ORIGINAL PAPER

A Comparison of Prognostic Value of the Levels of ProBNP and Troponin T in Patients with Acute Coronary Syndrome (ACS)

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ABSTRACT

Introduction: The propeptide of brain natriuretic peptide (ProBNP) is used for the diagnosis of left ventricle dysfunction and heart failure. In patients with an Acute Coronary Syndrome (ACS) it can contribute to both short and long term prognosis of cardiovascular events that could be very important for management and therapy of these patients. **Aim:** The aim of this study was to evaluate the prognostic value of ProBNP for the clinical course after an acute coronary syndrome, compared with that of cardiac troponine T (cTnT) and the risk stratification of patients with acute coronary syndrome, both during hospitalization and six months later. **Methods:** We studied 390 patients (256 men, 134 women, mean age 66.04$\pm$12.38) with an acute coronary syndrome who were hospitalized in the Coronary Unit of our cardiology clinic. We studied epidemiological and clinical data and biochemical markers were examined as prognostic factors for clinical course intrahospital and during six months follow-up. **Results:** In the majority of patients, a myocardial infarction without ST elevation was diagnosed (NSTEMI) (193 patients 49.49%) while 167 patients (42.82%) had a myocardial infarction with ST elevation (STEMI) and the remaining 30 patients (7.69%) had unstable angina. Patients had multiple risk factors for coronary heart disease. The levels of ProBNP were significantly elevated in patients with STEMI (p=0.003) and NSTEMI (p=0.002) who died or experienced an adverse event (angina, myocardial infarction, cardiogenic shock, congestive heart failure, arrhythmias) during hospitalization. After six months of follow-up, patients who had an adverse event had higher levels of ProBNP. There was no difference in troponine T levels in patients with STEMI and NSTEMI who had adverse events compared with the others, either during hospitalization or after six months. **Conclusion:** The level of ProBNP is an important predictor of cardiovascular events in patients with acute coronary syndrome. This study showed that it provides better predictive power than the troponine T.

Key words: ProBNP, troponin T, STEMI, NONSTEMI.

1. INTRODUCTION

The natriuretic peptides (NPs) are released from the cardiac myocardium as a result of pressure or volume overload. There are three types of natriuretic peptides, atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). ANP and BNP have varying biological actions including vasodilatation, natriuresis and diuresis (1). CNP may protect from myocardial remodeling after a myocardial infarction (2).

BNP is used in differentiating cardiac from non cardiac reasons of dyspnea (3) and has a prognostic role in chronic heart failure (4) and after an acute coronary syndrome (5). Elevated levels of NT-proBNP correlate with increased mortality of patients with acute coronary syndrome regardless of left ventricular function (6). ProBNP levels increase

early after the onset of symptoms in patients with acute coronary syndrome, which can be useful for risk stratification and for management decision (7).

2. THE AIM OF THE STUDY

The aim of this study was to assess the prognostic value of proBNP to determine cardiovascular risk in patients with acute coronary syndrome admitted in our Department. We compared levels of proBNP with levels of cardiac troponine T at presentation and six months later to accomplish risk stratification.

3. METHODS

A prospective study of patients admitted because of acute coronary syndrome in the Coronary Care Unit of Cardiology Department of our hospital was designed and conducted. The study enrolled 390 patients, 256 males and 134 females with a mean age of 66.04±12.38 years. Patients were treated according to the protocol of the Cardiology Department for acute coronary syndromes (for STEMI and UA/NSTEMI), given the absence of catheterization laboratory.

Epidemiological characteristics such as age, sex, weight, high, body mass index (BMI) as well as clinical characteristics, such as history of chronic heart disease, diabetes mellitus (DM), hypertension, dyslipidemia, smoking and family history of cardiovascular disease were studied and recorded.

The measurement of biochemical markers (cardiac enzymes–Pro BNP) was given at 0, 8, 24, 48 and 120 hours after admission and higher value was used for evaluation. Biochemical markers studied were: hemoglobin, white blood cell count, red blood cells, platelets, hematocrit, urea, electrolytes, creatine phosphokinase (CPK), creatine kinase isoenzyme MB (CK-MB), fasting blood glucose, glucosylated hemoglobin (HbAc%), total cholesterol, HDL, LDL and triglycerides.

Patients were followed up for six months. Primary endpoint was death or the occurrence of any major complication (reinfarction, cardiogenic shock, sustained ventricular tachycardia, ventricular fibrillation, angina, symptoms of left ventricular dysfunction) during hospitalization and six months later. Ejection fraction of the left ventricle (LVEF) was measured echocardiographically at the 4th day of hospitalization using the Simpson method and normal function defined to be LVEF$\geq$ 50%.

The levels of troponin T were measured using the third generation immunohistochemical assay (Elecsys 1010, Roche Diagnostics), with a detection range values 0.010-25.00 ng / ml and with values for myocardial infarction > 0.1 ng/ml (sensitivity 100% and specificity of 83.9% in the first 24 hours). The concentration of Pro BNP was evaluated using immunohistochemical method (Elecsys 1010, Roche Diagnostics), with detection range values 5-35000 pg / ml and with normal values < 194 pg / ml.

Statistical analysis was performed using the statistical package SPSS 18.00 (SPSS Inc., Chicago, Ill, USA). Originally, an estimation of the normality of the distribution of quantitative variables (troponin, BNP) was made using the Kolmogorov-Smirnov test (sample > 50 patients). Due to the highly asymmetric distribution nonparametric tests, such as Mann-Whitney and Kruskal-Wallis, were used for comparing two or three independent groups respectively.

To estimate the predictive value of the variables a model based on the Cox Regression analysis was used, which initially examined the univariate relationship of the variables with the combined endpoint (major complications as reinfarction, cardiogenic shock, sustained ventricular tachycardia, ventricular fibrillation, angina, symptoms of left ventricular dysfunction), both at hospital discharge and after six months. Variables showed significant association (male gender, age, Killip class, ProBNP, CPKMB and LVEF) were included in a multivariate model analysis (Cox Regression analysis), where the prognostic value of ProBNP as independent factor for adverse events was examined, both at hospital discharge and six months later. Then, ROC (Receiver–Operations Characteristic) curves were created, in order to identify and graphically display the cut off values, for the predictive role of ProBNP, for the two time periods. The results were presented as Area Under the Curve (AUC) and the best cut off values assigned the points of higher sensitivity and specificity. Finally, based on these values, Kaplan – Meier curves were created, which compared the predictive role of these values for the outcome of combined adverse effects during the follow up period, using the log-rank test.

Probability p < 0.05 (2- way) was considered statistically significant. The study protocol was approved by the Scientific Council of the Hospital.

4. RESULTS

Demographic characteristics–Risk factors

Table 1 contains the basic demographic, epidemiological, clinical and biochemical data of the patients.

	STEMI n=167	NSTEMI n=193	UA n=30	p
Age (years)	63.34±13,26	68.12±11.6	67.14±12.44	0.21
Gender – Male n (%)	104 (62.27)	133 (68.91)	26 (86.67)	0.5
Killip class	1.62±1.45	1.35±1.15	1.71±0.76	0.65
LVEF (%)	51.14±12.42	52.8±11.27	56.7±10.08	0.49
ProBNP (pg/ml)	4365±1277	3062±1116	2619±818	0.04
cTnT (ng/ml)	4.25±5.7	1.16±1.33	0.02±0.01	<0.001
CPK (IU)	1648±1111	966±796	248±129	0.001
CPK–MB (IU)	140.78±152.24	74.23±57.65	69.14±84.43	0.001

Table 1. Main characteristics of patients

	STEMI n=167	NSTEMI n=193	UA n=30	p
Hypertension n (%)	72 (43.11)	97 (50.26)	14 (46.67)	0.3
Smoking n (%)	76 (45.5)	95 (49.22)	17 (54.5)	0.4
Diabetes n (%)	84 (49.1)	107 (55.44)	12 (40)	0.61
Previous CAD n (%)	30 (17.96)	87 (45.1)	17 (56.67)	0.01
Dyslipidemia n (%)	75 (44.9)	106 (54.9)	20 (66.67)	0.03
Family History of CAD n (%)	78 (46.7)	85 (44.04)	3 (10)	0.03

Table 2. Risk Factors in Patients with Acute Coronary Syndromes

	Hospital Exit n=144	6 months follow up period, n=103
Death n (%)	11 (7.64)	16 (15.54)
VT–VF n (%)	27 (18.75)	–
CHF n (%)	67 (46.53)	7 (6.8)
Cardiogenic Shock n (%)	24 (16.7)	–
Angina n (%)	80 (55.6)	26 (25.4)
Reinfarction n (%)	11 (7.64)	14 (13.6)

Table 3. Cardiovascular events. VT: Ventricular Tachycardia, VF: Ventricular Fibrillation, CHF: Congestive Heart Failure

	Adverse Cardio-vascular events	No Adverse Cardiovascular events	p
During Hospi-talization	n=144	n=246	
ProBNP	4147.4+2826.5	752.5+532.8	0.003
TroponinT	2.33+1.48	1.43+3.68	0.5
6 months follow up	n=103	n=287	
ProBNP	1468.7+868.8	937.1+108.65	0.01
TroponinT	2.67+3.4	1.1+2.8	0.4

Table 4. Relationship of cardiac biomarkers with the occurrence of complications during hospitalization and the follow up period

	Odds Ratio (OR)	CI	p
During Hospitalization			
Age (years)	1.039	1.006–1.073	0.022
ProBNP	1.16	1.08–1.28	0.009
LVEF	1.4	1.31–1.48	<0.001
6 months follow up			
Gender (Male)	0.512	(0.262–0.93)	0.041
Age (years)	1.025	(1.01–1.33)	0.04
ProBNP	1.43	(1.02–1.56)	0.04
LVEF	1.38	(1.27–1.42)	<0.001

Table 5. Independent factors (multivariable analysis) for the occurrence of complications during hospitalization and the follow up period

There were 263 men (67.43%), while the mean age of the population was 66.04±12.38 years. Mean systolic blood pressure was 136+35.7 mmHg and diastolic blood pressure 82.7 +16.9 mmHg.

The majority of patients had a myocardial infarction without ST segment elevation ST (NSTEMI) (193 patients, 49.49%), 167 patients (42.82%) myocardial infarction with ST segment elevation ST (STEMI) and the remaining 30 patients (7.69%) unstable angina, diagnosis based on typical ischaemic precordial pain and ECG changes, without troponin T elevation. There were no significant differences in age and gender of the patients of all three groups. In contrast, significant differences of the peak values of ProBNP, troponin T and CPK- CPK/MB were observed.

The most common risk factors in the study population were hypertension (183 patients - 46.92%), smoking (188 patients - 48.2%), diabetes mellitus (201 patients - 51.53%), dyslipidemia (201 patients - 51.53%) and positive family history (166 patients - 42.56%), while patients with previous coronary disease were 134 (34, 36%). Table 2 lists the risk factors in the three patient groups. The analysis shows that patients with unstable angina were more likely to suffer from dyslipidemia and a history of any prior CHD and STEMI patients with a positive family history.

Cardiovascular events

During hospitalization 11 patients died (7.64%) while 144 patients (36.9%) experienced major end point events, most often reinfarction (80 patients - 55.6%) and congestive heart failure (67 patients - 46.53%). Respectively at six months after hospitalization 103 patients (26.4%) had complications. Table 3 shows the cardiovascular events during hospitalization and after six months follow up. Cardiac catheterization during hospitalization or during follow up was done in 276 (70.77%) of patients. Most of them (113 - 40.94%) had two-vessel disease, 105 (38.04%) had three-vessel disease and 58 patients (21.02%) had one vessel disease. Considered these data in 164 patients (59.42%) percutaneous coronary intervention was done, 79 patients (28.7%) had coronary artery bypass graft surgery while in 33 patients (11.96%) conservative treatment was recommended.

Cardiac biomarkers and cardiovascular events

Patients with major end point events during hospitalization and six months later had significantly higher levels of ProBNP. There was no difference in levels of cTnT in patients with STEMI and NSTEMI who had adverse outcomes compared with the others, during follow up period. Table 4 shows the relationship of cardiac biomarkers with complications. At the same time ProBNP levels were significantly elevated in patients with heart failure compared to those without heart failure (8078.69+9595.82 pg/ml vs 2830.3+6524.84 pg/ml,
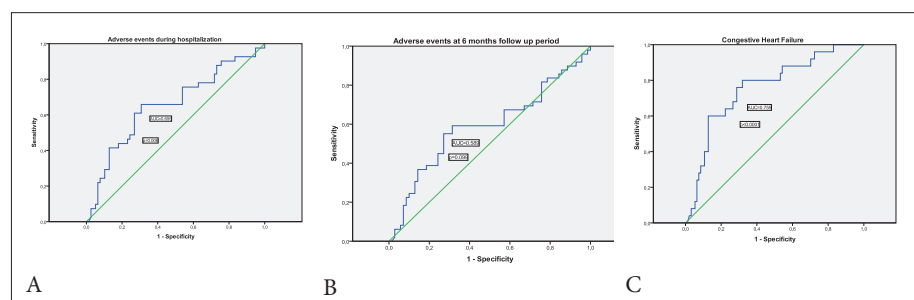

Figure 1. Characteristic ROC curves for BNP and adverse outcomes during hospitalization (A), during 6 months follow up period (B) and Congestive Heart Failure (C). AUC: Area Under the Curve

p=0.004). The same was observed for the troponin T levels (4.17+5.64 ng/ml vs 1.97+3.35 ng/ml) but was of borderline significance (p=0.058).

The independent predictive factors for the adverse effects occurrence during hospitalization were age, ProB-NP, and LVEF and during the 6-months follow up period were the female gender, age, ProBNP, and LVEF. All prognostic factors with the details of their analysis are recorded on Table 5.
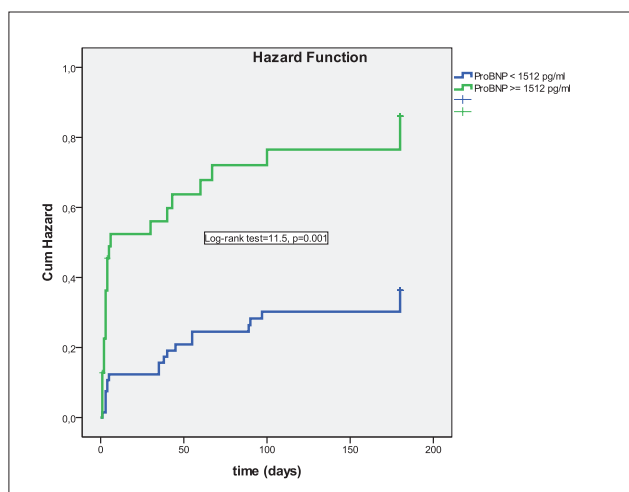
Figure 2. Kaplan – Meier curves where patients with ProBNP>1512 pg/ml were presented with worse clinical course at 6-months follow–up period

Figure 1 shows ROC curves presenting the relationship between ProBNP levels and the occurrence of adverse events during hospitalization (AUC=0.655, p=0.006) which became less predictive for adverse events during the six month follow up period (AUC=0.589, p=0.099), while for the outcome of congestive heart failure was significantly predictive (AUC=0.759, p<0.0001).

Analyzed the ROC curves a cut-off point of 1512 pg/ml for ProBNP was selected, which resulted in 65.5% sensitivity (95% CI, 54.7 - 76.2%) and 30.8% specificity (95% CI, 26.7 - 42.6%) for the occurrence of adverse effects during the hospitalization period. Similarly a cut-off point of 1436.5 pg/ml was selected, which resulted in 59.2% sensitivity (95% CI, 48 - 69.8%) and 31.4% specificity (95% CI, 26.9 - 40.6%) for the occurrence of adverse effects during the 6 months follow up period. For the outcome of congestive heart failure ProBNP was significantly predictive, with a cut-off point of 513.9 pg/ml, which resulted in 75.9% sensitivity (95% CI, 53.6 - 93.8%) and 64.1% specificity (95% CI, 46.9 - 80.6%).

Then Kaplan - Meier curves were created where patients with ProBNP values greater than 1512 pgr/ml ($\geq$ 1512 pgr/ml) were presented with worse clinical course at 6-months follow-up period (Figure 2).

5. DISCUSSION

The patients of the study had multiple cardiovascular risk factors such as hypertension, smoking, diabetes mellitus, dyslipidemia and family history, while significant number of them had coronary heart disease. According to coronary angiography findings many of them had diffuse coronary heart disease so they underwent a reperfusion therapy.

ProBNP levels in patients with ACS in our study increased very early while the maximum levels were observed in the first 48 hours. Previous studies showed this results too (8). Brain peptide (BNP) releases instantly after myocardial infarction reaching the peak after 16 hours. The mechanism of increasing ProBNP in patients with ACS and normal ejection fraction is not known yet. Probably the myocardial cells release natriuretic pep-

tides during a long ischaemia period before myocardial necrosis (9). Thus, ischaemia is probably an additional factor of releasing ProBNP, as illustrated by the results of this study.

Patients with STEMI and NSEMI had significantly higher levels of ProBNP compared with those with unstable angina, a fact that may be due to a larger ischaemia in myocardial infarction. A remarkable finding is that a large number of patients developed congestive heart failure during hospitalization (46.33%), confirming that ProBNP releases from left ventricle and depends on the level of wall stress and myocardial stretch of the left ventricle (10).

In patients with ACS, ProBNP level is an important prognostic factor for early and late cardiovascular events (11). It seems that the larger the ischaemic burden more ProBNP is released and the worst the prognosis is (6, 11, 12), as confirmed by our results. The same results were concluded by Bassan et al (13), ie the more extended ischaemia, the both higher levels of ProBNP released and worse clinical course.

On the contrary, the present study showed that the ProBNP is superior to troponin T as a prognostic factor for early and late cardiovascular events. In particular the troponin levels were higher in patients with STEMI and NSTEMI but they were the same between those who developed or not complications during follow up period. Probably this is due to intense treatment received by the patients (70.77% were subjected in catheterization and invasive treatment). It is known that the only quantitative prognostic markers for ACS were troponine and CPK/MB (14). Therefore increased levels leaded these patients faster to the hemodynamic laboratory. It seems that ProBNP differs from other biomarkers because its levels reflect the size of myocardial ischaemia before myocardial necrosis. This is proved by the fact that patients with unstable angina and normal ejection fraction had high levels of ProBNP which were prognostic marker of increased coronary events although troponineT was not raised. Similar results were seen in other trials too (15).

Study limitations

Significant limitation of our study is that the measurement of ProBNP was done only during hospitalization and the changes of the levels were not examined after medical or interventional treatment. In a recent study increased levels of ProBNP seven weeks after myocardial infarction stratified the risk in patients with ACS until ten moths with rates respectively compared with Pro BNP during hospitalization (16). Therefore it seems that does not offer qualitative information. Another limitation is that coronary angiography was not done in all patients. Lastly, patients with unstable angina had a history of previous coronary disease and this probably affected ProBNP measurements.

Generally, despite the limitations the study confirmed the relationship of elevated ProBNP levels with worse clinical course in patients with ACS or with reduced ejection fraction.

6. CONCLUSIONS

Plasma ProBNP is a significant prognostic risk factor in patients with ACS. It provides better predictive power than Troponine T. ProBNP testing should be involved in risk stratification in patients with ACS in order to guide a better treatment.

- Conflicts of interest: nothing to declare.

REFERENCES

1. Nakao K, Ogawa Y, Suga S, Imura H. Molecular biochemistry of the natriuretic peptide system. J Hypertens. 1992; 10: 1111-4.
2. Soeki T, Kishimoto I, Okumura H, et al. C-type natriuretic peptide, a novel antifibrotic and antihypertrophic agent prevents cardiac remodeling after myocardial infarction. J Am Coll Cardiol. 2005; 45: 608-16.
3. Morrison LK, Harrison A, Krishnaswamy P, et al. Utility of rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. J Am Coll Cardiol. 2002; 39: 202.
4. Sugimoto Y, Kinashita M. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: Prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation. 1997; 96: 509.
5. Morrow DA, de Lemos JA, Sabatine MS, et al. Evaluation of B-type natriuretic peptide for risk assessment in unstable angina/non-ST-elevation myocardial infarction: B-type natriuretic peptide and prognosis in TACTICS-TIMI 18.J Am Coll Cardiol. 2003; 41: 1264.
6. De Lemos JA, Morrow DA, Bantley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. N Eng J Med. 2001; 345: 1014-21.
7. Jernberg T, Stridsberg M, Venge P, et al. N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation. J Am Coll Cardiol. 2002; 40: 437-45.
8. Baxter GF. Natriuretic peptides and myocardial ischaemia. Basic Res Cardiol. 2004; 99: 90-3.
9. Goetze JP, Christoffersen C, Perko M, et al. Increased cardiac BNP expression associated with myocardial ischaemia. FASEB J. 2003; 17: 1105-7.
10. De Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet. 2003; 362: 316-22
11. Daniels L,Maisel A. Natriuretic peptides. J Am Coll Cardiol. 2007; 57: 2357-68.
12. Stein BC, Levin RI. Natriuretic peptides: Physiology, therapeutic potential, and risk stratification in ischaemic heart disease. Am Heart J. 1998; 135: 914.
13. Bassan R, Potch A, Maisel A. et al. B-type natriuretic peptide: a novel early blood marker of acute myocardial infarction in patients with chest pain and no ST-segment elevation. Eur Heart J. 2005; 26: 234-40.
14. Morrow DA, Braunwald E. Future of biomarkers in acute coronary syndromes: Moving toward a multimarker strategy. Circulation. 2003; 1208: 250.
15. Heeschen C, Hamm CW, Mitrovicn V. et al. N-terminal pro-B-type natriuretic peptide levels for dynamic risk stratification of patients with acute coronary syndromes. Circulation. 2004; 110: 3206-12.
16. Ang DS, Kong CF, Kao MP, Struthers AD. Serial bedside B-type natriuretic peptide strongly predicts prognosis in acute coronary syndrome independent of echocardiographic abnormalities. Am Heart J. 2009; 158(1): 133-40.