The Value of NT-PROBNP in Early Risk Stratification of Acute Coronary Syndromes [6]

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ABSTRACT

Introduction: The N-terminal portion of brain natriuretic peptide (NT-proBNP) has been identified as an indicator of prognosis in different cardiovascular diseases. Its role in risk stratification in patients with acute coronary syndromes (ACS) is still under evaluation.

Objective: We aimed to evaluate the prognostic value of NT-proBNP measured in the first 48 hours after admission due to an acute coronary syndrome.

Methods: Our study included 142 patients (aged 62.7 ± 12.0 years, 70.4 % males) admitted to a cardiology unit with an ACS. All laboratory evaluations were performed in the first 48 hours after admission. The mean follow-up was 200 days. Death from any cause or hospitalization because of a major acute cardiovascular event (whichever occurred first) was defined as the end-point.

Results: Cardiovascular risk factors were found in a significant proportion of our sample (hypertension in 56.3 %, diabetes mellitus in 38.0 %, current or previous smoking in 51.4 %, dyslipidemia in 67.6 %). Fifty-eight patients had left ventricular systolic dysfunction (LVSD). Serum levels of NT-proBNP were 2174 ± 4801 pg/ml. Variables associated with event-free survival in univariate analysis were: NT-proBNP (HR 1.007, 95 % CI 1.003-1.011, for each 100 pg/ml increment), serum glucose (hazard ratio [HR] 1.007, 95% CI 1.001-1.012, for each 1 mg/dl increment) and maximum cardiac troponin I (cTnI) level (HR 1.005, 95 % CI 1.001-1.009, for each 1 ng/ml

RESUMO

O valor do NT-PROBNP na estratificação de risco precoce das síndromes coronárias agudas

Introdução: O fragmento amino-terminal do peptídeo natriurético auricular (NT-proBNP) tem sido identificado como indicador de prognóstico em diferentes patologias cardiovasculares. O seu papel na estratificação de risco de doentes com síndromes coronárias agudas (SCA) continua em avaliação.

Objectivo: Avaliar o valor prognóstico do NT-proBNP medido nas primeiras 48 h após admissão por SCA.

Métodos: O estudo incluiu 142 doentes (62,7 ± 12,0 anos, 70,4 % do sexo masculino) internados em Unidade de Cardiologia por SCA. Todas as avaliações laboratoriais foram efectuadas nas primeiras 48 h após a admissão. O tempo médio de seguimento foi de 200 dias. O *end-point* definido foi a ocorrência de morte ou hospitalização por evento agudo cardiovascular *major*.

Resultados: Foram encontrados factores de risco cardiovascular numa grande parte da população estudada (56,3 % de hipertensos, 38,0 % de diabéticos, 51,4 % com história actual ou prévia de tabagismo, 67,6 % com dislipidemia). Cinquenta e oito doentes tinham disfunção sistólica do ventrículo esquerdo. O valor do NT-proBNP plasmático foi de 2174 ± 4801 pg/ml. As seguintes variáveis foram associadas a sobrevida livre do eventos cardiovasculares: NT-proBNP (HR 1,007; 95 %IC 1,003-1,011 por cada incremento de 100 pg/ml), glicemia na

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increment). The white blood count (WBC) was marginally associated with a poor prognosis (HR 1.152, 95% CI 0.994-1.335, for each 1000/mm^3 increment). After adjustment for the above variables, age, sex, left ventricular systolic dysfunction, diabetes, coronary anatomy and coronary revascularization using a forward likelihood ratio Cox regression model, NT-proBNP remained the only variable with significant prognostic value (HR 1.007, 95% CI 1.003-1.011, for each 100 pg/ml increment).

Conclusions: These data suggest that NT-proBNP is a strong clinical predictor of prognosis in acute coronary syndromes. Its early measurement should be included in the risk stratification strategy in this setting.

Palavras-Chave
NT-pro-BNP; Acute coronary syndromes; Prognosis

admissão (HR 1,007; 95%IC 1,001-1,012 por cada incremento de 1 mg/dl) e valor máximo de troponina I (HR 1,005, 95%IC 1,001--1,009 por cada incremento de 1 ng/ml). A contagem de glóbulos brancos apresentou associação quase significativa com a ocorrência do *end-point* (HR 1,152, 95%IC 0,994-1,335 por cada incremento de 1000/mm^3). Após ajustamento para as variáveis acima referidas, idade, sexo, disfunção sistólica do ventrículo esquerdo, diabetes, anatomia coronária e revascularização coronária usando um modelo de regressão de Cox tipo *forward likelihood ratio*, o valor do NT-proBNP foi o único parâmetro a manter valor prognóstico significativo (HR 1,007; 95%IC 1,003-1,011 por cada incremento de 100 pg/ml).

Conclusão: Os resultados sugerem que o NT-proBNP é um importante preditor clínico de prognóstico de doentes com SCA e que o seu doseamento precoce nesse contexto deverá ser incluído numa estratégia global de estratificação de risco.

Key words
NT-proBNP; Síndromes coronárias agudas; Prognóstico

INTRODUCTION

Acute coronary syndromes (ACS) remain a leading cause of morbidity and mortality in western countries. In the United States, an estimated 1.7 million patients with ACS are admitted each year [1]. These patients are not only prone to dire complications during the acute phase, but also experience higher risk of death and recurring major acute cardiovascular events after discharge. Risk stratification strategies have emerged to help select the most effective approach to treatment, incorporating data from history, physical exam and ancillary tests.

The natriuretic peptides are secreted by heart muscle mainly in response to wall stretch. Their biochemistry and physiology are reviewed elsewhere [2]. During the last decade, B-type natriuretic peptide (BNP) and its biologically inert amino-terminal fragment (NT-proBNP) have emerged as clinically useful biomarkers in management of cardiovascular disease [2, 3, 4]. In a seminal paper published in 2001, de Lemos et al. reported the value of BNP measurement in prognostication of 2525 patients with ACS [5]. Other studies also evaluated their role in early assessment of unstable coronary artery disease [6].

We aimed to evaluate the prognostic value of NT-proBNP soon after admission due to an acute coronary syndrome.

METHODS

This retrospective observational study was conducted in the Cardiology Unit of our institution (a tertiary care university hospital). We reviewed the medical records of all patients consecutively admitted for ACS in our Cardiology Unit from January to June 2004. Patients were eligible for inclusion if they had assessment of plasma NT-proBNP levels within the first 48 hours following onset of symptoms.

We enrolled 142 patients admitted for ACS

with baseline assessment of plasma NT-proBNP levels (Elecsys proBNP®, Roche Diagnostics), as well as other routine clinical and laboratory data. Dyslipidemia was considered in patients who reported previously documented high serum lipids, those under antidyslipidemic therapy or those with serum lipid profile meeting National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria for dyslipidemia. Hypertension was considered in patients with previous history of hypertension and/or under antihypertensive therapy. Left ventricular systolic function was assessed by transthoracic echocardiography and categorized as conserved (ejection fraction 50%), mildly compromised (ejection fraction 40% and <50%), moderately compromised (ejection fraction 30% and <40%) or severely compromised (ejection fraction <30%). After discharge, follow-up was established by telephone contact and review of the patients' medical records. Our end-point was defined as a composite of death from any cause and rehospitalization because of a major acute cardiovascular event (including new ACS or stroke).

Statistical analysis was performed using SPSS for Windows (v. 12.0). Association between the studied parameters and event-free survival was estimated by calculating unadjusted hazard ratios (HR) and 95% confidence intervals (95% CI) using the log rank test. The variables suspected to have statistically significant associations with the outcome after univariate analysis were included, together with other clinically relevant parameters, in multivariate analysis (using a forward likelihood ratio Cox regression model) to calculate adjusted HR. Statistical significance was defined at the $p<0.05$ level.

RESULTS

The baseline characteristics of our sample population are summarized in *Table I*.

Roughly 70% were male, with a mean age of 62 years. As expected, we found a high prevalence of cardiovascular risk factors and 40% had echocardiographic evidence of LVSD. Eighty patients had non-ST elevation ACS, 58 were admitted for ST segment elevation myocardial infarction (STEMI) and the remaining four had myocardial infarction of unknown location (comprising presumed new left bundle branch block or paced rhythms). Of the 117 patients with myocardial infarction, 91 evolved in Killip class I, 20 in Killip class II, four in Killip class III and the remaining two in Killip class IV. Most of these patients (86.6%) underwent coronary angiography and the majority of these had left main and/or multivessel disease. Eighty-nine (62.7%) underwent coronary revascularization during index hospitalization (66 by percutaneous coronary intervention and the remaining 23 by cardiac surgery). Most patients were started on standard medical treatment with antiplatelet drugs, statins, beta-blockers and angiotensin converting enzyme (ACE) inhibitors during hospitalization.

Baseline plasma levels of NT-proBNP and other laboratory parameters are summarized in *Table II*.

Mean follow-up time was 200 days, during which we recorded the occurrence of the defined end-point in 13 (9.4%) patients, namely five deaths and eight readmissions due

Table I
Baseline sample characteristics

	n (%)
Mean age (years)	62.712.0
Male gender	100 (70.4)
Hypertension	80 (56.3)
Diabetes	54 (38.0)
Dyslipidemia	96 (67.6)
Smoking (current or past)	73 (51.4)
Obesity	36 (25.4)
LVSF (echo)	
conserved	79 (55.6)
mildly compromised	15 (10.6)
moderately compromised	28 (19.7)
severely compromised	13 (9.2)
unknown	7 (4.9)
Type of ACS	
non-ST elevation ACS	80 (56.4)
STEMI	58 (40.8)
undetermined location	4 (2.8)
Coronary anatomy (angiography)	
no significant lesions*	8 (5.6)
single-vessel disease	42 (29.6)
multivessel disease§	56 (39.4)
left main disease	17 (12.0)
unknown	19 (13.4)
Coronary revascularization	89 (62.7)
percutaneous	66 (46.5)
surgical	23 (16.2)
In-hospital drug treatment	
aspirin	134 (94.4)
clopidogrel	89 (62.7)
beta-blockers	132 (93.0)
statins	138 (97.2)
ACE inhibitors	129 (90.8)

*Lesions considered significant if stenosis 50% (left main artery) or 70% (other epicardial arteries). § Except left main disease. LVSF: left ventricular systolic function. STEMI: ST segment elevation myocardial infarction.

Table II
Laboratory parameters (first 48h after admission)

Parameter	Median (inter-quartile range)
Hematocrit (%)	41.3 (37.2-44.0)
WBC (x109/l)	8.2 (6.5-11.6)
Glycemia (mg/dl)	143.5 (105.8-215.8)
Creatinine (mg/dl)	0.97 (0.81-1.14)
Troponin I (ng/ml)	14.2 (1.8-46.0)
NT-proBNP (pg/ml)	764 (283-1802)

Abbreviations as in text.

to a major acute cardiovascular event (all of them for a new ACS). Of the five deaths, one occurred during index hospitalization due to cardiogenic shock; the remaining four deaths occurred after discharge (two of unknown cause and two of non-cardiac cause). No patients were lost to follow-up.

We assessed possible associations between event-free survival from admittance and various baseline clinical and laboratory parameters, namely: plasma NT-proBNP levels, admission glycemia, maximum cTnI, WBC, hematocrit, plasma creatinine, age, sex, hypertension, diabetes, current or past smoking status, dyslipidemia, obesity (body mass index >30 kg/m^2), LVSD, angiographically significant coronary artery disease and coronary revascularization. Variables associated with event-free survival in univariate analysis were (*Table III*): NT-proBNP (HR 1.007, 95% CI 1.003-1.011, for each 100 pg/ml increment), serum glucose (HR 1.007, 95% CI 1.001-1.012, for each 1 mg/dl increment) and maximum cTnI level (HR 1.005, 95% CI 1.001-1.009, for each 1 ng/ml increment). The WBC was marginally associated with a poor prognosis (HR 1.152, 95% CI 0.994-1.335, for each 1000/mm^3 increment).

Table III
Association with event-free survival (univariate analysis)

Variable	HR	95% CI
Male gender	1.46	0.48-4.46
Age	1.01	0.96-1.06
Hypertension	0.88	0.29-2.61
Diabetes	1.39	0.47-4.14
Smoking	0.41	0.13-1.32
Dyslipidemia	0.98	0.31-3.31
Obesity	0.031	0.00-5.89
LVSD	2.49	0.81-7.61
Coronary revascularization	0.49	0.16-1.46
Significant coronary obstruction	1.12	0.38-3.34
Creatinine	1.70	0.78-3.71
Hematocrit	1.43	0.46-4.45
WBC (for each 109/l increment)	1.15	0.99-1.33
Glycemia (for each 1 mg/dl increment)	1.01	1.00-1.01
cTnI (for each 1 ng/ml increment)	1.01	1.00-1.01
NT-proBNP (for each 100 pg/ml increment)	1.01	1.00-1.01

Abbreviations as in text.

To adjust for potential confounders, we calculated adjusted HR and 95% CI for the above variables plus other clinical parameters widely accepted as prognostic markers in ACS patients, namely age, sex, history of diabetes, LVSD, coronary anatomy as documented by angiography, and coronary revascularization. After multivariate analysis, only plasma NT-proBNP levels remained as a significant predictor of event-free survival (HR 1.007, 95% CI 1.003-1.011 for each 100 pg/ml increase in plasma levels).

DISCUSSION

Despite the significant improvements in the approach to coronary artery disease in recent decades, ACS is still a cause of significant morbidity and mortality worldwide.

As early revascularization therapies become more widely available, with their increasing costs, care must be taken to select patients who will benefit most from an early aggressive approach in a cost-effective way. Furthermore, the efficacy of the currently most used risk stratifying strategies for early invasive versus conservative treatment remains unsettled[7,8].

In accordance with previously published data, our results have shown that plasma NT-proBNP levels soon after ACS onset are strong clinical predictors of event-free survival. In fact, they performed better than cTnI, a widely used biomarker in the diagnosis and risk stratification of ACS, and better than other routine clinical and laboratory parameters of established value as markers of prognosis in this setting, as they were the only independent predictor of a worse prognosis after multivariate analysis.

This being a small observational study with a short follow-up time, our results are fraught with limitations that must be acknowledged. We enrolled all of the sample patients after they were admitted to our Cardiology Unit, so this excluded some patients with ACS who might not have reached us for some reason, creating potential selection bias. We also included patients with STEMI and NSTEMI/unstable angina, which may be pathophysiologically distinct

entities and require different approaches in early management. These results have been driven by a small number of events (13 among 142 patients in a mean follow-up time of 200 days), which might have underestimated the association measures assessed. Lastly, being conducted in a tertiary care center with round-the-clock cardiac catheterization and cardiac surgery facilities available, with a high proportion of patients undergoing coronary revascularization during index hospitalization (62.7 %), the results of this study may not apply to different situations, with more limited availability of early invasive management.

Nonetheless, these data suggest that NT-proBNP must be considered as a tool for early risk assessment in ACS patients. Exactly how this should be done remains a matter of ongoing debate. This issue will have to be addressed in large-scale multicenter trials before we know with certainty the cost-effectiveness of routine NT-proBNP evaluation in ACS patients and how good it is in helping select the best therapeutic approach in this setting.

CONCLUSIONS

These data suggest that NT-proBNP is a strong clinical predictor of prognosis in ACS and that its early measurement might be included in an early risk stratification strategy in this setting, although the cost effectiveness of such an approach remains to be established. Larger studies are needed to specifically address this issue.

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