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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.

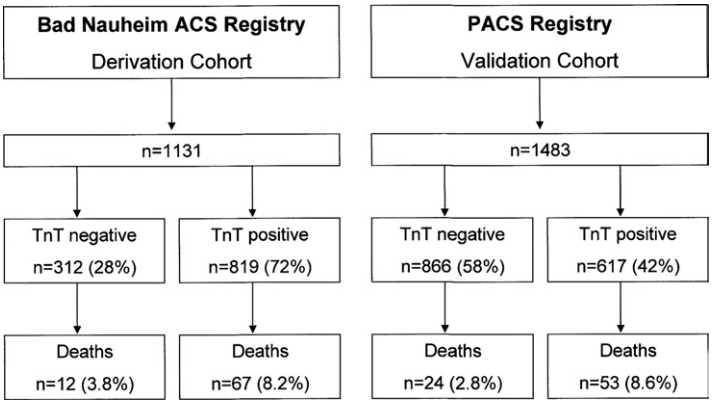

Figure 1 Study Outline

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