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Biomarkers

Minimally Elevated Cardiac Troponin T and Elevated N-Terminal Pro-B-Type Natriuretic Peptide Predict Mortality in Older Adults

Results From the Rancho Bernardo Study

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Objectives This study investigated the prognostic value of detectable cardiac troponin T (TnT) and elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in a population of community-dwelling older adults.

Background Minimally elevated levels of TnT, a marker of cardiomyocyte injury, have been found in small subsets of the general population, with uncertain implications. A marker of ventricular stretch, NT-proBNP has clinical utility in many venues, but its long-term prognostic value in apparently healthy older adults and in conjunction with TnT is unknown.

Methods Participants were 957 older adults from the Rancho Bernardo Study with plasma NT-proBNP and TnT measured at baseline (1997 to 1999) and followed up for mortality through July 2006.

Results Participants with detectable TnT (≥0.01 ng/ml, n = 39) had an increased risk of all-cause and cardiovascular death (adjusted hazard ratio [HR] by Cox proportional hazards analysis: 2.06; 95% confidence interval [CI]: 1.29 to 3.28, p = 0.003 for all-cause mortality; HR: 2.06, 95% CI: 1.03 to 4.12, p = 0.040 for cardiovascular mortality); elevated NT-proBNP also predicted an increased risk of all-cause and cardiovascular mortality (adjusted HR per unit-log increase in NT-proBNP: 1.85, 95% CI: 1.36 to 2.52, p < 0.001 for all-cause mortality; HR: 2.51, 95% CI: 1.55 to 4.08, p < 0.001 for cardiovascular mortality). Those with both elevated NT-proBNP and detectable TnT had poorer survival (HR for high NT-proBNP and detectable TnT vs. low NT-proBNP and any TnT: 3.20, 95% CI: 1.91 to 5.38, p < 0.001). Exclusion of the 152 participants with heart disease at baseline did not materially change the TnT mortality or NT-proBNP mortality associations.

Conclusions Apparently healthy adults with detectable TnT or elevated NT-proBNP levels are at increased risk of death. Those with both TnT and NT-proBNP elevations are at even higher risk, and the increased risk persists for years. (J Am Coll Cardiol 2008;52:450–9) © 2008 by the American College of Cardiology Foundation

Cardiac troponin T (TnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are two distinct biomarkers that have both emerged as valuable tools in confirming the diagnosis of cardiovascular disease (CVD) during the past decade. Cardiac TnT is a protein expressed by cardiac myocytes and released in the setting of myocardial injury. A sensitive and specific marker of myocardial injury, TnT is used clinically in the diagnosis of myocardial infarction. Elevations of TnT seen in acute coronary settings have helped guide risk stratification, prognosis, and therapeutic management (1–6) and have long-term prognostic value when present even months after an acute coronary syndrome (7). However, TnT levels can also be elevated and clinically meaningful in the absence of clinically suspected myocardial ischemia. For example, in the setting of disease states such as heart failure and chronic renal failure, even small elevations of TnT are associated with a poor prognosis (8–11). Minimally elevated levels of TnT have also been found in small subsets of the general population; the cause and significance of these rare elevations are unclear, but it seems to portend a worse prognosis (12,13).

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Natriuretic peptides are secreted from cardiac myocytes in response to ventricular wall stretch (14). The precursor protein is cleaved into the biologically active B-type natriuretic peptide (BNP) and the inactive N-terminal fragment (NT-proBNP), both of which have been shown to be useful in detecting abnormal ventricular function (15,16) and in diagnosing heart failure (17,18) in symptomatic patients. They also provide prognostic information in the setting of acute coronary syndromes (5,6,19,20), heart failure (21–23), and a variety of other settings (24–27). Emerging data suggest that natriuretic peptides may also be useful in screening asymptomatic populations for subclinical CVD (28–30).

The purpose of this study was to investigate the prognostic utility of minimally detectable TnT levels along with elevated NT-proBNP levels in predicting clinical outcomes in a population of community-dwelling older adults.

Abbreviations and Acronyms

AUC = area under the receiver-operator characteristic curve
BMI = body mass index
BUN = blood urea nitrogen
CHD = coronary heart disease
CVD = cardiovascular disease
HR = hazard ratio
NT-proBNP = N-terminal pro-B-type natriuretic peptide
ROC = receiver-operator characteristic
TnT = troponin T

Methods

Study population. The Rancho Bernardo Study is a prospective, population-based study of the epidemiology of chronic disease in older adults. Between 1972 and 1974, all community-dwelling residents ages 30 to 79 years of Rancho Bernardo, a community in Southern California, were invited to participate in a study of heart disease risk factors, and 82% (n = 5,052) enrolled. Nearly all were Caucasian, middle to upper-middle class, and relatively well-educated. The present analysis consists of the 957 of 1,096 surviving, locally resident participants who attended a study visit between 1997 and 1999, and who had frozen plasma available for analysis in 2006. One of the 957 participants had insufficient plasma available for measurement of TnT; all others had both TnT and NT-proBNP measured. Compared with the 139 individuals without NT-proBNP measured, the 957 participants studied were somewhat older and had a slightly higher prevalence of diabetes, hypertension, and cardiovascular disease, but did not differ by gender, body mass index (BMI), or lipid levels. All participants gave written informed consent, and the study protocol was approved by the human research protection program at the University of California at San Diego (La Jolla, California).

Data collection. Baseline data for these analyses were collected at the 1997 to 1999 Rancho Bernardo Study research clinic visit and included demographics, medical history (including history of cardiovascular events and revascularization procedures), and life-style information. Historical data and information on physical activity (exercise 3 or more times per week, yes or no), alcohol consumption (3 or more drinks per week vs. less or none), and current smoking (yes or no) were obtained using standard questionnaires developed by the Rancho Bernardo Research Group. Current medication use was validated by examination of pills and prescriptions brought to the clinic for that purpose. Blood pressure was measured in seated, resting subjects using the Hypertension Detection and Follow-up Program protocol (31); the mean of 2 readings was used in analyses. The BMI (kg/m^2) was derived from height and weight measured in the clinic with participants wearing light clothing and no shoes. Diabetes mellitus was defined as a fasting plasma glucose level ≥126 mg/dl, reported physician diagnosis, or use of diabetes medications. Hypertension was defined as use of antihypertensive medications, or resting blood pressure >140 mm Hg systolic or 90 mm Hg diastolic. Estimated creatinine clearance (eCrCl) was calculated using the Cockroft-Gault formula [creatinine clearance (ml/min) = weight (kg) × (140 − age)/(creatinine (mg/dl) × 72) × 0.85 (if female)], which may be more accurate than the Modification of Diet in Renal Disease equation in subjects with near-normal glomerular filtration rates (32,33). Participants were followed up for vital status with annual mailed questionnaires through June 1, 2006.

Laboratory methods. Blood samples were obtained after an overnight fast; serum and plasma were separated and stored frozen at −70° C. Total cholesterol and triglyceride levels were measured using an ABA-200 Biochromatic Analyzer (Abbott Laboratories, Irving, Texas). High-density lipoprotein was measured after precipitation of other lipoproteins with heparin and manganese chloride. Low-density lipoprotein was estimated using the Friedewald formula (34). Fasting plasma glucose levels were obtained in the morning after an overnight fast and were measured by the glucose oxidase method. In 2006, the Elecsys 2010 system (Roche Diagnostics, Indianapolis, Indiana) was used for analysis of TnT using the Elecsys Troponin T sandwich immunoassay (measurable range 0.010 to 25.00 ng/ml) (35) and NT-proBNP using the Elecsys proBNP sandwich immunoassay (measurable range 5 to 35,000 pg/ml) (36,37) in plasma that had been stored at −70°C. For TnT, the manufacturer has reported an interassay coefficient of variation of 10% at 0.03 ng/ml (35). Intra-assay and interassay coefficients of variation at various concentrations of NT-proBNP were as follows: at 175 pg/ml, 2.7% and 3.2%, respectively; at 355 pg/ml, 2.4% and 2.9%; at 1,068 pg/ml, 1.9% and 2.6%; and at 4,962 pg/ml, 1.8% and 2.3% (36).

Definition of end points. The primary outcome was all-cause mortality; the secondary end point was fatal CVD. Death certificates were obtained for decedents and coded by a certified nosologist using the International Classification of Disease–9th Revision criteria. The CVD death included deaths assigned codes 390 through 459. Prevalent coronary

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heart disease (CHD) was defined as a history of physician-diagnosed myocardial infarction or coronary revascularization. Prevalent CVD was defined as a history of CHD or stroke.

Statistical analysis. Continuous variables are presented as means ± standard deviation, and dichotomous variables as percentages. Participants were divided into groups based on TnT levels: undetectable (n = 917) and detectable (n = 39). Those with detectable levels were further divided into 2 groups: low (<0.03 ng/ml) and high (≥0.03 ng/ml), corresponding to the cut point suggested by current clinical guidelines, which recommend that TnT levels greater than the 99th percentile of a healthy population, in which imprecision is ≤10% (0.03 ng/ml), are considered abnormal (38). Participants were also grouped by NT-proBNP level into low (<450 pg/ml, n = 758) and high (≥450 pg/ml, n = 199). This cut point corresponds to the recommended decision threshold for the general age group represented in the Rancho Bernardo Study (36). Differences in baseline levels of risk factors and clinical characteristics between participants with and without detectable TnT or high NT-proBNP were analyzed with *t* tests and chi-square tests; the Fisher exact test was used as appropriate. High-density lipoprotein (HDL), triglycerides, blood urea nitrogen (BUN), and NT-proBNP were not normally distributed and were log transformed for analyses; geometric means are reported. The association between NT-proBNP and age was examined using Spearman rank-order correlation. The NT-proBNP levels and creatinine clearance levels were compared in participants with undetectable, low, and high TnT levels using analysis of variance and Tukey post-hoc tests. Multivariate covariates of elevated TnT and NT-proBNP were identified by logistic regression including variables with significant univariate associations; covariates that remained significant at $p < 0.05$ were retained in the final model. Multivariate Cox proportional hazards regression models were used to determine the association of TnT and/or NT-proBNP with all-cause and CVD mortality.

Table 1 Baseline Characteristics of the Study Population

	TnT*			NT-proBNP*		
Variable	Undetectable (n = 917)	Detectable (n = 39)	p Value	Low (n = 758)	High (n = 199)	p Value
Age, yrs	76.3 ± 8.4	83.5 ± 8.3	<0.001	74.9 ± 8.2	82.8 ± 6.6	<0.001
Male gender, %	38	62	0.003	40	37	0.44
Cardiovascular risk factors						
Hypertension, %	66	77	0.14	61	85	<0.001
Heart rate, beats/min	66 ± 10	64 ± 9	0.26	66 ± 9	65 ± 11	0.67
Systolic BP, mm Hg	138 ± 21	140 ± 18	0.65	136 ± 19	147 ± 25	<0.001
Diastolic BP, mm Hg	74 ± 9	69 ± 11	0.013	74 ± 9	72 ± 11	0.058
Current smoking, %	4	0	0.40	4	4	0.97
Ever smoked, %	54	64	0.20	54	56	0.58
Diabetes, %	11	26	0.018	11	14	0.36
Pre-existent disease, %						
MI	11	28	0.003	8	25	<0.001
CHD	15	38	<0.001	12	30	<0.001
Stroke	6	8	0.73	5	12	0.001
CVD	18	44	<0.001	15	37	<0.001
Medication use, %						
Aspirin	42	31	0.19	42	37	0.25
Lipid-lowering	18	18	0.96	19	13	0.037
Nutrition and activity						
Body mass index, kg/m^2	25.4 ± 4.1	24.7 ± 3.9	0.30	25.6 ± 4.1	24.4 ± 4.1	<0.001
Exercise ≥3×/week, %	74	62	0.086	76	62	<0.001
Alcohol ≥3×/week, %	49	46	0.69	49	48	0.76
Laboratory values						
Fasting glucose, mg/dl	103 ± 20	112 ± 30	0.076	104 ± 21	104 ± 21	0.90
BUN,† mg/dl	17	23	<0.001	17	19	<0.001
CrCl, ml/min	63 ± 23	44 ± 24	<0.001	66 ± 23	48 ± 18	<0.001
Total cholesterol, mg/dl	206 ± 36	200 ± 45	0.28	208 ± 36	199 ± 38	0.002
Triglycerides,† mg/dl	108	119	0.35	111	103	0.088
HDL cholesterol,† mg/dl	58	51	0.012	57	58	0.67
LDL cholesterol, mg/dl	121 ± 32	117 ± 39	0.48	123 ± 32	114 ± 34	<0.001
NT-proBNP,† pg/ml	164	863	<0.001	112	970	<0.001
Detectable troponin, %	N/A	N/A	N/A	2	15	<0.001

*For troponin groups, detectable is >0.01 ng/ml; for NT-proBNP groups, low is <450 pg/ml; high is >450 pg/ml. †Geometric mean.

BP = blood pressure; BPM = beats per minute; BUN = blood urea nitrogen; CHD = coronary heart disease; CrCl = creatinine clearance; CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TnT = troponin T.

Results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). For each analysis, 3 sequential Cox regression models were run. Model 1 adjusted for age and gender. For Model 2, life-style, risk factor, and laboratory covariates from Table 1 were analyzed, and univariate predictors of all-cause mortality were identified if significant at $p < 0.10$. This process yielded age, gender, hypertension, BMI, heart rate, systolic blood pressure, diastolic blood pressure, diabetes, physical activity, BUN, eCrCl, and logHDL, low-density lipoprotein, and total cholesterol as potential predictors. Backward stepwise Cox regression analysis was performed using these 14 covariates; those that remained significant at $p < 0.05$ (age, gender, systolic blood pressure, BMI, heart rate, physical activity, eCrCl, and total cholesterol) were retained in the final Model 2. Forward stepwise analysis yielded the same 8 covariates. The influence of prevalent CHD was tested by adjusting for a history of CHD in Model 3, and also by excluding those with CHD at baseline and repeating Models 1 and 2. Participants who were alive were censored at the date of their last follow-up. For survival analyses with CVD death as the outcome, subjects who died of non-CVD causes were censored at date of death.

Kaplan-Meier plots were constructed to compare survival in groups with detectable versus undetectable TnT and high versus low NT-proBNP. For analyzing the combination of TnT and NT-proBNP, 3 additional categories were defined: high NT-proBNP with detectable TnT (n = 27); high NT-proBNP but undetectable TnT (n = 171); and low NT-proBNP (with any TnT level, n = 758). Those with low NT-proBNP were grouped together regardless of TnT level because of the low number of participants with the combination of low NT-proBNP and detectable TnT (n = 12). All variables were treated as continuous variables except gender, hypertension, diabetes, history of CHD, smoking status, physical activity, and alcohol consumption, which were treated as dichotomous variables. Framingham risk scores were calculated based on published algorithms (39). Participants were classified into groups based on 3 Framingham risk categories (low, moderate, or high risk); HRs for all-cause mortality within each Framingham risk category, stratified by TnT or NT-proBNP level, were calculated using Cox regression analysis, with the low Framingham risk + low TnT/NT-proBNP as the reference group. Receiver-operator characteristic (ROC) curves were constructed to evaluate the incremental benefit of TnT or NT-proBNP, when combined with the Framingham risk score, for predicting all-cause mortality or CVD death. Areas under the receiver-operator characteristic curves (AUCs) were calculated and subsequent models were compared using the Delong-Delong Clarke-Pearson method (40). Interactions of biomarkers by gender were tested for all models, and none were found. A 2-tailed $p < 0.05$ was considered statistically significant. Data were analyzed using SPSS 12.0 (SPSS Inc., Chicago, Illinois) and Analyse-it v2.08 (Leeds, England, United Kingdom).

Results

Baseline characteristics. Baseline demographic, clinical, and laboratory characteristics of the study population by NT-proBNP and TnT groups are shown in Table 1. At baseline, the mean age of the 957 adults was 77 years (range 60 to 97 years); 39% were men. Overall, 12% of the population had diabetes mellitus, 66% had hypertension, and 16% had CHD. Over a median follow-up of 6.8 years (interquartile range 5.9 to 7.4 years, maximum 9.2 years), 220 deaths occurred; 42% were attributed to CVD.

Detectable TnT. The TnT levels were detectable in 4.1% of the population and ranged from 0.010 to 0.061 ng/ml. Compared with participants with undetectable TnT levels, those with detectable TnT were older and more likely to be male, hypertensive, and diabetic. They also had higher BUN and NT-proBNP levels, lower HDL cholesterol levels, and poorer renal function as estimated by creatinine clearance (Table 1). Across the 3 categories of TnT levels (undetectable, detectable but <0.03 ng/ml, and ≥0.03 ng/ml), higher TnT was associated with higher NT-proBNP levels and reduced creatinine clearance (Fig. 1).

Most participants with detectable TnT levels did not have a history of known CHD or CVD, even though such a history was more common in this group than in those without detectable levels (Fig. 2A). In multivariate analysis, covariates of having detectable TnT were male gender, lower creatinine clearance, and higher NT-proBNP levels (Table 2).

Elevated NT-proBNP levels. The NT-proBNP levels were higher in women than in men (207 pg/ml vs. 136 pg/ml, $p < 0.001$), and increased with age ($r = 0.56$, $p < 0.001$). Like those with detectable TnT levels, participants

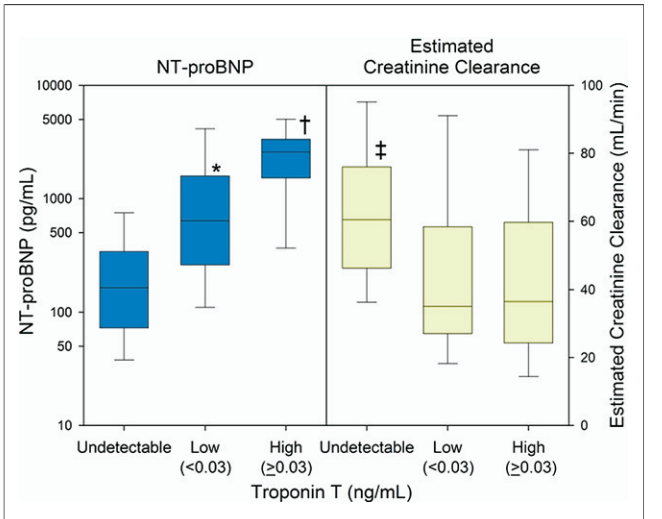

Figure 1 NT-proBNP Levels and Creatinine Clearance Levels by Troponin T Category

Troponin T categories: undetectable, n = 917; low, n = 30; high, n = 9. **Boxes** depict interquartile range, and **whiskers** represent 10th and 90th percentiles. *$p < 0.001$ versus undetectable. †$p < 0.001$ versus undetectable and $p = 0.03$ versus low. ‡$p < 0.001$ versus low and $p = 0.02$ versus high. NT-proBNP = N-terminal pro-B-type natriuretic peptide.

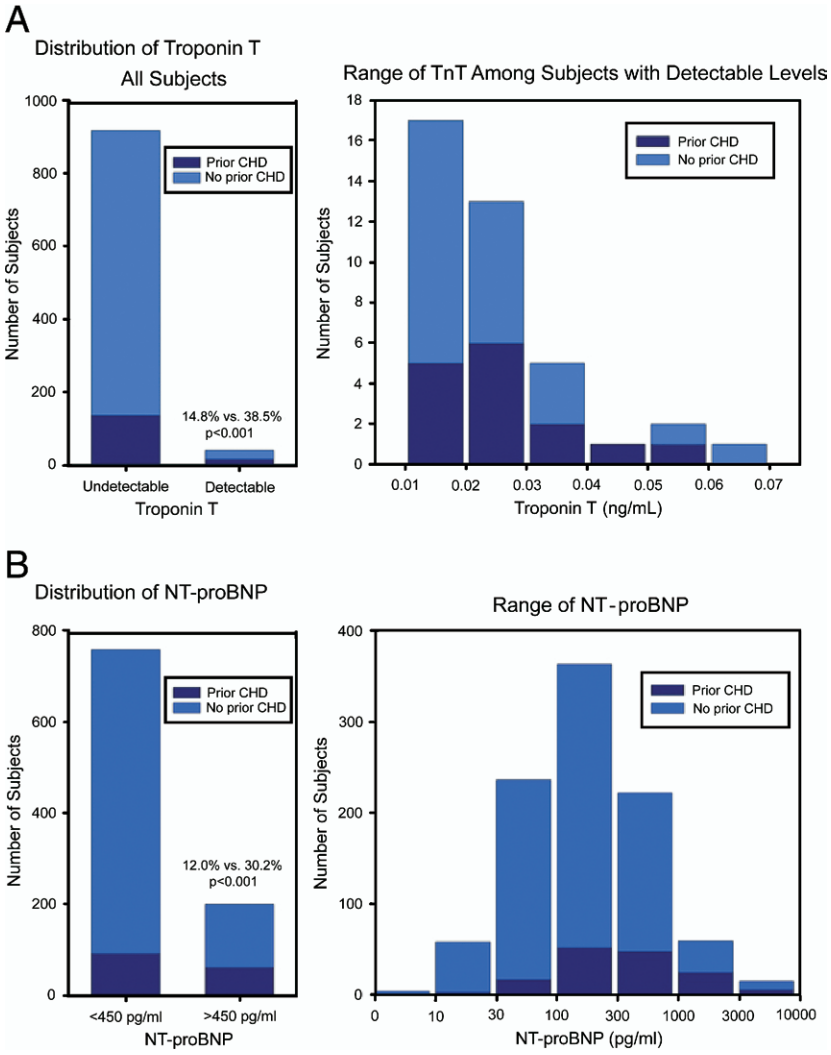

Figure 2 **Prevalence of Baseline CHD and Distribution of TnT and NT-proBNP**

(A) Prevalence of baseline coronary heart disease (CHD) in participants with undetectable and detectable TnT levels **(left)**, and distribution of TnT among those with detectable levels **(right)**. **(B)** Prevalence of baseline CHD in participants with low versus high NT-proBNP levels **(left)**, and distribution of NT-proBNP among all subjects **(right)**. NT-proBNP = N-terminal pro-B-type natriuretic peptide; prior CHD = myocardial infarction or revascularization; TnT = troponin T.

with higher NT-proBNP levels (≥450 pg/ml) were older than those with lower levels, had a higher prevalence of hypertension and CHD at baseline, and were more likely to have detectable TnT. They also had lower BMI, total and low-density lipoprotein cholesterol, and creatinine clearance levels; had higher systolic blood pressure and BUN; and were less likely to be taking lipid-lowering medications or to exercise regularly (Table 1).

Only 30% of those with elevated NT-proBNP levels had a history of CHD at baseline (Fig. 2B). In multivariate analysis, predictors of elevated NT-proBNP levels were age >70 years, higher systolic blood pressure, history of stroke, failure to exercise at least 3 times per week, lower creatinine clearance, and detectable troponin level (Table 2).

Outcomes. TNT AND RISK OF DEATH. Of the 220 participants who died during follow-up, 11% had detectable TnT levels, compared with only 2% of survivors ($p < 0.001$). Among all study participants, a detectable TnT level was associated with increased risk of all-cause death and of CVD death after adjusting for age and gender (Table 3, Model 1), and after further adjusting for other risk factors (Model 2). Further adjusting for the presence of CHD at baseline did not materially alter the findings (Model 3). When the analysis was restricted to the 806 participants without known CHD at baseline, detectable TnT remained a significant predictor of all-cause death. Figure 3 shows Kaplan-Meier survival curves by TnT group in all subjects (Fig. 3A) and in subjects without CHD at baseline (Fig.

Table 2 Multivariate Predictors of Detectable TnT or Elevated NT-proBNP

Risk Determinants	Odds Ratio (95% CI)	p Value
Risk determinants for detectable TnT		
Male gender	5.41 (2.50–11.6)	<0.001
CrCl*	0.45 (0.26–0.78)	0.004
log (NT-proBNP)*	3.47 (2.31–5.21)	<0.001
Risk determinants for elevated NT-proBNP		
Age >70 yrs	3.58 (1.76–7.27)	<0.001
Systolic blood pressure*	1.54 (1.29–1.83)	<0.001
History of stroke	3.43 (1.39–8.43)	0.007
Exercise <3 times per week	1.93 (1.31–2.83)	0.001
CrCl*	0.49 (0.38–0.63)	<0.001
Detectable TnT	7.49 (3.32–16.9)	<0.001

n = 953 in TnT model, and n = 949 in NT-proBNP model. *Per SD increase.
CI = confidence interval; other abbreviations as in Table 1.

3B); in both cases, mortality was higher for subjects with detectable TnT levels.

NT-PROBNP AND RISK OF DEATH. Forty percent of the 220 participants who died during follow-up had elevated NT-proBNP levels, compared with 15% of survivors ($p < 0.001$). After adjusting for age and gender, elevated NT-proBNP levels predicted all-cause and CVD mortality (Table 3). After further adjusting for other risk factors, NT-proBNP level remained a strong predictor of all-cause and of CVD mortality. In the 806 participants without baseline CHD, higher NT-proBNP levels were still significantly predictive of mortality, even after adjusting for other risk factors. Mortality was higher in subjects with NT-proBNP ≥450 pg/ml (Fig. 3C) even when the analysis was restricted to those participants without known CHD at baseline (Fig. 3D).

Combination of TnT and NT-proBNP for predicting death. When both TnT and NT-proBNP were included in the Cox regression model, each was independently predictive of all-cause mortality even after excluding participants with known CHD at baseline (Table 3).

Participants with both high NT-proBNP levels and detectable TnT levels had an increased risk of mortality (Fig. 4A) (adjusted HR for high NT-proBNP and detectable TnT vs. low NT-proBNP and any TnT: 3.20, 95% CI: 1.91 to 5.38). This association held true in analyses restricted to subjects without baseline CHD (Fig. 4B) (adjusted HR: 3.05, 95% CI: 1.52 to 6.12) and was even stronger when the outcome was limited to cardiovascular deaths (adjusted HR: 3.87, 95% CI: 1.83 to 8.15).

Framingham risk score stratification. An increased risk of death among participants with detectable TnT was evident in low-risk, intermediate-risk, and high-risk individuals, as classified by Framingham risk score (Fig. 5A). Use of TnT to stratify low-risk and intermediate-risk individuals resulted in reclassification of 4% of participants into a high-risk group, based on TnT detectability. Also, TnT significantly improved the AUC for the prediction of all-cause mortality and for CVD death compared with the Framingham risk score alone (AUC 0.625 vs. 0.575, $p = 0.011$ for all-cause mortality and 0.668 vs. 0.597, $p = 0.017$ for CVD death).

Similarly, elevated NT-proBNP levels were associated with an increased risk of death in each Framingham risk

Table 3 Multivariate Models for Predicting All-Cause and CVD Mortality

	All-Cause Mortality				CVD Mortality			
	All Subjects (n = 220 Deaths)		Baseline CHD Excluded (n = 157 Deaths)		All Subjects (n = 92 Deaths)		Baseline CHD Excluded (n = 52 Deaths)	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
TnT* (dichotomous)								
Model 1	2.25 (1.44–3.52)	<0.001	2.20 (1.23–3.93)	0.008	2.25 (1.17–4.32)	0.015	1.26 (0.39–4.09)	0.71
Model 2	2.06 (1.29–3.28)	0.003	2.38 (1.30–4.36)	0.005	2.06 (1.03–4.12)	0.040	1.42 (0.42–4.86)	0.58
Model 3	1.87 (1.16–3.00)	0.010	N/A		1.61 (0.79–3.28)	0.19	N/A	
NT-proBNP† (continuous)								
Model 1	2.29 (1.70–3.09)	<0.001	2.00 (1.38–2.88)	<0.001	3.50 (2.19–5.58)	<0.001	2.41 (1.25–4.65)	0.009
Model 2	1.85 (1.36–2.52)	<0.001	1.74 (1.19–2.55)	0.004	2.51 (1.55–4.08)	<0.001	1.85 (0.94–3.64)	0.078
Model 3	1.67 (1.21–2.29)	0.002	N/A		1.93 (1.17–3.19)	0.011	N/A	
TnT* and NT-proBNP†								
Model 1								
TnT	1.69 (1.06–2.68)	0.026	1.75 (0.96–3.18)	0.067	1.45 (0.74–2.87)	0.28	0.88 (0.26–2.98)	0.84
NT-proBNP	2.09 (1.54–2.84)	<0.001	1.82 (1.25–2.65)	0.002	3.27 (2.02–5.30)	<0.001	2.45 (1.25–4.82)	0.009
Model 2								
TnT	1.63 (1.00–2.66)	0.052	1.94 (1.03–3.66)	0.041	1.41 (0.68–2.94)	0.36	1.05 (0.29–3.80)	0.94
NT-proBNP	1.68 (1.22–2.31)	0.001	1.54 (1.04–2.29)	0.033	2.34 (1.41–3.89)	0.001	1.83 (0.90–3.72)	0.093
Model 3								
TnT	1.59 (0.97–2.59)	0.065	N/A		1.33 (0.64–2.74)	0.45	N/A	
NT-proBNP	1.53 (1.10–2.12)	0.011	N/A		1.84 (1.10–3.08)	0.020	N/A	

*Hazard ratios for TnT are for detectable versus undetectable levels. †Hazard ratios for NT-proBNP are per 1 unit log increase. Model 1, age and gender. Model 2, age, gender systolic blood pressure, body mass index, heart rate, physical activity, total cholesterol, and creatinine clearance. Model 3, Model 2 + baseline CHD.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

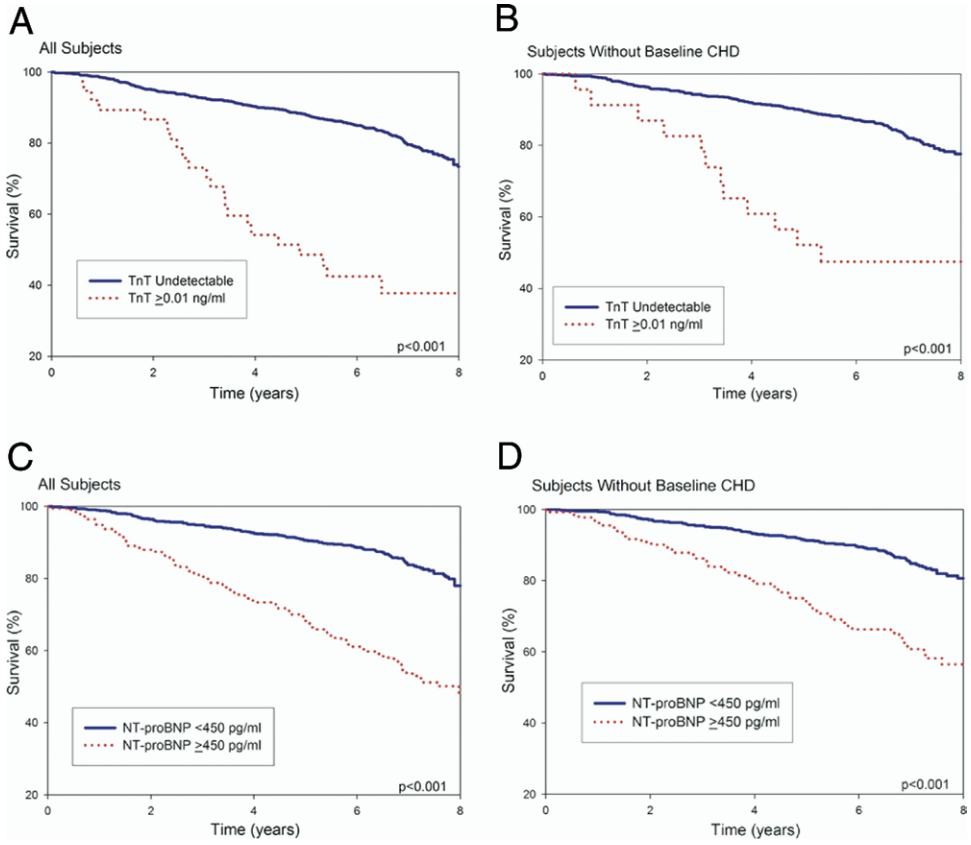

Figure 3 Kaplan-Meier Survival Plots by TnT or NT-proBNP Levels

(A) Survival in participants with undetectable versus detectable TnT levels. n = 196 deaths in the undetectable TnT group (of 917 participants with undetectable TnT) and n = 23 deaths in the detectable TnT group (of 39 participants with detectable TnT). **(B)** Survival in participants with undetectable versus detectable TnT levels, with analysis limited to those participants without baseline coronary heart disease (CHD). n = 143 deaths in the undetectable TnT group (of 781 participants with undetectable TnT) and n = 13 deaths in the detectable TnT group (of 24 participants with detectable TnT). **(C)** Survival in participants with low (<450 pg/ml) versus high (≥450 pg/ml) NT-proBNP levels. n = 132 deaths in the low NT-proBNP group (of 758 participants with low NT-proBNP) and n = 88 deaths in the high NT-proBNP group (of 199 participants with high NT-proBNP). **(D)** Survival in participants with low versus high NT-proBNP levels, with analysis limited to those participants without baseline CHD. n = 106 deaths in the low NT-proBNP group (of 667 participants with low NT-proBNP) and n = 51 deaths in the high NT-proBNP group (of 139 participants with high NT-proBNP). Abbreviations as in Figure 2.

group (Fig. 5B). The use of NT-proBNP would have reclassified 17% of participants as high risk, based on NT-proBNP ≥450 pg/ml. The addition of NT-proBNP to the Framingham risk score improved the AUC for prediction of all-cause mortality from 0.575 to 0.704, and for CVD death from 0.597 to 0.725 ($p < 0.001$ for each).

Similar results were seen when CVD death was used as the primary outcome measure (data not shown).

Discussion

In this cohort, apparently healthy community-dwelling adults with minimally detectable TnT were at increased risk of death. Elevated NT-proBNP levels also independently predicted death in this cohort. The predictive ability was improved by incorporating both TnT and NT-proBNP, and the prognostic value of each biomarker persisted for years after initial measurement.

Current guidelines recommend that TnT levels >0.03 ng/ml be considered abnormal (38). However, we have shown that individuals with any detectable TnT level, even those lower than this cut point, have clinical features suggestive of poor health, including higher NT-proBNP levels and poorer renal function. This is in agreement with the findings of Wallace et al. (12), who also noted that individuals with detectable TnT tended to have significant comorbidity. Importantly, in the present study more than 60% of those with detectable TnT did not have known prior heart disease, and the prognostic ability of TnT was independent of other CHD risk factors. Thus, cardiac TnT probably reflects subclinical heart disease in adults without known CHD. When analysis was limited to the subgroup of participants without prior CHD, the strength of the associations between detectable TnT or elevated NT-proBNP and all-cause mortality was not materially changed, suggest-

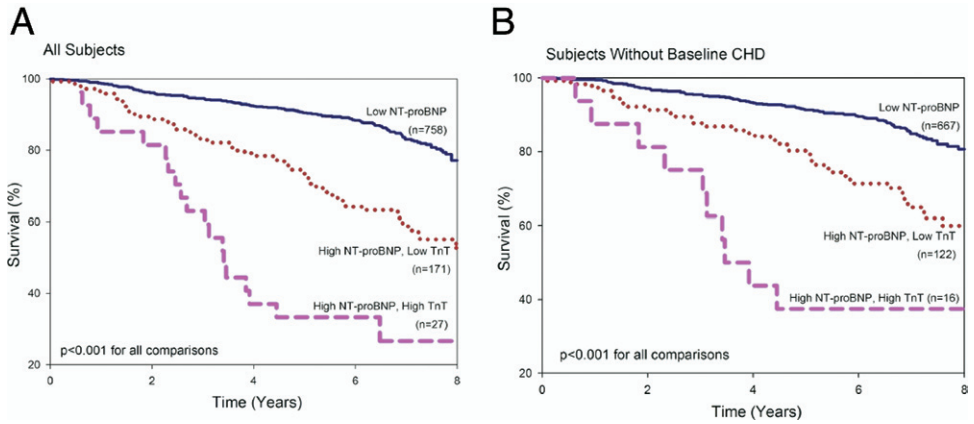

Figure 4 **Kaplan-Meier Survival Plots by Combined TnT and NT-proBNP Levels**

(A) n = 132 deaths in the high NT-proBNP/detectable TnT group, n = 68 deaths in the high NT-proBNP/undetectable TnT group, and n = 19 deaths in the low NT-proBNP group. **(B)** Analysis limited to those participants without baseline coronary heart disease (CHD). n = 106 deaths in the high NT-proBNP/detectable TnT group, n = 40 deaths in the high NT-proBNP/undetectable TnT group, and n = 10 deaths in the low NT-proBNP group. Abbreviations as in Figure 2.

ing that TnT and NT-proBNP are predictive even in an apparently heart disease–free population.

The prevalence of detectable TnT in the Rancho Bernardo cohort was 4.1%, higher than the prevalence of 0.7% estimated from the population-based Dallas Heart Study (12). This difference likely reflects the younger age of the Dallas cohort. Few studies have reported the clinical significance of minimally elevated troponin levels. Wallace et al. (12) reported that the presence of measurable troponin levels among the 3,557 subjects from the Dallas Heart Study was associated with a high-risk phenotype including underlying heart failure, left ventricular hypertrophy, chronic kidney disease, or diabetes, but did not report on how the presence of a measurable troponin level affected clinical outcomes. The only prior study that has reported minimally detectable troponin levels and outcomes in the general population was based on registry data and included only men; in this study Zethelius et al. (13) reported that cardiac troponin I predicted death and first CHD event over approximately 10 years of follow-up in 1,203 elderly men, and this association was independent of conventional risk factors.

The association of even minimally elevated TnT levels with mortality suggests that TnT is a marker of subclinical myocardial damage. Plausible mechanisms for the release of detectable TnT in the blood include silent ischemia, microvascular disease, left ventricular strain, impaired subendocardial perfusion, endothelial dysfunction, apoptosis, oxidative stress injury, inflammation, or other undetermined factors leading to microscopic myocardial cell necrosis or cellular membrane leak reflecting increased myocyte permeability (41–45). Until more sensitive tests become available, the relatively low prevalence of detectable TnT levels in the community may limit its utility as a screening agent.

In contrast, natriuretic peptides have been shown to predict cardiovascular disease in a variety of settings, including apparently healthy individuals. The NT-proBNP cut point of 450 pg/ml, derived from the recommended decision threshold for older outpatients with shortness of breath, also provided prognostic information in this community-based population of older adults. In the Framingham Offspring Study of 3,346 individuals with a mean age of 58 years, Wang et al. (29) found a 27% increased risk of death for each 1-SD increment in log BNP levels during 5.2 years of follow-up; higher BNP levels were also associated with increased risk of cardiovascular events, atrial fibrillation, heart failure, and stroke or transient ischemic attack. Kistorp et al. (46) measured NT-proBNP levels in a community-based cohort of 626 Danish adults (mean age 68 years) and reported a 43% increase in the adjusted risk of death from any cause per 1-SD increase in log NT-proBNP. These results are similar to the 39% increased risk of death per 1-SD increase in log NT-proBNP reported in the present study. Higher NT-proBNP levels were also associated with the first major cardiovascular event in the Danish cohort, in agreement with our finding of increased risk of cardiovascular death in individuals with elevated NT-proBNP.

In the present study, the coexistence of both elevated NT-proBNP and a detectable troponin level was uncommon, but was associated with a 3.2-fold increased risk of death. The effects of NT-proBNP and TnT were independent of each other, which is in accord with their differing pathophysiologic roles. It is likely that each marker identifies a distinct physiology, either of which confers increased risk. It is plausible that the simultaneous presence of subclinical myocardial ischemia and increased left ventricular wall stretch portends an outcome worse than either factor alone. Both NT-proBNP and TnT measurements may prove clinically useful in identifying a high-risk popu-

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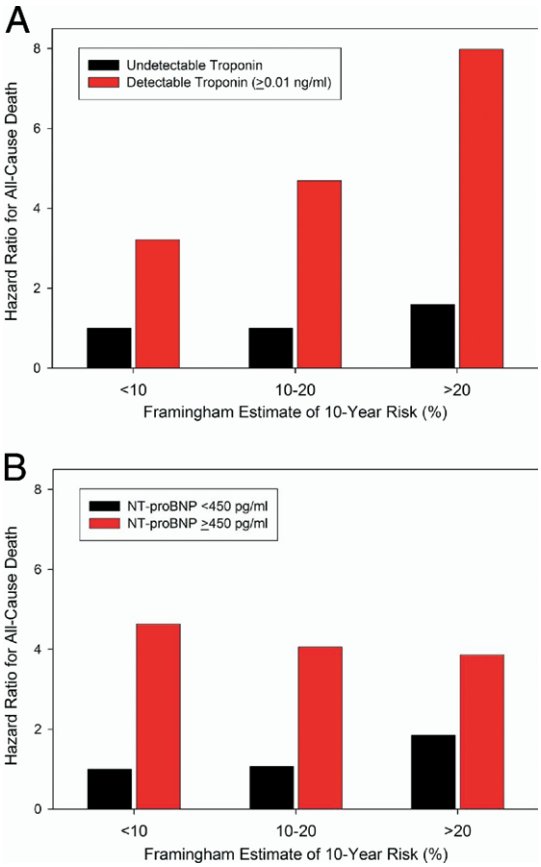

Figure 5 **Framingham Risk Score and Incremental Prognostic Value of Troponin T or NT-proBNP for Predicting Death**

Reference group in **(A)** is the group with low Framingham risk score (<10%) and undetectable troponin T. Reference group in **(B)** is the group with low Framingham risk scores and NT-proBNP <450 pg/ml. Framingham risk score was calculated as low risk (<10% risk of events over 10 years), moderate risk (10% to 20%), and high risk (>20%). Abbreviations as in Figure 2.

lation with subclinical CVD in whom aggressive preventive measures may be warranted. Further studies are needed to evaluate this possibility. Both TnT and NT-proBNP added significantly to risk prediction by the Framingham score, with elevated levels of either marker predicting an increased hazard of death, irrespective of Framingham risk level. Although both biomarkers improved the AUC for prediction of CVD death and all-cause mortality, NT-proBNP raised the AUCs more than TnT. Elevated NT-proBNP is also more prevalent than detectable TnT, and is therefore better suited to screening.

Study limitations. This study has several limitations. Because the Rancho Bernardo Study consists primarily of middle-class to upper-middle-class adults of European ancestry, the results may not be generalizable to other ethnic and socioeconomic groups. Baseline CHD events were based on self-report of prior coronary revascularization or of a physician diagnosis, which could have resulted in misclassification. However, at an earlier Rancho Bernardo study visit, 85% of reported cardiovascular events were confirmed in the 30% subset that had medical records permitting validation. Also, this study had small numbers of individuals with measurable TnT, limiting our ability to identify all important predictors of detectable TnT levels and our power to detect significant associations with CVD mortality after excluding participants with baseline CHD. Nonetheless, we were able to show a significant association for both TnT and NT-proBNP with all-cause mortality even after excluding participants with baseline CHD. In this case both TnT and NT-proBNP remained independent predictors of death.

Conclusions

Apparently healthy community-dwelling adults with minimally detectable TnT levels or elevated NT-proBNP levels are at an increased risk of death. Those with both TnT and NT-proBNP elevations are at even higher risk, and the increased risk adds significantly to the Framingham risk score prediction and persists for years. Further studies are needed to determine whether early interventions in individuals with elevated TnT or NT-proBNP levels could help improve long-term outcomes.

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REFERENCES

1. Newby LK, Roe MT, Chen AY, et al. Frequency and clinical implications of discordant creatine kinase-MB and troponin measurements in acute coronary syndromes. J Am Coll Cardiol 2006;47:312–8.
2. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996;335:1342–9.
3. Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. GUSTO IIA Investigators. N Engl J Med 1996;335:1333–41.
4. Steen H, Giannitsis E, Futterer S, Merten C, Juenger C, Katus HA. Cardiac troponin T at 96 hours after acute myocardial infarction correlates with infarct size and cardiac function. J Am Coll Cardiol 2006;48:2192–4.
5. Westerhout CM, Fu Y, Lauer MS, et al. Short- and long-term risk stratification in acute coronary syndromes: the added value of quantitative ST-segment depression and multiple biomarkers. J Am Coll Cardiol 2006;48:939–47.
6. James SK, Lindback J, Tilly J, et al. Troponin-T and N-terminal pro-B-type natriuretic peptide predict mortality benefit from coronary revascularization in acute coronary syndromes: a GUSTO-IV substudy. J Am Coll Cardiol 2006;48:1146–54.
7. Eggers KM, Lagerqvist B, Venge P, Wallentin L, Lindahl B. Persistent cardiac troponin I elevation in stabilized patients after an episode of acute coronary syndrome predicts long-term mortality. Circulation 2007;116:1907–14.
8. Hudson MP, O'Connor CM, Gattis WA, et al. Implications of elevated cardiac troponin T in ambulatory patients with heart failure: a prospective analysis. Am Heart J 2004;147:546–52.
9. Sato Y, Yamada T, Taniguchi R, et al. Persistently increased serum concentrations of cardiac troponin T in patients with idiopathic dilated cardiomyopathy are predictive of adverse outcomes. Circulation 2001;103:369–74.

10. Freda BJ, Tang WH, Van Lente F, Peacock WF, Francis GS. Cardiac troponins in renal insufficiency: review and clinical implications. J Am Coll Cardiol 2002;40:2065–71.
11. Latini R, Masson S, Anand IS, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation 2007;116:1242–9.
12. Wallace TW, Abdullah SM, Drazner MH, et al. Prevalence and determinants of troponin T elevation in the general population. Circulation 2006;113:1958–65.
13. Zethelius B, Johnston N, Venge P. Troponin I as a predictor of coronary heart disease and mortality in 70-year-old men: a community-based cohort study. Circulation 2006;113:1071–8.
14. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med 1998;339:321–8.
15. Maisel AS, Koon J, Krishnaswamy P, et al. Utility of B-natriuretic peptide as a rapid, point-of-care test for screening patients undergoing echocardiography to determine left ventricular dysfunction. Am Heart J 2001;141:367–74.
16. Groenning BA, Raymond I, Hildebrandt PR, Nilsson JC, Baumann M, Pedersen F. Diagnostic and prognostic evaluation of left ventricular systolic heart failure by plasma N-terminal pro-brain natriuretic peptide concentrations in a large sample of the general population. Heart 2004;90:297–303.
17. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161–7.
18. Januzzi JL, Jr., Camargo CA, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 2005;95:948–54.
19. de Lemos JA, Morrow DA, Bentley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. N Engl J Med 2001;345:1014–21.
20. James SK, Lindahl B, Siegbahn A, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. Circulation 2003;108: 275–81.
21. Maisel A, Hollander JE, Guss D, et al. Primary results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT). A multicenter study of B-type natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. J Am Coll Cardiol 2004;44:1328–33.
22. Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 2006; 27:330–7.
23. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol 2007;49: 1943–50.
24. Bibbins-Domingo K, Gupta R, Na B, Wu AH, Schiller NB, Whooley MA. N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP), cardiovascular events, and mortality in patients with stable coronary heart disease. JAMA 2007;297:169–76.
25. van Kimmenade RR, Januzzi JL, Jr., Baggish AL, et al. Amino-terminal pro-brain natriuretic peptide, renal function, and outcomes in acute heart failure: redefining the cardiorenal interaction? J Am Coll Cardiol 2006;48:1621–7.
26. Omland T, Sabatine MS, Jablonski KA, et al. Prognostic value of B-type natriuretic peptides in patients with stable coronary artery disease: the PEACE trial. J Am Coll Cardiol 2007;50:205–14.
27. Schnabel R, Lubos E, Rupprecht HJ, et al. B-type natriuretic peptide and the risk of cardiovascular events and death in patients with stable angina: results from the AtheroGene study. J Am Coll Cardiol 2006;47:552–8.
28. Nakamura M, Tanaka F, Sato K, Segawa T, Nagano M. B-type natriuretic peptide testing for structural heart disease screening: a general population-based study. J Card Fail 2005;11:705–12.
29. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350:655–63.
30. Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. JAMA 2006;296:2209–16.
31. The hypertension detection and follow-up program: hypertension detection and follow-up program cooperative group. Prev Med 1976; 5:207–15.
32. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
33. Vervoort G, Willems HL, Wetzels JF. Assessment of glomerular filtration rate in healthy subjects and normoalbuminuric diabetic patients: validity of a new (MDRD) prediction equation. Nephrol Dial Transplant 2002;17:1909–13.
34. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.
35. Roche Diagnostics. Elecsys Troponin T package insert. Indianapolis, IN: 2004.
36. Roche Diagnostics. Elecsys proBNP package insert. Indianapolis, IN: 2003.
37. Yeo KT, Wu AH, Apple FS, et al. Multicenter evaluation of the Roche NT-proBNP assay and comparison to the Biosite Triage BNP assay. Clin Chim Acta 2003;338:107–15.
38. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36:959–69.
39. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–47.
40. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–45.
41. Prabhu SD. Cytokine-induced modulation of cardiac function. Circ Res 2004;95:1140–53.
42. Narula J, Haider N, Virmani R, et al. Apoptosis in myocytes in end-stage heart failure. N Engl J Med 1996;335:1182–9.
43. Wu AH. Increased troponin in patients with sepsis and septic shock: myocardial necrosis or reversible myocardial depression? Intens Care Med 2001;27:959–61.
44. Olivetti G, Abbi R, Quaini F, et al. Apoptosis in the failing human heart. N Engl J Med 1997;336:1131–41.
45. Cheng W, Li B, Kajstura J, et al. Stretch-induced programmed myocyte cell death. J Clin Invest 1995;96:2247–59.
46. Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. JAMA 2005;293:1609–16.

Key Words: aging ■ cardiovascular diseases ■ epidemiology ■ natriuretic peptides ■ prognosis ■ risk factors ■ survival.