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FOCUS ISSUE: BIOMARKERS IN CARDIOVASCULAR DISEASE

# The Prognostic Value of N-Terminal Pro–B-Type Natriuretic Peptide for Death and Cardiovascular Events in Healthy Normal and Stage A/B Heart Failure Subjects

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**Objectives** Our objective was to determine the prognostic value of plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) for death and cardiovascular events among subjects without risk factors for heart failure (HF), which we term healthy normal.

**Background** Previous studies report that plasma NT-proBNP has prognostic value for cardiovascular events in the general population even in the absence of HF. It is unclear if NT-proBNP retains predictive value in healthy normal subjects.

**Methods** We identified a community-based cohort of 2,042 subjects in Olmsted County, Minnesota. Subjects with symptomatic (stage C/D) HF were excluded. The remaining 1,991 subjects underwent echocardiography and NT-proBNP measurement. We further defined healthy normal (n = 703) and stage A/B HF (n = 1,288) subgroups. Healthy normal was defined as the absence of traditional clinical cardiovascular risk factors and echocardiographic structural cardiac abnormalities. Subjects were followed for death, HF, cerebrovascular accident, and myocardial infarction with median follow-up of 9.1, 8.7, 8.8, and 8.9 years, respectively.

**Results** NT-proBNP was not predictive of death or cardiovascular events in the healthy normal subgroup. Similar to previous reports, in stage A/B HF, plasma NT-proBNP values greater than age-/sex-specific 80th percentiles were associated with increased risk of death, HF, cerebrovascular accident, and myocardial infarction ($p < 0.001$ for all) even after adjustment for clinical risk factors and structural cardiac abnormalities.

**Conclusions** These findings do not support the use of NT-proBNP as a cardiovascular biomarker in healthy normal subjects and have important implications for NT-proBNP–based strategies for early detection and primary prevention of cardiovascular disease. (J Am Coll Cardiol 2010;55:2140–7) © 2010 by the American College of Cardiology Foundation

The cardiac hormone B-type natriuretic peptide (BNP) has proved useful in the diagnosis and prognosis of heart failure (HF) (1–3). In addition, we (4) and others (5–7) have reported that plasma BNP, even in the absence of HF, has incremental prognostic value for future cardiovascular events and mortality beyond traditional cardiovascular risk factors when measured in large community-based samples. Importantly, the plasma BNP values associated with increased risk were below those observed in HF. These previous studies suggest, therefore, that there are mild although clinically significant elevations in plasma BNP before the onset of clinically recognizable disease that may aid in identifying at-risk subjects and help guide strategies to prevent adverse cardiovascular outcomes.

See page 2148

In recent studies, we further reported the clinical and echocardiographic phenotype of subjects with increased mortality risk as predicted by plasma BNP in a large community-based cohort of 1,991 subjects without symptomatic HF (4). Specifically, there was a significantly higher prevalence of important cardiovascular clinical risk factors

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and echocardiographic structural and functional abnormalities including hypertension, prior myocardial infarction, cardiovascular drug use, left atrial enlargement, left ventricular hypertrophy, and diastolic dysfunction among subjects with increased risk as predicted by plasma BNP. These findings suggested that subjects with increased mortality risk defined by elevated plasma BNP values were disproportionately represented by those with stages A and B HF as defined by the American College of Cardiology/American Heart Association (ACC/AHA) (8). Importantly, in-depth clinical examination and echocardiography permitted us to identify 703 subjects without clinical cardiovascular risk factors or structural abnormalities who we define as healthy normal subjects. To date, the prognostic significance of BNP in predicting adverse cardiovascular outcomes has not been determined in healthy normal subjects.

Based upon these previous findings, we hypothesized that plasma BNP would not have prognostic significance for increased mortality or adverse cardiovascular outcomes in the healthy normal subgroup. This is a significant question as healthy normal subjects represent 34% of the general population (9) and, to date, the prognostic value of BNP to predict increased mortality or cardiovascular morbidity in healthy normal subjects has not been addressed. Demonstration of a lack of prognostic value for BNP in healthy normal subjects is important because it may impact how we screen for at-risk populations as well as design interventional trials to decrease risk in such high-risk subjects.

To address this hypothesis, we utilized the comprehensive clinical and echocardiographic data from the PAVD (Prevalence of Asymptomatic Ventricular Dysfunction) study from Olmsted County, Minnesota, to identify a healthy normal cohort (n = 703) and a stage A/B HF cohort (1,288). Subjects with a history of symptomatic HF (stage C/D HF) were excluded. As amino-terminal pro-BNP (NT-proBNP) was the most prognostic of the BNP assays in our previous studies (4), NT-proBNP was used for all analyses in the current study. Our results establish that NT-proBNP lacks prognostic value in the absence of underlying disease and/or alterations in cardiac structure or function.

## Methods

This study was approved by the Mayo Foundation and Olmsted Medical Center institutional review board.

**Study sample.** Using the resources of the Rochester Epidemiology Project, a random sample of 2,042 Olmsted County, Minnesota, residents ages ≥45 years was identified. The design and selection criteria of the PAVD study as well as the characteristics of the Olmsted County population have been previously described (10–13). Of the 2,042 total participants, 45 were excluded because of symptomatic HF (stages C and D HF by ACC/AHA guidelines) and, consistent with previous reports (4,5,7), 6 because of plasma creatinine >2.0 mg/dl. The remaining 1,991 participants were used for all analyses in this study. Subjects were then characterized as healthy normal (n = 703) if they had no clinical risk factors or echocardiographic abnormalities. Clinical risk factors were defined as documented coronary artery disease (CAD), hypertension, diabetes mellitus, prior myocardial infarction, chronic obstructive pulmonary disease, history of cardiovascular drug use, peripheral vascular disease, hyperlipidemia, and absence of normal sinus rhythm. Echocardiographic abnormalities were left ventricular hypertrophy, left atrial enlargement, regional wall motion abnormalities, valvular dysfunction, ejection fraction <50%, and diastolic dysfunction. The remaining subjects (n = 1,288), with 1 or more clinical risk factors or echocardiographic abnormalities, were classified as stage A/B HF.

**Abbreviations and Acronyms**

**BMI** = body mass index
**BNP** = B-type natriuretic peptide
**CAD** = coronary artery disease
**CVA** = cerebrovascular accident
**HF** = heart failure
**IDI** = integrated discrimination improvement
**NT-proBNP** = N-terminal pro-B-type natriuretic peptide

**Main outcome measures.** The Rochester Epidemiology Project maintains a unified medical record including mortality data. For mortality, participants were followed up until death or May 2008, at which time they were censored. This provided a mean 8.9 years of mortality follow-up, with a median (25th, 75th percentile) of 9.1 (8.5, 9.9) years. In addition to all-cause mortality, participants were monitored with respect to HF, myocardial infarction, stroke, and transient ischemic attack. Heart failure was defined as International Classification of Diseases-Ninth Revision (ICD-9) code 402 or 428. Stroke and transient ischemic attack were grouped together under the term cerebrovascular accident (CVA) and included ICD-9 codes 430 to 438. Myocardial infarction was defined as ICD-9 code 410 or 412. For HF, CVA, and myocardial infarction participants were followed up until an event or May 1, 2008, at which time they were censored. This provided a median (25th, 75th percentile) of 8.7 (7.4, 9.8), 8.8 (6.3, 9.7), and 8.9 (7.3, 9.8) years of follow-up for HF, CVA, and myocardial infarction, respectively. Because of the low number of events in the healthy normal cohort, we assessed a combined end point of death, HF, CVA, and myocardial infarction with a median follow-up of 8.8 years. The combined end point was not assessed in the stage A/B HF cohort because of a sufficient number of individual events.

**Doppler echocardiography.** All echocardiograms were performed with the same echocardiographic instrument (HP-2500, Hewlett-Packard, Palo Alto, California) and were interpreted by a single echocardiologist blind to NT-proBNP values. Two-dimensional and color Doppler imaging were performed to screen for valvular stenosis and regurgitation. In each subject, ejection fraction was measured and diastolic function categorized, as previously described (11,14). Left ventricular mass was calculated accord-