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B-Type Natriuretic Peptide and the Risk of Cardiovascular Events and Death in Patients With Stable Angina

Results From the Athero*Gene* Study

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OBJECTIVES The aim of this study was to assess the predictive value of the cardiac hormone B-type natriuretic peptide (BNP) for long-term outcome in a large cohort of stable angina patients.

BACKGROUND Recent data suggest a role of BNP in stable ischemic heart disease beyond its known value in heart failure and acute coronary syndromes.

METHODS In 1,085 patients with coronary artery disease (CAD) baseline levels of BNP were prospectively associated with cardiovascular (CV) events during a mean follow-up of 2.5 years.

RESULTS BNP concentrations were significantly elevated in patients with future CV events (median [25th/75th interquartile range] 119.2 [43.6/300.4] pg/ml vs. 36.2 [11.3/94.6] pg/ml; $p < 0.001$). Kaplan-Meier survival analysis showed a stepwise decrease in event-free survival across quartiles of BNP baseline concentration ($p_{log\ rank} < 0.001$). Patients in the highest quartile revealed a 6.1-fold increased risk ($p = 0.001$) compared to patients in the lowest quartile after adjustment for potential confounders. For a cut-off value of 100 pg/ml, an independently increased risk of adverse outcome (hazard ratio [HR] 4.4; $p < 0.001$) could be demonstrated. One standard deviation (SD) decrease in ejection fraction implied the most prominent increase in risk of future CV events (HR 1.69; $p < 0.001$) followed by one SD increase in BNP (HR 1.53; $p < 0.001$). The highest prognostic accuracy could be demonstrated for BNP (area under the curve 0.671).

CONCLUSIONS The data of this large group of CAD patients provide independent evidence that BNP is a strong predictor of cardiovascular risk in patients with stable angina independent of left ventricular systolic performance and known risk factors. (J Am Coll Cardiol 2006;47: 552–8) © 2006 by the American College of Cardiology Foundation

The degree of cardiac neurohormonal activation as indicated by B-type natriuretic peptide (BNP) has been extensively investigated in cardiac disease, primarily in mechanistic disorders of cardiac function. As a hormone indicator of myocardial stretch (1) BNP is an excellent marker of heart failure and has already entered international guidelines. Its reliable characteristics as a biomarker have spurred further investigations in other cardiovascular disease entities. Indeed, there is an increasing body of evidence for the concept that BNP might be an indicator of hypoxia and ischemia itself which may result in myocyte stress under ischemic conditions despite constancy in measurable hemodynamic parameters (2–4). For patients with acute coronary syndromes, impressive data have been generated for BNP in the prediction of outcome. Under these conditions BNP provides information on survival and incident heart failure incremental to that of anthropometric data and clinical variables (5,6). For long-term mortality assessment BNP has proved to be superior to necrosis markers (7). Elevated BNP obviously does not depend on acute necrosis but may also indicate stable states of coronary artery disease (CAD) characterized by repetitive microischemia under stress without significant rise of creatine kinase or troponins (8).

There is also evidence that N-terminal B-type natriuretic peptide (Nt-proBNP), the inactive fragment of the prohormone, might also be a robust indicator of cardiovascular risk in patients with stable coronary disease (9–13).

The aim of the current study was to examine the prognostic impact of BNP in a large group of consecutively enrolled stable angina patients on short-term as well as long-term cardiovascular (CV) outcome to evaluate the potential clinical applicability of BNP measurements in CAD.

METHODS

During the enrollment phase 1,085 consecutive patients presenting with stable angina and at least one stenosis >30% in the larger coronary arteries entered the observational Athero*Gene* registry at the two recruitment centers: Department of Medicine II of the Johannes Gutenberg University, Mainz, and the Bundeswehrzentralkrankenhaus, Koblenz, Germany.

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Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CAD = coronary artery disease
CRP = C-reactive protein
CV = cardiovascular
EF = left ventricular ejection fraction
HR = hazard ratio

Further details on the concept of the Athero*Gene* study have been previously described (14). In the present substudy, exclusion criteria were clinical signs of instability (unstable angina Braunwald classification class B or C, acute ST-segment elevation, and non–ST-segment elevation myocardial infarction). Further reasons for exclusion were clinical or echocardiographic signs of severe heart failure and additional known hemodynamically relevant cardiac abnormalities which might generate myocyte stress in addition to overt CAD, including severe valvular heart disease, surgery or trauma within the previous month, known cardiomyopathy, manifest carcinoma, chronic inflammatory disease states and febrile conditions, and use of oral anticoagulant therapy within the previous four weeks. These exclusion criteria were met by up to 30% of the eligible patients.

The history of classic risk factors was assessed as follows. Patients who had received antihypertensive treatment or who had received a diagnosis of hypertension (blood pressure above 160/90 mm Hg) were considered to have hypertension. Patients were classified as currently smoking, as having smoked in the past (if they had stopped more than 4 weeks and less than 40 years earlier), or as never having smoked (if they had never smoked or had stopped 40 or more years earlier). Patients who were receiving dietary treatment or medication for diabetes or who presented with fasting blood glucose levels above 125 mg/dl were defined as diabetic.

In 769 patients, left ventricular ejection fraction (EF) was determined by angiography and off-line analysis according to the area-length method (15).

Among the 1,085 patients, survival status remained unknown in 11 subjects (1%) who were lost during follow-up, and the data of 2 patients for whom EF was not available were excluded from analysis owing to a BNP concentration over 1,500 pg/ml, which might indicate severe heart failure. The final study population consisted of 1,072 individuals who were followed over a median of 2.5 ± 1.2 years (skewness <1). During this time, 35 cardiovascular deaths, 15 deaths from other causes, and 17 nonfatal myocardial infarctions were registered. The primary end point was nonfatal myocardial infarction and cardiovascular death. Follow-up information was obtained from patient charts and death certificates. All data were evaluated by an independent adjudication committee consisting of experienced physicians who were blinded to BNP concentrations.

The study was approved by the local ethics committee of the University of Mainz. All patients were Caucasian. Participation was voluntary, and patients were enrolled after written informed consent was obtained.

Laboratory methods. Blood samples were drawn under standardized conditions before coronary angiography was performed when the patients entered the catheterization lab after a minimum 12-h fast. Serum lipids and creatinine were measured immediately by routine methods; low-density lipoprotein was calculated by the Friedewald formula. For all other biomarkers measured in the study population, plasma and serum were stored at −80°C immediately after centrifugation.

Plasma B-type natriuretic peptide was determined using a fluorescence immunoassay (Biosite, San Diego, California). The detection limit reported is <5 pg/ml, the upper limit 5,000 pg/ml. The assay has an interassay coefficient of variation of near 10%, and a recovery of 100% of added peptide was found. Cross-reactivity with other natriuretic peptides is negligible (16). C-reactive protein (CRP) was determined by a highly sensitive, latex particle-enhanced immunoassay (detection range 0 to 20 mg/l; Roche Diagnostics, Mannheim, Germany).

Statistical considerations. The mean values and proportions of baseline cardiovascular risk factors, clinical variables, and biomarkers were calculated for study participants according to occurrence of future cardiovascular events. The statistical significance of differences between the means for the two subgroups was assessed with Student *t* test, and the significance of differences in proportions was tested with the chi-squared statistic. Variables with a skewed distribution were presented as medians and Wilcoxon rank sum test was applied. Patients were divided into four subgroups on the basis of their BNP level at the time of enrollment. The cumulative event plots according to quartiles of BNP concentration were estimated by the Kaplan-Meier method and compared with use of the log rank test. All survival analyses were conducted for the primary end point of nonfatal myocardial infarction and cardiovascular death. Data from patients who died from causes not related to cardiovascular disease were censored at the time of death. Hazard ratios for future CV events were estimated by Cox regression models adjusted for potential confounders. All models included the adjustment for age and sex. Further adjustment was performed for classic risk factors (body mass index, high-density lipoprotein cholesterol levels, a history of hypertension, diabetes, and smoking). The second model further comprised clinical variables such as presence of multivessel disease and cardiac medication with angiotensin-converting enzyme inhibitors and statins and the inflammatory marker CRP. The final analyses included EF into the regression models. To compare the predictive power of BNP to known risk measures in stable angina patients, the hazard ratios (HR) found for one standard deviation increase of BNP, CRP, fibrinogen, and EF were presented for two Cox regression models. A backward stepwise Cox regression approach was taken for the multi-