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Accuracy of N-Terminal Probrain Natriuretic Peptide to Predict Mortality or Detect Acute Ischemia in Patients with Coronary Artery Disease

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Key Words
Coronary artery disease · Mortality · Myocardial ischemia · Natriuretic peptide

Abstract
Objective: The aim of the study was to assess the accuracy of N-terminal probrain natriuretic peptide (NT-proBNP) to predict mortality or detect acute ischemia in patients with coronary artery disease (CAD). ***Methods:*** This study included 1,552 patients with stable (n = 1,059) or unstable (n = 493) CAD undergoing percutaneous coronary intervention. NT-proBNP was measured before percutaneous coronary intervention. The primary endpoint of the study was mortality. Patients were followed for 3.6 years. ***Results:*** There were 171 deaths (11%) during follow-up. In the entire group of patients, NT-proBNP had the best accuracy to predict mortality (area under receiver operating characteristic curve 0.76, 95% CI 0.72–0.80). In patients without congestive heart failure (n = 760) there were 46 deaths (6%). The area under receiver operating characteristic curve of NT-proBNP was reduced to 0.70 (95% CI 0.63–0.79) which was not better than the area under curve of age (p = 0.981) or C-reactive protein (p = 0.082) regarding mortality. NT-proBNP showed limited power to detect patients with acute ischemia (area under curve 0.63, 95% CI 0.60–0.66) among consecutive patients with stable and unstable CAD. ***Conclusions:*** NT-proBNP has a moderate accuracy to predict mortality and does not assist in the diagnosis of acute myocardial ischemia in patients with CAD.

Brain natriuretic peptide (BNP) and N-terminal probrain natriuretic peptide (NT-proBNP) are cardiac biomarkers with an established role in identifying patients with congestive heart failure [1]. Numerous studies have demonstrated that levels of BNP or NT-proBNP are increased across the entire spectrum of coronary artery disease (CAD), including ST segment elevation acute myocardial infarction [2, 3], non-ST segment elevation acute coronary syndromes [4, 5] and stable CAD [6–8], and that they are closely linked to prognosis. The regional or global left ventricular dysfunction leading to left ventricular wall stretch [9] and myocardial ischemia [10] are recognized stimuli for increased BNP (and consequently NT-proBNP) circulating levels. Several studies have suggested that circulating levels of BNP or NT-proBNP correlate with severity of angiographic CAD [11, 12] and that atherosclerotic plaques contain abundant amounts of na-

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triuretic peptides and their receptors [13]. Ischemia provoked by exercise testing [14] or balloon angioplasty [15] has been associated with increased levels of plasma natriuretic peptides. In clinical practice, left ventricular dysfunction and CAD may overlap and there is conflicting evidence regarding the accuracy and value of natriuretic peptide measurements to detect myocardial ischemia in emergency conditions [16, 17]. Furthermore, despite almost unanimous confirmation that elevated levels of BNP (or NT-proBNP) independently predict prognosis in patients with various presentations of CAD, limited information is available regarding the predictive accuracy of NT-proBNP as a marker of mortality [18]. The present study has a two-fold objective. First, we assessed the accuracy of NT-proBNP as a predictor of mortality and its dependence on the presence of congestive heart failure or left ventricular systolic dysfunction. Second, we tested the diagnostic accuracy of NT-proBNP to detect acute coronary syndromes (acute ischemia) in a consecutive series of patients with stable and unstable CAD.

Methods

Patients

This study included 1,552 patients with CAD who underwent coronary angiography and percutaneous coronary intervention (PCI) in the Deutsches Herzzentrum and Klinikum rechts der Isar in Munich between September 1999 and February 2002. Of them, 1,059 patients had stable CAD and 493 acute coronary syndromes (unstable angina or non-ST segment elevation acute myocardial infarction). Patients were recruited in prospective studies to investigate the prognostic value of biochemical markers in patients with CAD [7, 19]. The diagnosis of stable CAD was based on the presence of angina symptoms in a patient already diagnosed as having CAD, that had been occurring without a change in their pattern during the preceding 2 months. Unstable angina was diagnosed when characteristic chest pain of longer than 20 min was associated with either ST segment depression of $\geq$0.1 mV and/or T-wave inversion in 2 continuous leads in the electrocardiogram and with documentation of significant CAD in the coronary angiography. Diagnosis of non-ST segment elevation acute myocardial infarction was based on the above-mentioned criteria plus increased levels of troponin T (>0.03 μg/l). These patients were considered to have acute myocardial ischemia. Patients with advanced renal disease (serum creatinine >2 mg/dl or those on dialysis), acute inflammatory states or malignancies were not included in this study. Congestive heart failure was graded according to the New York Heart Association (NYHA) classification. Other cardiovascular risk factors were defined using previously described criteria [20]. All patients gave written consent for the angiographic examination, stent implantation and participation in the study. The study protocol was approved by the institutional ethics committee and conformed to the Declaration of Helsinki.

Angiographic Examination and Stent Implantation

CAD was diagnosed in the presence of coronary stenoses $\geq$50% lumen obstruction in at least 1 of the 3 major coronary arteries. Digital angiograms were analyzed offline with an automated edge detection system (CMS; Medis Medical Imaging Systems, Nuenen, The Netherlands). The complexity of lesions was defined according to the modified American College of Cardiology/American Heart Association grading system [21]. Class B2 and C lesions were considered complex. Left ventricular end-diastolic pressure was measured before angiography. Global left ventricular ejection fraction was determined using the area-length method [22]. PCI (mostly stent implantation) and periprocedural care were performed according to the standard criteria. Bare metal stents were used. Antiplatelet therapy consisted of clopidogrel (300–600 mg as a loading dose followed by 75 mg/day for at least 4 weeks) and aspirin (200 mg/day administered orally and continued indefinitely).

Laboratory Measurements

Blood was collected before angiography in tubes containing EDTA (Sarstedt, Nümbrecht, Germany) and promptly centrifuged at 1,550 *g* for 10 min. After separation, plasma aliquots were stored frozen at –80°C until assayed within batches. Blood count, serum lipids and other metabolites were determined immediately after collection, using standard methods.

NT-proBNP measurements were performed on a Roche Elecsys 1010 automated analyzer (Roche Diagnostics, Mannheim, Germany). The measuring range, provided by the manufacturer and defined by the lower detection limit and the maximum of the master curve, is 5–35,000 ng/l (Roche Diagnostics ProBNP technical bulletin for Elecsys systems). The functional sensitivity, that is the lowest analyte concentration that can be reproducibly measured with a between-run coefficient of variation of 20%, is <50 ng/l. NT-proBNP concentrations in healthy subjects depend on age and sex. In women, the 95th percentile of NT-proBNP concentration increases from 152 ng/l (at <55 years of age) to 265 ng/l (at >65 years of age). In men of the same age, the 95th percentile of NT-proBNP concentration increases from 75.8 to 157 ng/l [23].

High-sensitivity C-reactive protein (CRP) was measured fully automated with a latex-enhanced immunoturbidometric assay on a Cobas Integra analyzer (Roche Diagnostics). The CRP assay has an analytical sensitivity of 0.085 mg/l and a measuring range of up to 160 mg/l. The upper limit of the reference range in healthy adults is 5 mg/l.

Troponin T was measured by a third-generation electrochemiluminescence immunoassay on an Elecsys 2010 analyzer (Roche Diagnostics). The lower detection limit of this assay is 0.01 μg/l. Our current performance data show coefficient of variation values ranging from 0.82% at a concentration of 2.52 μg/l to 1.29% at 0.12 μg/l using commercial control sera (PreciControl Troponin; Roche Diagnostics). The upper limit of the normal range is 0.03 μg/l.

Laboratory measurements were performed by laboratory personnel unaware of clinical or angiographic outcome.

Study Endpoints and Follow-Up

Clinical follow-up consisted of telephone interviews at 1 month, 1 year and 3–5 years after the initial procedure. All patients were advised to contact our outpatient clinic or their refer-

ring physicians whenever they experienced cardiac symptoms. Patients with cardiac complaints underwent a complete clinical, electrocardiographic and laboratory checkup. The primary endpoint of the study was all-cause mortality. Information on mortality was obtained from hospital records, death certificates, or phone contact with relatives of the patient or attending physicians. Collection of baseline characteristics of the patients, follow-up information as well as adjudication of adverse events was performed by medical staff unaware of laboratory measurements.

Statistical Analysis

Data are presented as median (with 25th and 75th percentiles) or counts and proportions (percentages). The distribution of the data was analyzed with the one-sample Kolmogorov-Smirnov test. Continuous data were compared with the Wilcoxon rank-sum test. Categorical data were compared with the χ^2 test. Receiver operating characteristic (ROC) curves were constructed to assess the predictive accuracy of NT-proBNP and other variables such as age, left ventricular ejection fraction and high-sensitivity CRP regarding 1-year mortality. Area under ROC curve and 95% confidence intervals (CI) were used to assess the overall diagnostic accuracy for mortality. Differences between the areas under curve were assessed for statistical significance according to the method by DeLong et al. [24]. Multiple linear regression analysis was used to assess the independent influence of various factors on the NT-proBNP concentration. The Cox proportional hazards model was used to assess the independent correlates of mortality. All analyses were performed using the S-PLUS statistical package (Insightful Corp., Seattle, Wash., USA). $p < 0.05$ was considered to indicate statistical significance.

Results

Baseline Characteristics

A total of 1,552 patients (1,059 patients with stable CAD and 493 patients with non-ST segment elevation acute coronary syndromes) were included in the study. During a median of 3.6 years (interquartile range 3.3–4.6 years), 171 patients (11%) died. Baseline characteristics of patients who survived (survivors) and those did not survive (nonsurvivors) are shown in table 1. Expectedly, nonsurvivors had a worse demographical and clinical profile, including more advanced NYHA class, worse left ventricular function, and higher circulating levels of NT-proBNP, CRP, cardiac troponin T and serum creatinine.

Correlates of NT-proBNP Level

The linear regression model was used to define independent correlates of increased circulating level of NT-proBNP. The following parameters were included into the model: age, sex, diabetes, arterial hypertension, body mass index, hypercholesterolemia, smoking, previous myocardial infarction, previous coronary artery bypass surgery, presentation with acute coronary syndrome, atrial fibrillation, heart rate, NYHA class, NT-proBNP, CRP, creatinine, troponin T, left ventricular ejection fraction, left ventricular end-diastolic pressure, number of narrowed coronary arteries and complex lesions. NT-proBNP was entered into the model as a continuous variable. The model showed that 14 variables were independently associated with increased elevated levels of NT-proBNP. A list of independent correlates of elevated level of NT-proBNP is shown in table 2. The overall R^2 for the model was 0.36.

The linear regression model was used to identify the independent correlates of NT-proBNP in patients without congestive heart failure. Patients presenting with NYHA class >1, patients with a history of congestive heart failure or those with a left ventricular ejection fraction <55% were excluded from this analysis. According to these criteria, 792 patients (51%) had to be excluded. Thus, 760 patients (49%) were used for this analysis. Among them, 46 patients (6%) died during follow-up. The remaining 125 deaths (73% of the total number of deaths) occurred in patients with evidence of congestive heart failure of left ventricular dysfunction. The same variables as for the entire group were entered into the model. The model showed that age, sex, current smoking, atrial fibrillation, CRP, troponin level and left ventricular ejection fraction were independently associated with increased levels of NT-proBNP (table 2). The overall R^2 for the model was 0.17. Smoking was an independent correlate of elevated NT-proBNP level only in patients without congestive heart failure. Contrary to the model for the entire group of patients, presentation with acute coronary syndromes or number of narrowed coronary arteries was not independently associated with elevated NT-proBNP level. Troponin independently predicted elevated NT-proBNP level in both models.

Independent Correlates of Mortality

The Cox proportional hazards model was used to identify independent correlates of mortality among variables shown in table 1. The above-mentioned parameters plus β-blocker therapy which differed significantly between survivors and nonsurvivors were included into the model. The following variables were independently associated with mortality: age [hazard ratio (HR) 1.42, 95% CI 1.29–1.57; $p < 0.001$ for 5-year increase], NT-proBNP (HR 1.10, 95% CI 1.06–1.15; $p < 0.001$ for 1,000-ng/l increase in concentration), female sex (HR 0.67, 95% CI 0.45–0.99; $p = 0.043$), diabetes (HR 1.58, 95% CI 1.14–2.20; $p = 0.006$), body mass index (HR 0.79, 95% CI 0.45–

Table 1. Baseline demographic, clinical and coronary angiographic characteristics

	Survivors (n =1,381)	Nonsurvivors (n = 171)	p value
Age, years	65.5 [58.9; 73.0]	73.0 [66.4; 78.9]	<0.001
Women	324 (23.5)	43 (25.1)	0.624
Diabetes	341 (24.7)	65 (38.0)	<0.001
Arterial hypertension	749 (54.2)	90 (52.6)	0.691
Body mass index	26.8 [24.7; 29.3]	25.3[23.4; 28.7]	<0.001
Hypercholesterolemia (≥240 mg/dl)	647 (46.9)	63 (36.8)	0.013
Current smoking	221 (16.0)	31 (18.1)	0.477
Previous myocardial infarction	521 (37.7)	80 (46.8)	0.021
Previous CABG	209 (15.7)	35 (20.5)	0.070
Acute coronary syndrome	428 (31.0)	65 (38.0)	0.063
Atrial fibrillation	56 (4.1)	27 (15.8)	<0.001
Heart rate, beats/min	69 (61; 77)	74 (65; 81)	<0.001
Systolic blood pressure, mm Hg	150.0 [130.0; 170.0]	145.0 [120.0; 161.5]	0.108
NYHA class			<0.001
1	1,027 (74.4)	82 (47.9)	
2	274 (19.8)	57 (33.3)	
3	65 (4.7)	26 (15.2)	
4	15 (1.1)	6 (3.6)	
NT-proBNP, ng/l	315.8 [126.6; 881.7]	1,601.5 [494.6; 4,016.5]	<0.001
CRP, mg/l	1.2 [0.9; 2.2]	1.9 [1.1; 5.5]	<0.001
Creatinine, mg/dl	1.1 [0.9; 1.2]	1.2 [1.0; 1.4]	<0.001
Cardiac troponin T, μg/l	0.0 [0.0; 0.01]	0.01 [0.0; 0.099	<0.001
Cholesterol level, mg/dl	195.0 [166.0; 229.0]	190.0 [156.0; 222.0]	0.057
LV ejection fraction, %	59.0 [48.0; 67.0]	50.0 [35.0; 60.0]	<0.001
LV end-diastolic pressure, mm Hg	18.0 [12.0; 20.0]	18.0 [12.0; 22.0]	0.774
Number of affected vessels			0.012
1	311 (22.5)	33 (19.3)	
2	449 (32.5)	39 (22.8)	
3	621 (45.0)	99 (57.9)	
Vessel treated			0.093
Left main coronary artery	26 (1.9)	4 (2.3)	
Left anterior descending artery	543 (39.3)	69 (40.3)	
Right coronary artery	412 (29.8)	36 (21.1)	
Left circumflex coronary artery	317 (22.9)	46 (26.9)	
Bypass graft	83 (6.1)	16 (9.4)	
Complex lesions	1,013 (73.4)	135 (78.9)	0.116
Therapy at discharge			
Statins	1,199 (86.8)	140 (81.9)	0.076
ACE inhibitors	1,146 (83.0)	136 (79.5)	0.261
β-Blockers	1,259 (91.2)	143 (83.6)	0.002

Data are medians [25th; 75th percentiles] or numbers of patients (%). CABG = Coronary artery bypass grafting; LV = left ventricle.

0.99; p = 0.038 for increase of 5), current smoking (HR 2.62, 95% CI 1.68–4.08; p < 0.001), NYHA class (HR 1.37, 95% CI 1.10–1.70; p = 0.004 for increase of 1 class), CRP (HR 1.02, 95% CI 1.01–1.03; p = 0.001 for 1-mg/l increase) and left ventricular ejection fraction (HR 1.10, 95% CI 1.03–1.17; p = 0.004 for 5% decrease).

Accuracy of NT-proBNP as a Predictor of Mortality

Diagnostic accuracy of continuous variables that were independent correlates of mortality in the Cox proportional hazards model was tested by ROC curve analysis. On ROC curve analysis, 4 variables – age, NT-proBNP, left ventricular ejection fraction and CRP – had areas under ROC curve significantly greater than 0.5 (table 3).

Table 2. Results of multivariable analysis showing independent correlates of NT-proBNP level in the whole group of patients and in those without congestive heart failure

	All patients (n = 1,552)		Patients without congestive heart failure (n =760)	
	coefficient	p value	coefficient	p value
Age	35.6	<0.001	17.5	<0.001
Female	420.2	<0.001	216.1	0.003
Body mass index	–31.3	0.013	1.3	0.865
Hypercholesterolemia	–227.8	0.020	–62.8	0.274
Current smoking	144.3	0.310	283.9	<0.001
Atrial fibrillation	1,569.1	<0.001	1,031.9	<0.001
NYHA class	627.3	<0.001	–	–
Acute coronary syndrome	306.0	0.005	105.2	0.120
Number of narrowed coronary arteries	151.3	0.023	70.5	0.069
Heart rate	12.6	<0.001	2.4	0.282
CRP level	13.7	0.003	9.2	0.001
Creatinine level	159.3	<0.001	17.9	0.366
Troponin level	400.5	<0.001	235.3	<0.001
Left ventricular ejection fraction	–37.7	<0.001	–8.3	0.050
Left ventricular end-diastolic pressure	174.7	0.001	2.2	0.636

Table 3. ROC curve analysis showing areas under curve for NT-proBNP, age, left ventricular ejection fraction and CRP as predictors of all-cause mortality

Characteristic	Area under ROC curve	p value	p value[1]
All patients (n = 1,552)			
NT-proBNP	0.76 (0.72–0.80)	<0.001	–
Age	0.70 (0.66–0.74)	<0.001	0.006
Left ventricular ejection fraction	0.65 (0.61–0.71)	<0.001	0.005
CRP	0.63 (0.59–0.68)	<0.001	<0.001
Patients without CHF (n = 760)			
NT-proBNP	0.70 (0.63–0.79)	<0.001	–
Age	0.71 (0.64–0.79)	<0.001	0.981
Left ventricular ejection fraction	0.52 (0.43–0.62)	0.296	0.082
CRP	0.60 (0.51–0.70)	0.015	0.007
Patients with stable CAD (n = 1,059)			
NT-proBNP	0.77 (0.72–0.82)	<0.001	–
Age	0.68 (0.63–0.73)	<0.001	0.001
Left ventricular ejection fraction	0.66 (0.59–0.72)	<0.001	0.017
CRP	0.64 (0.58–0.70)	<0.001	<0.001
Patients with ACS (n = 493)			
NT-proBNP	0.73 (0.67–0.80)	<0.001	–
Age	0.73 (0.66–0.79)	<0.001	0.818
Left ventricular ejection fraction	0.65 (0.58–0.72)	<0.001	0.141
CRP	0.62 (0.55–0.69)	<0.001	0.006

Figures in parentheses are 95% CI. ACS = Acute coronary syndrome; CHF = congestive heart failure.

[1] Comparison of areas under ROC curve with the area under ROC curve of NT-proBNP.

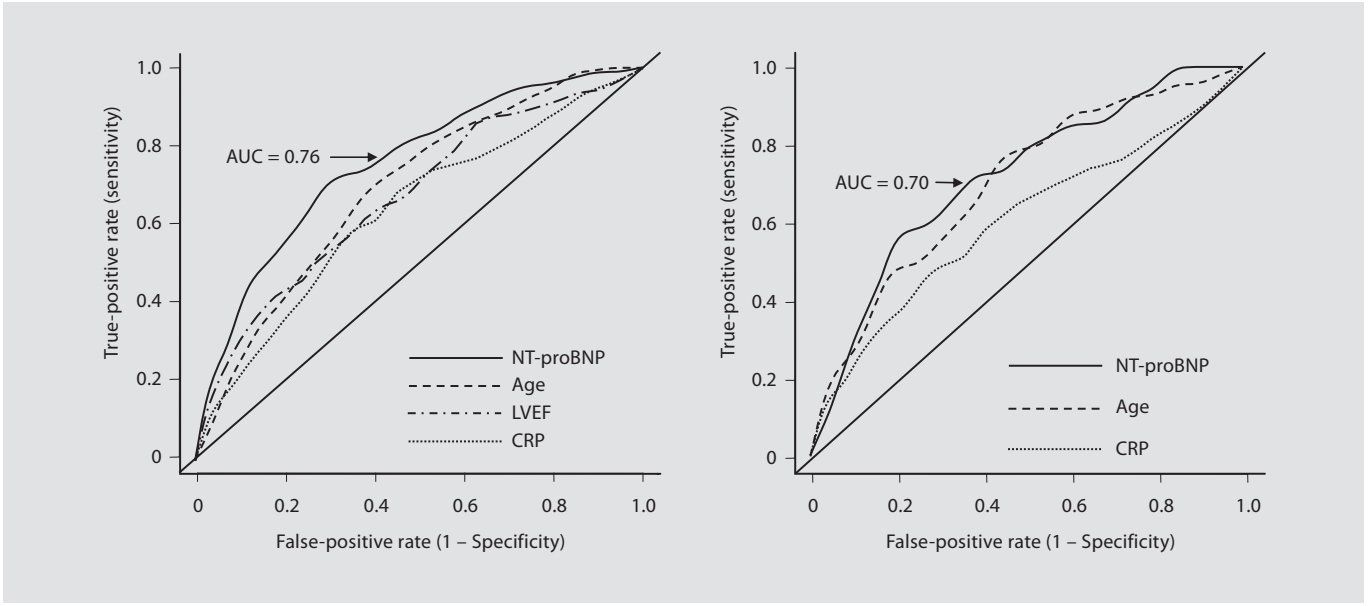

Fig. 1. ROC curves showing ability of NT-proBNP, age, left ventricular ejection fraction and CRP to predict mortality in the entire group of patients (left panel) and in patients without congestive heart failure (right panel). AUC = Area under curve; LVEF = left ventricular ejection fraction.

NT-proBNP had the greatest area under ROC curve which was significantly greater than the area under ROC curve of age, left ventricular ejection fraction and CRP (table 3; fig. 1).

Accuracy of NT-proBNP Level as a Predictor of Mortality in Patients without Congestive Heart Failure

ROC curve analysis in this group of patients showed that age and NT-proBNP had almost the same diagnostic accuracy (areas under curve 0.71 and 0.70, respectively) as predictors of mortality (table 3). The area under ROC curve of NT-proBNP was reduced compared with the area under ROC curve of the entire group. Comparison of the area under ROC curve of NT-proBNP with those of age, left ventricular ejection fraction and CRP is shown in table 3.

Accuracy of NT-proBNP to Predict Mortality in Patients with Stable CAD and Acute Coronary Syndromes

In patients with stable CAD (1,059 patients), there were 106 deaths during follow-up. ROC curve analysis showed that NT-proBNP has the greatest area under ROC curve and thus the best predictive accuracy regarding mortality. The area under ROC curve of NT-proBNP was significantly greater than those of age, left ventricular ejection fraction and CRP (table 3).

In patients with acute coronary syndromes (493 patients), there were 65 deaths during follow-up. ROC curve analysis showed that NT-proBNP and age have similar areas under ROC curve and thus similar predictive accuracy regarding mortality. The area under ROC curve of left ventricular ejection fraction was smaller than those of NT-proBNP and age but statistical significance was not achieved. The area under ROC curve of NT-proBNP was significantly greater than that of CRP (table 3).

Diagnostic Accuracy of NT-proBNP to Detect Acute Ischemia

In the entire group of patients, ROC curve analysis was performed to assess the predictive accuracy of NT-proBNP and CRP as predictors of acute ischemia (i.e. patients with an acute coronary syndrome). The area under ROC curve of NT-proBNP was 0.63 (95% CI 0.60–0.66; $p < 0.001$). The area under ROC curve of CRP was 0.56 (95% CI 0.53–0.59; $p < 0.001$), which was significantly smaller than that of NT-proBNP ($p < 0.001$).

ROC curve analysis was performed to assess the diagnostic accuracy of NT-proBNP and CRP to detect acute ischemia in patients without congestive heart failure as well. The area under ROC curve of NT-proBNP was 0.61

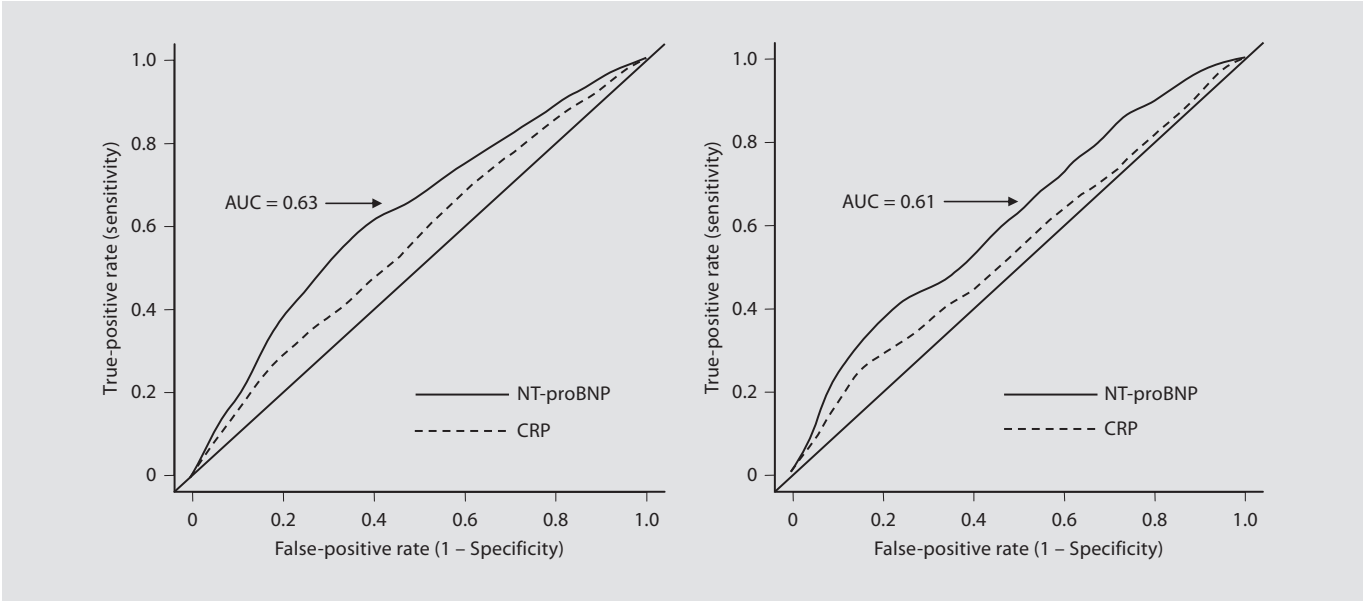

Fig. 2. ROC curves showing ability of NT-proBNP and CRP to detect acute ischemia in the entire group of patients (left panel) and in patients without congestive heart failure (right panel). AUC = Area under curve.

(95% CI 0.56–0.65; $p < 0.001$). The area under ROC curve of CRP was 0.54 (95% CI 0.49–0.59; $p = 0.05$; fig. 2) which was significantly smaller than that of NT-proBNP ($p = 0.021$).

Discussion

In the present study we tested the accuracy of NT-proBNP to predict mortality or acute ischemia in a large and well-characterized consecutive series of patients with stable and unstable CAD by using ROC curve analysis. The area under the ROC curve is widely accepted as a measure of the discriminatory power of a diagnostic test [25]. This study showed that among all parameters studied, the area under ROC curve of NT-proBNP was greatest, implying that NT-proBNP has the best accuracy to predict mortality in this consecutive series of patients with CAD. Although an area under ROC curve of 0.76 may be considered as clinically relevant, a test with such an area under ROC curve is considered to have a moderate predictive (or diagnostic) accuracy. The moderate accuracy of NT-proBNP as a predictor of death may be related to the complexity and multitude of factors underlying mortality. Although NT-proBNP is an integrative marker that accumulates risk from multiple sources, some cardiovascular risk factors may be out of reach or poorly presented by this biomarker. It has recently been demonstrated that at least in patients with heart failure, BNP level did not correlate with health status [26], which has been identified as an independent correlate of mortality in patients with CAD [27]. Other studies have reported that elevated levels of NT-proBNP do not predict future development of myocardial infarction [7, 28] because natriuretic peptides are not involved in the genesis of instable atherosclerotic plaques or their disruption. Consequently, elevated levels of NT-proBNP may be a poor predictor of mortality related to future myocardial infarction. Furthermore, PCI resulting in durable restoration of coronary blood flow and amelioration of myocardial ischemia potentially contributing to increased NT-proBNP level may attenuate the prognostic power of NT-proBNP or, at least, of that portion of NT-proBNP level that has been produced by myocardial ischemia not progressing to necrosis or serving as an unstable substrate due to effective coronary intervention.

Analysis of NT-proBNP level and predictivity according to the presence of congestive heart failure overlapping with CAD brought to attention 2 interesting findings. First, elevated levels of NT-proBNP may preferentially predict mortality related to congestive heart failure. Two facts may support this conclusion. First, exclusion of pa-

tients with congestive heart failure was associated with a 73% reduction (125 of 171 patients) in mortality and second, exclusion of patients with congestive heart failure or left ventricular dysfunction was associated with a reduction in the area under ROC curve of NT-proBNP. Second, exclusion of patients with congestive heart failure attenuated the independent association of various clinical variables with NT-proBNP beyond parameters considered typical of congestive heart failure. By excluding patients with congestive heart failure or left ventricular systolic dysfunction, 7 of 14 independent correlates of NT-proBNP level, among them the number of narrowed coronary arteries and presentation with acute coronary syndrome, lost their independent association with NT-proBNP. Our data suggest that apparent association between severity of CAD and elevated NT-proBNP level [11, 12] may result from underadjustment for congestive heart failure. It may be possible that worse left ventricular function and more advanced congestive heart failure that associates advanced CAD rather than the severity of coronary artery narrowing may be the primary source of elevated NT-proBNP level. Our data warrant caution in interpreting any association of NT-proBNP (or BNP) with clinical status without careful consideration of the potential impact of impaired left ventricular function or congestive heart failure.

Our study showed that NT-proBNP measurement was of little help in identifying patients with acute ischemia (acute coronary syndrome diagnosed by characteristics of chest pain and ST segment depression or elevated troponin T level). The area under ROC curve of NT-proBNP to detect those with spontaneously occurring acute myocardial ischemia was in the range of no clinical value. This finding is at variance with a recent study that has reported that NT-proBNP level at rest as well as ΔNT-proBNP during exercise stress testing predicted inducible myocardial ischemia [29]. However, we concur with a study by Campbell et al. [17] that reported that NT-proBNP level did not assist in the diagnosis of acute myocardial ischemia in unselected patients presenting to the emergency department. Reasons for the poor predictive power to predict spontaneously occurring acute ischemia should be sought in the multitude of factors that intervene in determining the NT-proBNP level. As multivariable analysis showed, 14 variables were independently associated with NT-proBNP level. Other studies have also reported multiple correlates of NT-proBNP level as well [28]. Thus, the multisource origin of NT-proBNP level weakens the predictive accuracy of the marker to detect any individual conditions increasing NT-proBNP level including acute myocardial ischemia.

In conclusion, although NT-proBNP was the best predictor of increased risk of death, the marker has a moderate power to predict long-term mortality in a consecutive series of patients with stable and unstable CAD. NT-proBNP does not assist in the diagnosis of acute myocardial ischemia (or acute coronary syndrome) in unselected consecutive patients with CAD.

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