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ORIGINAL ARTICLE

Does admission NT-proBNP increase the prognostic accuracy of GRACE risk score in the prediction of short-term mortality after acute coronary syndromes?

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Abstract

Background: NT-proBNP has prognostic implications in heart failure. In acute coronary syndromes (ACS) setting, the prognostic significance of NT-proBNP is being sought. We studied short-term prognostic impact of admission NT-proBNP in patients admitted for ACS and in association with GRACE risk score (GRS). *Methods and Results:* We studied 1035 patients admitted with ACS. Patients were divided in quartiles according to NT-proBNP levels on admission: Q1 <180 pg/ml; Q2 180–691 pg/ml; Q3 696–2664 pg/ml; Q4 2698–35 000 pg/ml. Groups were compared in terms of short-term all-cause mortality. Patients with higher NT-proBNP had worst GRS on admission. They also received less aggressive treatment. In-hospital mortality was 0.8%, 3.0%, 5.8% and 12.8% ($P<0.001$) and 30-day mortality 1.6%, 4.6%, 6.5% and 16.7% ($P<0.001$) respectively. In multivariate logistic regression analysis, NT-proBNP is an independent predictor of in-hospital (OR 2.35; 95% CI: 1.12–4.93, $P=0.022$) and 30-day mortality (OR 2.20; 95% CI: 1.17–4.12, $P=0.014$). However, NT-proBNP does not add any incremental benefit to GRS for prediction of outcome by ROC curve analysis. *Conclusions:* NT-proBNP is an independent predictor of in-hospital and 30-day mortality after ACS, independently of left ventricular function, but does not increase the prognostic accuracy of GRS.

Key Words: *Admission N-terminal-proBNP, GRACE risk score, acute coronary syndromes, prognosis*

Introduction

During the last decade, B-type natriuretic peptide (BNP) has been recognized as a useful marker for the detection of acute and chronic left ventricular dysfunction (1,2). Acute regional diastolic and/or systolic left ventricular dysfunction is a hallmark of sudden and prolonged myocardial ischaemia (3). In fact, natriuretic peptides have been found to be elevated in the setting of acute coronary syndromes (ACS). In ST-segment elevation, peak values are observed 16 hours after admission with over one-half of the patients developing a second peak by the fifth day (4). BNP is produced by myocardial cells when submitted to wall stress or overload, especially if systolic dysfunction is present (1,4).

N-terminal-pro-BNP (NT-proBNP) is the amino terminal product after cleavage of the precursor peptide of BNP (4). This molecule has a longer half-life that may allow for greater accumulation of NT-proBNP and a greater sensitivity in detecting more subtle structural and functional changes (5).

Risk prediction based on clinical, ECG, and biochemical (cardiac troponin) markers, is relatively inaccurate (6). The development of risk scores, such as GRACE risk score, associating several variables, improved the predictive capacity, but requires several measurements on admission (7).

In the present study, we evaluated the short-term prognostic value of an early measurement of NT-proBNP in a wide cohort of patients encompassing the whole spectrum of ACS. We also studied if NT-proBNP has any incremental value when associated with GRACE risk score for the prediction of outcome.

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Materials and methods

The present study is a retrospective analysis of an internal registry of ACS (based on GRACE registry) that included consecutive patients from January 2005 to July 2007, admitted at our Intensive Care Unit for ACS. Inclusion criteria were—clinical history consistent with new onset or a worsening pattern of characteristic ischemic chest pain in the previous 24 h, occurring at rest or with minimal exertion (lasting longer that 10 min) and at least one of the following: ECG changes compatible with ischemia (ST-segment depression, elevation or T wave inversion) or elevated cardiac enzymes or biomarkers (Troponin T) above the upper limit of normal. Baseline demographics, clinical history, and objective assessment of clinical signs were obtained. Follow-up was performed in all surviving patients by telephone interview 30 days after admission. All cause mortality was evaluated at 30 days of the follow-up period.

Plasma NT-proBNP was incorporated into the diagnostic protocol and obtained on admission and serial measurements were made until discharge. Venous blood samples were obtained by direct venous puncture. Blood samples were collected in tubes without anticoagulant, centrifuged, and serum was analysed within 3 hours. Serum NT-proBNP was determined, with an electrochemiluminescence immunoassay (ECLIA) on an Elecsys 2010 analyser (Roche Diagnostics). The analytical range of this assay extended from 5 to 35 000 pg/ml. At our laboratory, total precision has a coefficient of variation of 2.9% and 1.9% using Roche Precicontrol II, 1 and 2 respectively. Serum creatinine was analysed by a Jaffe timed rate method, and estimated creatinine clearance was calculated with the Cockcroft-Gault equation (8).

The study complies with the principles outlined in the Declaration of Helsinki and patients gave informed consent for inclusion in the registry and for follow-up contact.

Statistical analysis

Continuous data were presented as mean $\pm$ SD (median and 25–75th percentile for skewed variables) and were compared with ANOVA test or Kruskal–Wallis test. Categorical variables were presented as frequencies and percentages and were compared using Chi-square test.

Patients were divided in quartiles according to NT-proBNP levels on admission: Q1 (<180 pg/ml), Q2 (180–691 pg/ml), Q3 (696–2664 pg/ml) and Q4 (>2698 pg/ml). Blood glucose, estimated creatinine clearance (eCrCl), admission and peak NT-proBNP levels and peak creatinine kinase were much skewed. A 10-base logarithmic transformation was done and log-transformed variables were used throughout.

Pearson's correlation coefficient and linear regression analysis was computed to examine the association between NT-proBNP and other variables. Receiver operating characteristics (ROC) curves were generated and the area under the curve (AUC) (and its 95% confidence intervals) calculated to determine the best discriminating level of NT-proBNP for predicting in-hospital and 30-day mortality. Optimal discrimination limits were identified at the cut-point that maximizes sensitivity and specificity. ROC curves were constructed for NT-proBNP, GRACE risk score and a combination of both (as continuous variables) for the prediction of all-cause mortality.

Univariate analysis was performed to evaluate the significance of all variables for prediction of outcome. All variables with a *P*-value <0.10 were then entered into a multivariable logistic regression analysis. We also included variables that could influence NT-proBNP levels, identified by linear regression analysis.

To compare overall diagnostic performance, comparing the AUC of two ROC curves (admission NT-proBNP and GRACE risk score), we used the bivariate chi-square test with ROCKIT 1.1B2 software β version (Chicago, Illinois). All the other data analysis was performed using SPSS version 10.0 (SPSS Inc. Chicago, Illinois). A *P*-value <0.05 was considered statistically significant.

Results

Study population consisted of 1035 patients with NT-proBNP measurements (out of a total of 1113 patients included in our registry), 72% males, aged 63 ± 13 years. The median time from the beginning of symptoms to first blood collection for NT-proBNP assessment was 8.5 h (4–17.5) in the overall population, 5.5 h (3–13) in the group with ST-segment elevation and 14 h (7.5–23.5) in the group with ACS with non-ST-segment elevation. Patients' characteristics are shown in Table I. Age, hypertension, previous myocardial infarction (MI), previous percutaneous coronary intervention (PCI) and blood glucose on admission increased along with the quartiles. Male gender, smoking, total cholesterol, LDL-cholesterol, triglycerides and eCrCl decreased. ST-segment elevation acute MI and a lower Killip class was more frequent in lower quartiles. Patients in the highest quartiles received less clopidogrel, beta-blockers, statins and PCI (Table II). The unadjusted mortality rate (in-hospital and 30-day mortality) increased directly across quartiles of NT-proBNP ($P<0.001$) (Figure 1).

In bivariate analysis, higher baseline levels of NT-proBNP were directly associated (with fair correlation) with age ($r=0.46$, $p<0.001$), history of hypertension ($r=0.24$, $P<0.001$), diabetes ($r=0.18$, $P<0.001$) and smoking ($r=0.29$, $P<0.001$).

Table I. Baseline characteristics for each admission NT-proBNP quartile.

	Quartile 1 $n=258$	Quartile 2 $n=260$	Quartile 3 $n=260$	Quartile 4 $n=257$	*P*-value
Age (years)	56±11	62±13	66±12	73±11	<0.001
Male gender	223 (86)	199 (76)	166 (64)	124 (48)	<0.001
BMI (kg/m2)	27±3	27±8	27±5	27±4	NS
Hypertension[a] *n* (%)	118 (46)	168 (65)	187 (72)	195 (76)	<0.001
Hyperlipidemia[b] *n* (%)	145 (56)	116 (45)	125 (48)	119 (46)	0.04
Diabetes *n* (%)	40 (15)	54 (21)	75 (29)	90 (35)	<0.001
Smoking *n* (%)	143 (55)	100 (38)	82 (31)	43 (17)	<0.001
Previous MI *n* (%)	27 (10)	36 (14)	47 (18)	52 (20)	0.01
Prev. revascularization *n* (%)	30 (11)	38 (14)	43 (16)	38 (15)	NS
ST-segment elevation *n* (%)	180 (70)	162 (62)	146 (56)	124 (48)	<0.001
Killip class >1 *n* (%)	13 (5)	19 (7)	32 (12)	74 (29)	<0.001
LVEF <40% *n* (%)	5 (2)	11 (4)	28 (11)	49 (19)	<0.001
Blood glucose (mg/dl)	129 (112–167)	132 (107–170)	141 (112–180)	151 (121–204)	<0.001
eCrCl (ml/min)	95 (78–115)	86 (66–108)	74 (57–95)	52 (37–73)	<0.001
Total cholesterol (mg/dl)	202±47	194±46	188±53	171±41	<0.001
HDL-cholesterol (mg/dl)	38±12	39±12	40±16	40±12	NS
LDL-cholesterol (mg/dl)	135±44	130±37	122±43	110±35	<0.001
Peak CK (UI/ml)	1132 (349–2952)	804 (230–2262)	906 (236–2414)	755 (242–2235)	NS
Peak Troponin T (ng/ml)	2.74 (0.39–7.13)	2.04 (0.4–6.29)	2.46 (0.6 –5.75)	2.93 (0.97–7.63)	0.059
Ad. NT-proBNP (pg/ml)	65 (30–111)	361 (242–518)	1431 (1007–1995)	6073 (3707–12004)	<0.001
P. NT-proBNP (pg/ml)	458 (115–1407)	2129 (383–1834)	3420 (1289–3779)	12040 (4199–16128)	<0.001
GRACE risk score	124±29	137±33	148±32	174±35	<0.001

[a]History of hypertension according to the patient.
[b]History of hyperlipidemia that required medical therapy according to the patient.
BMI, body mass index; MI, myocardial infarction; LVEF, left ventricular ejection fraction; eCrCl, estimated creatinine clearance; CK, creatinine kinase; Ad., admission; P., peak.

An inverse association was seen with eCrCl ($r=-0.51$, $P<0.001$) and weight ($r=-0.20$, $P<0.001$). No correlation was found with BMI. There was also a significant correlation between GRACE risk score and NT-proBNP ($R=0.51$, $P<0.001$).

ROC curve analysis showed that admission NT-proBNP measurements are predictive of in-hospital and 30-day mortality (Figure 2). The AUC for in-hospital mortality was 0.74 (95% CI: 0.67–0.81; $P<0.001$) and for 30-day mortality, 0.73 (95% CI: 0.67–0.79; $P<0.001$). The results were similar for peak NT-proBNP: in-hospital mortality AUC 0.82 (95% CI: 0.76–0.89; $P<0.001$); 30-day mortality, AUC 0.80 (95% CI: 0.74–0.86; $P<0.001$). The curves were used to determine cut points to evaluate the likelihood of death for admission NT-proBNP. Decision limits yielding 57% sensitivity are 2884 pg/ml (79% specificity) for in-hospital death and 2818 pg/ml (78% specificity) for 30-day mortality. The same analysis was done for GRACE risk score in the present population of patients, with more significant results (Table III). The AUC of NT-proBNP for in-hospital mortality is significantly lower when compared with GRACE risk score AUC (Chi-square statistic $=12.91$, $P<0.001$) as well as for 30-day mortality (Chi-square statistic $=11.18$, $P=0.0037$). The combined index of GRACE risk score and NT-proBNP was studied by ROC curve analysis and the combination did not yield incremental value over GRACE risk score alone (Table III).

Univariate analysis showed that admission NT-proBNP levels (for the cut-offs obtained before) are predictors of in-hospital death (OR 4.76; 95% CI: 2.77–8.19; $P<0.001$) and 30-day death (OR 4.68; 95% CI: 2.90–7.55; $P<0.001$). Patients with high GRACE risk score—high NT-proBNP (GRACE risk score patients divided in tertiles and admission NT-proBNP divided by the cut-off values identified by ROC curve analysis) were more likely to have

Table II. Treatment given to the patient after hospital admission.

	Quartile 1 $n=258$	Quartile 2 $n=260$	Quartile 3 $n=260$	Quartile 4 $n=257$	*P*-value
Aspirin *n* (%)	253 (98)	256 98)	250 (96)	247 (96)	NS
Clopidogrel *n* (%)	241 (93)	242 (93)	235 (90)	216 (84)	0.001
ACEI *n* (%)	210 (81)	216 (83)	229 (88)	226 (88)	0.07
Beta-blocker *n* (%)	228 (88)	212 (81)	210 (81)	187 (73)	<0.001
Statin *n* (%)	248 (96)	243 (93)	234 (90)	227 (88)	0.005
PCI *n* (%)	174 (67)	130 (50)	114 (44)	81 (32)	<0.001
IIb/IIIa antagonists *n* (%)	143 (55)	107 (41)	88 (34)	64 (25)	<0.001

ACEI, angiotension converting enzyme inhibitor; PCI, percutaneous coronary intervention.

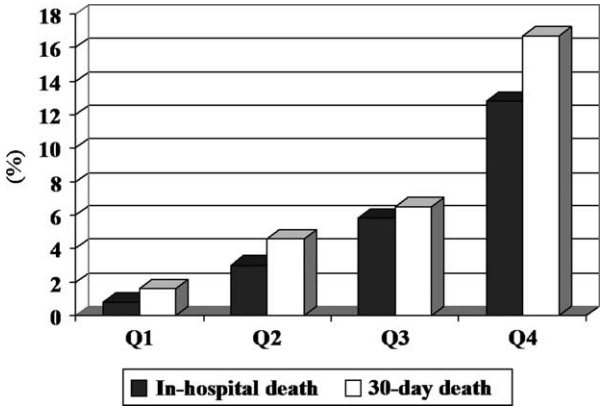

Figure 1. In-hospital and 30-day mortality across quartiles of admission NT-proBNP ($P<0.001$).

in-hospital (RR 1.56; 95% CI: 0.93–2.61; $P=0.09$) and particularly 30-day death (RR 1.98; 95% CI: 1.22–3.22; $P=0.007$) when compared to patients with high GRACE risk score—low admission NT-proBNP.

In a multivariate logistic regression model adjusted for other predictors of death (identified by univariate analysis) or related to an elevated NT-proBNP (including age, weight, hypertension, diabetes, smoking, stage 2 or worse chronic kidney disease—eCrCl <90 ml/min/m^2, Killip class ≥ 2, ST elevation myocardial infarction, ACE inhibitor, beta-blocker, statins, LVEF $\leq 40\%$, blood glucose on admission, peak CK and admission NT-proBNP), NT-proBNP levels on admission were an independent predictor of in-hospital death (OR 2.02; 95% CI: 1.21–3.39; $P=0.008$) and 30-day mortality (OR 1.86; 95% CI: 1.20–2.88; $P=0.005$) (Tables IV and V).

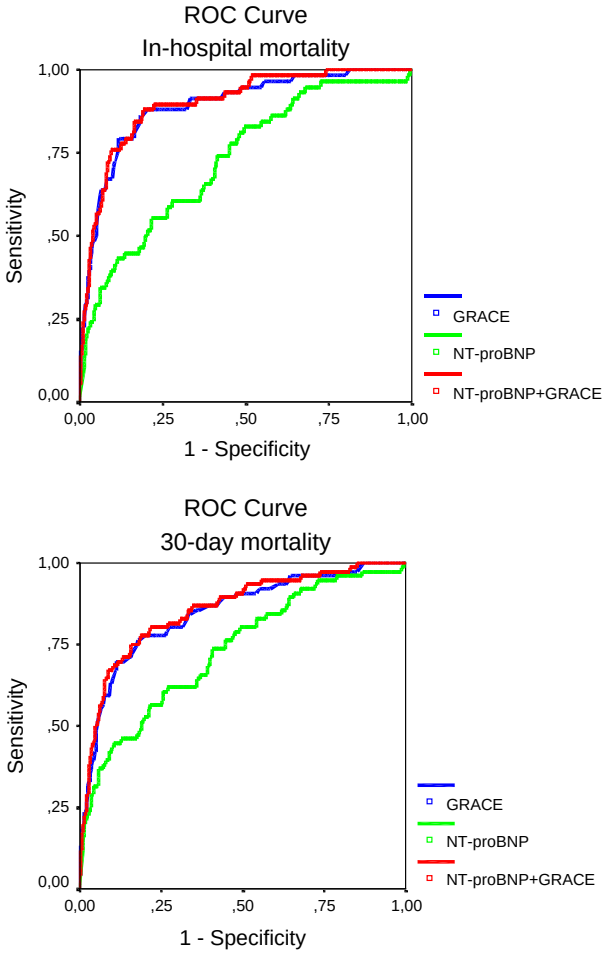

Figure 2. ROC curves for admission NT-proBNP, GRACE risk score and a combination index to predict in-hospital and 30-day mortality.

Table III. ROC curves analysis for admission NT-proBNP and GRACE risk score for the prediction of death and a combination score: AUC (95% CI), *P*-value.

	In-hospital mortality	30-day mortality
Admission NT-proBNP	0.73 (0.66–0,80), <0.001	0.73 (0.67–0.80), <0.001
GRACE risk score	0.89 (0.85–0.94), <0.001	0.85 (0.80–0.90), <0.001
GRACE+ NT-proBNP[a]	0.90 (0.86–0.94), <0.001	0.86 (0.81–0.91), <0.001

[a]Combination of increasing GRACE risk score and increasing admission NT–proBNP.

Discussion

The roles of BNP and NT-proBNP are well established for heart failure (1,2). However, their utility in ACS is still evolving. BNP has a well-defined mechanism of elimination: degradation by circulating endopeptidases, clearance by cellular binding receptors and to a lesser degree by renal excretion (9). Recent reports showed that NT-proBNP and BNP are equally dependent on renal function for clearance, suggesting also a saturable clearance mechanism for NT-proBNP degradation independent of glomerular filtration, yet unknown (10). NT-proBNP has a longer half-life (70–120 min) that may allow for greater accumulation and potentially greater sensitivity in detecting more subtle structural and functional changes (9,10). In our population, NT-proBNP was directly correlated with age, hypertension, diabetes and smoking and inversely

Table IV. Multivariate analysis for in–hospital mortality (independent predictors).

	OR	95% CI	*P*-value
Admission NT-proBNP	2.02	1.21–3.39	0.008
Age	1.05	1.01–1.09	0.023
ST-elevation MI	2.74	1.14–6.54	0.024
Beta-blocker	0.19	0.09–0.39	<0.001
LVEF <40%	4.54	2.07–9.95	<0.001
Blood glucose	24.47	3.57–167.69	0.001

MI, myocardial infarction; LVEF, left ventricular ejection fraction. Variables included in the model: age, weight, hypertension, smoking, diabetes, eCrCl <90 ml/min, Killip class ≥ 2, ST elevation myocardial infarction, ACE inhibitor, beta-blocker, statins, LVEF $\leq 40\%$, blood glucose on admission, peak CK and admission NT-proBNP.

Table V. Multivariate analysis for 30–day mortality (independent predictors).

	OR	95% CI	*P*-value
Admission NT-proBNP	1.86	1.20–2.88	0.005
Beta-blocker	0.25	0.14–0.46	<0.001
Statin	0.44	0.21–0.96	0.038
LVEF <40%	3.59	1.78–7.23	<0.001
Blood glucose	23.67	4.43–126.53	<0.001

LVEF, left ventricular ejection fraction.
Variables included in the model: age, weight, hypertension, smoking, diabetes, eCrCl <90 ml/min, Killip class ≥2, ST elevation myocardial infarction, ACE inhibitor, beta-blocker, statins, LVEF ≤40%, blood glucose on admission, peak CK and admission NT-proBNP.

correlated with eCrCl and weight, confirming previous studies, particularly on eCrCl and obesity (11,12).

Acute regional diastolic and/or systolic left ventricular dysfunction is a hallmark of sudden and prolonged myocardial ischemia, and is one of the first steps in the ischemic cascade that leads to cell necrosis (3). The prognostic accuracy of early measurement of NT-proBNP was greater than that of early measurements of troponin T in the study by Galvani, suggesting that NT-proBNP might be considered an early ischemic marker (13). Such early increases may reflect the amount of the ischaemic insult to the myocardium, rather that the actual extent of myocardial necrosis. Myocardial cell death (and the release of its necrosis markers) is a final event (3). BNP was found to be very useful in the emergency department for the diagnosis of acute MI in patients with chest pain, particularly when standard cardiac markers are non-diagnostic (14). In fact, BNP has been found to increase in the setting of MI with peak levels occurring 14 to 40 h after the ischemic event (4). The degree of natriuretic peptide elevation is related to the size of the ischaemic injury (4).

Patients in the highest quartiles were treated less aggressively. The explanation for that is related to the fact that the majority of patients in these groups had non ST-segment elevation ACS and underwent PCI less often (as usual in non ST-segment elevation compared with ST-segment elevation ACS). This fact in association with the high in-hospital mortality rate in these groups (in most cases very soon after admission, not allowing for appropriate treatment to be provided) can explain the lowest rate of PCI, clopidogrel, beta-blockers and statins.

Analysis of the sensitivity and specificity of using NT-proBNP to predict death was accomplished by evaluating ROC curves. Admission NT-proBNP was found to be useful for assessing prognosis as well as peak NT-proBNP; however, peak values are a later marker. We demonstrated that as a single prognostic marker, admission NT-proBNP has a good overall diagnostic performance for the prediction of death in short-term follow-up. When we evaluated the overall diagnostic performance by comparing the areas under the ROC curves for NT-proBNP and GRACE risk score (a score that includes several prognostic variables), the second one had a better overall performance.

Previous studies showed that BNP and NT-proBNP provided additional prognostic information beyond that of TIMI risk score, both in ST-segment and non-ST-segment elevation acute myocardial infarction (15–18). In our study, combining GRACE risk score to admission NT-proBNP had no incremental value over GRACE risk score alone for predicting outcome. TIMI risk score has been derived from a database of clinical trial. It is possible that it would have excluded high-risk patients and may not be fully representative of broad spectrum patients encountered in clinical practice. GRACE risk score is a mortality model that span the entire spectrum of ACS, based in a relatively unselected patient-population, representing those seen in general practice and incorporates new variables that add considerable predictive information such as renal dysfunction (one of the most important variables to predict prognosis in ACS) as well as Killip class. These variables also correlate with NT-proBNP. This might explain the fact that combining GRACE risk score with NT-proBNP did not improve prognostic accuracy. Multivariate analysis confirmed that admission NT-proBNP can predict in-hospital and 30-day mortality independently of other variables that can predict death and adjusted for the variables that influence NT-proBNP levels.

Our results (with a larger patient population) are consistent with those of Bazzino et al., who showed that baseline NT-proBNP is an important prognostic variable in non-ST-elevation ACS and Grabowski et al, in patients with ST-elevation MI treated with primary angioplasty (this last study with BNP) (15,16). The results were also consistent with those of Galvani et al that compared the whole spectrum of ACS as our study (13). In fact, higher BNP concentrations are associated with tighter culprit lesions, diameter stenosis, left descending artery or proximal culprit lesion location, slow flow in culprit artery and no-reflow phenomenon after PCI (19,20). All of these findings support the hypothesis that ischemia leads to altered myocardial stretch and causes active secretion of BNP (21). In fact, Goetze demonstrated that myocardial ischemia in the absence of left ventricular dysfunction augments cardiac BNP gene expression and increases plasma NT-proBNP concentrations. Quantitative analysis of BNP mRNA in ventricular biopsies revealed close association of plasma NT-proBNP to BNP mRNA levels (22).

Limitations

One limitation of this study is the relatively heterogeneous population, since we included the entire

spectrum of ACS. However, a correction was made by the inclusion of ST-segment elevation MI in the multivariate model. The results are also consistent with Galvani results with the same type of population; however, our results were obtained from a registry that represents a real life population and not from a trial as in Galvani paper.

Another limitation is that we did not analyse the influence of time frames in NT-proBNP levels. The time between the beginning of the acute event and admission was not specifically analysed. However, all patients were admitted in the first 24 h of ACS evolution. Serial measurements of NT-proBNP in patients with ACS might by used more rapidly to identify patients suitable for early discharge or more intensive therapy. An early (at 48 h) and significant decline (48 h: −24%; 72 h: −49%) compared to admission, indicates clinical stabilization and a better 30-day prognosis (23). This aspect was not analysed due to the fact that our registry only collected admission and peak NT-proBNP, although it was not possible to draw any conclusions about the dynamic evolution of NT-proBNP levels and impact on prognosis.

A longer follow-up could also show a more significant impact on prognosis.

Conclusions

In the present study, we demonstrated that early measurements of NT-proBNP provide important and independent information for risk stratification (in-hospital and 30-day mortality) across the entire spectrum of ACS. This impact is independent of degree of myocardial damage, left ventricular function and other clinical risk factors. However, admission NT-proBNP does not increase the prognostic accuracy of GRACE risk score. We also confirmed the relation between NT-proBNP and age, renal function, body weight, hypertension, smoking and diabetes.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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