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ORIGINAL ARTICLE

Prognostic value of brain natriuretic peptide in ST-elevation myocardial infarction patients: A Portuguese registry

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KEYWORDS
Brain natriuretic peptide;
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Abstract
Introduction: Brain natriuretic peptide (BNP) is a highly sensitive and specific biomarker for the extent of myocardial infarction that is strongly related to short- and long-term prognosis in patients with acute coronary syndromes.
Objective: To assess the prognostic value of BNP levels in a Portuguese cohort of ST-elevation myocardial infarction (STEMI) patients.
Methods: We performed a retrospective analysis of patients admitted with STEMI included in the Portuguese Registry of Acute Coronary Syndromes (ProACS) between 2010 and 2019. Patients were divided into three groups according to BNP level (<100 pg/ml, 100-399 pg/ml and ≥400 pg/ml) and compared. Independent predictors of a composite of all-cause mortality and rehospitalization for cardiovascular causes were assessed by multivariate logistic regression. For sample homogenization, propensity score matching and pairwise matching with a tolerance level of 0.005 were performed.
Results: A total of 1650 patients were included, of whom 21.5% presented high BNP levels (≥400 pg/ml). These were older and had more comorbidities, lower admission systolic blood pressure and hemoglobin, higher heart rate, Killip class and creatinine, worse left ventricular systolic function and severe coronary anatomy. Higher BNP was associated with more in-hospital complications, in-hospital mortality and adverse outcomes at one year.

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Conclusion: BNP levels during the index hospitalization were a powerful prognostic biomarker for all-cause mortality and major adverse cardiac events in patients admitted with STEMI to Portuguese hospitals.

PALAVRAS-CHAVE
BNP;
SCA com supradesnivelamento ST;
Mortalidade;
Prognóstico;
Enfarte do miocárdio

Valor prognóstico do BNP no enfarte agudo do miocárdio com supradesnivelamento de ST: um registo português

Resumo
Introdução: O peptídeo natriurético cerebral (BNP) é um biomarcador de elevada sensibilidade e especificidade relativamente à extensão do enfarte do miocárdio, estando fortemente relacionado com o prognóstico a curto e longo prazo em doentes com síndrome coronária aguda.
Objetivo: Avaliar o valor diagnóstico e prognóstico dos níveis de BNP numa coorte portuguesa de doentes com enfarte do miocárdio com elevação de ST (STEMI).
Métodos: Realizámos uma análise retrospectiva de pacientes admitidos com STEMI incluídos no Registo Português de Síndromes Coronarianas Agudas (ProACS) entre 2010 e 2019. Os pacientes foram divididos em três grupos de acordo com o nível BNP (<100 pg/ml, 100-399 pg/ml e ≥400 pg/ml) e comparados. Preditores independentes de um composto de mortalidade por todas as causas e re-hospitalização para causas cardiovasculares foram avaliados por regressão logística multivariada. Para a homogeneização da amostra, foi realizada uma correspondência de propensão e uma correspondência em pares com um nível de tolerância de 0,005.
Resultados: Foram incluídos 1650 doentes; 21,5% apresentaram níveis elevados de BNP (≥400 pg/ml). Estes doentes eram mais velhos; apresentavam mais comorbilidades; menor pressão arterial sistólica e hemoglobina à admissão; frequência cardíaca, classe Killip e creatinina mais elevados; pior função sistólica ventricular esquerda e anatomia coronária mais grave. A elevação de BNP associou-se a maior taxa de complicações intra-hospitalares, mortalidade intra-hospitalar e *outcomes* adversos a ano.
Conclusão: Os níveis de BNP durante a hospitalização index foram um poderoso biomarcador prognóstico para mortalidade por todas as causas e eventos cardíacos adversos *major* (MACE) em doentes com STEMI.

Introduction

ST-elevation myocardial infarction (STEMI) remains an important cause of death, especially in developed countries, despite significant advances in its prevention and management.[1] Primary percutaneous coronary intervention (PCI) has been shown to reduce death, reinfarction and stroke in STEMI patients.[2] Accurate risk stratification plays an important role in appropriate therapeutic decision-making for these patients. The Global Registry of Acute Coronary Events (GRACE) and Thrombolysis in Myocardial Infarction (TIMI) risk scores are helpful in the identification of high-risk patients, however they require complex calculation methods that are not easily applicable before hospital admission or in the emergency department, and are therefore not widely used in clinical practice.

Brain natriuretic peptide (BNP) measurement is a simple tool that has been proposed to assist in risk stratification. BNP is secreted in response to cardiac hemodynamic stress mediated by volume and pressure overload.[1] The inflammatory response that is triggered leads to myocyte necrosis and apoptosis, collagen deposition, fibrosis, hypertrophy and dilatation, resulting in left ventricular (LV) systolic dysfunction.[1,3] Exogenous BNP infusion has proved to have a cardioprotective effect, preventing unfavorable LV remodeling through generation of 3′,5′-cyclic guanosine monophosphate and nitric oxide synthase, leading to reduced myocardial oxygen consumption, enhancement of myocardial relaxation, retardation of adrenergic activation, induction of vascular regeneration, and inhibition of cardiac fibroblast collagen synthesis and proliferation.[3,4]

BNP is a highly sensitive and specific indicator of the extent of myocardial infarction (MI) and remodeling that is strongly related to short-term (LV systolic dysfunction, ventricular arrhythmias, LV aneurysm) and long-term clinical outcomes, including heart failure (HF) and mortality.[2,5–8] BNP's prognostic value is due to the fact that it is the sum of different risk markers. Detection of LV dysfunction during the early phase of MI through elevated plasma BNP levels should prompt close clinical follow-up and imaging studies to

guide the therapeutic strategy needed in order to improve the long-term clinical outcome.[5] After MI, BNP levels rise rapidly, reaching a peak after 16-18 hours, and usually fall over the next 2-3 days in a monophasic pattern. However, a biphasic pattern, with BNP levels rising once more within five days of MI, is observed in about half of patients and predicts worsening cardiac function and clinical HF.[9] With the advent of primary PCI, the importance of remodeling has decreased significantly, however a significant proportion of STEMI patients still suffer impaired LV function, and rates of mortality and progression to HF remain high.[3]

The current guidelines recommend the use of BNP as a biomarker to provide additional prognostic information in patients with non-STEMI; however, no European or universal risk model has incorporated it for use in STEMI patients.[1] To the best of our knowledge, there has been a single Dutch study evaluating a multimarker approach that includes BNP to improve mortality prognostication in STEMI patients.[10] There is no evidence on this issue in the Portuguese population, despite its significant impact on clinical practice. The present study aims to assess the added prognostic value of BNP levels in a Portuguese cohort of STEMI patients regarding all-cause mortality and major adverse cardiac events (MACE).

Methods

The Portuguese Registry of Acute Coronary Syndromes (ProACS) is a national multicenter voluntary registry of patients admitted with acute coronary syndromes. Baseline demographic data, cardiovascular risk factors and other relevant personal background, clinical, laboratory, echocardiographic and angiographic data, and medications of all patients are recorded. The present analysis is a retrospective cohort study, but all data were collected prospectively during the index hospitalization. Fifteen Portuguese centers contributed to this study (four in the North region, four in the Center region, three in the Greater Lisbon area and four in the Lower Alentejo). Primary PCI was performed using standard techniques according to the institution's protocol and European guidelines for the management of patients with STEMI. The use of antiplatelet agents, beta-adrenergic blocking agents, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), statins or inotropic drug support was left at the clinician's discretion according to clinical protocols.

A total of 8036 consecutive STEMI patients were enrolled in this registry between October 2010 and January 2019. Of these, 2695 patients were excluded due to lack of information related to LV systolic function and coronary artery disease characterization, 22 due to lack of follow-up data and 3669 due to lack of BNP quantification. The remaining patients were stratified according to BNP levels: <100 pg/ml, 100-399 pg/ml and $\geq$400 pg/ml. These cut-off values were established in accordance with the upper limit of normal values in an acute setting set out in the European guidelines on heart failure.

The population was thus composed of 1650 subjects, of whom 1287 (78%) were followed for at least one year after the index hospitalization. Follow-up data were obtained by reviewing medical records or through telephone interviews with patients. The clinical outcomes analyzed were in-hospital adverse events and mortality and a composite of all-cause mortality and rehospitalization for cardiovascular causes at one year after discharge.

Statistical analysis

Continuous variables were expressed as means $\pm$ standard deviation and categorical variables as percentages. Categorical data were analyzed by the chi-square test and continuous data by the Kruskal-Wallis test. Two-sided p-values <0.05 were considered statistically significant. Logistic regression models were used to assess independent predictors of the clinical outcomes. Propensity score matching and pairwise matching with a tolerance level of 0.005 were performed. The patients were paired taking in account the following characteristics: age, body mass index (BMI), gender, LV ejection fraction (LVEF), previous myocardial infarction, chronic kidney disease (CKD), previous HF, creatinine level, atrial fibrillation at admission, Killip class and admission blood pressure (BP). The final matched groups (n=351 patients, 21.3% of the total population) were as follows: BNP <100 pg/ml (n=116, 7.0%); 100-399 pg/ml (n=117, 7.1%) and BNP $\geq$400 pg/ml (n=118, 7.2%).

Ethical considerations

Patient identities were anonymized at all times, and the registry was authorized by the national authorities and registered on the clinicaltrials.gov site (NCT01642329). All ethical requirements in the Helsinki Declaration of 1975 were met for studies not involving human and/or animal experimentation. Written informed consent for the introduction of patient data into the registry has been available since 2010 and was applied after approval by the ethics committee of each center.

Results

Clinical and demographic characterization

The population was composed of 1650 patients, mean age 64 $\pm$ 13 years, mostly male (75.4%). There was a high prevalence of cardiovascular risk factors, particularly hypertension (61.7%), dyslipidemia (50.9%) and smoking (36.0%). BNP levels were <100 pg/ml in 39.0% (n=643), 100-399 pg/ml in 39.5% (n=652) and $\geq$400 pg/ml in 21.5% (n=355). Baseline characteristics differed substantially between groups (Table 1). Patients with higher BNP levels were significantly older and had more classic cardiovascular risk factors, except for smoking status and family history of premature cardiovascular disease. BMI did not differ significantly between groups. A previous history of cardiovascular disease (coronary, cerebrovascular and peripheral arterial disease), CKD, chronic obstructive pulmonary disease (COPD) and cancer was more common in patients with higher BNP, and before hospitalization, they were more medicated for cardiovascular risk factors and disease.

Table 1 Baseline characteristics of patients admitted with ST-elevation myocardial infarction according to brain natriuretic peptide levels.

	All (n=1650)	BNP <100 pg/ml (n=643)	BNP 100-399 pg/ml (n=652)	BNP ≥400 pg/ml (n=355)	P
Demographic					
Age, years	64 ± 13 (1649/1650)	58 ± 11 (643/643)	66 ± 13 (651/652)	72 ± 12 (355/355)	<0.001
Male, %	75.4 (1244/1650)	85.2 (548/643)	71.6 (467/652)	64.5 (229/355)	<0.001
BMI, kg/m^2	27.2 ± 4.4 (1487/1650)	27.5 ± 4.4 (610/643)	27.1 ± 4.4 (572/652)	26.8 ± 4.4 (305/355)	0.039
CV risk factors					
Smoking, %	36.0 (592/1643)	49.1 (314/639)	31.6 (206/651)	20.4 (72/355)	<0.001
Hypertension, %	61.7 (997/1615)	54.7 (343/627)	63.4 (405/639)	71.3 (249/349)	<0.001
Diabetes, %	25.6 (411/1603)	21.4 (134/625)	25.8 (162/629)	33.0 (115/349)	<0.001
Dyslipidemia, %	50.9 (787/1547)	56.1 (342/610)	46.5 (282/607)	49.4 (163/330)	0.003
Family history of CAD, %	9.3 (140/1504)	12.9 (80/618)	8.4 (49/583)	3.6 (11/303)	<0.001
Previous history					
Angina, %	19.6 (322/1642)	19.4 (124/640)	19.4 (126/649)	20.4 (72/353)	0.915
MI, %	12.1 (199/1642)	13.9 (89/640)	9.9 (64/648)	13.0 (46/354)	0.073
PCI, %	10.5 (173/1647)	12.6 (81/642)	8.6 (56/651)	10.2 (36/354)	0.061
CABG, %	1.3 (21/1648)	0.9 (6/642)	0.8 (5/651)	2.8 (10/355)	0.013
HF, %	2.2 (36/1647)	0.5 (3/642)	1.8 (12/651)	5.9 (21/354)	<0.001
Stroke/TIA, %	5.6 (92/1648)	3.4 (22/642)	5.2 (34/651)	10.1 (36/355)	<0.001
CKD, %	3.1 (51/1631)	1.3 (8/638)	2.5 (16/647)	7.8 (27/346)	<0.001
PAD, %	4.2 (68/1634)	2.0 (13/637)	4.6 (30/649)	7.2 (25/348)	<0.001
COPD, %	4.2 (69/1639)	2.8 (18/637)	4.5 (29/649)	6.2 (22/353)	0.035
Cancer, %	3.9 (64/1638)	2.5 (16/639)	3.4 (22/649)	7.4 (26/350)	<0.001

BMI: body mass index; BNP: brain natriuretic peptide; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CCB: calcium channel blocker; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CV: cardiovascular; HF: heart failure; MI: myocardial infarction; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention; TIA: transient ischemic attack.

Clinical, laboratory, echocardiographic and angiographic characteristics

Anterior STEMI was the most frequent location of STEMI for all groups. Patients with higher levels of BNP presented with lower systolic BP and higher heart rate and Killip class. They also presented the highest creatinine levels and the lowest hemoglobin levels at admission and during hospitalization. Mean LVEF was lower in patients with higher BNP, and a higher proportion of these patients had severely compromised LVEF (Table 2).

Table 3 summarizes the coronary anatomy in the BNP stratification groups. Multivessel disease was more common in patients with higher BNP. In this group, a higher proportion of patients were proposed for medical therapy. In the patients proposed for revascularization, there was a trend towards surgical revascularization or a hybrid approach, although this was not statistically significant. These patients also more frequently required advanced therapeutic devices and ventilatory support.

In-hospital outcomes and medication

Table 4 shows that in-hospital complications, especially HF (mean 18.9% vs. 45.4%, p<0.001), were more frequent in patients with higher BNP levels. Atrial fibrillation (AF) and cardiogenic shock were the second and third most observed complications. Sustained ventricular tachycardia was also frequent in patients with higher BNP. In-hospital mortality was seven times greater in the higher BNP group than in the lower BNP group (1.2% vs. 8.5%, p<0.001).

Although HF was the most frequent complication in patients with higher BNP levels, during hospitalization they were less medicated with standard HF therapies (except aldosterone antagonists) but more often received diuretic therapy. As AF was the most prevalent condition in this group, a higher percentage received anticoagulant and antiarrhythmic drugs. Medication at discharge also followed these tendencies (Table 5).

One-year outcomes

Higher BNP was associated with higher rates of one-year mortality and rehospitalization due to cardiovascular disease (p=0.001) (Figure 1). One-year mortality was 4.6% and the rate of rehospitalization for cardiovascular causes was 9.0%. The composite endpoint of one-year mortality and cardiovascular rehospitalization occurred in 12%. After propensity score matching for sample homogenization, the

Table 2 Clinical presentation and laboratory and echocardiographic findings.

	All (n=1650)	BNP <100 pg/ml (n=643)	BNP 100-399 pg/ml (n=652)	BNP ≥400 pg/ml (n=355)	p
STEMI location					
Anterior, %	51.1 (843/1650)	46.2 (297/643)	49.5 (323/652)	62.8 (223/355)	<0.001
Inferior, %	48.2 (796/1650)	53.5 (344/643)	50.0 (326/652)	35.5 (126/355)	<0.001
New-onset LBBB, %	0.7 (11/1650)	0.3 (2/643)	0.5 (3/652)	1.7 (6/355)	0.029
Vital signs					
HR, bpm	78 ± 20 (1650/1650)	76 ± 17 (643/643)	77 ± 19 (652/652)	84 ± 26 (355/355)	<0.001
SBP, mmHg	136 ± 30 (1649/1650)	136 ± 30 (643/643)	140 ± 31 (651/652)	131 ± 28 (355/355)	<0.001
DBP, mmHg	80 ± 18 (1650/1650)	81 ± 19 (643/643)	81 ± 18 (652/652)	77 ± 18 (355/355)	0.007
Killip class >I, %	12.1 (1648/1650)	5.6 (642/643)	9.5 (651/652)	28.5 (355/355)	<0.001
Laboratory findings					
Cr (admission), mg/dl	1 ± 0.5 (1643/1650)	0.9 ± 0.4 (641/643)	1 ± 0.4 (649/652)	1.2 ± 0.7 (353/355)	<0.001
Cr (maximum), mg/dl	1.2 ± 0.8 (1354/1650)	1 ± 0.5 (572/643)	1.2 ± 0.9 (499/652)	1.5 ± 1 (283/355)	<0.001
Hb (admission), g/dl	14.1 ± 1.8 (1639/1650)	14.5 ± 1.5 (639/643)	14.1 ± 1.8 (648/652)	13.5 ± 2 (352/355)	<0.001
Hb (minimum), g/dl	12.8 ± 2 (1357/1650)	13.5 ± 1.6 (584/643)	12.6 ± 1.9 (501/652)	11.7 ± 2.1 (272/355)	<0.001
LVEF					
Mean, %	53 ± 13 (1650/1650)	58 ± 11 (643/643)	53 ± 12 (652/652)	44 ± 13 (353/355)	<0.001
>50%, %	63.2 (1043/1650)	81.2 (522/643)	61.5 (401/652)	33.8 (120/355)	<0.001
40-49%, %	21.2 (350/1650)	13.1 (84/643)	23.9 (156/652)	31.0 (110/355)	<0.001
30-39%, %	11.8 (195/1650)	5.1 (33/643)	12.4 (81/652)	22.8 (81/355)	<0.001
<30%, %	3.8 (62/1650)	0.6 (4/643)	2.1 (14/652)	12.4 (44/355)	<0.001

BNP: brain natriuretic peptide; bpm: beats per min; Cr: creatinine; DBP: diastolic blood pressure; Hb: hemoglobin; HR: heart rate; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; TG: triglycerides.

one-year endpoint of total mortality and cardiovascular rehospitalization occurred in 20.3%.

Factors predicting the endpoint, assessed through Cox multivariate regression (Table 6), were previous HF, multivessel disease, LVEF <30% and the use of nitrates and aldosterone antagonists. The use of aspirin was a protective factor.

Discussion

We observed higher BNP levels in elderly patients and in those with classic cardiovascular risk factors and previous history of cardiovascular disease, CKD, COPD and cancer. Patients with higher BNP levels had lower systolic BP at admission, higher heart rate and Killip class, and higher creatinine and lower hemoglobin levels, which are known predictors of worse outcome. Their coronary anatomy was more complex, with multivessel disease, left main and left anterior descending lesions, also features associated with a worse prognosis. A higher proportion of these patients were proposed for medical therapy, probably reflecting significant surgical risk and frailty. In patients referred for revascularization, there was a trend, albeit not statistically significant, toward coronary artery bypass grafting or a hybrid approach, probably reflecting more severe coronary disease. These features were also in accordance with the more frequent need for advanced therapeutic devices and ventilatory support in this group.

BNP is a polypeptide secreted by the ventricles in response to excessive stretching of cardiomyocytes, and increased BNP may represent a greater extent of myocardial ischemic territory, which would explain the positive correlation between elevated BNP and MACE in MI patients.[5] In our study, patients with high BNP levels had lower LVEF. Previous studies have shown an association between elevated BNP level and multivessel disease, independently of LV systolic dysfunction and congestive HF.[4]

Higher BNP is associated with short-term complications, including HF, ventricular arrhythmias and LV aneurysm formation, which is in accordance with our results, although we did not specifically assess the presence of LV aneurysms.[11] HF was the most frequent in-hospital complication, followed

Table 3 Characterization of coronary anatomy and planned revascularization and other therapeutic interventions.

	All (n=1650)	BNP <100 pg/ml (n=643)	BNP 100-399 pg/ml (n=652)	BNP ≥400 pg/ml (n=355)	p
No. of diseased vessels					
0	1.0 (16/1650)	1.2 (8/643)	0.8 (6/652)	0.8 (3/355)	0.657
1	56.7 (936/1650)	63.9 (411/643)	54.4 (355/652)	47.9 (170/355)	<0.001
2	28.5 (470/1650)	25.0 (161/643)	30.5 (199/652)	31.0 (110/355)	0.046
3	13.8 (228/1650)	9.8 (63/643)	14.3 (93/652)	20.3 (72/355)	<0.001
Multivessel (2-3) disease	42.3 (698/1650)	34.8 (224/643)	44.8 (292/652)	51.3 (182/355)	<0.001
Planned revascularization					
None (%)	4.3 (71/1650)	2.8 (18/643)	3.5 (23/652)	8.5 (30/355)	<0.001
PCI (%)	93.0 (1535/1650)	95.8 (616/643)	93.7 (611/652)	86.8 (308/355)	<0.001
CABG (%)	1.2 (20/1650)	0.3 (2/643)	1.5 (10/652)	2.3 (8/355)	0.017
PCI+CABG (%)	1.5 (24/1650)	1.1 (7/643)	1.2 (8/652)	2.5 (9/355)	0.155
Other interventions					
Swan-Ganz (%)	1.5 (24/1650)	0.0 (0/643)	0.6 (4/652)	5.6 (20/355)	<0.001
IABP (%)	0.5 (9/1650)	0.3 (2/643)	0.8 (5/652)	0.6 (2/355)	0.556
IMV	4.0 (66/1650)	3.7 (24/643)	3.2 (21/652)	5.9 (21/355)	0.103
NIMV	2.1 (34/1650)	0.2 (1/643)	1.4 (9/652)	6.8 (24/355)	<0.001
Temporary PM	3.8 (63/1650)	2.2 (14/643)	3.8 (25/652)	6.8 (24/355)	0.001
Ventricular assistance	0.0 (0/1650)	0.0 (0/643)	0.0 (0/652)	0.0 (0/355)	–

BNP: brain natriuretic peptide; CABG: coronary artery bypass grafting; IABP: intra-aortic balloon pump; IMV: invasive mechanical ventilation; LAD: left anterior descending; LCX: left circumflex; LM: left main; NIMV: non-invasive mechanical ventilation; PCI: percutaneous coronary intervention; PM: pacemaker.

Table 4 Adverse outcomes during hospitalization.

	All (n=1650)	BNP <100 pg/ml (n=643)	BNP 100-399 pg/ml (n=652)	BNP ≥400 pg/ml (n=355)	p
Reinfarction, %	0.7	0.5	0.6	1.1	0.447
HF, %	18.9	6.5	16.7	45.4	<0.001
Shock, %	6.9	3.3	5.1	16.9	<0.001
AF, %	7.5	3.0	6.4	17.5	<0.001
Mechanical complication, %	0.6	0.2	0.3	2.0	0.001
AV block, %	5.0	3.3	5.1	7.9	0.006
SVT, %	3.5	1.6	3.7	6.8	<0.001
Cardiac arrest, %	7.9	9.8	6.3	7.3	0.058
Stroke, %	0.8	0.5	0.6	2.0	0.032
Major bleeding, %	2.8	1.6	2.6	5.4	0.002
Blood transfusion, %	1.9	0.3	1.8	5.1	<0.001
Death, %	3.3	1.2	2.6	8.5	<0.001

AF: atrial fibrillation; AV: atrioventricular; BNP: brain natriuretic peptide; HF: heart failure; SVT: sustained ventricular tachycardia.

by AF and cardiogenic shock. In-hospital mortality was more than seven times higher in the highest than in the lowest BNP group. At discharge, patients with higher BNP were more likely to be prescribed drugs to control cardiovascular risk factors (aspirin and statins) and for AF control and anticoagulation. The rate of neurohormonal therapy was lower in the high BNP group, except for aldosterone antagonists, probably as a result of their in-hospital clinical course requiring greater use of inotropes and levosimendan, which could have limited the use of neurohormonal HF drugs. The 30-day mortality of patients with STEMI treated with PCI ranges between 5.3 and 7.3%, and is higher in patients with HF (16.5%).[12] Although overall mortality in our study was low, it proved that high BNP was associated not only with worse in-hospital outcomes but also with one-year outcomes, which is in line with previous studies.[13] BNP levels probably represent the sum of well-known prognostic markers in coronary artery disease, the presence and extent of LV ischemia and dysfunction, suggesting that BNP therapy-guided interventions might improve mortality after STEMI.[14] Furthermore, in patients with type 2 diabetes and renal dysfunction, independently of glomerular filtration rate, BNP is an important

Table 5 In-hospital and discharge medication.

	All (n=1650)	BNP <100 pg/ml (n=643)	BNP 100-399 pg/ml (n=652)	BNP ≥400 pg/ml (n=355)	p
In-hospital medication, %					
Aspirin	98.8 (1631/1650)	99.4 (639/643)	98.2 (640/652)	99.2 (352/355)	0.100
Clopidogrel	83.9 (1384/1650)	83.4 (536/642)	84.4 (550/652)	83.9 (298/355)	0.887
Ticagrelor	25.4 (321/1264)	27.1 (136/502)	24.2 (121/499)	24.3 (64/263)	0.531
Glycoprotein inhibitor	56.3 (928/1649)	74.5 (479/643)	49.0 (319/651)	36.6 (130/355)	<0.001
UFH	33.0 (544/1646)	20.6 (132/642)	38.9 (253/651)	44.9 (159/354)	<0.001
LMWH	39.0 (643/1647)	19.0 (122/642)	47.9 (312/651)	59.0 (209/354)	<0.001
ACEI/ARB	85.2 (1405/1649)	83.8 (539/643)	89.7 (585/652)	79.4 (281/354)	<0.001
Beta-blocker	76.8 (1268/1650)	80.7 (519/643)	76.2 (497/652)	71.0 (252/355)	0.002
Aldosterone antagonist	14.9 (246/1650)	11.4 (73/643)	14.3 (93/652)	22.5 (80/355)	<0.001
Statin	95.1 (1569/1650)	95.5 (614/643)	95.2 (621/652)	94.1 (334/355)	0.600
VKA	3.0 (49/1650)	1.4 (9/643)	3.4 (22/652)	5.1 (18/355)	0.004
Other OAC	1.7 (19/1650)	0.9 (6/643)	2.3 (7/652)	1.7 (6/355)	0.576
Amiodarone	9.1 (150/1650)	3.7 (24/643)	8.7 (57/652)	19.4 (69/355)	<0.001
Digoxin	1.6 (26/1650)	0.2 (1/643)	29.0 (9/652)	32.7 (16/355)	<0.001
Nitrate	26.7 (441/1649)	21.2 (136/643)	31.4 (189/651)	4.5 (116/355)	<0.001
CCB	3.8 (63/1650)	2.8 (18/643)	4.1 (27/652)	5.1 (18/355)	0.172
Diuretic	445/1647 (27.0)	12.5 (80/642)	25.2 (16/651)	56.8 (201/354)	<0.001
Inotropic support	143/1650 (8.7)	3.3 (21/643)	6.6 (43/652)	22.3 (79/355)	<0.001
Levosimendan	6/1650 (0.4)	0.0 (0/643)	0.0 (0/652)	1.7 (6/355)	<0.001
Discharge medication, %					
Aspirin	96.1 (1502/1563)	97.6 (615/630)	97.1 (600/618)	91.1 (287/315)	<0.001
Clopidogrel	77.3 (1208/1563)	75.9 (478/630)	79.8 (493/618)	75.2 (237/315)	0.161
Ticagrelor	24.0 (289/1205)	28.0 (138/493)	22.9 (109/475)	17.7 (42/237)	0.008
ACEI/ARB	85.0 (1329/1564)	84.2 (531/631)	88.4 (547/619)	79.9 (251/314)	0.002
Beta-blocker	76.8 (1399/1562)	79.5 (501/630)	75.7 (467/617)	73.3 (231/315)	0.075
Aldosterone antagonist	12.7 (198/1562)	7.3 (46/630)	13.5 (83/617)	21.9 (69/315)	<0.001
Statin	95.8 (1499/1565)	97.3 (614/631)	96.1 (595/619)	92.1 (290/315)	<0.001
VKA	3.7 (58/1563)	1.7 (11/631)	3.7 (23/617)	7.6 (24/315)	<0.001
Other OAC	4.4 (45/1563)	1.9 (11/631)	3.6 (12/617)	7.7 (22/315)	<0.001
Amiodarone	3.6 (56/1562)	1.6 (10/630)	3.4 (21/617)	7.9 (25/315)	<0.001
Digoxin	0.8 (12/1562)	0.0 (0/630)	0.8 (5/617)	2.2 (7/315)	0.001
Nitrate	7.9 (124/1562)	8.6 (54/630)	6.2 (38/617)	10.2 (32/315)	0.076
CCB	4.8 (75/1562)	2.4 (15/630)	6.8 (42/617)	5.7 (18/315)	<0.001
Diuretic	21.2 (331/1563)	9.0 (57/630)	20.1 (124/618)	47.6 (150/315)	<0.001

ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BNP: brain natriuretic peptide; CCB: calcium channel blocker; LMWH: low molecular weight heparin; OAC: oral anticoagulation; UFH: unfractionated heparin; VKA: vitamin K antagonist.

Table 6 Influence of brain natriuretic peptide on the primary endpoint, a composite of all-cause mortality and rehospitalization for cardiovascular causes at one year.

Predictor	Beta-coefficient	Statistical significance	p	HR	95% CI
BNP ≥400 vs. BNP <100 pg/ml	0.730	0.400	0.007	2.07	0.95-4.54
Previous HF	1.740	0.437	<0.001	5.69	2.42-13.42
Multivessel disease	0.850	0.326	0.009	0.43	0.23-0.81
LVEF <30%	1.561	0.594	0.009	4.76	1.49-15.25
Discharge medication: nitrates	2.575	0.749	0.001	13.13	3.02-56.98
Discharge medication: aldosterone antagonists	2.180	0.572	<0.001	8.85	2.89-27.14
Discharge medication: aspirin	−1.923	0.391	<0.001	0.15	0.07-0.31

BNP: brain natriuretic peptide; CI: confidence interval; HF: heart failure; HR: hazard ratio; LVEF: left ventricular ejection fraction.

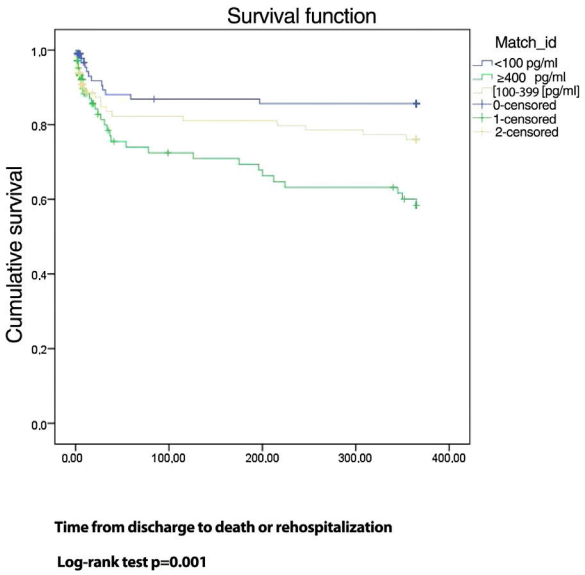

Figure 1 Kaplan-Meier curve for one-year all-cause mortality and rehospitalization for cardiovascular causes.
Time discharge - death/CV rehospitalization.
p value of Log-Rank test 0.001.

predictor of mortality, cardiovascular death, MI, HF, and stroke.[15] In survivors, patients' quality of life after hospital discharge is affected primarily by the development of HF, recurrence of ischemic events, and death. Close monitoring of STEMI patients enables the identification of high-risk patients who might benefit from more regular attention and long-term follow-up.[12] One-year mortality in our study was 4.6% and 9.0% were hospitalized for cardiovascular causes.

The results of our study are supported by the findings of previous studies aiming to identify STEMI patients at high risk of poor clinical outcomes. Accurate, comprehensive and simple risk assessment plays an important role in appropriate therapeutic decision-making for these patients. Higher-intensity treatments may be appropriate in patients with higher risk scores; however, their inappropriate use in low-risk patients may expose them to adverse effects. Although existing risk scores present good predictive value, their use is limited due to their complexity, the need to carry out various calculations, and the effect of procedure-related variables. BNP can be rapidly measured during admission and is increasingly shown to be predictive of short- and long-term outcomes following STEMI, independently of the presence of clinical HF during hospitalization, providing significant prognostic information in addition to that of Killip class and TIMI risk score in STEMI patients.[16–18]

Our study presents some limitations. First, it was a retrospective observational study and thus susceptible to inherent limitations, including selection bias. Since this is a voluntary registry, it does not represent all the cardiology centers in Portugal and, even in the centers that did participate, we cannot guarantee that all STEMI patients are included. Also, STEMI patients suffering out-of-hospital death were probably not included. Second, BNP was collected for clinical reasons and this decision was made at the discretion of the attending physician, thus there was only one measurement, which does not allow an analysis of BNP kinetics, and the timing of the measurements was variable. BNP values may have been determined at admission, reflecting the baseline severity of the population, during hospitalization, or at discharge, reflecting the evolution of STEMI itself and implemented therapies. Thirdly, there were no data regarding adherence to medical treatment after discharge.

Conclusion

Patients with higher BNP levels were significantly older, had more cardiovascular risk factors and comorbidities, more severe clinical presentation and complications, and needed more aggressive treatment. These differences might explain their higher in-hospital and one-year mortality and adverse outcomes. Importantly, BNP levels during the index hospitalization were a powerful prognostic biomarker for one-year all-cause mortality and MACE in patients with STEMI, which may indicate a need for more regular monitoring of these patients at follow-up.

Conflicts of interest

The authors have no conflicts of interest to declare.

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