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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.

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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-

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ing to the Devereux formula (15) and indexed to body surface area. Presence of left ventricular hypertrophy was defined on the basis of left ventricular mass index >130 g/m^2 for men and >100 g/m^2 for women (16). Presence of left atrial enlargement was defined as left atrial volume index >33 ml/m^2 in men and >30 ml/m^2 in women (17).

Analysis of NT-proBNP. All 1,991 participants underwent NT-proBNP measurement with the Elecsys NT-proBNP electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, Indiana), as described previously (13,18). Interassay and intra-assay coefficients of variation for NT-proBNP were 3.1% and 2.5%, respectively.

Statistical analysis. Descriptive statistics were used to summarize the data, continuous variables were expressed as a mean ± SD, and categorical variables by the percentage of the category among the total group. The Wilcoxon rank-sum test was used to compare variables between the healthy normal cohort and stage A/B HF cohort. Survival and event-free rates after entry into the study were estimated using the Kaplan-Meier method. The association of outcomes with clinical and echocardiographic variables and NT-proBNP levels was assessed using Cox proportional hazards regression.

As both sex and age significantly impact NT-proBNP plasma values (13,19), we used cut points corresponding to age- and sex-adjusted 80th percentile values for NT-proBNP (Fig. 1) in all analyses. The age- and sex-adjusted 80th percentile cut point values were obtained from the total study sample (n = 1,991), excluding subjects with stages C and D HF or creatinine >2.0 mg/dl. Hazard ratios and 95% confidence intervals were calculated from unadjusted analyses, after adjustment for age, sex, and body mass index (BMI) as well as from multivariable models with traditional cardiovascular risk factors (age, sex, BMI, diabetes mellitus, hypertension, serum total cholesterol, CAD, and serum creatinine) and finally from multivariable models with both traditional cardiovascular risk factors and echocardiographic abnormalities (ejection fraction <50%, diastolic dysfunction, valvular dysfunction, left ventricular hypertrophy, left atrial enlargement, and wall motion abnormalities).

The discriminative value of the NT-proBNP biomarker for each outcome beyond known risk factors was evaluated using the integrated discrimination improvement (IDI) approach, as proposed by Pencina et al. (20,21). The IDI is the difference in discriminative ability between 2 models according to their predicted event probabilities. For instance, in comparing 1 mortality model to another, an

Table 1 Baseline Characteristics of the Healthy Normal and Stage A/B HF Subgroups

	Healthy Normal (n = 703)	Stage A/B HF (n = 1,288)
Age, yrs	56 ± 7*	65 ± 10
Female, n (%)	370 (53)	667 (53)
BMI	28 ± 4*	29 ± 5
Systolic BP, mm Hg	124 ± 17*	138 ± 22
Diastolic BP, mm Hg	72 ± 9*	75 ± 10
Serum cholesterol, mg/dl		
Total	208 ± 35*	201 ± 36
HDL	47 ± 14†	46 ± 15
Serum Cr, mg/dl	1.0 ± 0.2*	1.1 ± 0.2
LA volume index, ml/m^2	21 ± 5*	27 ± 11
LV mass index, g/m^2	88 ± 14*	101 ± 23
Ejection fraction, %	64 ± 4	63 ± 7

Data are presented as mean ± 1 SD. *$p < 0.001$ compared to stage A/B heart failure (HF) subgroup. †$p = 0.031$ compared to stage A/B HF subgroup.
BMI = body mass index; BP = blood pressure; Cr = creatinine; HDL = high-density lipoprotein; LA = left atria; LV = left ventricle.

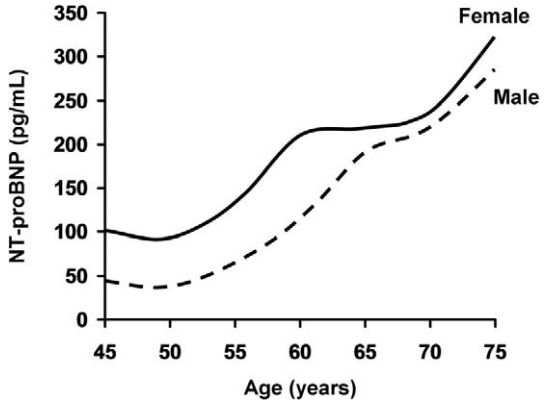

Figure 1 Age- and Sex-Specific 80th Percentile Values for Plasma NT-proBNP

Age- and sex-specific 80th percentile values for plasma N-terminal pro–B-type natriuretic peptide (NT-proBNP) in the total study sample excluding subjects with stages C and D heart failure or creatinine >2.0 (n = 1,991). **Solid line** = female; **dashed line** = male.

Table 2 Prevalence of Clinical and Echocardiographic Characteristics in the Stage A/B Heart Failure Subgroup

	Prevalence (%) in the Stage A/B HF Subgroup (n = 1,288)
Coronary artery disease	16
Hypertension	42
Diabetes mellitus	11
Angina	10
Unstable angina	6
Prior myocardial infarction	6
Atrial fibrillation/flutter	6
Cardiomyopathy	1
COPD	6
Cardiovascular drug	54
Ejection fraction ≤50%	8
Valvular disease	6
Wall motion abnormality	6
Diastolic dysfunction	47
Left ventricular hypertrophy	18
Left atrial enlargement	24

COPD = chronic obstructive pulmonary disease; other abbreviations as in Table 1.

increased probability of death among subjects who died and a decreased probability of death among subjects who survived implies better predictive ability, whereas the opposite implies worse predictive ability. These 2 changes are summed (improvement always considered positive), and the standard error is calculated based on the sum of squares of the standard errors for each mean change. Based on these estimates, a 1-sample *t* test was used to test for a significant IDI. A 2-sided p value of <0.05 was deemed statistically significant. The ability to classify risk was further assessed with the use of the c-statistic (22). The statistical software package SAS version 8.2 (SAS Institute, Cary, North Carolina) was used for all analyses.

Results

Study sample characterization. Baseline characteristics of the healthy normal subgroup (n = 703) and stage A/B HF subgroup (n = 1,288) are shown in Table 1. Healthy normal subjects were younger and had lower BMI levels than stage A/B HF subjects. Systolic and diastolic blood pressure, creatinine, left atrial volume, and left ventricular mass were significantly lower in the healthy normal subgroup compared with the stage A/B HF subgroup. Interestingly, total cholesterol and high-density lipoprotein were higher in healthy normal subjects as compared with stage A/B HF subjects. The prevalence of the traditional clinical risk factors and structural/functional cardiac abnormalities that define the stage A/B HF subgroup are shown in Table 2. Importantly, the healthy normal subgroup by definition was free of traditional clinical risk factors and structural/functional changes of the heart. Age- and sex-specific 80th percentile values for plasma NT-proBNP in the total study sample (n = 1,991 [excluding stage C/D HF]) are shown in Figure 1. Female sex and increasing age were both associated with higher 80th percentile values, but all age- and sex-specific 80th percentile values were below the HF diagnosis threshold (23–25). There was a greater prevalence of subjects with NT-proBNP value above the 80th percen-

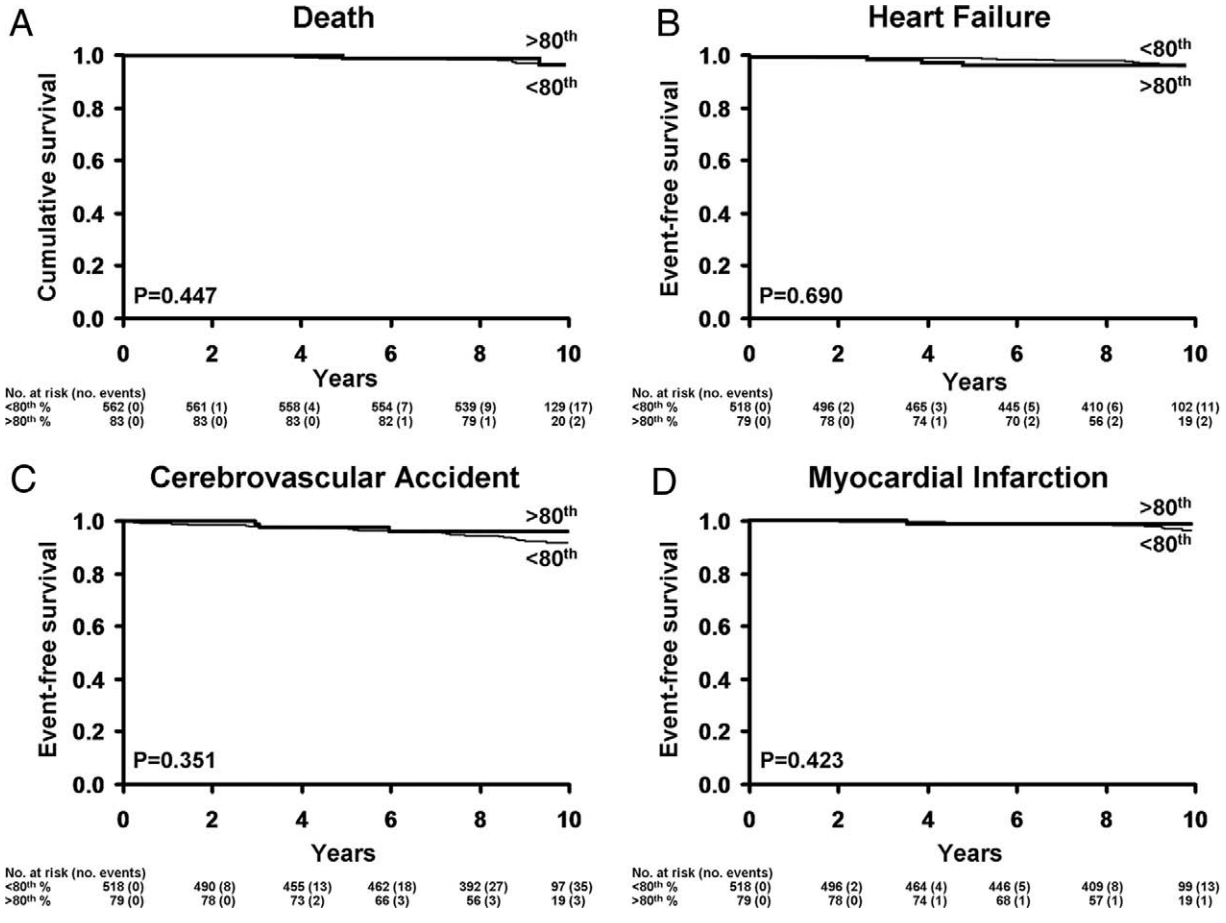

Figure 2 **Cumulative Survival and Event-Free Survival in the Healthy Normal Subgroup**

Kaplan-Meier curves for unadjusted cumulative incidence in the healthy normal subgroup (n = 703) for **(A)** death, **(B)** heart failure, **(C)** cerebrovascular accident, and **(D)** myocardial infarction according to plasma N-terminal pro–B-type natriuretic peptide (NT-proBNP) values above the age- and sex-specific 80th percentile **(thick line)** and below it **(thin line)**. Follow-up results are truncated after 10 years. Age- and sex-specific 80th percentile NT-proBNP values are shown in Figure 1. The average overall 80th percentile value was 196 pg/ml for women and 125 pg/ml for men.

tile in the stage A/B HF subgroup (24.7%) compared with the healthy normal subgroup (12.8%). The average overall NT-proBNP 80th percentile value was 196 pg/ml and 125 pg/ml for women and men, respectively.

Mortality and cardiovascular morbidity. HEALTHY NORMAL SUBGROUP. In the healthy normal subgroup, a cohort of 703 subjects free of traditional clinical risk factors and structural/functional cardiac abnormalities, there were 19 all-cause deaths, 13 HF events, 38 CVA, and 14 myocardial infarctions. Kaplan-Meier plots for the unadjusted incidence of death, HF, CVA, and myocardial infarction in the healthy normal subgroup according to plasma NT-proBNP levels above and below the age- and sex-adjusted 80th percentile are shown in Figure 2. In the healthy normal subgroup, there was no increased risk of death, HF, CVA, or myocardial infarction among subjects with plasma NT-proBNP levels greater than the age- and sex-specific 80th percentile. Age-, sex-, and BMI-adjusted hazard ratios for death, HF, CVA, and myocardial infarction according to baseline plasma NT-proBNP (greater than the age- and sex-adjusted 80th percentile as well as a continuous variable) are presented in Table 3. Because of the relatively small number of end points in the healthy normal group, we evaluated a combined end point including death, HF, CVA, and myocardial infarction. There were 72 combined events in the healthy normal cohort, and there was no increase in the cumulative incidence of the combined end point among subjects with NT-proBNP values above the age- and sex-specific 80th percentile or when NT-proBNP was analyzed as a continuous variable (Table 3).

Mortality and cardiovascular morbidity. STAGE A/B HF SUBGROUP. In contrast to the healthy normal subgroup, there were 170 all-cause deaths, 156 HF events, 236 CVA, and 133 myocardial infarctions among the 1,288 participants in the stage A/B HF subgroup. Figure 3 shows Kaplan-Meier plots for the unadjusted cumulative incidence of death, HF, CVA, and myocardial infarction in the stage A/B HF subgroup according to plasma NT-proBNP levels above and below the age- and sex-specific 80th percentile. There was a significantly higher cumulative incidence for each outcome among subjects with plasma NT-proBNP levels above the age- and sex-specific 80th percentile. Age-, sex-, and BMI-adjusted as well as multivariable analysis hazard ratios for death, HF, CVA, and myocardial infarction according to baseline plasma NT-proBNP (greater than the age- and sex-adjusted 80th percentile as well as a continuous variable) are presented in Table 4. In the stage A/B HF subgroup, plasma NT-proBNP was independently associated with increased death, HF, CVA, and myocardial infarction even after adjustment for traditional clinical risk factors and structural/functional cardiac abnormalities (Table 4).

The IDI was estimated to assess the discriminative value of NT-proBNP beyond known traditional clinical risk factors for each outcome. When adding NT-proBNP to a model including age, sex, BMI, total cholesterol, serum creatinine, diabetes mellitus, hypertension, and CAD, the increase in IDI (± SE) was 1.23 ± 0.45%, 1.41 ± 0.59%, 0.65 ± 0.41%, and 0.56 ± 0.25% for death, HF, CVA, and myocardial infarction, respectively. The improvement was significant ($p < 0.05$) for all outcomes except myocardial infarction ($p = 0.11$). Respective c-statistics for models with the above traditional clinical risk factors alone and with clinical risk factors plus NT-proBNP were 0.79 and 0.80 for death, 0.76 and 0.78 for HF, 0.71 and 0.72 for CVA, and 0.76 and 0.77 for myocardial infarction.

Discussion

The current study is the first to analyze the prognostic significance of NT-proBNP in a large, entirely normal sample free of traditional clinical cardiovascular risk factors

Table 3 Mortality and Cardiovascular Morbidity in the Healthy Normal Subgroup (n = 703) During 10 Years of Follow-Up According to Baseline NT-proBNP

Outcome (No. of Events)	HR (95% CI) per 1 SD Increase in Log Variable	p Value	HR (95% CI) for Values Above 80th Percentile	p Value
Death (19)				
Unadjusted model	1.52 (0.88–2.62)	0.132	0.72 (0.17–3.09)	0.655
Age-, sex-, BMI-adjusted	0.95 (0.47–1.92)	0.881	1.06 (0.24–4.74)	0.938
Heart failure (13)				
Unadjusted model	1.21 (0.63–2.35)	0.564	1.19 (0.26–5.38)	0.819
Age-, sex-, BMI-adjusted	1.36 (0.61–3.01)	0.452	1.69 (0.36–7.96)	0.507
Myocardial infarction (14)				
Unadjusted model	0.71 (0.40–1.28)	0.255	0.45 (0.06–3.39)	0.435
Age-, sex-, BMI-adjusted	0.72 (0.33–1.59)	0.421	0.66 (0.08–5.23)	0.697
Cerebrovascular accident (38)				
Unadjusted model	1.06 (0.74–1.52)	0.738	0.61 (0.22–1.73)	0.356
Age-, sex-, BMI-adjusted	0.79 (0.49–1.26)	0.320	1.06 (0.37–3.05)	0.915
Combined end point (72)				
Unadjusted model	1.04 (0.79–1.37)	0.765	0.76 (0.36–1.57)	0.454
Age-, sex-, BMI-adjusted	0.93 (0.65–1.33)	0.688	1.14 (0.53–2.42)	0.736

CI = confidence interval; HR = hazard ratio; NT-proBNP = N-terminal pro–B-type natriuretic peptide; other abbreviations as in Table 1.

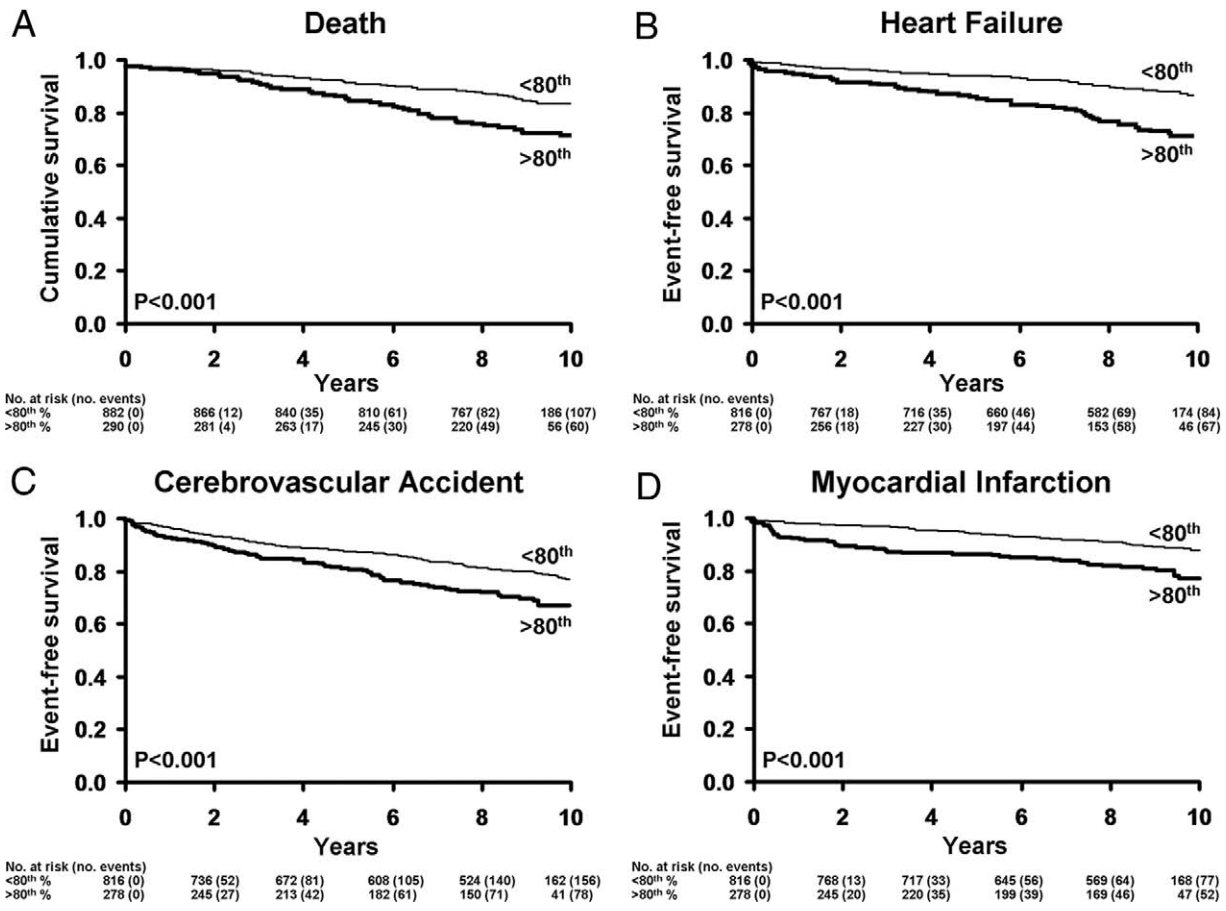

Figure 3 **Cumulative and Event-Free Survival in the Stage A/B Heart Failure Subgroup**

Kaplan-Meier curves for unadjusted cumulative incidence in the stage A/B heart failure subgroup (n = 1,228) for **(A)** death, **(B)** heart failure, **(C)** cerebrovascular accident, and **(D)** myocardial infarction according to plasma N-terminal pro–B-type natriuretic peptide (NT-proBNP) values above the age- and sex-specific 80th percentile **(thick line)** and below it **(thin line)**. Follow-up results are truncated after 10 years. Age- and sex-specific 80th percentile NT-proBNP values are shown in Figure 1. The average overall 80th percentile value was 196 pg/ml for women and 125 pg/ml for men.

and structural/functional echocardiographic abnormalities (healthy normal subjects). In this subgroup, which represented 34% of the 2,042 subjects in a community-based sample and 703 of 1,991 subjects in the current analysis, the prognostic significance of plasma NT-proBNP for mortality, HF, CVA, and myocardial infarction was absent, suggesting that NT-proBNP lacks prognostic significance in healthy normal subjects. Similar to previous reports, NT-proBNP had significant prognostic value for mortality, HF, CVA, and myocardial infarction among subjects with stage A/B HF. It should be noted that the NT-proBNP values associated with increased risk were well below those seen with HF (23–25), and that the prognostic value remained significant even after adjustment for traditional clinical cardiovascular risk factors and structural/functional echocardiographic abnormalities, including diastolic dysfunction.

The important observation from our investigations that NT-proBNP lacks prognostic value in the healthy normal cohort has clear implications on the use of NT-proBNP as a biomarker to identify subjects at increased risk for mortality and cardiovascular morbidity. First, an elevated plasma NT-proBNP alone does not appear sufficient to predict subjects at increased risk. Detailed history and echocardiographic examination are also necessary, and only in the presence of traditional risk factors or echocardiographic abnormalities (i.e., stage A/B HF) does NT-proBNP have prognostic value. Again, this is underscored by our observation that the healthy normal subgroup had subjects with plasma NT-proBNP values above the 80th percentile, but such values were of no prognostic significance. Second, these findings will have important implications as future proof-of-concept and interventional trials are planned to identify at-risk subjects based on elevated NT-proBNP levels. Only subjects with at-risk NT-proBNP values and either risk factors and/or structural or functional changes of the heart (stage A/B HF) should be candidates for more aggressive risk management. Importantly, we advocate stud-

Table 4 Mortality and Cardiovascular Morbidity in the Stage A/B Heart Failure Subgroup (n = 1,228) During 10 Years of Follow-Up According to Baseline NT-proBNP

Outcome (No. of Events)	HR (95% CI) per 1 SD Increase in Log Variable	p Value	HR (95% CI) for Values Above 80th Percentile	p Value
Death (170)				
Unadjusted model	2.65 (2.23–3.14)	<0.001	1.70 (1.25–2.33)	<0.001
Age-, sex-, BMI-adjusted	1.76 (1.45–2.13)	<0.001	2.01 (1.47–2.75)	<0.001
Multivariable model 1*	1.75 (1.43–2.14)	<0.001	2.02 (1.45–2.81)	<0.001
Multivariable model 2†	1.55 (1.23–1.96)	<0.001	1.60 (1.10–2.32)	0.014
Heart failure (156)				
Unadjusted model	1.75 (1.52–2.01)	<0.001	1.60 (1.22–2.09)	<0.001
Age-, sex-, BMI-adjusted	1.38 (1.18–1.62)	<0.001	1.77 (1.35–2.32)	<0.001
Multivariable model 1*	1.28 (1.09–1.52)	0.004	1.56 (1.18–2.06)	0.002
Multivariable model 2†	1.26 (1.05–1.51)	0.015	1.51 (1.12–2.03)	0.007
Myocardial infarction (133)				
Unadjusted model	2.77 (2.29–3.35)	<0.001	2.49 (1.82–3.41)	<0.001
Age-, sex-, BMI-adjusted	2.30 (1.87–2.84)	<0.001	3.00 (2.18–4.12)	<0.001
Multivariable model 1*	2.16 (1.72–2.70)	<0.001	2.63 (1.87–3.68)	<0.001
Multivariable model 2†	1.63 (1.27–2.09)	<0.001	1.74 (1.20–2.53)	0.004
Cerebrovascular accident (236)				
Unadjusted model	1.68 (1.39–2.02)	<0.001	2.22 (1.58–3.14)	<0.001
Age-, sex-, BMI-adjusted	1.61 (1.31–1.99)	<0.001	2.49 (1.76–3.52)	<0.001
Multivariable model 1*	1.36 (1.07–1.71)	0.011	2.03 (1.41–2.91)	<0.001
Multivariable model 2†	1.33 (1.03–1.73)	0.029	2.05 (1.39–3.03)	<0.001

*Adjustment for age, sex, body mass index (BMI), total cholesterol, serum creatinine, presence of diabetes mellitus, hypertension, and coronary artery disease. †Adjustment for variables in model 1 in addition to presence of ejection fraction <50%, diastolic dysfunction, valvular dysfunction, left ventricular hypertrophy, left atrial enlargement, and wall motion abnormalities.

Abbreviations as in Table 3.

ies be undertaken to determine if reduction of NT-proBNP in stage A/B HF by more aggressive risk management improves outcomes and survival.

The mechanism for the absence of prognostic value of NT-proBNP (both above the age- and sex-adjusted 80th percentile and as a continuous variable) in healthy normal subjects remains to be elucidated. One explanation would be too few individual events in the healthy normal subgroup to predict mortality and cardiovascular morbidity based on plasma NT-proBNP. Indeed, for the combined end point of death, HF, CVA, and myocardial infarction, for which there were 72 total events in the healthy normal subgroup, the current study was powered to detect an HR of 2.29. While underpowered because of the low event rate to detect a moderate association (hazard ratios of 1.5 to 2.0) of NT-proBNP with adverse outcomes in the healthy normal subgroup, the absolute risk is so low that it is difficult to justify the widespread use of NT-proBNP in clinically normal subjects. It is also possible that a mild elevation in BNP is cardioprotective in the absence of stage A/B HF. Another potential explanation is that subjects in the healthy normal subgroup who have elevated NT-proBNP levels may have a greater frequency of a recently reported BNP gene (NPPB) single-nucleotide polymorphism (rs198389), which results in greater circulating levels of BNP in the absence of cardiovascular disease (26,27). Although these hypotheses require further investigation, our findings suggest that in a large, well-characterized community-based cohort, NT-proBNP lacks prognostic value in healthy normal subjects.

A strength of the current investigation was the median follow-up of almost 9 years' duration and in-depth documentation of mortality and cardiovascular events. The seminal study of Wang et al. (5) documented the utility of atrial natriuretic peptide and BNP in predicting adverse cardiovascular outcomes in the general community (healthy normal and stage A/B HF combined) over a 5.2-year period of follow-up. The important Heart and Soul study of patients with CAD and without HF reported the prognostic significance of NT-proBNP over 3.5 years of follow-up (28,29). When all 3 studies are taken together, they reinforce the utility of the native cardiac natriuretic peptides as biomarkers for cardiovascular disease in the general population without HF. However, the current study would again state that NT-proBNP is not prognostic for mortality or cardiovascular morbidity in healthy normal subjects.

Conclusions

We report the first large community-based sample study of healthy normal subjects and stage A/B HF subjects to determine the prognostic value of NT-proBNP in predicting mortality and cardiovascular morbidity over a median 8.9 years of follow-up. Importantly, the prognostic value of NT-proBNP in healthy normal subjects as verified by in-depth clinical and echocardiographic examination was absent. Thus, our studies do not support the use of NT-

proBNP as a cardiovascular biomarker in healthy normal subjects.

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