markedly low value of BNP (<100 pg/mL) at T2 was observed in 26 pts of the whole population (17%): 0 of Group 1, 9 (25%) of Group 2, and 17 (33%) of Group 3 (Chi-square test, $p<0.01$).

3.3. Events

No clinical events occurred in the time interval between discharge and first ambulatory control. During the six-month of follow-up after the first ambulatory visit 40 pts died and 19 pts were re-admitted to the hospital for worsening HF. A high rate of hospital readmission and death was observed in Group 1 (45/62 pts, 72%); on the other hand, only 8 out of 36 pts (26%) of Group 2 and 6 out of 52 pts of Group 3 (12%) were readmitted to the hospital or died. These differences were statistically significant (Table 2).

Cox proportional hazards regression analysis shows that a BNP cut-off value of 250 pg/mL obtained at discharge (T1) was superior as a prognostic index compared with other variables such as New York Heart Association classification, restrictive pattern on Doppler echocardiogram, LV ejection fraction, age and serum creatinine (Table 3).

Kaplan–Meier cumulative survival curves separated according to cut-off BNP levels of 250 pg/mL are presented in Fig. 2.

ROC curves are shown in Fig. 3: area under curve (AUC) progressively increased from T0 to T2, confirming the greater prognostic value of BNP measurements obtained after therapy optimization compared to BNP levels at admission.

Finally, no events were recorded among 26 pts in whom a BNP value<100 pg/mL was observed at T2.

4. Discussion

The principal findings of this study of BNP levels during treatment of severe HF, three distinct patterns of BNP change were observed. These patterns were associated with distinct clinical outcomes. We believe that these data permit

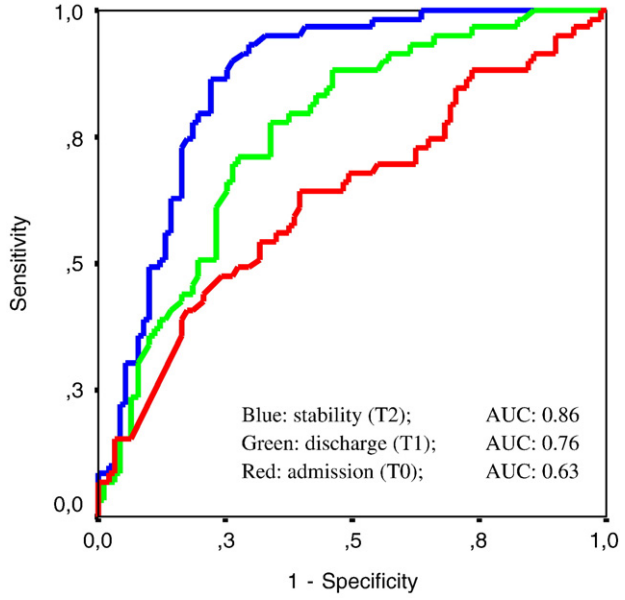

Fig. 3. ROC curves for BNP obtained at admission (T0), at discharge (T1) and at the first ambulatory control (T2). Area under the curve (AUC) progressively increases from T0 to T2. See the text for details.

identification of high-risk patients — those who will die or will be hospitalized again for worsening HF within the next six months. The prognostic role of BNP level, specially that obtained at discharge after in-hospital medical therapy optimization (T1), appears to add incremental value to clinical evaluation alone, since though all pts in our study were considered clinically improved and stable ("ready for discharge"), cardiac events were observed mainly among those pts with high BNP values at discharge and/or persisting high BNP values at the first ambulatory control. The superiority of BNP values >250 pg/mL over other widely used prognostic markers, such as NYHA functional class, restrictive filling pattern, LVEF and renal function, has been confirmed by Cox analysis performed in our study. Thus, elevated BNP levels at discharge, might be used as justification for prolongation of the hospital stay and/or to prescribe a more aggressive therapeutic approach, despite symptom improvement and absence of evident fluid overload. In this way, BNP levels at the first ambulatory visit may further contribute to modify clinical strategy in these pts.

There has been much recent interest in the potential role of plasma natriuretic peptides (BNP and NTproBNP) in monitoring the severity of clinical picture and in risk stratification of HF patients [6–15]. Considering the limitations of conventional assessment of clinical status (symptoms, signs of fluid congestion, body weight changes) in evaluating the short and mid-term changes, it has been suggested that plasma BNP level might be to the heart what glycated haemoglobin is to diabetes [5].

Data from the literature support the notion that absolute BNP levels, specially at discharge, or changes in BNP levels from the initial evaluation, are related to subsequent hospital readmission and death [8,10–15]. Several studies have demonstrated that high *predischarge* BNP assay is a strong independent predictor of death or re-admission after decompensated HF, more important than usual clinical or Doppler-echocardiographic parameters (including restrictive filling pattern and Doppler tissue imaging) and more relevant than changes in BNP levels during in-hospital treatment [9,22,23].

Bettencourt et al. found that variations of natriuretic peptides during hospitalization (a reduction greater of 30% from baseline level) and predischarge absolute levels are predictors of hospital readmission and death within six months of discharge [13,14]. Thus, serial measurements of BNP levels may be helpful to decide the optimal time to discharge HF pts after medical therapy optimization.

However, the optimal number and time collection intervals for natriuretic peptide measurements remain to be established, with obvious implications on laboratory resources and health costs [24]. The results of our work suggest that, at least in pts hospitalized for acute severe HF, three BNP assessment, two of which during hospital stay (at admission and at discharge) and one at an early ambulatory visit, could represent a useful compromise between the need of an accurate short-term risk stratification and cost containment. We hypothesized that the use of a BNP cut-off value (250 pg/mL in this work, according to results of previous studies) to optimize medical therapy at recommended maximal dosages, or even above, might allow to improve six-month outcome of pts with acute severe HF. In our study, a BNP level <250 pg/mL was obtained in 83 out of 150 pts, corresponding to 59% of whole population, 35% at discharge (Group 3) and 24% at first ambulatory control (Group 2), after further drug therapy optimization. Although the event rate reduction induced by treatment was not an endpoint of our study, relatively few events were observed in those pts in whom therapy optimization was successful in reducing BNP levels at less than 250 pg/mL, i.e. in Groups 2 and 3, compared with Group 1.

Of interest, Jourdain et al. recently demonstrated, in pts with stable HF, that a strategy of intensive medical therapy directed to the goal of decreasing BNP levels <100 pg/mL was associated with a significant reduction of HF-related deaths or hospitalizations, compared to conventional treatment [25]. In their study mean BNP levels decreased from 384±260 to 284±180 at 3-month follow-up, with 33% of pts reaching the target of <100 pg/mL [25]: our Groups 2 and 3 pts showed lower mean BNP values at 3–4 weeks after discharge (see Fig. 1), with 25% and 33%, respectively, reaching BNP values <100 pg/mL; furthermore, no death or hospital readmission were observed in these pts at 6-month of follow-up. Accordingly, the strategy of an intensive medical therapy directed at very low BNP levels could allow to improve the prognosis of high-risk HF pts.

4.1. Study limitations

Our data did not allow to compare a *BNP-guided approach* with other strategies, such as Doppler echocardiography, right heart catheterization, exercise test, for optimizing treatment in

pts with acute severe HF during the in-hospital stay and at home; this end-point was not included in the study protocol. However, the data presented seems to support the validity of a BNP-oriented therapy to improve outcome in HF pts, and should be confirmed by further studies ad-hoc planned.

Our study population was mostly male and with LV systolic dysfunction, similar to randomized studies and differently from HF registries, in whom female sex and diastolic dysfunction are increasingly prevalent. Accordingly, our results only apply to the population included. However, pts of Group 1 were older, with worse renal function and more frequent isolated diastolic dysfunction than pts of other groups: the persistently high BNP levels observed despite medical therapy optimization correctly identified patients with a worse outcome, confirming previous data [18,26,27].

Although only four HF centers were involved in this study and a previously used and validated methodology to assess the clinical stability of pts was adopted, we cannot exclude a relevant variability in the medical therapy optimization and in the assessment of pre-discharge clinical status.

In conclusion, in patients hospitalized for acute severe HF, three serial measurements of blood BNP levels, performed at critical intervals, could allow to identify pts at high risk for early hospital readmission or death during six-month follow-up, despite medical therapy optimization. Admission BNP assay is usually markedly elevated in these pts, *discharge* BNP assay seems to have a relevant value in order to identify pts with different six-month prognosis, with *early post-discharge* BNP assay having an additive value for risk stratification.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [28].

References

[1] Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme — a survey on the quality of care among patients with heart failure in Europe. Part 1. Patient characteristics and diagnosis. Eur Heart J 2003;24:442–63.
[2] Maisel A, Krishnaswamy P, Nowak R, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. NEJM 2002;347(3):161–7.
[3] de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003;362:316–22.
[4] Morita E, Yasue H, Yoshimura M, et al. Increased plasma levels of brain natriuretic peptide in patients with acute myocardial infarction. Circulation 1993;88:82–91.
[5] Kazanegra R, Cheng V, Garcia A, et al. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. J Card Fail 2001;7:21–9.
[6] Feola M, Aspromonte N, Canali C, et al. Prognostic value of plasma brain natriuretic peptide, urea nitrogen and creatinine in outpatients >70 years of age with heart failure. Am J Cardiol 2005;96:705–9.
[7] Cowie MR. B-type natriuretic peptide testing: where we are now? Heart 2004;90:725–6.
[8] Richards AM, Doughty R, Nicholls MG, et al. Neurohumoral predictors of benefit from carvedilol in ischemic left ventricular dysfunction. Circulation 1999;99:786–97.
[9] Logeart D, Thabut G, Jourdain P, et al. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. J Am Coll Card 2004;43:635–41.
[10] Logeart D, Saudubray C, Beyne P, et al. Comparative value of Doppler echocardiography and B-type natriuretic peptide assay in the etiologic diagnosis of acute dyspnea. J Am Coll Card 2002;40:1794–800.
[11] 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.
[12] Cheng V, Kazanegra R, Garcia A, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. J Am Coll Cardiol 2001;37:386–91.
[13] 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.
[14] Bettencourt P, Frioes F, Azevedo A, et al. Prognostic information provided by serial measurements of brain natriuretic peptide in heart failure. Int J Cardiol 2004;93:45–8.
[15] Troughton RW, Frampton M, 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.
[16] Yu CM, Sanderson JE. Plasma brain natriuretic peptide — an independent predictor of cardiovascular mortality in acute heart failure. Eur J Heart Fail 1999;1(1):59–65.
[17] Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. J Am Coll Cardiol 1998;32:865–75.
[18] Valle R, Aspromonte N, Feola M, et al. B-type natriuretic peptide can predict the medium-term risk in patients with acute heart failure and preserved systolic function. J Card Fail 2005;11:498–502.
[19] Valle R, Bagolin E, Canali C, et al. The BNP assay does not identify mild left ventricular diastolic dysfunction in asymptomatic diabetic patients. Eur J Echocardiog 2006;7:40–4.
[20] The Task Force for the Diagnosis and Treatment of Chronic Heart Failure. European Society of Cardiology guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527–60.
[21] Valle R, Aspromonte N, Carbonieri E, et al. Fall in readmission rate for heart failure after implementation of B-type natriuretic peptide testing for discharge decision: a retrospective study. Int J Cardiol 2008;126:400–6.
[22] Dokainish H, Zoghbi WA, Lakkis NM, et al. Incremental predictive power of B-type natriuretic peptide and tissue Doppler echocardiography in the prognosis of patients with congestive heart failure. J Am Coll Cardiol 2005;45:1223–6.
[23] Gackowski A, Isnard R, Goldmard JL, et al. Eur Heart J 2004;25:1788–96.
[24] Wu AHB, Smith A, Apple FS. Optimum time collection intervals for B-type natriuretic peptide testing in patients with heart failure. Am J Cardiol 2004;93:1562–3.
[25] Jourdain P, Jondeau G, Fucnk F, et al. Plasma natriuretic peptide-guided therapy to improve outcome in heart failure. The STARS-BNP Multicenter Study. J Am Coll Cardiol 2007;49:1733–9.
[26] Heywood JT, Fonarow GT, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J, ADHERE Scientific Advisory committee and Investigators. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. J Card Fail 2007;13:422–30.
[27] Metra M, Nodari S, Parrinello G, et al. Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance. Eur J Heart Fail 2008;10:188–95.
[28] Coats AJ. Ethical authorship and publishing. Int J Cardiol 2009;131:149–50.