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USEFULNESS OF NT-proBNP IN THE FOLLOW-UP OF PATIENTS AFTER MYOCARDIAL INFARCTION

ZNAČAJ NT-proBNP-A U PRAĆENJU BOLESNIKA POSLE AKUTNOG INFARKTA MIOKARDA

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Summary

Background: Since serial analyses of NT-proBNP in patients with acute coronary syndromes have shown that levels measured during a chronic, later phase are a better predictor of prognosis and indicator of left ventricular function than the levels measured during an acute phase, we sought to assess the association of NT-proBNP, measured 6 months after acute myocardial infarction (AMI), with traditional risk factors, characteristics of in-hospital and early postinfarction course, as well as its prognostic value and optimal cut-points in the ensuing 1-year follow-up.
Methods: Fasting venous blood samples were drawn from 100 ambulatory patients and NT-proBNP concentrations in lithium-heparin plasma were determined using a one-step enzyme immunoassay based on the »sandwich« principle on a Dimension RxL clinical chemistry system (DADE Behring-Siemens). Patients were followed-up for the next 1 year, for the occurrence of new cardiac events.
Results: Median (IQR) level of NT-proBNP was 521 (335–1095) pg/mL. Highest values were mostly associated with cardiac events during the first 6 months after AMI. Negative association with reperfusion therapy for index infarction confirmed its long-term beneficial effect. In the next one-year follow-up of stable patients, multivariate Cox regression analysis revealed the independent prognostic value of NT-

Kratak sadržaj

Uvod: Serijska merenja natriuretskih peptida kod pacijenata sa akutnim koronarnim sindromom su pokazala da su njihove vrednosti u kasnijoj, hroničnoj fazi bolji prediktor prognoze i pouzdaniji indikator funkcije leve komore nego one u akutnoj fazi. Stoga je cilj ovog rada da se ustanove vrednosti NT-proBNP-a 6 meseci nakon akutnog infarkta miokarda (AIM), njihova udruženost sa tradicionalnim faktorima rizika, karakteristikama intrahospitalnog i ranog postinfarktnog toka, kao i njegov prognostički značaj i optimalne prediktivne vrednosti, tokom narednog jednogodišnjeg praćenja.
Metode: Uzorci krvi su uzeti našte kod 100 ambulantnih pacijenata. Koncentracije NT-proBNP-a u litijum-heparinskoj plazmi su određivane korišćenjem jednostepenog enzimskog imunoeseja, baziranog na »sendvič« principu, na uređaju »Dimension RxL clinical chemistry system« (DADE Behring-Siemens). Pacijenti su praćeni narednih godinu dana radi registrovanja novih srčanih događaja.
Rezultati: Medijana (IQR) NT-proBNP-a u našoj populaciji bila je 521 (335–1095) pg/mL. Najviše vrednosti NT-proBNP-a bile su značajno pozitivno udružene sa srčanim događajima tokom prvih 6 meseci nakon AIM; nasuprot tome, negativna udruženost sa reperfuzionom terapijom u lečenju indeks infarkta potvrdila je njen dugotrajni povoljan efekat. Tokom jednogodišnjeg praćenja stabilnih pacijena-

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List of abbreviations: AMI, acute myocardial infarction; IQR, interquartile range; AUC, area under ROC curve; ROC, receiver operating characteristic; HF, heart failure; CAD, coronary artery disease; NCE, new coronary events; EDTA, ethylene diamine-tetraacetic acid; EF, ejection fraction.

proBNP for new-onset heart failure prediction (p=0.014), as well as for new coronary events prediction (p=0.035). Calculation of the AUCs revealed the optimal NT-proBNP cut-points of 800 pg/mL and 516 pg/mL, respectively.
Conclusions: NT-proBNP values 6 months after AMI are mainly associated with the characteristics of early infarction and postinfarction course and can predict new cardiac events in the next one-year follow-up.

Keywords: prognostic neurohumoral testing, postinfarction period, N-terminal pro-brain natriuretic peptide, myocardial infarction

ta, multivarijantna regresiona Coxova analiza pokazala je nezavisan prognostički značaj NT-proBNP-a u predviđanju novonastale srčane insuficijencije (SI) (p=0,014), kao i novih koronarnih događaja (NKD) (p=0,035). Analizom ROC krive dobijene su optimalne prediktivne vrednosti NT-proBNP-a: 800 pg/mL za SI i 516 pg/mL za NKD.
Zaključak: Vrednosti NT-proBNP-a 6 meseci nakon AIM su značajno udružene sa karakteristikama infarktnog i ranog postinfarktnog toka i nezavisno predviđaju najvažnije nove srčane događaje tokom narednih godinu dana.

Ključne reči: prognostičko neurohumoralno testiranje, postinfarktni period, N-terminalni promoždani natriuretski peptid, infarkt miokarda

Introduction

During the last decade, B type-natriuretic peptides have moved on »from bench to bedside« very quickly. Originally, they were introduced in clinical practice as a diagnostic tool for heart failure (HF) (1). Later, their independent prognostic value was also shown, especially concerning mortality and heart failure, in patients with stable and unstable coronary artery disease (CAD) (2–5). On the other hand, data about acute coronary events prediction are still conflicting; in contrast to the »PEACE« trial (2), in which neither BNP nor NT-proBNP significantly increased the risk of myocardial infarction (MI), »The Heart and Soul Study« found an independent association of both markers with the individual outcomes of heart failure, myocardial infarction and cardiovascular death (6). Also, NT-proBNP was found to be a useful biomarker for distinguishing patients with long-standing hypertension who are at risk of heart failure, allowing optimization and proper treatment of these patients (7).

Patients with previous myocardial infarction represent a heterogenous group, whose prognosis differs significantly. Since traditional risk factors have less prognostic value in this secondary prevention population, they are important candidates for neurohumoral testing. Serial analyses of NT-proBNP in patients with non-ST segment elevation acute coronary syndromes (FRISC-II substudy) showed that levels measured during a chronic, relatively stable phase are a better predictor of mortality than those measured during an acute, unstable phase (8). Also, assessment of NT-proBNP level 6 months after ST-elevation MI was a better indicator of infarct size and left ventricular function measured by cardiac magnetic resonance than baseline (admission) NT-pro BNP values (9).

Although previously thought to be equally effective for diagnostic and prognostic purposes (10), recently published data from »The Heart and Soul Study« found NT-proBNP to be superior to BNP, when added to clinical risk factors, for net reclassification of the risk for major adverse cardiac events in patients with stable CAD (6).

Meta-analysis of nine prospective studies, which indicated strong association between the circulating concentration of NT-proBNP and long-term prognosis of patients with stable CAD, pointed out that although most of the included studies grouped the population according to the median or quartiles of NT-proBNP, the specific NT-proBNP levels varied greatly among different studies, making it impossible to give a precise cut-point (11).

Therefore, we designed this study to assess the association of NT-proBNP, measured 6 months after AMI, with traditional risk factors, characteristics of in-hospital and early postinfarction course, as well as its prognostic value and optimal cut-points in the next one-year follow-up.

Material and Methods

Study population and design

We enrolled prospectively 114 consecutive ambulatory patients, who were treated for AMI six months ago in our coronary care unit. Of them, 14 patients met exclusion criteria based on data from the literature about other potential sources of natriuretic peptides such as: age >70, renal failure, liver disease, known malignant disease, chronic systemic illness or trauma or surgery in the last 2 months. Finally, 100 participants gave informed consent for study enrollment and underwent a baseline study appointment, which included a medical history interview, physical examination, and resting echocardiogram. Fasting venous blood samples were drawn and EDTA plasma was frozen at –80 °C until measurement. Patients were followed-up for the next one year, for the occurrence of new cardiac events; the relevant endpoints were new-onset HF and new coronary events (NCE), defined as a composite of myocardial reinfarction or unstable angina (according to standard definitions) (12). New-onset heart failure was defined as a clinical syndrome involving at least 2 of the following: paroxysmal nocturnal dyspnoea, orthopnea, elevated jugular venous pressure, pulmonary rales and third heart sound. These clinical signs and symptoms had to be accompanied by intravenous diuretic or vasodilator therapy. The study protocol was

approved by the Ethical Committee of School of Medicine, University of Belgrade and conformed to applicable institutional and national guidelines for research on human subjects, as well as to the Declaration of Helsinki.

Blood sampling procedures and biochemical assays for measurement of NT-proBNP levels

Samples of EDTA – anticoagulated venous blood were obtained in the morning and centrifuged at 2000 rpm. Plasma was aspirated and frozen at –80 °C until measurement. The NT-proBNP concentrations in lithium-heparin plasma were determined using a one step enzyme immunoassay based on the »sandwich« principle on a Dimension RxL clinical chemistry system (DADE Behring-Siemens) with commercial reagents (13). The interassay coefficient of variation was 3.1% at a concentration of 50 pg/mL (n=60), 2.5% at a concentration of 12000 pg/mL (n=60). The measuring range for the assay was 10–30000 pg/mL.

Fasting baseline glucose, creatinine, and serum lipids (total cholesterol, HDL cholesterol and triglycerides) were determined by use of routine methods of the respective study centers. All biochemical analyses were performed blinded to the patients' status.

Echocardiography

Two dimensional ultrasound resting echocardiography was performed using a commercially available imaging system (VIVID 4, General Electrics Healthcare) for each subject by an expert sonographer, blinded to patient data, at study entry. Determination of systolic ejection fraction (EF) of the left ventricle was done by planimetry of the left ventricle (biplane Simpson method) (14).

Statistical analysis

Statistical analysis was performed with SPSS 13.5 for Windows. Since the distribution of NT-proBNP values was skewed, their original values were described as medians with interquartile range and were log-transformed to enable the application of parametric tests. Normally distributed data were expressed as mean ± standard deviation (SD); categorical data were summarized as frequencies and percentages. Since this investigation is a longitudinal study in which patients were followed for one year (and therefore a control group to themselves), there was no healthy control group. Logistic regression analysis was used to investigate the association of NT-proBNP values (as highest vs. other 3 quartiles) with demographic and risk factors, as well as with in-hospital and early postinfarction course. Cox proportional hazards regression model, adjusted for variables known to be important predictors of HF or NCE was used for prognostic analysis, i.e. to examine the independent association of NT-proBNP with new cardiac events during the one-year follow-up. Receiver-operating characteristic (ROC) analysis was used to estimate the overall prognostic accuracy of NT-proBNP and to define its optimal predictive cut-off values. Finally, Kaplan-Meier survival curves with log rank tests were used for comparisons of the occurence of new cardiac events in patient groups stratified according to optimal cut-points.

Results

Baseline characteristics of study population and association of NT-proBNP with demographic and traditional risk factors, characteristics of in-hospital and early postinfarction course

The final study group consisted of 100 ambulatory patients (81 men and 19 women, mean age 59±9 years) who had survived an AMI six months earlier. At least one risk factor was present in 88% of patients; most of them had hypertension (68%) and hyperlipidaemia (67%), followed by smoking (60%), family history (41%) and diabetes (20%). ST segment elevation at index event was present in 83% of patients and reperfusion therapy was given to 67% of patients. The localization of infarction was anterior in 42% of patients and 19% of patients had heart failure (Killip class > 1) during initial hospitalization. Multivessel disease was found at coronary angiography in 41% of patients. During the first 6 months after AMI (early postinfarction course), 12% of patients had heart failure (NYHA > I), 8% had a new coronary event and 6% of patients were surgically revascularized (all coronary events and procedures happened at least 2 months before study inclusion); beta blockers were used by 75% and ACE inhibitors by 79% of patients. The mean LVEF was 46±8%.

Median (IQR) level of NT-proBNP was 521 (335,1095) pg/mL. Factors significantly associated with the highest NT-proBNP quartile among demographic and risk factors, as well as in-hospital and early postinfarction course are presented in *Table I*. Older age was independently associated with highest NT-proBNP values, together with all cardiac events during the first 6 month after AMI, and the strongest association was found, as expected, with actual heart failure. Negative association was observed with reperfusion therapy for index AMI (during initial hospitalization).

Prognostic significance of NT-proBNP

Because of the known relationship of NT-proBNP and heart failure, only patients without any signs and

Table I Independent associations of the highest NT-proBNP quartile with demographic and risk factors (model 1), in-hospital characteristics (model 2) and early postinfarction (6 months) course (model 3).

	B	SE	OR	95% CI	*p*
Model 1*					
Age	1.12	0.56	3.07	1.03–9.14	0.044
Model 2 †					
STEMI[a]	1.61	0.69	4.62	1.28–16.68	0.019
Reperfusion therapy	–1.70	0.73	0.18	0.04–0.76	0.020
Model 3‡					
NYHA[b]>1	1.59	0.61	4.90	1.49–16.15	0.009
Rec. ischem. event	1.35	0.57	3.86	1.25–11.86	0.018
Revascularization	1.30	0.60	3.69	1.13–12.0	0.031

[a]STEMI indicates ST-elevation myocardial infarction; [b]NYHA indicates New York Heart Association (classification of heart failure).
*Adjusted for sex, diabetes, hypertension, smoking, hyperlipidaemia and family history of CAD.
†Adjusted for infarct localization, peak creatine-kinase, Killip class and multivessel disease.
‡Adjusted for actual ejection fraction and medications use.

Table II Independent predictors of new coronary events (NCE) and new-onset heart failure (HF)*.

Variable	NCE			New-onset HF		
	HR	95% CI	p	HR	95% CI	p
Diabetes	1.19	1.045–1.360	0.009	1.15	0.99–1.34	0.050
Rec. ischem. event				1.08	1.01–1.15	0.023
Statin use	0.30	0.094–0.977	0.046			
ln (NT-proBNP) (highest quartile)	2.03	1.052–3.923	0.035	3.29	1.27–8.54	0.014

* adjusted for age, risk factors, reperfusion therapy and EF

symptoms of heart failure, as well as without radiographic signs of HF, were included in the prognostic analysis (88 patients, mean age 57±9, female 14, male 74, mean EF 48±8; median (IQR) NT-proBNP 490 (296,950) pg/mL). During one-year follow-up (11–14 months), 2 patients died (2.3%), 10 (11.3%) patients had NCE and 15 (17%) had new-onset HF. Multivariate Cox regression analysis revealed the independent prognostic value of NT-proBNP (as log-transformed continuous variable) for new-onset HF and NCE prediction (*Table II*).

ROC analysis and optimized NT-proBNP cut-off values

Calculation of the areas under the ROC curves, as a measure of overall prognostic accuracy, demonstrated that NT-proBNP performed better for new-onset HF than for NCE, although the accuracy was satisfactory for both events (*Figure 1*). Therefore, further analysis of the ROC curve, in order to assess the optimal predictive cut-off values of NT-proBNP, was done. The value with the highest sensitivity and specificity was 800 pg/mL for new-onset HF (sensitivity 78%, specificity 79%, negative predictive value 92%) and 516 pg/mL for NCE (sensitivity 75%, specificity 58%, negative predictive value 91%).

When patients were stratified into two groups, according to optimized cut-off values, Kaplan-Meier analysis showed a highly significant difference in the rates of new-onset HF and a clear trend toward higher incidence of NCE (*Figure 2*).

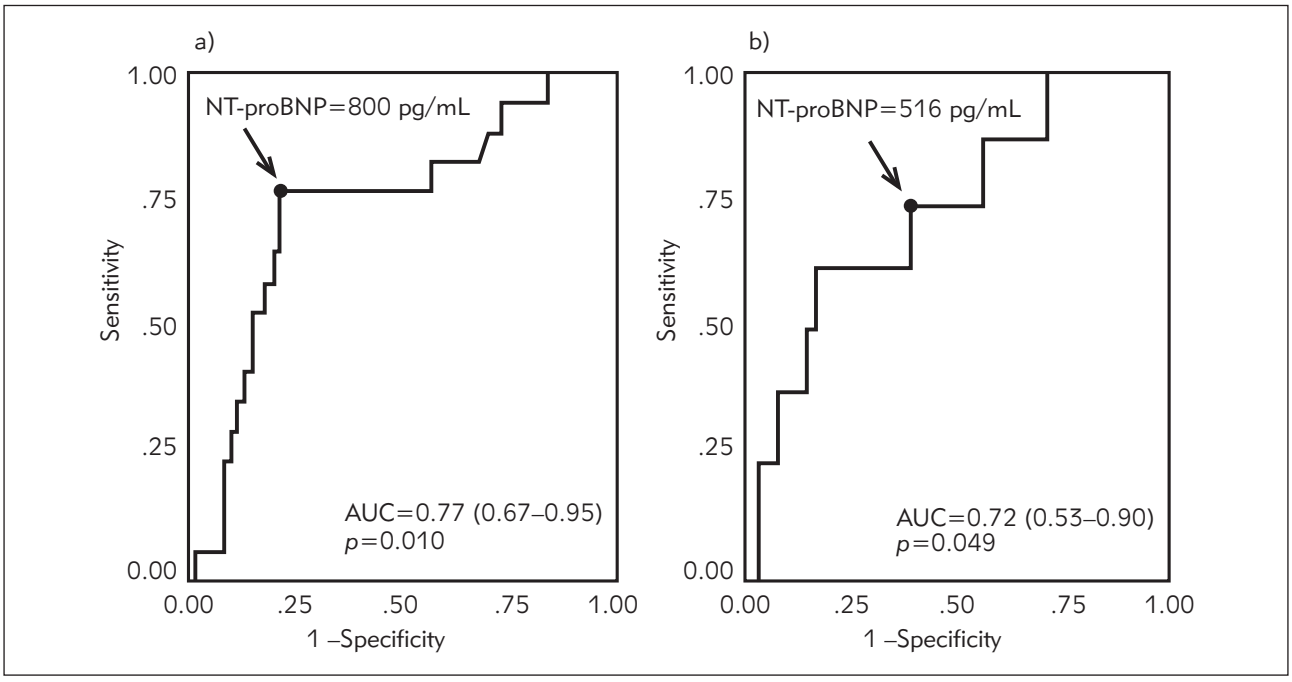

Figure 1 Receiver operating characteristic (ROC) curves showing prognostic accuracy of NTproBNP for new-onset heart failure prediction (a.) and new coronary events prediction (b.), together with the optimal cut-off values.

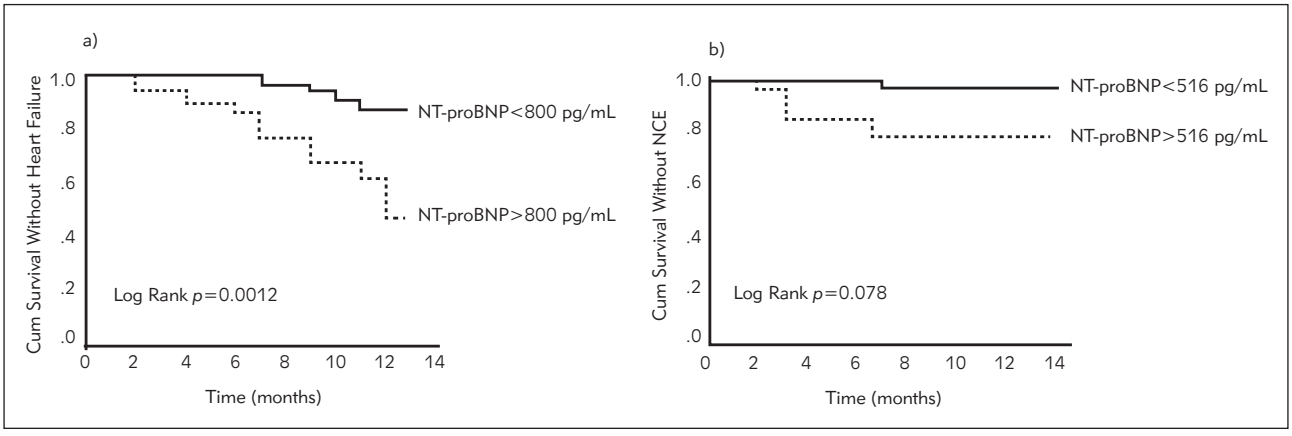

Figure 2 Kaplan-Meier survival curves without new-onset heart failure (a.) and new coronary events (NCE) (b.), according to optimal cut-off values of NT-proBNP.

Discussion

The main findings of our study are: a.) NT-proBNP values are higher in outpatients with previous MI than in the healthy population, as well as in the patients with stable CAD; b.) none of the traditional risk factors for CAD (apart from age) was independently associated with NT-proBNP; conversely, all cardiac events during the first 6 months after AMI were associated with highest NT-proBNP values, the strongest one being the association with heart failure. Negative association with reperfusion therapy for index infarction during initial hospitalization confirmed its long-term beneficial effect, by reducing the infarct size; c.) NT-proBNP accurately predicted new-onset HF in the next one-year follow-up and, to a lesser extent, NCE as well; d.) the optimal NT-proBNP values were: 800 pg/mL for new-onset HF and 516 pg/mL for NCE.

Patients with previous MI are usually classified as chronic CAD patients, together with those with stable angina or previous coronary artery bypass grafting (CABG). This may not stand true because the existence of previous myocardial infarction is usually associated with worse angiographic findings (more

widespread CAD), as well as more frequent appearance of heart failure and recurrent ischemic events, which influences quality of life and life expectancy (15, 16). Our data support these findings by showing a significantly higher NT-proBNP median value (521; IQR 335,1095 pg/mL) compared to the one described for a healthy population by Melander et al. (17) (61; IQR 34,110 pg/mL), ($p<0.001$), as well the one described for patients with chronic stable CAD (6) (174; IQR 74,460 pg/mL), ($p<0.01$). Apart from increased ventricular stretch and wall tension, natriuretic peptides synthesis has been shown in atherosclerotic coronary plaques as well (18) and NT-proBNP levels might reveal the prevalence and severity of coronary stenoses (19, 20). Multivessel disease was present in almost half of the patients in our study, possibly contributing to the higher median NT-proBNP level.

The reason for choosing 6 months after AMI for NT-proBNP measurement was based on the results of Lindahl et al. (8) showing that its levels decrease markedly in the first 24 h and then decrease more gradually over the following 6 months. Distribution of NT-proBNP levels, shown on *Figure 1*, justifies the common use of the highest quartile for correlations and prognostic purposes. Highest NT-proBNP values in our study were expectedly associated with age, HF and recurrent ischemic event in the early postinfarction period, as well as with index ST-elevation MI which usually represents larger myocardial necrosis and subsequent left ventricular remodelling compared to non-ST-elevation MI. In contrast, reperfusion therapy for index event was expectedly associated with lower NT-proBNP values, since it definitely reduces the infarct size and consequent remodeling of the left ventricle. Highest NT-proBNP values were also found in revascularized patients, which can be partially explained by transitory periprocedural ischemia directly stimulating its synthesis (21), but other potential stimuli related to revascularization are also possible, such as inflammation and modified neuroendocrine function.

Having in mind the fact that about 19% of men and 26% of women older than 45 years having a myocardial infarction will die within one year, whereby survivors will have a 1.5 to 15 times higher risk for illness and death compared to the general population (22), use of a simple blood test for NT-proBNP level that could improve risk stratification and possibly tailor the therapy becomes essential. Furthermore, it has been shown that beneficial effects of adequate therapeutic protocol for heart failure were accompanied by a significant reduction of BNP (23).

Patients included in the prognostic analysis in this study were those surviving 6 months after myocardial infarction, free of coronary events or interventions for at least two months, and with relatively preserved left ventricular function, therefore representing a homogenous intermediate risk group of postinfarction patients. In the next one-year follow-up, multivariate Cox regression analysis revealed the independent prognostic value of NT-proBNP for new-onset HF prediction (together with reccurent coronary event), as well as for new coronary events prediction (together with diabetes and statin non-use). This is in accordance with the recently published data on participants in cardiac rehabilitation, of whom 50% had AMI and 50% had coronary artery bypass surgery (24). They showed that 12-months NT-proBNP levels after an acute cardiovascular event are strongly associated with subsequent long-term events and may provide numerically better reclassification of risk for an adverse cardiovascular event compared to NT-proBNP levels shortly after the acute event, after adjustment for the established risk factors.

In our study, patients with high NT-proBNP values had 3 times higher risk for incident HF. Similar findings have been shown among ambulatory patients with stable CAD and preserved left ventricular function, among which more than half had a history of prior MI (25). The overall prognostic accuracy (AUC) for incident HF of NT-proBNP in our study was 0.77 and the optimal cut-off value was 800 pg/mL. Compared to the limit of the highest NT-proBNP quartile in our stable patients (950 pg/mL), it was associated with a higher sensitivity (78% vs 63%), which is important in the secondary prevention populations, especially as that was at an expense of somewhat lower specificity (79% vs 84%). Negative predictive values were high for both cut-offs and almost the same (~90%).

Although to a lesser extent, NT-proBNP was also predictive of NCE in our study (AUC=0.72). The explanation could be in transitory hypoxia, stimulating cardiac natriuretic peptides expression by increasing the tissue content of natriuretic peptide messenger RNA, as shown by Goetze et al. (26). Also, silent ischemia was found to increase natriuretic peptides in patients with type 2 diabetes (27). One of the first authors reporting an independent association of NT-proBNP with the coronary events in fully adjusted models of secondary prevention population were investigators of the HOPE study (28). Previously mentioned study on ambulatory patients with stable CAD and preserved left ventricular function also observed an association between an elevated NT-proBNP level and the risk of MI, although the magnitude was less than for the other cardiovascular events and was significantly attenuated after adjusting for the other prognostic markers (25). On the contrary, Mishra et al. (6) found NT-proBNP to be significantly associated with MI, fully adjusted for all relevant clinical, labaratory and echocardiographic variables. The optimal cut-off value in our study was 516 pg/mL, which is very close to the one mentioned by Bibbins-Domingo et al. (25) (500 pg/mL) to indicate patients with highest risk for future events among those with

stable CAD. The fact that Kaplan-Meier analysis showed only a trend toward higher risk of NCE when patients were stratified according to optimal cut-off value may reflect the relatively small number of NCE in this population and possibly become significant in a larger study population, with more NCE.

Since current recommendations for the use of natriuretic peptides (29) leave the question of optimal time for risk stratification after acute coronary syndrome open, our results propose NT-proBNP values 6 months after AMI to be reliable and useful for identification of patients who could profit from more intensive monitoring and timely treatment options toward reducing future adverse cardiovascular events. The absence of association with traditional risk factors, together with its prognostic significance may reinforce its role in the secondary prevention after AMI.

Limitations of the study

Due to the limited sample size, the results should be prospectively validated in a larger group of patients, including more women. Second, most high-risk patients were excluded because they fulfilled the exclusion criteria (i.e. other potential sources of NT-proBNP secretion) or died during the first 6 months after AMI, so the results may not be generalized to the whole post-myocardial infarction population. Nevertheless, our prespecified study group fulfilled the important criteria of homogeneity. Finally, minimization of the potential biases could be obtained by measuring each NT-proBNP sample in triplicate or duplicate.

Conclusions

In this secondary prevention population of post-myocardial infarction patients, highest NT-proBNP values were associated mostly with heart failure and recurrent ischemic events in the first 6 months after AMI. Long term beneficial effect of reperfusion therapy was confirmed by significantly lower NT-proBNP values 6 months after AMI. NT-proBNP accurately predicted new-onset HF in the next one-year follow-up, at the optimal cut-off value of 800 pg/mL and, to a lesser extent NCE, at 516 pg/mL.

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Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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