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RESEARCH ARTICLE

Prognostic prediction in acute heart failure patients with extreme BNP values

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ABSTRACT

Background: Some patients have good prognosis despite elevated B-type natriuretic peptide (BNP), while others have ominous outcome with low BNP. We aimed at characterising these groups of patients.

Methods: We analysed patients prospectively included in an acute HF registry. Vital status within 1-year post discharge was ascertained. A receiver–operating characteristic curve was used to define discharge BNP cut-offs for 1-year death prediction. Among survivors, we compared patients with low and not-low BNP (cut-off 400 pg/mL); and among non-survivors those with high vs not-high BNP (cut-off 2000 pg/mL). In the specific subgroups of patients with low and high BNP, mortality predictors were assessed with multivariate Cox-regression analysis.

Results: We studied 584 patients, median age 78 years, 62.5% had HF with reduced ejection fraction; and 199 (34.1%) died during the first year. Non-survivors were very homogeneous irrespective of BNP, survivors were substantially different. In patients discharged with BNP <400 pg/mL, increasing age independently predicted death; when BNP ≥2000 pg/mL death predictors were higher NYHA class, and non-use of evidence-based therapy. BNP was outcome associated in both groups.

Conclusions: Different prognostic predictors may play a role in different BNP levels. We suggest that risk stratification in HF would probably be more accurate if made on top of BNP knowledge.

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KEYWORDS

Acute heart failure; natriuretic peptides; relative insufficiency; prognosis

Introduction

Natriuretic peptides have known beneficial effects: diuretic, natriuretic, vasodilation, suppression of the renin–angiotensin–aldosterone axis and sympathetic tone reduction; they also have anti-fibrotic, and anti-hypertrophic actions (Levin *et al.* 1998, Kjaer and Hesse 2001, Daniels and Maisel 2007, Calvieri *et al.* 2012). Increased levels are a hallmark in heart failure (HF), both acute and chronic (Maisel *et al.* 2002, McGeoch *et al.* 2002, Tang *et al.* 2003, Januzzi *et al.* 2005). Natriuretic peptides are useful for diagnostic purposes and they are also considered the gold standard for prognostic prediction in HF (Berger *et al.* 2002, Gardner *et al.* 2003, Januzzi *et al.* 2006, Latini *et al.* 2006, van Kimmenade *et al.* 2006, Masson *et al.* 2008). Despite their beneficial actions it is recognised that high and increasing natriuretic peptide levels predict worse outcome and that low and decreasing levels associate with better survival. It seems that HF is a state of relative insufficiency of natriuretic peptides since the system is activated but their protective effects are no longer sustained (Cody *et al.* 1986, Nakamura *et al.* 1998). This loss of effect does not seem to be observed in all HF patients. Among patients with better outcome in one hand and patients with a more adverse outcome on the other, there is a wide range of possible, and sometimes

overlapping, natriuretic peptide levels. Some patients have good prognosis despite elevated B-type natriuretic peptide (BNP) levels and, on the contrary, others have a gloomy outcome with low BNP levels (Miller *et al.* 2005, Sun *et al.* 2007).

In order to better understand the apparently paradoxical association of natriuretic peptides with worse outcome we compared patients with different neuro-humoral activation but the same outcome. To comprehend why in some situations this paradoxical association is not maintained we also characterised two well-known groups of patients in clinical practice: HF patients with good prognosis despite high levels of natriuretic peptides and HF patients with ominous outcome despite low natriuretic peptide levels.

Our guiding hypothesis was that in subgroups of patients with extreme (high or low) natriuretic peptide levels, different variables would be outcome associated. Predictors of survival and predictors of death were respectively studied in these subgroups.

Clinical significance

We characterise two HF subgroups well known in everyday clinical practice: patients that have poor outcome despite

low natriuretic peptide levels and those with good outcome despite elevated natriuretic peptide levels.

HF patients with low BNP have specific death predictors while those with elevated BNP have different survival predictors. The added knowledge may help physicians that treat HF patients in their daily practice

Our study tries to build knowledge on the natriuretic peptide relative insufficiency phenomenon in HF. Future studies should address mechanisms of natriuretic peptide system resistance and/or relative insufficiency.

Methods

We analysed patients from a registry of acute HF that was conducted in the Internal Medicine department of São João Hospital Centre, which a tertiary care academic hospital, between January 2009 and December 2010. Physicians treating acute HF patients were aware of the ongoing HF registry. The patients' treatment strategy, timing of discharge and discharge medication were at the discretion of the attending physician. As part of the registry's protocol all patients admitted to our department with the primary diagnosis of acute HF (both *de novo* and worsening chronic) were eligible for inclusion in the registry. The 2008 European Society of Cardiology guidelines were used for the diagnosis of HF (Dickstein *et al.* 2008). Both patients with systolic dysfunction and those with HF with preserved ejection fraction were included in the registry.

A complete physical examination at admission and in the discharge day was performed. A 12-lead electrocardiogram was performed at admission. Demographic characteristics, medications in use upon hospitalisation, discharge medication and comorbidities were recorded. All patients were also drawn a venous blood sample within the first 48 h of hospital admission as well as in the discharge day. BNP determination is a routine laboratory procedure in our hospital; an Abbott[®] (Lisbon, Portugal) chemiluminescent microparticle immunoassay (two-step immunoassay) is used. The measurement range of this assay is 10–5000 pg/mL. Percentage of BNP variation (% Δ BNP) was calculated as: [(admission BNP – discharge BNP)/admission BNP] \times 100. Renal function was assessed using the glomerular filtration rate as estimated by the modification of diet in renal disease (MDRD) formula. An echocardiogram was performed to all patients during hospitalisation; left ventricular ejection fraction $>50\%$ was considered normal systolic function. Patients' vital status at 12 months was ascertained by consulting hospital registries and by telephone contact with the patients or their relatives.

The registry's protocol conformed to the ethical guidelines of the declaration of Helsinki and it was approved by the local ethics committee. Patients provided informed consent.

A retrospective analysis was conducted in this prospectively recruited patient cohort. Patients with missing data regarding discharge BNP were excluded from the analysis; only a small subgroup of 27 (4.4%) patients had no BNP measured at discharge. In patients surviving the first year post discharge, those with low (<400 pg/mL) and not-low (≥ 400 pg/mL) were compared; and in patients not-surviving

this period those with high and not-high BNP (cut-off 2000 pg/mL) were also compared. We also studied two specific subgroups: 1) patients with low discharge BNP (<400 pg/mL); and 2) patients with high discharge BNP (>2000 pg/mL).

Statistical analysis

We used a receiver–operating characteristic (ROC) curve to define a discharge BNP cut-off below which there was a high negative predictive value of 1-year death and a discharge BNP cut-off above which there was a reasonably high positive predictive value of 1 year death. Cut-offs chosen was 400 and 2000 pg/mL, respectively.

We first analysed 12-month survivors and non-survivors separately. In the group of survivors those with discharge BNP below and above 400 pg/mL were compared; and in subset of non-survivors at 12 months those with BNP below and above 2000 pg/mL were also compared. Chi-square test was used to compare categorical variables and Student's *t*-test to compare continuous variables.

We then studied two specific subgroups: 1) patients with low discharge BNP (<400 pg/mL); and 2) patients with high discharge BNP (>2000 pg/mL). A Cox regression analysis was used to assess predictors of death in the subgroup of patients with low neuro-humoral activation and to assess predictors of survival in those with high neuro-humoral activation. Multivariate models were built. Variables included in the model were those that differed between survivors and non-survivors in each subgroup.

The *p* value considered for statistical significance was 0.05. Data was stored and analysed using SPSS software (IBM Corp, version 20.0, Armonk, NY).

Results

We studied 584 patients, 45.2% were male, 62.5% had HF with reduced ejection fraction and in 41.1% of the patients the HF was of ischaemic aetiology. Median patients age was 78 years (range from 32 to 100). In a 12-month follow-up period 199 (34.1%) patients died. Median discharge BNP in survivors was 519.7 (230.6–1034.8) pg/mL and in non-survivors was 1233.0 (679.9–2553.0), $p < 0.001$. The distribution of death and survival according to BNP categories is depicted in the bar graph of [Figure 1](#).

The area under the ROC curve of discharge BNP for 1-year mortality prediction was 0.75 (0.70–0.79), $p < 0.001$. Probability trees for the chosen discharge BNP cut-offs 400 and 2000 pg/mL are shown in [Figure 2](#). The negative predictive value for 12-month death in patients with discharge BNP <400 pg/mL was of 87.3%. The positive predictive value of being dead by 1 year for patients discharged with BNP ≥ 2000 pg/mL was of 71.6%. As expected, patients had increasingly worse prognosis with progressively higher discharge BNP (data not shown).

[Table 1](#) shows the comparison between patients with low (<400 pg/mL) and not-low discharge BNP among the 385 1-year survivors. Those with higher discharge BNP were

predominantly male, older aged, more often had HF with reduced ejection fraction, and they had higher admission BNP. They were also discharged on higher NYHA classes and with lower systolic blood pressure, lower haemoglobin and total cholesterol, as well as with worse renal function. Patients with lower discharge BNP were also less often discharged with beta blocker. Table 1 also shows the comparison between patients with high (≥ 2000 pg/mL) and not high discharge BNP among the 199 1-year non-survivors. Patients not surviving the first year post discharge were more homogenous irrespective of discharge BNP. They had higher admission BNP, more often had HF with reduced ejection fraction and they were discharged on higher NYHA classes and with worse renal function. In the whole patient population there was a weak negative correlation between BNP and

glomerular filtration rate as estimated by the MDRD formula ($p = -0.220, p < 0.001$)

We then specifically analysed two subgroups separately: those with low discharge BNP (lower than 400 pg/mL) and those with high discharge BNP (≥ 2000 pg/mL). One hundred and eighty nine patients (32.4%) were discharged with BNP lower than 400 pg/mL: 165 survived a 12-month period and 24 died. Patients discharged with low BNP corresponded to an overall group of younger aged (mean age 74 years vs 77 in those discharged with >400 pg/mL) women (64.6% vs 50.1% in those discharged with higher BNP) with HF with preserved ejection fraction (52.7% vs 30.1%). Table 2 shows their characteristics and compares survivors and non-survivors. Non-survivors were more often older patients with preserved ejection fraction; there was also a non-significant trend towards more women not surviving the first follow-up year. However, the only independent death predictors were age with a HR of 1.05 (95% CI 1.00–1.10) per each 1 year increase and discharge BNP with a HR of 1.57 (95% CI 1.00–2.48) per each 100 pg/mL increase. Eighty four patients (14.4%) were discharged with BNP ≥ 2000 pg/mL: 60 died during the first year post discharge and 24 survived. Their characteristics and comparison is shown in Table 3. Independent predictors of death were: being discharged in NYHA class ≥ 3 with a HR of 2.51 (95% CI 1.42–4.43) and not under prognostic modifying therapy – those discharged without beta blocker had a HR of death of 1.99 (95% CI 1.13–3.52) and those discharged without ACEi or ARB had a HR of death of 2.25 (95% CI 1.24–4.08). Higher discharge BNP still predicted death in this high discharge BNP group with a HR of 1.10 (95% CI 1.03–1.19) per each 1000 pg/mL increase. Importantly, in patients discharged with extreme BNP values no significant differences existed nor in BNP variation during hospitalisation neither in the glomerular filtration rate between 1 year survivors and non-survivors; renal function and BNP change were also not outcome associated in these patient subgroups.

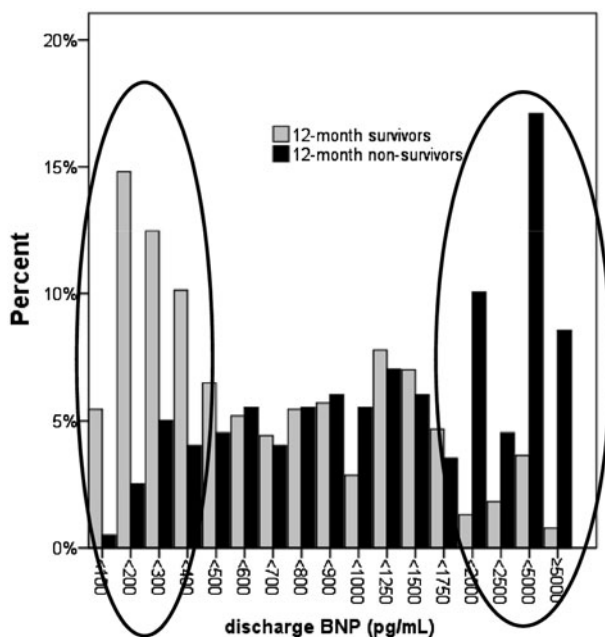


Figure 1. Distribution of death and survival according to BNP categories. Approximately below 400 pg/mL discharge BNP, there is a clear imbalance favouring survival; and above 2000 pg/mL, there is a strong imbalance favouring mortality.

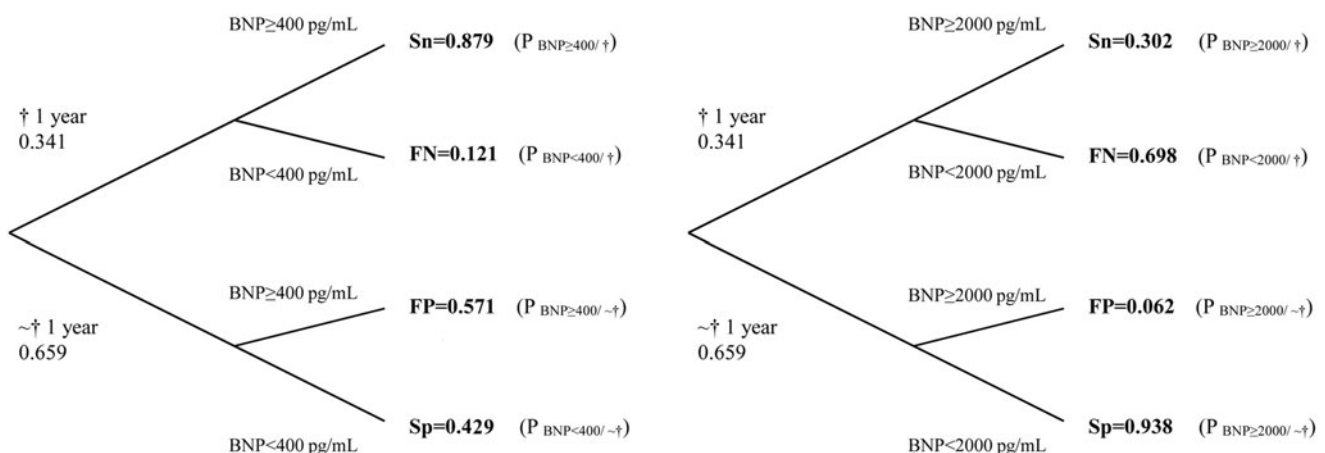


Figure 2. Survival probability trees when BNP cut offs are set at 400 and 2000 pg/mL. †: death; FN: false negative; FP: false positive; P: probability; Sn: sensitivity; Sp: specificity.

Discussion

Acute HF patients surviving the first year post discharge were substantially different depending on neuro-humoral

Table 1. Characteristics of the 385 patients surviving the first 12 months post discharge and comparison between those with low and not-low BNP (cut-off: 400 pg/mL) and of the 199 patients not surviving the first 12 months post discharge and comparison between those with high and not-high BNP (cut-off: 2000 pg/mL).

Characteristics	385 patients surviving follow-up	BNP <400pg/mL (n = 165)	BNP ≥400pg/mL (n = 220)	p Value	199 patients not surviving follow-up	BNP <2000 pg/mL (n = 139)	BNP ≥2000 pg/mL (n = 60)	p Value
Demographic data and comorbidities								
Male sex, n (%)	172 (44.7)	61 (37.0)	111 (50.5)	0.008	92 (46.2)	65 (46.8)	27 (45.0)	0.82
Age, mean (SD)	74 (12)	73 (13)	76 (12)	0.02	79 (11)	80 (11)	78 (11)	0.27
Arterial hypertension, n (%)	296 (76.9)	130 (78.8)	166 (75.4)	0.19	138 (69.3)	95 (68.3)	43 (71.7)	0.65
Diabetes mellitus, n (%)	71 (43.0)	71 (43.0)	96 (43.6)	0.90	82 (41.2)	57 (41.0)	25 (41.7)	0.93
Atrial fibrillation, n (%)	165 (42.9)	65 (39.4)	100 (45.5)	0.23	97 (48.7)	73 (52.5)	24 (40.0)	0.13
Ischaemic aetiology, n (%)	164 (42.6)	62 (37.6)	102 (46.4)	0.08	76 (38.2)	52 (37.4)	24 (40.0)	0.73
Left ventricular systolic dysfunction, n (%)	235 (61.0)	82 (49.7)	153 (65.9)	<0.001	119 (59.8)	73 (52.5)	46 (76.7)	<0.001
Admission parameters								
NYHA I (vs II/III)	235 (61.0)	102 (61.8)	133 (60.4)	0.71	119 (59.8)	82 (59.0)	37 (61.7)	0.77
Acute pulmonary oedema, n (%)	75 (19.5)	38 (23.0)	37 (16.8)	0.13	18 (9.0)	14 (10.1)	4 (6.7)	0.59
BNP (pg/mL), mean (SD)	1768.6 (1425.1)	1088.1 (966.8)	2282.2 (1500.1)	<0.001	3091.2 (2872.1)	2059.6 (1474.6)	5481.3 (3778.9)	<0.001
Discharge parameters								
NYHA ≥ III, n (%)	58 (15.1)	17 (10.3)	41 (18.6)	0.02	60 (30.8)	34 (24.8)	26 (44.8)	0.006
Systolic blood pressure (mmHg), mean (SD)	117 (19)	119 (18)	115 (19)	0.02	111 (19)	112 (20)	110 (18)	0.74
Heart rate (bpm), mean (SD)	74 (13)	73 (12)	75 (13)	0.27	74 (13)	74 (14)	76 (12)	0.36
Haemoglobin (g/dL), mean (SD)	12.1 (2.1)	12.4 (2.0)	11.9 (2.1)	0.02	11.7 (1.9)	11.8 (2.0)	11.4 (1.8)	0.24
Sodium (mEq/L), mean (SD)	137 (4)	137 (4)	138 (4)	0.75	137 (4)	137 (4)	137 (4)	0.81
Creatinine (mg/dL), mean (SD)	1.48 (0.72)	1.34 (0.66)	1.57 (0.75)	0.002	1.58 (0.78)	1.47 (0.67)	1.82 (0.96)	0.01
Glomerular filtration rate (mL/min/1.73m ²), mean (SD)	51.4 (22.2)	55.0 (21.4)	48.7 (22.4)	0.005	47.5 (20.7)	50.2 (21.0)	41.4 (18.8)	0.006
C-reactive protein (mg/L), mean (SD)	20.7 (25.1)	19.3 (21.3)	21.7 (27.6)	0.36	24.3 (27.3)	23.8 (26.1)	25.6 (30.0)	0.67
Total cholesterol (mg/dL), mean (SD)	159 (44)	169 (48)	152 (40)	<0.001	149 (42)	154 (43)	140 (38)	0.05
BNP (pg/mL), mean (SD)	794.1 (919.6)	215.9 (95.8)	1227.7 (1017.5)	<0.001	2141.5 (2629.5)	947.7 (535.1)	4907.0 (3376.3)	<0.001
ΔBNP (%), mean (SD)	51.6 (37.1)	70.5 (23.2)	37.4 (39.3)	<0.001	25.0 (69.0)	41.1 (43.4)	-12.4 (97.5)	<0.001
Discharge medication								
ACEi or ARB, n (%)	330 (85.7)	147 (89.1)	183 (83.2)	0.07	129 (64.8)	94 (67.6)	35 (58.3)	0.18
Beta blocker, n (%)	312 (81.0)	119 (72.1)	193 (87.7)	<0.001	137 (68.8)	100 (71.9)	37 (61.7)	0.13

ACEi: angiotensin converting enzyme inhibitors, ARB: Angiotensin receptor blockers; BNP: B-type natriuretic peptide; HF: heart failure; NYHA: New York Heart Association; SD: standard deviation.

Table 2. Characteristics of 189 patients discharged with BNP <400 pg/mL and comparison between 1 year survivors and non-survivors.

Characteristics	Survivors (n = 165)	Non-survivors (n = 24)	p
Demographic data and comorbidities			
Male sex, n (%)	61 (37.0)	6 (25.0)	0.25
Age, mean (SD)	73 (13)	81 (13)	0.003
Arterial hypertension, n (%)	130 (78.8)	17 (70.8)	0.37
Diabetes mellitus, n (%)	71 (43.0)	10 (41.7)	0.90
Atrial fibrillation, n (%)	65 (39.4)	12 (50.0)	0.32
Ischaemic aetiology, n (%)	62 (37.6)	7 (29.2)	0.42
Left ventricular systolic dysfunction, n (%)	82 (49.7)	5 (20.8)	0.008
Admission parameters			
NYHA IV (vs II/III)	102 (61.8)	17 (70.8)	0.43
Acute pulmonary oedema, n (%)	38 (23.0)	3 (12.5)	0.30
BNP (pg/mL), mean (SD)	1088.1 (966.8)	1272.1 (741.5)	0.37
Discharge parameters			
NYHA \geq III, n (%)	17 (10.3)	5 (20.8)	0.17
Systolic blood pressure (mmHg), mean (SD)	119 (18)	117 (19)	0.56
Heart rate (bpm), mean (SD)	73 (12)	71 (12)	0.45
Haemoglobin (g/dL), mean (SD)	12.4 (2.0)	11.8 (2.3)	0.16
Sodium (mEq/L), mean (SD)	137 (4)	137 (4)	0.74
Creatinine (mg/dL), mean (SD)	1.34 (0.66)	1.36 (0.74)	0.93
Glomerular filtration rate (mL/min/1.73m ²), mean (SD)	55.0 (21.4)	53.4 (21.4)	0.72
C-reactive protein (mg/L), mean (SD)	19.3 (21.3)	24.5 (31.0)	0.31
Total cholesterol (mg/dL), median (IQR)	169 (48)	166 (45)	0.81
BNP (pg/mL), mean (SD)	215.9 (95.8)	259.7 (87.4)	0.04
Δ BNP (%), mean (SD)	70.5 (23.2)	71.8 (21.4)	0.80
Discharge medication			
ACEi or ARB, n (%)	147 (89.1)	18 (75.0)	0.04
Beta blocker, n (%)	119 (72.1)	16 (66.7)	0.55

ACEi: angiotensin converting enzyme inhibitors, ARB: Angiotensin receptor blockers; BNP: B-type natriuretic peptide; HF: heart failure; NYHA: New York Heart Association; SD: standard deviation.

Table 3. Characteristics of 84 patients discharged with BNP \geq 2000 pg/mL and comparison between 1 year survivors and non-survivors.

Characteristics	Survivors (n = 24)	Non-survivors (n = 60)	p
Demographic data and comorbidities			
Male sex, n (%)	11 (45.8)	27 (45.0)	0.94
Age, mean (SD)	78 (12)	78 (11)	0.88
Arterial hypertension, n (%)	15 (62.5)	43 (71.7)	0.29
Diabetes mellitus, n (%)	12 (50.0)	25 (41.7)	0.49
Atrial fibrillation, n (%)	9 (37.5)	24 (40.0)	0.79
Ischaemic aetiology, n (%)	9 (37.5)	24 (40.0)	0.79
Left ventricular systolic dysfunction, n (%)	22 (91.7)	46 (76.7)	0.27
Admission parameters			
NYHA IV (vs II/III)	13 (54.2)	37 (61.7)	0.53
Acute pulmonary oedema, n (%)	3 (12.5)	4 (6.7)	0.40
BNP (pg/mL), mean (SD)	4426.6 (2682.1)	5481.3 (3778.9)	0.17
Discharge parameters			
NYHA \geq III, n (%)	5 (20.8)	26 (43.3)	0.04
Systolic blood pressure (mmHg), mean (SD)	108 (15)	110 (18)	0.65
Heart rate (bpm), mean (SD)	76 (12)	76 (12)	0.97
Haemoglobin (g/dL), mean (SD)	11.4 (1.3)	11.4 (1.8)	0.87
Sodium (mEq/L), mean (SD)	137 (4)	137 (4)	0.69
Creatinine (mg/dL), mean (SD)	1.84 (0.84)	1.82 (0.96)	0.92
Glomerular filtration rate (mL/min/1.73m ²), mean (SD)	40.4 (19.8)	41.4 (18.8)	0.84
C-reactive protein (mg/L), mean (SD)	22.5 (21.7)	25.6 (30.0)	0.65
Total cholesterol (mg/dL), mean (SD)	132 (23)	140 (38)	0.25
BNP (pg/mL), mean (SD)	3477.3 (1615.1)	4907.0 (3376.3)	0.01
Δ BNP (%), mean (SD)	15.8 (30.6)	-12.4 (97.5)	0.19
Discharge medication			
ACEi or ARB, n (%)	21 (87.5)	35 (58.3)	0.01
Beta blocker, n (%)	21 (87.5)	37 (61.7)	0.04

ACEi: angiotensin converting enzyme inhibitors, ARB: Angiotensin receptor blockers; BNP: B-type natriuretic peptide; HF: heart failure; NYHA: New York Heart Association; SD: standard deviation.

activation. Non-survivors were very homogeneous irrespective of discharge BNP. Our results reinforce the importance of natriuretic peptides and their association with outcome more than other proposed variables. As expected, non-survivors

had significantly higher BNP than survivors. However, among survivors, patients with higher natriuretic peptide activation differed substantially from those with less activation without outcome differences. This observation is in line with the

hypothesis that the classically suggested association of many variables with outcome may reflect their association/interaction with the natriuretic peptide system. This hypothesis is further supported by the fact that, among non-survivors, there was a somehow unexpected homogeneity in variables other than the natriuretic peptide system activation.

An unanswered question is the paradoxical association with worse morbidity and mortality along with the activation of a counter-regulatory, “friendly” system like the natriuretic peptide system. Natriuretic peptides are known to play an important role in the regulation of electrolytes and water balance as well as to the regulation and preservation of cardiac hemodynamic and performance (Levin *et al.* 1998, Kjaer and Hesse 2001, Daniels and Maisel 2007, Calvieri *et al.* 2012). HF is a condition that presents with natriuretic peptide system activation early in its course and it is increasingly recognised as a state of relative deficiency or response attenuation to natriuretic peptides (Chen 2007). Somewhere in HF progression, natriuretic peptides may ‘lose’ their effect. Response attenuation has multiple potential contributions: increased natriuretic peptides degradation resulting from clearance receptors or neutral endopeptidase upregulation (Andreassi *et al.* 2001, Knecht *et al.* 2002); down-regulation of the natriuretic peptide receptor A (Tsutamoto *et al.* 1993, Bryan *et al.* 2007); second messenger – cGMP – response attenuation (Lourenco *et al.* 2009), alternate processing after secretion and degradation into a multitude of less active forms (Hawkridge *et al.* 2005, Liang *et al.* 2007, Martinez-Rumayor *et al.* 2008). Dipeptidyl-peptidase IV cleaves the functional and active BNP1-32 into the less active BNP3-32 form and has gained increasing attention has part of this alternate processing and inactivation of natriuretic peptides in HF (Brandt *et al.* 2006, Lourenco *et al.* 2013).

Figure 1, that represents the survival and death distributions according to BNP categories, shows that somewhere below 400 pg/mL there is a clear imbalance favouring survival and that somewhere above 2000 pg/mL there is also a clear imbalance, this time favouring mortality. These cut offs for survival and death prediction were supported by the ROC curve. As it is shown in the survival probability trees according to these discharge BNP cut offs: the probability of not-dying at 1-year once the discharge BNP was <400 pg/mL was of 87.3%, and the probability of dying once the patient had a discharge BNP \geq 2000 pg/mL was of 71.6%.

One important key to halt HF progression would be to better understand the natriuretic peptides resistance phenomenon. Such resistance or relative natriuretic peptides insufficiency does not appear to be universal in HF since it is recognised that some patients have good outcome despite elevated natriuretic peptide levels. These patients probably represent a group in which natriuretic peptides increase and are still able to perform their beneficial actions. On the other hand, there is a group of patients in which natriuretic peptides response is “blocked” or simply inappropriately not activated and, in this particular group, even low BNP levels associate with ominous outcome.

In the second part of our study we intended to characterise these particular HF patient subgroups (patients discharged with low or very high BNP) in order to better

understand the natriuretic peptide system attenuation phenomenon. Our results sustain the hypothesis that in a subgroup of patients in which the natriuretic peptide system is appropriately activated there is some kind of “resistance” to inactivation and they retain their beneficial actions.

HF patients with high BNP that survived the first year post discharge for an acute HF episode were more often in lower NYHA classes (\leq II). Among patients with BNP \geq 2000 pg/mL, those with better outcome in a multivariate analysis were patients in less symptomatic NYHA classes (\leq II), with a 60% decrease in the risk of death at 1 year. This suggests that natriuretic peptides maintained their “functionality” and the ability to sustain their diuretic and natriuretic actions keeping HF patients more euvoletic and less symptomatic. In this subgroup of patients, the use of evidence-based therapy also portended a clear survival benefit: those discharged under beta blocker and ACEi or ARB with a 50 and 56% decrease in the 1-year death risk, respectively. Importantly, in these patients with elevated discharge BNP, 1-year survivors and non-survivors were similar concerning age, major comorbidities, systolic blood pressure and heart rate, and also similar concerning renal impairment. This ultimately means that those patients had no objective reason not to have been discharged on evidence-based therapy; the gap between guidelines and the daily practice is recognised and still an important issue to address in order to improve HF prognosis (de Groote *et al.* 2007). Higher BNP independently predicted death in this subgroup of high BNP patients - 10% increase in the 1 year death risk per 1000 pg/L increase.

In the subgroup of patients that died despite a low discharge BNP, age was an independent mortality predictor – per each 1-year increase in age there was a 5% increased 1-year death risk. The 24 patients that died with a BNP <400 pg/mL corresponded to a subgroup of HF patients in which the natriuretic peptide system appears not to have been activated despite need: they had low BNP despite older age, known to be associated with higher BNP levels (Daniels and Maisel 2007). Besides older, non-survivors were also more often women (trend) with preserved ejection fraction; however, none of these latter variables was independently associated with mortality. Effectively, HF patients with reduced and preserved ejection fraction have already been reported to portend a similarly ominous prognosis (Abebe *et al.* 2016) and women and men have an also comparable gloomy outcome (Fonarow *et al.* 2009). Higher BNP still independently predicted death in this subgroup of low BNP patients, reinforcing the already known prognostic impact of BNP.

It is interesting to note that, despite the association of higher discharge BNP with worse prognosis even in extremes of natriuretic peptide activation at discharge; BNP changes during hospitalisation did not, as expected (Di Somma *et al.* 2010), predict outcome; probably, these discharge BNP extremes – low and high – are already a mirror of response and non-response, respectively.

Prognostic modifying therapy appeared to have differential relevance depending on BNP, with utmost importance the higher the BNP. This is a curious, still not that surprising finding. Higher activation of a counter-regulatory system as

natriuretic peptides may simply reflect an also higher activation of regulatory, vasoconstrictor and anti-natriuretic mechanisms and therefore a more favourable field for prognostic-modifying drugs to show their beneficial effects. Future studies should address mechanisms of natriuretic peptide system relative insufficiency: whether non-activation when needed or inactivation and loss of effect.

The single centre nature of the study poses generalisability concerns. Despite the prospective recruitment of the patients, this specific analysis was retrospective with all its inherent setbacks. Another limitation is the short sample size, particularly in the second part of the study in which we only included the subgroups of patients with low or high discharge BNP. Also important to strain is the fact that the data presented only support associations and not causality or pathophysiological links.

Conclusions

Different prognostic predictors may play a role in different BNP levels. We reinforce the prognostic importance of BNP even in subgroups of very low or very high BNP; and suggest that risk stratification in HF would probably be more accurate if made on top of BNP knowledge. The use of prognostic-modifying therapy appeared to be of utmost importance the higher the BNP.

Disclosure statement

The authors report no conflicts of interest

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