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N-Terminal B-Type Natriuretic Peptide Assessment Provides Incremental Prognostic Information in Patients With Acute Coronary Syndromes and Normal Troponin T Values Upon Admission

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Objectives The purpose of this study was to determine the prognostic value of N-terminal B-type natriuretic peptide (NT-proBNP) in two independent samples of patients presenting with acute coronary syndromes (ACS) and normal troponin T (TnT) values.

Background Recently assessment of NT-proBNP has been studied in patients with ACS. However, the clinical relevance in patients who present without troponin elevation is unclear.

Methods We included 2,614 patients from two independent registries, one serving as a derivation cohort comprising patients with evident ACS (Bad Nauheim ACS registry, n = 1,131) and the other serving as a validation cohort including chest pain patients (PACS [Prognosis in Acute Coronary Syndromes] registry, n = 1,483). NT-proBNP and TnT were measured upon admission. Clinical outcome has been assessed over a 6-month period.

Results In both cohorts, the mortality rate was significantly lower among TnT negative patients: 3.8% versus 8.2% ($p = 0.009$) in the Bad Nauheim ACS registry, and 2.8% versus 8.6% ($p = 0.009$) in the PACS registry. Among TnT negative patients, receiver-operating characteristics curve analysis yielded an optimal cutoff value of 474 pg/ml for NT-proBNP that was able to discriminate patients at higher risk in the Bad Nauheim ACS and PACS registries (mortality rate 12.3% vs. 1.3%, $p < 0.001$ and 8.5% vs. 1.5%, $p < 0.001$, respectively). By Kaplan-Meier analysis, patients with NT-proBNP values over 474 pg/ml were at higher risk for death in the Bad Nauheim ACS registry (log-rank 19.01, $p < 0.001$, adjusted hazard ratio [HR] 9.56 [95% confidence interval (CI) 2.42 to 37.7], $p = 0.001$) and in the PACS registry (log-rank 23.16, $p < 0.001$, adjusted HR 5.02 [95% CI 2.04 to 12.33], $p < 0.001$).

Conclusions Among patients with suspected ACS considered to be at low risk because of normal troponin values, NT-proBNP above 474 pg/ml is able to discriminate individuals at higher risk. Because of its incremental prognostic value, NT-proBNP assessment should be considered in clinical routine for risk stratification of patients with normal troponin. (J Am Coll Cardiol 2008;51:1188–95) © 2008 by the American College of Cardiology Foundation

In numerous large-scale trials on non–ST-segment elevation acute coronary syndromes (NSTE-ACS), it has been consistently demonstrated that cardiac troponins, namely troponin I (TnI) and troponin T (TnT), add strong prognostic information beyond that provided by traditional predictors such as symptoms or electrocardiographic (ECG) alterations. Furthermore, an elevation of TnI or TnT indicates that an early aggressive strategy including coronary angiography, revascularization if appropriate, and the application of a glycoprotein (GP) IIb/IIIa inhibitor will be beneficial (1–3). For this reason, the assessment of troponins has become the gold standard for risk stratification and therapeutic decision making in accordance with treatment guidelines (4). However, in the subset of patients presenting with suspected acute coronary syndromes (ACS)

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and normal troponin levels, initial risk stratification is less accurate because it relies only on clinical and ECG variables.

B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are neurohormones synthesized and secreted mainly from the ventricular myocardium in response to an increase in left ventricular wall stress (5). In patients with congestive heart failure, elevated levels of BNP and NT-proBNP have proven to be highly predictive for an adverse outcome (6). Recently, several clinical and experimental studies have shown that both neurohormones are also released in response to myocardial ischemia (7–11). Furthermore, there are data available showing consistently that in patients presenting with ACS, BNP and NT-proBNP provide independent prognostic information for mortality irrespective of the troponin status (12–15). However, further assessment of the utility of NT-proBNP in troponin negative patients is required. Most of the information available comes from subsidiary analysis of clinical trials. More importantly, the additive predictive value of NT-proBNP over traditional prognostication schemes such as the Thrombolysis In Myocardial Infarction (TIMI) risk score in troponin negative patients has not been studied.

Therefore, it was our aim to evaluate the incremental prognostic value of NT-proBNP assessment in patients with suspected ACS and normal troponin values on admission and to calculate and validate a cutoff value that could be applicable in clinical routine.

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
AUC = area under the curve
BNP = B-type natriuretic peptide
CABG = coronary artery bypass grafting
ECG = electrocardiographic
GP = glycoprotein
HR = hazard ratio
NSTE-ACS = non–ST-segment elevation acute coronary syndromes
NT-proBNP = N-terminal pro–B-type natriuretic peptide
PCI = percutaneous coronary intervention
ROC = receiver-operating characteristic
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction
TnT = troponin T

Methods

Patients. For this study, we analyzed data from two independent patient cohorts, the Bad Nauheim ACS registry and the PACS (Prognosis in Acute Coronary Syndromes) registry with a total of 2,614 patients. Both cohorts were different, with the Bad Nauheim ACS registry comprising a higher risk cohort with confirmed ACS and the PACS registry comprising a low risk chest pain cohort. Accordingly, we analyzed both populations separately, with the Bad Nauheim ACS registry serving as a derivation cohort and the PACS cohort as a validation sample (Fig. 1). The two cohorts were independent with differences of the patient demographics. In addition, hypothesis generation and statistical methods were developed before analysis of the data.

The Bad Nauheim ACS registry included all consecutive patients (n = 1,131) from April 2003 until March 2005 who were referred for early coronary angiography or primary percutaneous coronary intervention (PCI) because of an ACS with an episode of chest pain within the last 48 h. Blood drawing for TnT and NT-proBNP assessment was performed on admission directly before angiography and revascularization. Patients either were admitted directly by the emergency medical system or were transferred from community hospitals. Pre-treatment with clopidogrel or a GP IIb/IIIa inhibitor was left to the discretion of the treating physicians or the emergency staff. Medical history was assessed as the patients reported it or if available from the medical records. All patients gave informed consent that included consent for biomarker analysis prior to inclusion into the study, and the study was approved by the local ethical board.

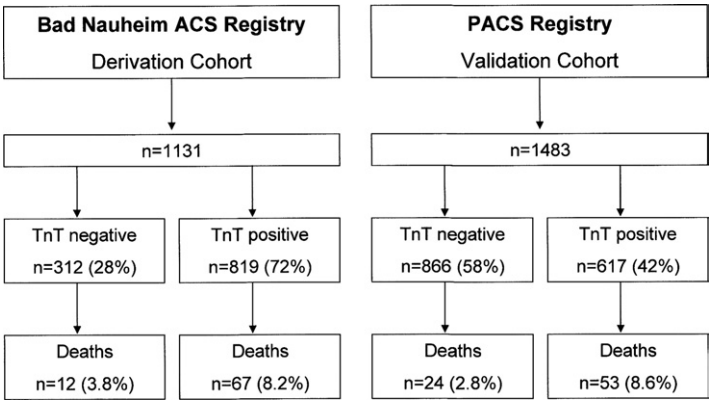

Figure 1 Study Outline

Composition of the 2 different study cohorts and clinical outcome. ACS = acute coronary syndromes; PACS = Prognosis in Acute Coronary Syndromes; TnT = troponin T.

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The PACS registry (16), a multicenter registry performed in Argentina, included 1,483 consecutive patients from January 2000 to July 2001 admitted to the coronary care units with resting chest pain within the 24 h before admission. Patients who were candidates for reperfusion therapy on admission because of ischemic chest pain >20 min with ST-segment elevation, or patients who had coronary angioplasty performed during the previous 6 months were excluded. Patients with an active cancer or autoimmune inflammatory disease were also excluded. Blood drawing for TnT and NT-proBNP assessment was performed on admission. The ethics committee of each center approved the study protocol and patients provided written informed consent that included consent for biomarker analysis.

In both cohorts, all investigators were blinded to NT-proBNP results until the study was completed. Simultaneous levels of TnT and of creatine kinase-myocardial band (activity or mass) were measured at each center and were used for diagnosis and prognostic analysis. Creatinine clearance was calculated according to the Cockroft-Gault equation. All patients were followed for at least 6 months from hospital admission or until death, whichever occurred first. The average follow-up time was 213 ± 57 days for the Bad Nauheim ACS registry and 173 ± 31 days for the PACS registry.

The TIMI risk score (NSTE-ACS and ST-segment myocardial infarction [STEMI]) was calculated in both cohorts for the assessment of clinical risk and defined as low (scores 0, 1, and 2), moderate (scores 3 and 4), and high (scores 5, 6, and 7) risk categories for NSTE-ACS and as low (scores 0 to 3), moderate (scores 4 to 7), and high (scores ’8) risk categories for STEMI (17,18).

Laboratory measurements. From all patients, venous blood was taken from an antecubital vein in gel-filled tubes. The specimens were centrifuged within 1 h and serum was frozen at −70° until they were analyzed either at a core laboratory in Buenos Aires or at Bad Nauheim. Cardiac TnT was measured by an electrochemiluminescence immunoassay (third generation for cTnT, Elecsys, Roche Diagnostics, Mannheim, Germany). A TnT value of equal to or less than 0.01 ng/ml was considered as normal troponin. The NT-proBNP was measured by an electrochemiluminescence-immunoassay (Elecsys proBNP,

Table 1 Baseline Characteristics of the Study Population

	Bad Nauheim ACS Registry			PACS Registry		
	TnT Negative	TnT Positive	p Value	TnT Negative	TnT Positive	p Value
n	312	819		866	617	
Gender (female)	92 (30%)	254 (31%)	NS	390 (45%)	150 (24%)	<0.001
Age (yrs)	64.5 ± 12.5	64.0 ± 12.2	NS	65.2 ± 11.9	68.6 ± 11.7	<0.001
Rhythm atrial fibrillation	21 (7%)	66 (8%)	NS	805 (7%)	53 (9%)	NS
Systolic blood pressure (mm Hg)	139 ± 32	133 ± 35	0.012	137 ± 24	138 ± 25	NS
Heart rate (beats/min)	73 ± 20	76 ± 22	0.031	67 ± 19	73 ± 21	<0.001
Diabetes mellitus	62 (20%)	196 (24%)	NS	136 (16%)	139 (23%)	<0.001
Hypertension	219 (70%)	543 (66%)	NS	582 (67%)	411 (67%)	NS
Hyperlipidemia	135 (43%)	346 (42%)	NS	475 (55%)	313 (51%)	NS
Current smoker	92 (30%)	273 (33%)	NS	233 (27%)	168 (27%)	NS
Previous CAD	87 (28%)	167 (20%)	0.009	252 (29%)	179 (29%)	NS
STEMI	129 (41%)	361 (44%)	NS	0	0	NS
Treatment						
PCI	169 (54%)	653 (80%)	<0.001	115 (13%)	203 (33%)	<0.001
CABG	11 (4%)	50 (6%)	NS	49 (6%)	73 (12%)	<0.001
Conservative	132 (42%)	116 (14%)	<0.001	702 (81%)	341 (55%)	<0.001
TIMI risk						
Low	224 (72%)	427 (52%)	<0.001	571 (66%)	220 (36%)	<0.001
Moderate	85 (27%)	344 (42%)		286 (33%)	310 (50%)	
High	3 (1%)	48 (6%)		9 (1%)	87 (14%)	
Killip class II to IV	29 (9%)	116 (14%)	0.029	ND	ND	
Time from onset of symptoms (h)	3.4 (1.7–8.5)	7.0 (3.2–14.3)	<0.001	3.3 (2.0–6.0)	3.0 (1.3–6.0)	NS
Creatinine clearance (ml/min)	96 ± 37	95 ± 41	NS	82 ± 32	89 ± 33	<0.001
Left ventricular EF <45%	101 (32%)	448 (55%)	<0.001	ND	ND	
NT-proBNP (pg/ml)	157 (60–452)	815 (243–2244)	<0.001	120 (55–317)	611 (231–1621)	<0.001
NT-proBNP >474 pg/ml	73 (28%)	505 (61%)	<0.001	153 (18%)	357 (58%)	<0.001
Deaths	12 (3.8%)	67 (8.2%)	0.009	24 (2.8%)	53 (8.6%)	0.009
Lost to follow-up	1 (0.3%)	7 (0.9%)	NS	0	0	NS

Values are expressed as absolute numbers (%), means ± SD, or as medians (interquartile ranges).

ACS = acute coronary syndromes; CABG = coronary artery bypass graft; CAD = coronary artery disease; EF = ejection fraction; nd = no data; ns = not significant; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PACS = Prognosis in Acute Coronary Syndromes; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction; TnT = troponin T.

Roche Diagnostics). The analytical range extends from 5 to 35,000 pg/ml. The total coefficient of variation was 3.3% (n = 28) at a level of 252.6 pg/ml and 3.7% (n = 25) at a level of 6130.8 pg/ml of NT-proBNP.

Statistical analysis. All results for continuous variables are expressed as mean ± SD, and skewed variables are expressed as median and interquartile range. Kolmogorov-Smirnov test was used to test for normal distribution. For groupwise comparisons of continuous variables, Mann-Whitney *U* (2 groups) or Kruskal-Wallis (n groups) tests were used for skewed variables, and Student *t* test (2 groups) or 1-way ANOVA (n groups) were used for normally distributed variables. For categorical variables, Fisher's exact test or the chi-square test were used. For the correlation of NT-proBNP to TnT, creatinine clearance, and age, the Spearman rank correlation coefficient was calculated. To evaluate the performance of NT-proBNP as a predictor for mortality, the area under the curve (AUC) of the receiver-operating characteristic (ROC) curve has been calculated and an optimal cutoff level has been derived from the ROC analysis according to the Youden criterion (19,20). For survival analysis, Kaplan-Meier survival curves according to NT-proBNP values dichotomized at the calculated cutoff value were plotted and log-rank test was used. An adjusted hazard ratio (HR) was calculated by a Cox regression analysis including the confounding factors age and gender and in a second model adjusting for all factors that proved to be related to elevated NT-proBNP values in the univariate analysis.

All tests were performed 2-sided and a significance level of $p < 0.05$ was considered to indicate statistical significance. For all statistical analyses, the statistical software SPSS 10.0 (SPSS Inc., Chicago, Illinois) for Windows was used.

Results

Baseline characteristics. A total of 2,614 patients were included, 1,131 patients in the Bad Nauheim ACS registry and 1,483 patients in the PACS cohort. In the Bad Nauheim ACS registry, 312 (28%) patients had normal TnT levels on admission. In turn, in the PACS registry, normal baseline TnT levels were observed in 866 (58%) patients (Fig. 1).

Table 1 shows the relationship between troponin values and the baseline characteristics of both study cohorts. In the Bad Nauheim ACS registry, TnT negative patients had a significantly higher blood pressure and lower heart rate, more frequently had a history of coronary artery disease (previous myocardial infarction, PCI, or coronary artery bypass grafting [CABG]) had a shorter delay from onset of symptoms until blood sampling, and had a lower frequency of reduced left ventricular function (ejection fraction <45%) as compared to the TnT positive patients. In the PACS registry, TnT negative patients were more often female, were younger, had a lower heart rate on admission, were more frequently diabetics, and had a lower creatinine clearance compared with TnT positive patients.

Revascularization therapy, either PCI or CABG, was performed more often in the Bad Nauheim ACS registry (883 patients, 78%) as compared to the PACS registry (440 patients, 30%). However, in both cohorts, revascularization procedures (PCI or CABG) were performed less frequently in patients with negative TnT levels as compared to patients with elevated TnT values (58% vs. 86%, $p < 0.001$ in the Bad Nauheim ACS registry and 19% vs. 35%, $p < 0.001$ in the PACS registry, respectively).

Mortality rate was significantly lower among the TnT negative patients (3.8% vs. 8.2%; $p = 0.009$; and 2.8% vs. 8.6%; $p = 0.009$; Fisher's exact test), in the Bad Nauheim ACS and the PACS registries, respectively (Table 1, Fig. 1)

N-terminal BNP levels. In both study cohorts, median NT-proBNP values were lower in TnT negative patients as compared to troponin positive patients: 157 (60 to 452) pg/ml versus 815 (243 to 2244) pg/ml; ($p < 0.001$; Mann-Whitney *U* test) in the Bad Nauheim registry, and 120 (55 to 317) pg/ml versus 611 (231 to 1621) pg/ml; ($p < 0.001$; Mann-Whitney *U* test) in the PACS registry. There was a moderate but significant correlation of NT-proBNP to TnT ($\rho = 0.389$; $p < 0.001$ in the Bad Nauheim registry and $\rho = 0.508$; $p < 0.001$ in the PACS registry), to age ($\rho = 0.430$; $p < 0.001$ in the Bad Nauheim registry and $\rho = 0.513$; $p < 0.001$ in the PACS registry), and to creatinine clearance ($\rho = -0.355$; $p < 0.001$ in the Bad Nauheim registry and $\rho = -0.351$; $p < 0.001$ in the PACS registry).

Predictive value of NT-proBNP in TnT negative patients. Compared with patients who survived, TnT negative patients who deceased during the follow-up period showed higher baseline NT-proBNP median values (2,047 [209 to 3,906] pg/ml vs. 154 [59 to 407] pg/ml; $p < 0.001$; Mann-Whitney *U* test) in the Bad Nauheim ACS registry and (637 [181 to 2,205] pg/ml vs. 117 [54 to 310] pg/ml; $p < 0.001$; Mann-Whitney *U* test) in the PACS registry (Fig. 2).

In the cohort of troponin negative patients from the Bad Nauheim ACS registry, the area of the ROC curve for NT-proBNP as a predictor for 6-months mortality was 0.80 ($p < 0.001$). From the ROC curve, we were able to derive an optimal cutoff value for NT-proBNP of 474 pg/ml. Levels of NT-proBNP above or below this cutoff value of 474 pg/ml were associated with a mortality rate of 12.3% versus 1.3%, respectively ($p < 0.001$; Fisher's exact test) (Fig. 3). Applying this cutoff value, we found a sensitivity of 75%, a specificity of 79%, a negative predictive value of 99%, and a positive predictive value of 12% to predict subsequent death. Consequently, by Kaplan-Meier analysis, NT-proBNP values dichotomized at this cutoff were able to discriminate patients with an adverse outcome (log-rank 19.01; $p < 0.001$; adjusted HR 9.56 [95% confidence intervals (CI) 2.42 to 37.7]; $p = 0.001$) (Fig. 4A).

Similarly, applying this cutoff value to the cohort of troponin negative patients from the PACS registry, we

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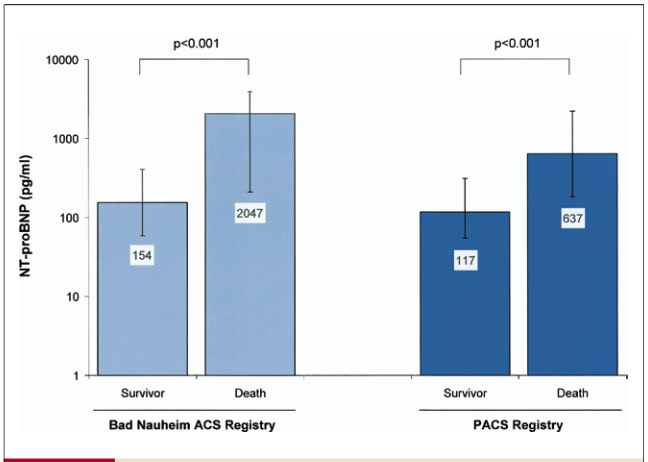

Figure 2 NT-proBNP Values in Relation to Clinical Outcome

N-terminal pro–B-type natriuretic peptide (NT-proBNP) values of survivors and those who deceased during follow-up. Values are expressed as median and interquartile range. Other abbreviations as in Figure 1.

found a higher mortality rate in patients with NT-proBNP values above the cutoff value of 474 pg/ml (8.5% vs. 1.5%; $p < 0.001$; Fisher's exact test) (Fig. 3), yielding a sensitivity of 54%, a specificity of 83%, a negative predictive value of 98%, and a positive predictive value of 8%. By Kaplan-Meier analysis, NT-proBNP values over 474 pg/ml were discriminative for subsequent death (log-rank 23.16; $p < 0.001$: adjusted HR 5.02 [95% CI 2.04 to 12.33]; $p < 0.001$) (Fig. 4B). However, from the ROC curve analysis of the PACS cohort (AUC 0.77; $p < 0.001$) the optimal cutoff value that could be calculated was 586 pg/ml, providing a better test accuracy with an increased specificity of 87%, negative predictive value of 99% and positive predictive value of 10%, and an adjusted HR of 6.86 (95% CI 2.81 to 16.78); $p < 0.001$ (Table 2).

Table 3 shows the relationship between baseline characteristics and NT-proBNP status. After adjusting for all baseline parameters significantly associated with elevated NT-proBNP levels, NT-proBNP remained a strong and independent predictor for mortality in a multivariate Cox regression model (HR 11.9 [95% CI 1.9 to 73.4], $p = 0.007$ for the Bad Nauheim ACS registry and HR 4.4 [95% CI 1.7 to 11.3], $p = 0.001$ for the PACS registry).

The predictive value associated with NT-proBNP above a threshold of 474 pg/ml, as shown by a significant HR, could also be demonstrated consistently in various clinically relevant subgroups such as age <65 and ≥65 years, male and female gender, diagnosis of STEMI or NSTE-ACS, TIMI risk score, time from onset of symptoms <6 h and ≥6 h, and diabetes mellitus. The only exceptions were found for female patients in the Bad Nauheim ACS registry (HR 2.3 [95% CI 0.9 to 5.7]; $p = 0.067$) and for patients over 65 years of age in the PACS registry (HR 2.5 [95% CI 0.7 to 8.2]; $p = 0.140$). However, in both above-mentioned subgroups, a strong trend toward an increased risk of patients with elevated NT-proBNP was present.

Discussion

The present study aimed to evaluate the prognostic information provided by NT-proBNP assessment in patients with an ACS and normal troponin values at baseline. For this purpose, we analyzed the data derived from two distinct cohorts, one including patients presenting with evident ACS, the other cohort including patients with chest pain. Our major finding was that among patients with normal TnT values, elevated NT-proBNP identifies a higher risk population adding substantial prognostic information beyond that provided by traditional risk predictors. Furthermore, we were able to determine and validate an optimal cutoff value for NT-proBNP of 474 pg/ml, thereby identifying patients with normal troponin values who are at higher risk.

The adverse prognostic meaning of elevated cardiac troponin in patients with clinical suspicion for a NSTE-ACS has been previously demonstrated (21–23). Conversely, as a group, troponin negative patients are considered to be at low risk of serious complications (24,25). In fact, in the present study, the 6-month mortality rate of TnT negative patients was significantly lower as compared to patients with elevated TnT. These findings are consistent with previous reports on the prognostic value of cardiac troponins either in the setting of clinical trials or in cohort studies (21).

However, our findings clearly indicate that patients with normal troponin levels have a heterogeneous prognosis. The NT-proBNP was able to discriminate patients with increased risk among troponin negative patients. As shown, those patients with negative TnT but elevated NT-proBNP had a mortality rate that was identical to or even higher than the mortality rate of TnT positive patients.

The two cohorts of this study were different from each other. The Bad Nauheim ACS registry consisted of a higher risk population with evident ACS treated mostly by an early

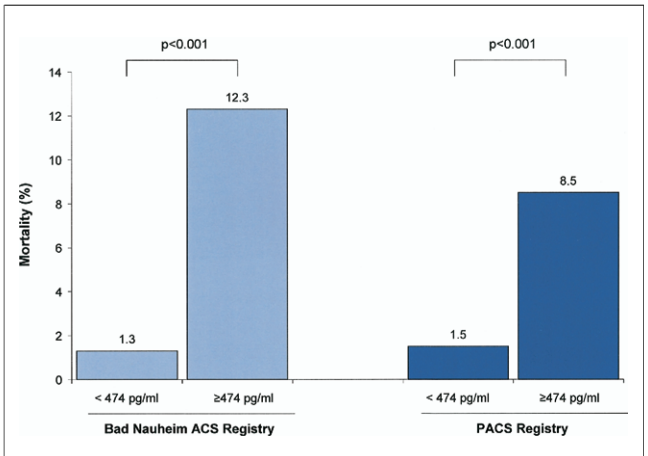

Figure 3 Mortality Rate in Relation to NT-proBNP Values

Mortality rate in association with NT-proBNP values dichotomized at the calculated cutoff value of 474 pg/ml. Abbreviations as in Figures 1 and 2.

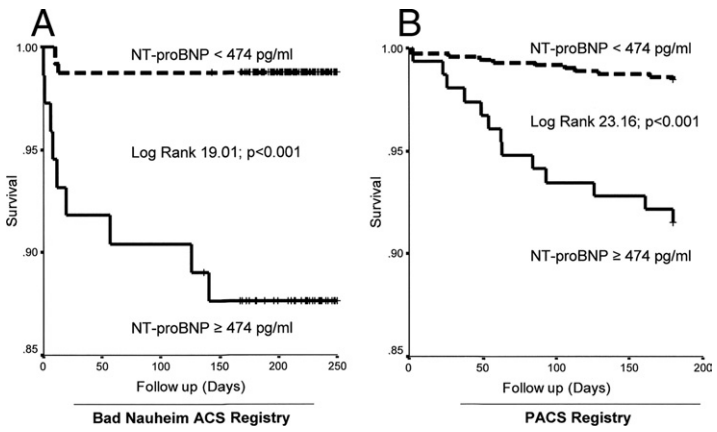

Figure 4 **Survival According to NT-proBNP Levels**

Kaplan-Meier survival curves according to NT-proBNP values above **(dashed lines)** and below **(solid lines)** a cutoff value of 474 pg/ml. **(A)** Bad Nauheim ACS registry; **(B)** PACS registry. Abbreviations as in Figures 1 and 2.

interventional strategy, and the PACS registry consisted of a low risk chest pain population with a low rate of invasive diagnostic and revascularization procedures. Interestingly, the results that we obtained from these distinct cohorts were very consistent with almost identical calculated cutoff values for NT-proBNP of 474 pg/ml and 586 pg/ml, respectively. Therefore, these data suggest that NT-proBNP at a practical decision limit of approximately 500 pg/ml may be useful in clinical routine to triage patients with evident or suspected ACS.

Our findings also agree with previous reports on the prognostic value of BNP and NT-proBNP in patients with ACS. In these studies, both markers were consistently found to be independently predictive for an increased risk, especially for increased mortality (26). However, in none of these studies has an optimal cutoff value been calculated for the subgroup of patients with normal troponin values.

What are the clinical implications of these findings? Patients without troponin elevation represent a large proportion of those admitted with suspected NSTE-ACS, with some studies reporting frequencies as high as 60% to 79% (21). In contrast with the situation of troponin positive patients, risk stratification in patients with normal troponin values is considerably more uncertain because clinical variables alone are not precise enough to adequately stratify patients with suspected ACS (24). As shown in the PACS cohort, even refined prognostication schemes, such as the TIMI risk score, failed to identify a significant number of patients at higher risk (16).

Therefore, our study with data derived from two different large-scale registries comprising a wide spectrum of patients reflecting everyday clinical routine adds important information. It underscores the incremental prognostic value of NT-proBNP in troponin negative patients with suspected ACS and provides a cutoff value applicable for clinical routine.

Study limitations. This analysis is partially retrospective. Nevertheless, the prognostic value of NT-proBNP was assessed prospectively in the Bad Nauheim registry as well as in the PACS study.

It must also be noted that we used a single baseline NT-proBNP measurement; therefore, we cannot exclude that serial measurements may provide better prognostic information.

Table 2 **Hazard Ratio for Mortality of Patients in Relation to NT-proBNP Dichotomized at Various Cutoff Values**

NT-proBNP Cutoff	HR	95% CI	p Value
Bad Nauheim ACS registry			
300 pg/ml	4.97	1.24–19.88	0.024
450 pg/ml	8.60	2.17–34.03	0.002
474 pg/ml	9.56	2.42–37.7	0.001
600 pg/ml	7.39	2.02–27.01	0.002
750 pg/ml	6.35	1.81–22.24	0.004
PACS registry			
300 pg/ml	3.15	1.27–7.80	0.013
450 pg/ml	4.78	1.95–11.75	0.001
474 pg/ml	5.02	2.04–12.33	<0.001
600 pg/ml	6.86	2.81–16.78	<0.001
750 pg/ml	4.97	2.05–12.05	<0.001

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

Conclusions

Patients with negative troponin values, a large proportion of those presenting with an ACS, are usually considered at low risk. However, this is a heterogeneous group that includes individuals at higher risk of serious complications that cannot be identified by applying current risk stratification schemes. Our data, obtained from 2 distinct populations representing a wide spectrum of clinical presentations of ACS, indicates that NT-proBNP at a decision limit of 500 pg/ml adds substantial information

Table 3 Baseline Characteristics of Troponin Negative Patients in Relation to NT-proBNP Levels

	Bad Nauheim ACS Registry			PACS Registry		
	NT-proBNP ≤474 pg/ml	NT-proBNP >474 pg/ml	p Value	NT-proBNP ≤474 pg/ml	NT-proBNP >474 pg/ml	p Value
n	239	73		713	153	
Gender (female)	60 (25%)	32 (44%)	0.003	301 (42%)	89 (58%)	0.003
Age (yrs)	61.4 ± 12.2	70.5 ± 10.8	<0.001	63.3 ± 11.3	74.0 ± 10.5	<0.001
Systolic blood pressure (mm Hg)	138 ± 29	140 ± 41	NS	136 ± 23	142 ± 28	0.028
Heart rate (beats/min)	72 ± 18	75 ± 27	NS	68 ± 18	66 ± 29	NS
Diabetes mellitus	45 (19%)	17 (23%)	NS	104 (15%)	32 (21%)	0.065
Hypertension	164 (69%)	55 (75%)	NS	462 (65%)	120 (78%)	0.001
Hyperlipidemia	110 (46%)	25 (34%)	NS	404 (57%)	71 (46%)	0.025
Current smoker	80 (36%)	12 (16%)	0.005	214 (30%)	19 (12%)	<0.001
Previous CAD	59 (25%)	28 (38%)	0.026	183 (26%)	69 (45%)	0.001
NSTE-ACS	131 (55%)	52 (71%)	0.014	713 (100%)	153 (100%)	NS
Treatment						
PCI	134 (56%)	35 (48%)	NS	92 (13%)	23 (15%)	NS
CABG	4 (2%)	7 (10%)	0.004	38 (5%)	11 (7%)	NS
Conservative	101 (42%)	31 (43%)	NS	583 (82%)	119 (78%)	NS
TIMI risk						
Low	182 (76%)	42 (58%)	0.008	507 (71%)	64 (42%)	<0.001
Moderate	55 (23%)	30 (41%)		199 (28%)	87 (57%)	
High	2 (1%)	1 (1%)		7 (1%)	2 (1%)	
Time from onset of symptoms (h)	3.2 (1.7, 7.4)	4.3 (2.1, 11.4)	0.048	3.2 (2.0, 6.0)	4.0 (2.0, 7.0)	NS
Creatinine clearance (ml/min)	102 ± 36	76 ± 34	<0.001	92 ± 31	76 ± 34	<0.001
Left ventricular EF <45%	60 (25%)	41 (56%)	<0.001	ND	ND	
Deaths	3 (1.3%)	9 (12.3%)	<0.001	11 (1.5%)	13 (8.5%)	<0.001

Values are expressed as absolute numbers (%), means ± SD, or as medians (interquartile ranges).
NSTE-ACS = non–ST-segment elevation acute coronary syndromes; other abbreviations as in Table 1.

to identify those patients who are at higher risk for subsequent death. Therefore, our study in combination with previously published data, strongly suggests the implementation of NT-proBNP assessment for risk stratification of patients with chest pain or suspected NSTE-ACS and negative troponin values.

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APPENDIX

For a list of the PACS study group of investigators and centers, please see the online version of this paper.