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Prognosis of Post-Acute Myocardial Infarction Patients with Preserved Left Ventricular Ejection Fraction

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RESUMO

Introdução: A fração de ejeção do ventrículo esquerdo é um dos parâmetros mais usados na estratificação do risco dos doentes após enfarte agudo do miocárdio. Apesar daqueles que evoluem com uma fração de ejeção do ventrículo esquerdo preservada parecerem ter um melhor prognóstico, em oposição àqueles com fração de ejeção do ventrículo esquerdo reduzida, os primeiros têm uma taxa de eventos cardiovasculares significativa. Com este trabalho pretendemos descrever o prognóstico e os fatores de risco deste subgrupo de doentes.

Métodos: Estudamos doentes referenciados para o programa de reabilitação cardíaca após enfarte agudo do miocárdio, entre Janeiro de 2010 e Dezembro de 2012. Estes tinham de ter fração de ejeção do ventrículo esquerdo >=50% à data da alta (medida por ecocardiografia transtorácica) e completado o programa de reabilitação cardíaca. Os dados laboratoriais foram colhidos a partir de medição de análises sanguíneas durante o internamento. O *outcome* composto foi definido como morte de qualquer causa, hospitalização por insuficiência cardíaca, diagnóstico de novo ou agravamento da insuficiência cardíaca no doente seguido em ambulatório.

Resultados: Os 235 doentes estudados tinham uma média de idades de 60±11 anos e 80% eram homens. Durante o seguimento de 3.2±4.1 anos, 31 (13%) sofreram o *outcome* composto (19 diagnósticos de novo de insuficiência cardíaca, 6 hospitalizações e 6 mortes). Os doentes que tiveram um evento eram mais velhos (68 anos vs 59 anos, P = 0.001), e tinham uma maior prevalência de hipertensão (81% vs 62%, P = 0.044) e diabetes (55% vs 28%, P = 0.003). Houve menos enfartes agudos do miocárdio sem supra-ST no grupo de doentes que tiveram um evento (32% vs 41%, P = 0.001). Estes tiveram uma classe *Killip* superior durante o internamento (classe II-IV: 28% vs 4.9%; P < 0.001) e doença coronária arterial mais grave (55% com doença de três vasos vs 30%, P = 0.06). Houve também maior prevalência de doença renal crónica (26% vs 6%, P < 0.001) e anemia (45% vs 18%, P < 0.001) neste subgrupo. Não foram encontradas diferenças significativas nos dados ecocardiográficos entre os dois grupos. Os níveis plasmáticos de péptido natriurético do tipo-B N-terminal durante o internamento foram mais altos nos doentes que eventualmente tiveram um evento (mediana 408 [207-799] ng/mL vs 342 [124-569] ng/mL; P = 0.018). Depois de ajustados para o sexo e idade, apenas a diabetes (HR-1.93; 95% CI: 1.12-4.24) e a classe *Killip* (HR-2.15; 95% CI: 1.15-4.02) mantiveram-se significativamente associados ao *outcome* incidente. O péptido natriurético do tipo-B N-terminal não manteve o seu valor prognóstico significativo (HR-1.24; 95%CI: 0.88-1.76).

Conclusão: Os doentes pós-enfarte agudo do miocárdio não têm o prognóstico benigno sugerido pela fração de ejeção do ventrículo esquerdo preservada. São necessários mais estudos que avaliem a utilidade da diabetes, níveis plasmáticos de péptido natriurético do tipo-B N-terminal e novos parâmetros ecocardiográficos de forma a identificar aqueles com maior risco dentro deste grupo específico de doentes.

Palavras-chave: fração de ejeção do ventrículo esquerdo preservada; pós-enfarte agudo do miocárdio; péptido natriurético.

ABSTRACT

Introduction: Left ventricular ejection fraction (LVEF) has long been the key parameter used to stratify the risk in patients after an acute myocardial infarction (AMI). Although patients evolving with a preserved LVEF seem to have a better prognosis opposed to those with a reduced LVEF, they may have a significant rate of cardiovascular (CV) events. We aimed to describe the prognosis and its risk factors in this often overlooked subgroup of patients.

Methods: We studied patients referred to a cardiac rehabilitation (CR) program after an acute myocardial infarction (AMI) between January 2010 and December 2012. They had to have a LVEF >=50% at the time of hospital discharge (measured by transthoracic echocardiography) and completed CR program. The laboratorial data was collected from blood analysis measurement during hospitalization. The composite outcome was defined as all-cause death, heart failure hospitalization, *de novo* diagnosis or worsening HF at the outpatient clinic, and it was assessed by chart review.

Results: The 235 studied patients had a mean age of 60±11 years and 80% were male. During a follow-up of 3.2±4.1 years, 31 (13%) had a composite outcome (19 *de novo* HF diagnosis, 6 HF hospitalizations and 6 deaths). Patients who had an event were older (68 years vs 59 years, P = 0.001), and had a higher prevalence of hypertension (81% vs 62%, P = 0.044) and diabetes (55% vs 28%, P = 0.003). There were fewer STEMIs in the group with an event (32% vs 41%, P = 0.001). They had higher Killip class during hospitalization (class II-IV: 28% vs 4.9%; P < 0.001) and more severe CAD (55% with three-vessel disease vs 30%, P = 0.06). Higher prevalence of chronic kidney disease (CKD) (26% vs 6%, P < 0.001) and anemia (45% vs 18%, P < 0.001) was also present in this subgroup. No significant difference regarding echocardiographic data was present between groups. N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) plasma levels during hospitalization were higher in the subset of patients that eventually had an event (median 408 [207-799] ng/mL vs 342 [124-569] ng/mL; P = 0.018). After adjusting for sex and age, only diabetes (HR-1.93; 95% CI: 1.12-4.24) and Killip class (HR-2.15; 95% CI: 1.15-4.02) remained significantly associated with incident outcome. NT-pro-BNP did not keep its significant prognostic value (HR-1.24; 95%CI: 0.88-1.76).

Conclusions: These post-AMI patients did not have the benign prognosis that could be suggested by the preserved LVEF. Further studies are needed to examine the utility of diabetes, NT-pro-BNP plasma levels and new echocardiographic parameters to identify those at higher risk among this specific group of post-AMI patients.

Key-words: Preserved left ventricle ejection fraction; post-acute myocardial infarction; natriuretic peptide.

INTRODUCTION

Heart failure (HF) is a major cause of morbidity and mortality in developed countries, as well as impaired quality of life. Moreover, it is rapidly becoming a serious economic burden for the healthcare systems across Western societies.

For the past decades, HF and its two subtypes, HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), had been the aim of many studies [1-3]. HFpEF represents half of HF diagnosis and its prevalence is increasing, particularly among the elderly and women [4-6]. Despite all efforts, there’s no treatment available capable of modifying the prognosis of these patients [7-10]. Their heterogeneity has led the scientific community to approach HFpEF’s different phenotypes, that are generally based on their comorbidities, such as arterial hypertension, diabetes, obesity, coronary heart disease (CAD), chronic kidney disease (CKD), among others. [11, 12].

CAD seems to play a key role, with a prevalence that ranges from 35% to 53% in HFpEF patients [5, 13] In fact, acute coronary syndromes often lead to HF decompensation and subsequently to hospitalisation [14]. As expected, patients with CAD and HFpEF suffer a greater left ventricular (LV) dysfunction and have a worse prognosis, when compared to HFpEF patients without CAD [15, 16]. In parallel, the clinical landscape of post-AMI patients had been changing during the last decades due to the efficacy and the greater availability of emergent percutaneous coronary revascularization. Along with improvements in pharmacological therapy, this led to an increased prevalence of acute myocardial infarctions (AMI) evolving with a preserved left ventricular ejection fraction (LVEF) [17]. Despite the major advances in the treatment of this condition, studies have shown that patients with a preserved LVEF post-AMI still have a significant number of cardiovascular events, such as progression to HF in up to one third [18] and sudden cardiac death (SCD), the main cause of death in post-AMI with preserved LVEF [19].

Similarly to HF, LVEF is an important prognostic factor in CAD patients. This key parameter is commonly used to assess prognosis. However, LVEF alone is a very limited tool, because post-AMI patients with a LVEF above 50% can be a rather heterogeneous group, holding significant different prognosis. For this reason, it is important to look for other tools to better prognosticate these patients. Little data is available on the utility of other clinical, echocardiographic and plasma biomarkers to stratify either the mortality and HF incidence in this subgroup of patients.

The present study aimed to investigate the prognostic value of clinical features, cardiac phenotype and serum levels of N-terminal pro-brain natriuretic peptide (NT-pro-BNP) in post-AMI patients with preserved LVEF.

METHODS

We studied 235 consecutive patients referred to a cardiac rehabilitation (CR) program after an acute myocardial infarction (AMI) between January 2010 and December 2012 at Hospital Santo António, Centro Hospitalar do Porto, who presented a LVEF >=50% at the time of discharge and completed that same program. Clinical, laboratorial, and echocardiographic data were collected by chart review. This study conforms with the principles outlined in the Declaration of Helsinki and was approved by the institution's ethical committee (N/REF.ª 2016.236(199-DEFI/188-CES).

Supine transthoracic echocardiography was performed in all patients before the hospital discharge. LVEF was either calculated using the biplane Simpson method or eye-balling. We excluded patients with a reported LVEF lower than 50%. Dimensions and volumes of cardiac chambers and left ventricular mass were measured according to current international recommendations [20]. The laboratorial data was collected from blood analysis measurement during hospitalization. NT-pro-BNP was measured using the Roche® NT-pro-BNP assay. Anemia was defined as hemoglobin less than 12 g/dL for women and less than 13 g/dL for men. CKD was defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/ 1.73 m2.

Incident outcome events were defined as the first occurrence of all-cause death, heart failure hospitalization, or *de novo* diagnosis (if explicitly stated at clinical notes of assistant physician or diuretics were uptitrated). All events were collected by chart review.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation for normally distributed data or median [25th, 75th percentiles] for non-normally distributed data. Categorical variables are expressed as number of subjects and proportion [n (%)]. Comparisons between groups were performed using 2-sided unpaired or paired t tests or Wilcoxon rank sums test for normally and non-normally distributed data, respectively. Fisher's exact test was applied to compare proportions. One-way ANOVA with Bonferroni correction was used to perform multiple group comparisons. Correlations between hemodynamic and metabolic variables were determined using Pearson or Spearman correlation for normally and non-normally distributed data, respectively. We used univariate and multivariable Cox proportional hazards regression models to assess the unadjusted and adjusted association of clinical and echocardiography features and pro-BNP with the composite outcome. The proportional hazards assumption was assessed by visual inspection of Schoenfeld residuals. Statistical analysis was performed using Stata software Version 12.1 (Stata Corp LP, College Station, TX, USA). A two-sided p-value <0.05 was considered significant.

RESULTS

Studied population

The 235 patients included in this analysis had a mean age of 60±11 years and were predominantly male (80%). Their baseline clinical characteristics are shown in Table 1. Patients with an event were older and had a higher prevalence of several cardiovascular risk factors such as hypertension and diabetes. They were also more inclined to have known CAD, history of atrial fibrillation, and stroke, but presented similar prevalence of other comorbidities such as dyslipidemia, COPD and OSA.

Regarding the ACS event, the group that didn't suffer an event tended to have a higher proportion of ST-segment elevation myocardial infarction (STEMI) (41%). On the other hand, significant differences were found regarding the Killip class, with patients who had an event post-AMI presenting with a higher class (24% in class II and 4% at class III). We also found an increased severity of CAD, with 55% of patients who had an event suffering of a three-vessel disease. We did not observe any difference regarding the culprit coronary lesion. Patients that eventually had an event were more likely to have atrial fibrillation during hospitalization.

Regarding laboratory data, patients who eventually had an event had a worse renal function, with a significant GFR value lower than those who didn't have an event, as well as a higher proportion of patients with CKD. Hemoglobin levels at discharge were also lower in this subgroup, with 45% of patients presenting anemia, as well as higher values of NT-pro-BNP (available in 72% of the overall patients, ordered by physician assistant discretion). In contrast, no differences in peak CK and TnT were found in our analysis.

No significant discrepancies were observed at discharge medications, but diuretics were more often prescribed to patients that eventually had an event.

Echocardiographic data

Patients that developed a clinical event trended to have an increased LV mass and larger left atria. No other differences were found between these groups relating structural and functional variables in transthoracic echocardiography – Table 2.

Outcomes

Of the 235 patients, 31 (13%) had a composite outcome (19 *de novo* HF diagnosis, 6 HF hospitalizations and 6 deaths) over a 3.2±4.1 years of follow-up. The overall incidence was 3.4 (95% CI: 2.3-4.9) 100 person-years. The unadjusted analysis is displayed in Table 3. After adjusting for sex and age, only diabetes (HR-1.93; 95%CI: 1.12-4.24) and Killip class (HR-2.15; 95%CI: 1.15-4.02) remained significantly associated with incident outcome. NT-pro-BNP did not keep its significant prognostic value (HR-1.24; 95%CI: 0.88-1.76).

DISCUSSION

Our analysis yield four key findings. Firstly, post-AMI patients with preserved LVEF have a significant rate of CV events. Secondly, our studied population was older and had a high prevalence of comorbidities, namely diabetes, an important prognosis factor for this subgroup of patients. Thirdly, NT-pro-BNP was independently associated with composite outcomes, but, after adjusting for demographic features in a multivariate analysis, only Killip class during hospitalizations prevailed as an independent prognostic marker. Finally, conventional echocardiographic measurements couldn't predict outcome in this subgroup of patients with preserved LVEF.

In this study, post-AMI patients with preserved LVEF had a significant CV event rate of 5% per year. Since post-AMI patients with preserved LVEF have a better prognosis than the ones with reduced LVEF [21], this rate may be higher than expected. This reminds us that although they presented with preserved LVEF at the time of discharge, some of them had clinical features that significantly influenced their prognosis. Some studies that compared outcomes in HFpEF and HFrEF concluded that patients with preserved EF had a lower death rate (13% vs 21%) and were significantly associated with a better survival after adjusting for demographic features. The proportion of deaths attributed to cardiovascular events is also lower in HFpEF (ranging from 50%-70% vs 60%-80%) [22]. Others state that, regarding all-cause readmission or HF hospitalization, there wasn't an association between preserved EF and this increased risk (HR 1.01 and HR 0.77, respectively) [23]. Despite that, the comparison with previous studies is problematic, because we used a composite outcome that included all-cause death and HF-related events. However, we may be underestimating the prognosis severity as we only included post-AMI patients who were enrolled and completed CR program, who usually are the healthiest ones among post-AMI cohorts.

Diabetes is a common comorbidity in CAD patients and it was more prevalent in patients who eventually developed the composite event, remaining significantly associated with the incident outcome, after adjusting for demographic features. It is well known that patients with diabetes have a poorer short-term and long-term prognosis after an AMI, when compared to non-diabetic patients [24, 25]. In fact, despite the management of diabetic and non-diabetic patients after an acute coronary syndrome (ACS) being comparable, studies have not demonstrated a similar reduction in cardiovascular mortality, even though they're subjected to the most modern therapy available [26, 27]. This might be explained by the fact that diabetes constitutes a major risk factor for atherosclerosis, which in turn leads to coronary artery disease. Moreover, hyperglycemia and insulin-resistance have also been associated with the dysregulation of several signalling pathways responsible for platelets reactivity, leading to an increase of thrombotic events, such as AMI [28]. This dysregulation also contributes to a lower success rate of antithrombotic therapies and a lesser extent of STEMI resolution [29]. Besides the prognostic implications in post-ACS patients, diabetes also plays a role in the development of HF, particularly HFpEF, which appears to be more common among diabetic patients [30-32]. Pathophysiological mechanisms such as cardiac hypertrophy and fibrosis, metabolic dysfunction of the muscle, which lead to relaxation and microvascular abnormalities, might explain the increased prevalence of HFpEF in this subgroup. Other studies name the processes that impact negatively the cardiac muscle of diabetic patients with no other comorbidities “diabetic cardiomyopathy” [33], which highlights the need for a tighter control of the glycemia. Even patients without known CAD are at higher risk of developing a fatal or nonfatal CV event when diabetes and microalbuminuria, as well as elevated NT-pro-BNP, are present [34].

In this study, another key parameter analyzed was NT-pro-BNP, an important biomarker whose plasma levels tend to be elevated in patients with left ventricular impairment. Increased wall stress and LV volume overload, with consequent cardiomyocyte stretching and neurohormonal activation, upregulates the release of the peptide in response to these stimuli [35, 36]. It is also the cornerstone parameter for the diagnosis and management of HF, as well as a potent predictor of short and long-term mortality in this subset of patients [37-41]. In our study, higher values of NT-pro-BNP were associated with a higher rate of events in the studied population (Figure 1). However, this significant association with composite outcome did not persist after adjusting for age and sex, remaining only significantly associated diabetes and Killip class. Previous studies have shown that NT-pro-BNP is able to independently predict incident heart failure and death, regardless of LVEF and, for those with systolic dysfunction, it signals the risk of developing new ischemic events [42]. Others concluded that NT-pro-BNP was a valuable marker to predict the severity of CAD, namely the number of vessels involved and the degree of stenosis [43, 44] Accordingly, our data shows that the majority of patients in the events subset had a significant rate of three-vessels disease (54.8%). In spite of not showing statistical significance after adjusting for demographic features, our results show some correlation between NT-pro-BNP and incident outcome (Figure 2). This suggests that the natriuretic peptide might have a potential benefit in reducing the underdiagnosis of HF during hospital stay, as well as stratifying risk in these populations, which would help assess those in need of a more aggressive treatment approach. Multiple studies have already proven the usefulness of this biomarker. The risk assessment and MACE prediction in patients undergoing diagnostic coronary angiography with a score that included NT-pro-BNP [45] and it’s use complemented with high-sensitivity C-reactive protein (hs-CRP) to predict mortality risk and MI risk in patients with non–ST-segment elevation ACS [46] are some examples of this.

Another relevant finding of this study was that none of the conventional echocardiographic measurements predicted the outcome in this subgroup of patients. As traditional echocardiographic parameters depend on single measurements, they are representative only in normally shaped ventricles and may be blind to more subtle shape distortions, not visible in the 2 or 4 chambers planes. Moreover, since adverse remodelling develops in a complex process over weeks to months after AMI, the initial abnormalities may be so tenuous that they do not reflect structure changes at this time. Lately, new imaging tools have emerged as a more sensitive index of LV function and mechanics after AMI. Myocardial strain measures the relative change in length of myocardium through the cardiac cycle. As global longitudinal strain is less susceptible to factors that limit EF [21], it may be a better indicator for LV contractile function and mechanics than LVEF [22]. Global longitudinal strain measured acutely by Speckle Tracking Echocardiography post-STEMI had been shown to be independently associated with LV dilatation at follow-up [23] and strongly correlated with adverse events [24]. However, despite being proved to be predictive for LV remodelling, this tool is not currently widely available and limited data is available regarding the prognostic utility in HFpEF patients [25-27]. Further research is needed to better stratify these patients’ risks.

Our study has several limitations that need to be considered. We cannot avoid the inherent biases to the retrospective design. By selecting patients who underwent cardiac rehabilitation program, we can’t extrapolate our findings to all ACS patients. The single center data limits inference to a broader population. The small sample size and reduced event rate limits our statistical power to examine the prognostic effect of some of the studied variables. Therefore, we cannot exclude the possibility of a type 2 error in those negative associations we found, such as NT-pro-BNP. We analysed a composite outcome that may hamper more straightforward interpretation of our survival data.

CONCLUSION

These post-AMI patients did not have the benign prognosis that could be suggested by the preserved LVEF. Further studies are needed to examine the utility of diabetes, NT-pro-BNP plasma levels and new echocardiographic parameters to identify those at higher risk among this specific group of post-AMI patients.

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TABLES

Table 1 – Clinical characteristics of studied patients.

Characteristic	**Overall (N=235)**	**Without event (n=204)**	**With event (n=31)**	**P-value**
Age, y	59.81 ± 10.80	58.64 ± 10.52	67.55 ± 9.48	< 0.001
Male, n (%)	187 (79.6%)	168 (82.4%)	19 (61.3%)	0.007
BMI, Kg/m2	26.56 ± 4.01	26.51 ± 4.13	26.89 ± 3.16	0.63
Hypertension, n (%)	151 (64.5%)	126 (62.1%)	25 (80.6%)	0.044
Smoking status				0.013
Never smoked, n (%)	86 (36.6%)	68 (33.3%)	18 (58.1%)	
Past smoker, n (%)	87 (37.0%)	82 (40.2%)	5 (16.1%)	
Current smoker, n (%)	62 (26.4%)	54 (26.5%)	8 (25.8%)	
Diabetes, n (%)	74 (31.6%)	57 (28.1%)	17 (54.8%)	0.003
Dyslipidemia, n (%)	174 (74.4%)	150 (73.9%)	24 (77.4%)	0.68
History of atrial fibrillation, n (%)	5 (2.1%)	3 (1.5%)	2 (6.5%)	0.07
Stroke, n (%)	7 (3.0%)	5 (2.5%)	2 (6.5%)	0.22
CAD, n (%)	44 (18.7%)	35 (17.2%)	9 (29.0%)	0.11
COPD, n (%)	9 (3.8%)	8 (3.9%)	1 (3.2%)	0.85
OSA, n (%)	4 (1.7%)	4 (2.0%)	0 (0.0%)	0.43
ACS hospitalization features				
STEMI, n (%)	92 (39.5%)	82 (40.6%)	10 (32.3%)	0.38
Killip class				< 0.001
II, n (%)	11 (5.9%)	5 (3.1%)	6 (24.0%)	
III, n (%)	3 (1.6%)	2 (1.2%)	1 (4.0%)	
IV, n (%)	1 (0.5%)	1 (0.6%)	0 (0.0%)	
Number of coronaries with significant disease				0.06
One-vessel, n (%)				

Two-vessel, n (%) Three-vessel, n (%)	85 (37.0%) 67 (29.1%) 77 (33.5%)	78 (39.2%) 60 (30.2%) 60 (30.2%)	7 (22.6%) 7 (22.6%) 17 (54.8%)	
Culprit coronary				0.95
LAD, n (%)	90 (39.8%)	79 (40.3%)	11 (36.7%)	
RCA, n (%)	90 (39.8%)	77 (39.3%)	13 (43.3%)	
LCx, n (%)	45 (19.9%)	39 (19.9%)	6 (20.0%)	
PCI, n (%)	204 (87.6%)	176 (86.7%)	28 (93.3%)	0.77
Atrial fibrillation, n (%)	10 (4.3%)	7 (3.4%)	3 (10.0%)	0.10
Blood analysis at discharge				
GFR, mL/min/1.73 m2	85.82 ± 17.44	87.55 ± 16.47	75.02 ± 19.65	< 0.001
GFR < 60 mL/min/1.73 m2, n (%)	20 (8.5%)	12 (5.9%)	8 (25.8%)	< 0.001
Hb, g/dL	13.56 ± 1.37	13.68 ± 1.24	12.75 ± 1.82	< 0.001
Anemia, n (%)	50 (21%)	36 (18%)	14 (45%)	<0.001
Peak CK, U/L	636.16 ± 910.38	647.97 ± 862.62	561.38 ± 1184.31	0.63
Peak TnT, ng/mL	1.19 ± 1.54	1.22 ± 1.56	1.01 ± 1.47	0.57
NT-pro-BNP, ng/mL	347 [129-632]	342 [124-569]	408 [207-799]	0.018
Medication at discharge				
Aspirin, n (%)	231 (98.7%)	200 (98.5%)	31 (100.0%)	0.50
Clopidogrel/Ticagrelor, n (%)	227 (97.0%)	196 (96.6%)	31 (100.0%)	0.29
Statin, n (%)	223 (95.3%)	193 (95.1%)	30 (96.8%)	0.68
B-Blocker, n (%)	209 (89.3%)	182 (89.7%)	27 (87.1%)	0.67
ACEI/ARB, n (%)	159 (68.5%)	137 (68.2%)	22 (71.0%)	0.75
Diuretic, n (%)	14 (6.0%)	6 (2.9%)	8 (25.8%)	< 0.001
MRA, n (%)	2 (0.9%)	2 (1.0%)	0 (0.0%)	0.58

Caption: BMI, Body Mass Index; HF, Heart Failure; CAD, Coronary Artery Disease; COPD, Chronic Obstructive Pulmonary Disease; OSA, Obstructive Sleep Apnea; ACS, Acute Coronary Syndrome; STEMI, ST Segment Elevation Myocardial Infarction; LAD, Left Anterior Descending Artery; RCA, Right Coronary Artery; LCx, Left Circumflex Artery; PCI, Percutaneous Coronary Intervention; GFR, Glomerular Filtration Rate; Hb, Hemoglobin; CK, Creatine Kinase; TnT, Troponine T; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; ACEI/ARB, Angiotensin-converting-enzyme Inhibitor/Angiotensin II Receptor Blocker; MRA, Mineralocorticoid Receptor Antagonist.

Table 2 – Echocardiographic features of studied patients.

Characteristic	**Overall (N=235)**	**No event (n=204)**	**Event (n=31)**	**P-value**
IVS, mm	11.77 ± 1.99	11.81 ± 2.04	11.57 ± 1.65	0.54
PWT, mm	10.50 ± 1.33	10.50 ± 1.31	10.53 ± 1.50	0.89
LV mass indexed, g/m2	102±22	102±22	106±25	0.29
LVEDD, mm	46.02 ± 4.80	45.93 ± 4.88	46.60 ± 4.31	0.48
LVESD, mm	29.63 ± 4.94	29.64 ± 5.11	29.57 ± 3.60	0.95
LA diameter, mm	38.74 ± 4.63	38.49 ± 4.61	40.40 ± 4.54	0.035
LA area, cm2	20.21 ± 4.17	19.98 ± 3.99	21.81 ± 5.03	0.032
Segmental motion abnormalities				
Anterior, n (%)	52 (22.2%)	46 (22.5%)	6 (20.0%)	0.75
Posterior, n (%)	87 (37.0%)	75 (36.8%)	12 (38.7%)	0.83
Inferior, n (%)	131 (55.7%)	112 (54.9%)	19 (61.3%)	0.50
Moderate/severe MR, n (%)	3 (1.3%)	3 (1.5%)	0 (0.0%)	0.49
RV systolic dysfunction, n (%)	4 (1.7)	3 (1.5%)	1 (3.2%)	0.50
LV remodelling pattern				
Normal, n (%)	51 (21.7%)	44 (21.6%)	7 (22.6%)	0.40
Concentric, n (%)	98 (41.7%)	87 (42.6%)	11 (35.5%)	
Concentric LVH, n (%)	66 (28.1%)	54 (26.5%)	12 (38.7%)	

Eccentric LVH, n (%)	20 (8.5%)	19 (9.3%)	1 (3.2%)	

Caption: IVS, Interventricular Septum; PWT, Posterior Wall Thickness; LVEDD, Left Ventricular End Diastolic Diameter; LVESD, Left Ventricular End Sistolic Diameter; LA, Left Auricle; MR, Mitral Regurgitation; LV, Left Ventricle; LVH, Left Ventricular Hypertrophy.

Table 3 – Unadjusted hazard ratios for incident composite outcome.

	Univariate Hazard Ratio (95% CI)	P-value
Age	1.09 (1.05-1.13)	<0.001
Male sex	0.40 (0.18-0.85)	0.017
Hypertension	2.09 (0.84-5.17)	0.112
Diabetes	2.43 (1.14-5.17)	0.021
STEMI	0.92 (0.41-2.05)	0.838
Killip class	2.20 (1.24-3.91)	0.007
Hemoglobin	0.68 (0.54-0.85)	0.001
GFR	0.97 (0.95-0.99)	0.001
NT-pro-BNP*	1.45 (1.01-2.07)	0.04
LV mass	1.01 (0.99-1.03)	0.212
LA area	1.09 (1.01-1.17)	0.024

Caption: *log-NT-pro-BNP.

FIGURES

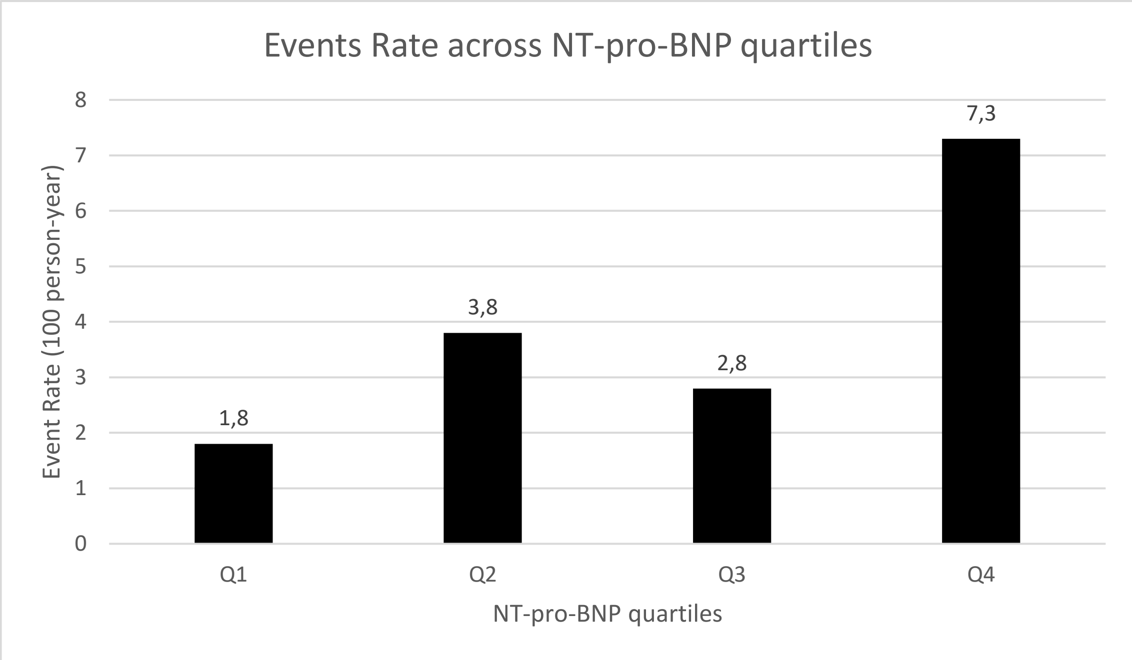

Figure 1 - Events rate across NT-pro-BNP quartiles. Q1 = 68 [41-102] ng/mL; Q2 = 228 [177-292] ng/mL; Q3 = 426 [388-528] ng/mL; Q4 – 1042 [809-1620] ng/mL.

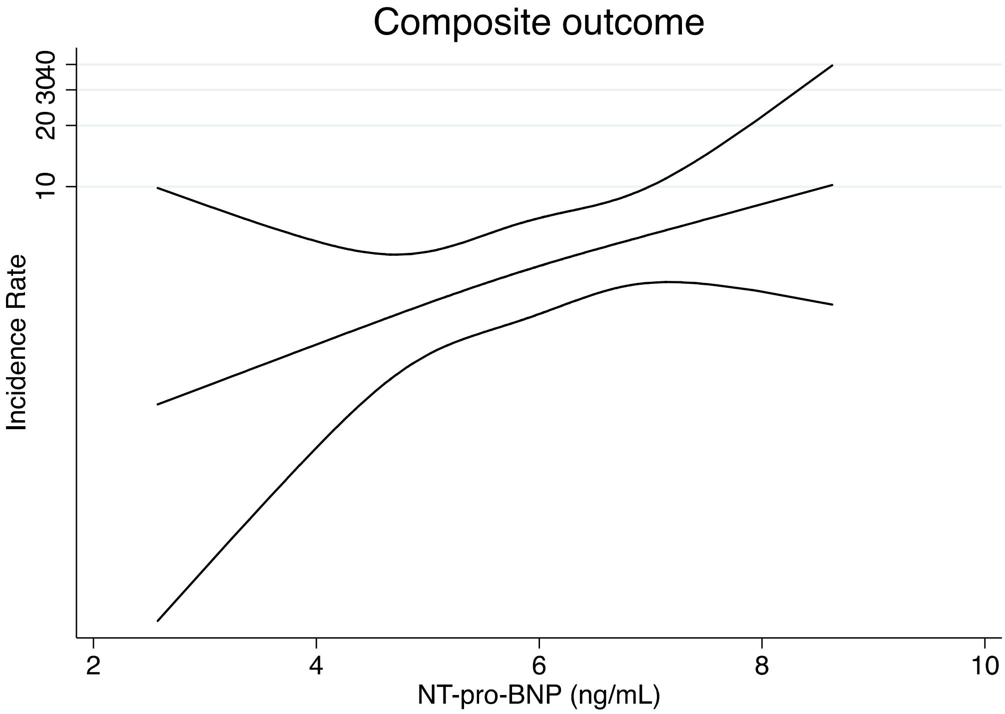

Figure 2 - Incidence spline of NT-pro-BNP and composite event rate. Incidence rate's unit is 100 person-year and NT-pro-BNP was converted to logNT-pro-BNP.

Appendix 1 – Institutional Ethics Committee Deliberation

centro hospitalar
do Porto

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Largo Prof. Abel Salazar
4099-001 PORTO
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Exmo. Sr.

Filipe Santos

Aluno do ICBAS

ASSUNTO: Trabalho Académico - MIM - **"Doença cardíaca isquémica e insuficiência cardíaca com fração de ejeção preservada"** - N/ REF.ª 2016.236(199-DEFI/188-CES)

O Conselho de Administração do CHP autoriza a realização do estudo acima mencionado a realizar no Serviço de Cardiologia, desta Instituição e tendo como Investigador Principal, o aluno do ICBAS, Filipe Santos.

O estudo foi previamente analisado pela Comissão de Ética para a Saúde, pelo Gabinete Coordenador de Investigação, pela Direção do Departamento de Ensino, Formação e Investigação e pelo Presidente do Conselho de Administração tendo obtido parecer favorável.

Cumprimentos,

CONSELHO DE ADMINISTRAÇÃO

0 9 FEV. 2017

Dr. PAULO BARBOSA
Presidente

Dr.ª ÉLIA GOMES
Vogal Executiva

Prof. Doutor JOSÉ BARROS
Diretor Clínico

Dr. RUI PEDROSO
Vogal Executivo

Enf.º EDUARDO ALVES
Enfermeiro Diretor

* Em todas as eventuais comunicações posteriores sobre este estudo é indispensável indicar a nossa ref.ª.