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Dynamic Cardiovascular Risk Assessment in Elderly People

The Role of Repeated N-Terminal Pro–B-Type Natriuretic Peptide Testing

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Objectives This study sought to determine whether serial measurement of N-terminal pro–B-type natriuretic peptide (NT-proBNP) in community-dwelling elderly people would provide additional prognostic information to that from traditional risk factors.

Background Accurate cardiovascular risk stratification is challenging in elderly people.

Methods NT-proBNP was measured at baseline and 2 to 3 years later in 2,975 community-dwelling older adults free of heart failure in the longitudinal CHS (Cardiovascular Health Study). This investigation examined the risk of new-onset heart failure (HF) and death from cardiovascular causes associated with baseline NT-proBNP and changes in NT-proBNP levels, adjusting for potential confounders.

Results NT-proBNP levels in the highest quintile (>267.7 pg/ml) were independently associated with greater risks of HF (hazard ratio [HR]: 3.05; 95% confidence interval [CI]: 2.46 to 3.78) and cardiovascular death (HR: 3.02; 95% CI: 2.36 to 3.86) compared with the lowest quintile (<47.5 pg/ml). The inflection point for elevated risk occurred at NT-proBNP 190 pg/ml. Among participants with initially low NT-proBNP (<190 pg/ml), those who developed a >25% increase on follow-up to >190 pg/ml (21%) were at greater adjusted risk of HF (HR: 2.13; 95% CI: 1.68 to 2.71) and cardiovascular death (HR: 1.91; 95% CI: 1.43 to 2.53) compared with those with sustained low levels. Among participants with initially high NT-proBNP, those who developed a >25% increase (40%) were at higher risk of HF (HR: 2.06; 95% CI: 1.56 to 2.72) and cardiovascular death (HR: 1.88; 95% CI: 1.37 to 2.57), whereas those who developed a >25% decrease to ≤190 pg/ml (15%) were at lower risk of HF (HR: 0.58; 95% CI: 0.36 to 0.93) and cardiovascular death (HR: 0.57; 95% CI: 0.32 to 1.01) compared with those with unchanged high values.

Conclusions NT-proBNP levels independently predict heart failure and cardiovascular death in older adults. NT-proBNP levels frequently change over time, and these fluctuations reflect dynamic changes in cardiovascular risk. (J Am Coll Cardiol 2010;55:441–50) © 2010 by the American College of Cardiology Foundation

Heart failure (HF) is associated with high mortality risk and hospitalization in older adults, accounting for more than 875,000 annual hospital admissions (1). Despite declines in the rates of cardiovascular deaths in the general population, more than 80% of cardiovascular deaths occur in elderly people (2). Traditional cardiovascular risk factors, although adept at predicting cardiovascular events in middle-aged populations, are less predictive in elderly people (3). Subclinical cardiovascular disease is common in elderly

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people and is associated with an increased risk of cardiovascular events, including HF (4). Furthermore, the develop-

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Abbreviations and Acronyms

CI = confidence interval
ECG = electrocardiogram
HF = heart failure
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
NT-proBNP = N-terminal pro–B-type natriuretic peptide
ROC = receiver-operator characteristic

ment of new subclinical disease on repeated measures is associated with increased risk compared with that for subjects who remain without identifiable disease (4).

Blood-based biomarkers provide an attractive adjunctive methodology for identifying older individuals at higher risk of adverse cardiovascular events. Natriuretic peptide levels (B-type natriuretic peptide and N-terminal pro–B-type natriuretic peptide [NT-proBNP]) are associated with long-term cardiovascular outcomes in the general community (5–9). However, it is controversial whether a natriuretic peptide level provides additional prognostic information beyond traditional risk factors in this population (7,10). The CHS (Cardiovascular Health Study) trial cohort of elderly participants with long-term follow-up, detailed risk factor assessment, and electrocardiographic and echocardiographic data allows for the opportunity to test whether measurement of NT-proBNP provides independent and additive information. Nevertheless, a single measurement of NT-proBNP cannot reflect change in subclinical disease, and therefore may not optimally stratify long-term cardiovascular outcomes (4).

We hypothesized that NT-proBNP, in an ambulatory elderly population free of HF, would be independently associated with new-onset HF and cardiovascular death after adjusting for prevalent comorbidities and cardiovascular risk factors. Furthermore, we anticipated that serial measurements of NT-proBNP, as a possible surrogate for change in subclinical disease status, identify a dynamic change in long-term risk of incident HF and cardiovascular mortality. Specifically, we hypothesized that individuals showing increases in NT-proBNP over time would have elevated risks independent of baseline NT-proBNP levels and cardiovascular risk factors.

Methods

Study population. The CHS trial is a multicenter, prospective, observational cohort study of cardiovascular disease in elderly people. A detailed description of the study methods has been published previously (11). For the present analysis, participants with prior HF at study entry were excluded; HF was identified by self-report and confirmed by medical record review and/or physician interview as described previously (12).

Of the 5,888 CHS trial participants, prevalent HF was present in 275 (4.7%), and sufficient serum for NT-proBNP measurement was available in 4,312 (76.8%) (Fig. 1). Comparing those with and without sufficient sera volumes, there were no significant differences in demographics and most clinical measures. Modest but statistically significant differences were observed between those with and without NT-proBNP measurements in the frequency of diabetes (17.7% vs. 8.6%), hypertension (59.4% vs. 54.9%), and current smoking (11% vs. 15%).

The CHS trial was approved by the institutional review boards of the University of Washington and the participating centers. The current analysis was approved by the institutional review board of the University of Maryland, Baltimore.

Assay methods. NT-proBNP was measured in serum collected at baseline in the main CHS trial cohort (1989 to 1990) and the supplemental cohort (1992 to 1993). A second measure of NT-proBNP was performed on sera collected 3 years later for the main cohort (1992 to 1993) and 2 years later for the supplemental cohort (1994 to 1995). NT-proBNP was measured on the Elecsys 2010 system (Roche Diagnostics, Indianapolis, Indiana). The coefficient of variation for the NT-proBNP assay was 2% to 5% during the testing period, and the analytical measurement range for NT-proBNP was 5 to 35,000 pg/ml. All samples were stored at −70°C to −80°C and were thawed before testing (maximum of 3 freeze–thaw cycles). Measurements of NT-proBNP using this assay do not change after 5 freeze–thaw cycles (13).

Primary outcomes. Outcomes were incident HF and cardiovascular mortality. Incident HF events were ascertained by participant interview at semiannual study visits and through examination of Medicare claims data. Potential HF events and determination of cause of death were determined by an expert adjudication panel (14). Cardiovascular death was defined as death related to atherosclerotic heart disease

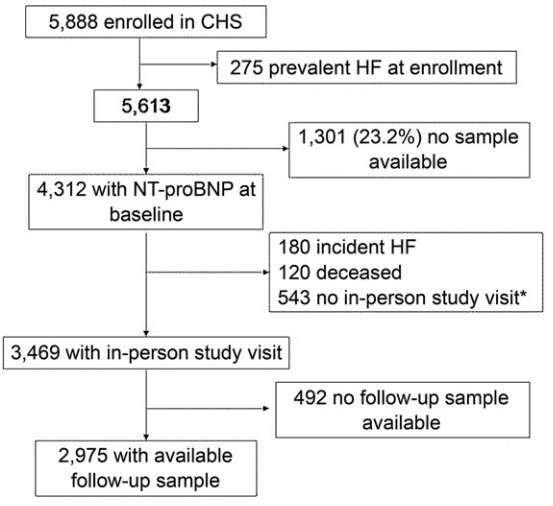

Figure 1 Flow Diagram of CHS Participants

The CHS (Cardiovascular Health Study) trial participants with blood samples available for N-terminal pro–B-type natriuretic peptide (NT-proBNP) testing at baseline and follow-up visits. *No study visit or only phone-based visit. HF = heart failure.

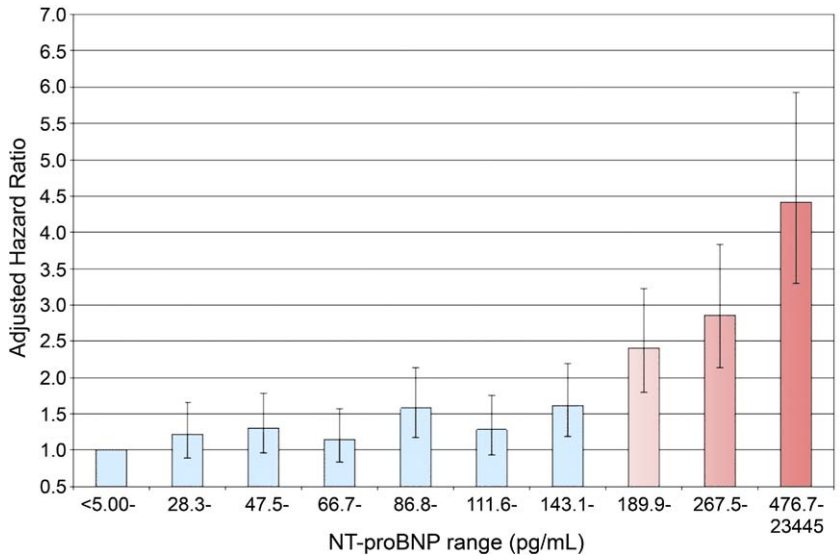

Figure 2 **Hazard Ratios for New-Onset HF by Decile of NT-proBNP**

Demographic-adjusted hazard ratios for developing new-onset HF by decile of baseline NT-proBNP level. Abbreviations as in Figure 1.

(fatal myocardial infarction and definite and possible fatal coronary heart disease), death after cerebrovascular disease (fatal stroke), or death from other atherosclerotic and cardiovascular diseases as described in detail previously (14).

Other covariates. Clinical characteristics were obtained from the initial CHS study visit for each cohort (for the analysis of baseline NT-proBNP and outcomes) or at the study visit of the follow-up NT-proBNP measurement (for the analysis of change in NT-proBNP and outcomes). The methodology for assessing cardiovascular risk factors has been described previously (12).

Coronary heart disease was defined as a history of angina, myocardial infarction, coronary angioplasty, or coronary artery bypass surgery. An electrocardiogram (ECG) was performed annually; left ventricular (LV) mass was estimated from the ECG, and major ECG abnormalities, including atrial fibrillation, were defined according to previously described methods (15,16). Echocardiography was performed in the main cohort in 1989 to 1990 and in both cohorts in 1995 to 1996. Measures of interest for this analysis included left atrial diameter and qualitative left ventricular ejection fraction (LVEF) (normal, borderline, or abnormal) (17).

Statistical methods. Characteristics by quintile of baseline NT-proBNP were compared by chi-square tests or 1-way analysis of variance as appropriate. Cumulative incidence of HF and cardiovascular death were estimated using the Kaplan-Meier method and compared with log-rank tests, and multivariate analyses were performed using Cox proportional hazards models. Three sets of adjustment covariates were chosen a priori among factors with an established role in predicting cardiovascular events and known or likely to influence natriuretic peptide levels: 1) traditional cardiovascular risk factors as defined by the Framingham risk score (18); 2) clinically available risk factors, an expanded set of factors readily ascertained in a general outpatient clinical care setting; and 3) measures of cardiac structure (LV mass by ECG, LVEF, and left atrial diameter by echocardiogram). The NT-proBNP was modeled both as a linear variable (after logarithmic transformation) and as quintiles. The optimal threshold of NT-proBNP for increased HF risk was determined by receiver-operator characteristic (ROC) analyses and by plotting the adjusted risk of HF for each decile of NT-proBNP; this threshold was identified at 190 pg/ml, the cut-point separating the seventh from eighth decile (Fig. 2). The corresponding sensitivity and specificity for incident HF were derived by ROC analyses.

The association of change in NT-proBNP with subsequent HF and cardiovascular death was examined in 2 ways. First, change in NT-proBNP was considered as a categorical predictor. Among those with an initial NT-proBNP of $<$190 pg/ml, risk of HF and cardiovascular death were examined associated with: 1) a decrease in NT-proBNP of at least 25%; and 2) an increase of at least 25% to a level $\geq$190 pg/ml, compared with those with neither change. The cut-point of 190 pg/ml was derived from the decile analysis described above, and the 25% threshold for change was based on the reported intraindividual variability in NT-proBNP in stable HF patients (19). Likewise, among those with a baseline NT-proBNP $\geq$190 pg/ml, HF and cardiovascular death risk were examined associated with: 1) a decline of at least 25% to a level $<$190 pg/ml; and 2) an increase of $>$25%, compared with those with neither change. Second, continuous changes in NT-proBNP levels

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Table 1 Baseline Characteristics of Study Population by NT-proBNP Quintile

	All	Q1	Q2	Q3	Q4	Q5	Test for Trend
Range (pg/ml)		<5–47.5	47.5–86.8	86.9–143.1	143.2–267.5	267.7–23,445	
Age (yrs)	72.7 (5.5)	70.5 (4.1)	71.1 (4.5)	72.2 (5.0)	73.7 (5.6)	76.1 (6.3)	<0.001
Male	40.6%	48.1%	38.4%	38.5%	34.7%	43.2%	0.01
African American	15.9%	21.7%	17.4%	13.6%	14.5%	12.4%	<0.001
CHD	17.6%	10.0%	12.1%	15.2%	19.4%	31.5%	<0.001
Diabetes	17.7%	20.2%	16.8%	18.2%	15.2%	18.1%	0.20
Hypertension	59.4%	50.1%	54.4%	54.7%	65.2%	72.8%	<0.001
Smoker	11.1%	12.4%	12.5%	9.5%	10.8%	10.4%	0.02
eGFR (ml/min/1.73 m^2)	78.8 (22.7)	83.7 (22.9)	81.7 (21.6)	79.5 (21.7)	77.4 (23.0)	70.1 (24.7)	<0.001
BMI (kg/m^2)	26.7 (4.7)	27.6 (4.6)	27.1 (4.8)	26.7 (4.7)	26.5 (4.7)	25.8 (4.6)	<0.001
LDL-C	3.38 (0.91)	3.46 (0.86)	3.48 (0.93)	3.38 (0.90)	3.31 (0.91)	3.27 (0.95)	<0.001
Total cholesterol	5.49 (1.01)	5.59 (0.96)	5.61 (1.01)	5.51 (1.00)	5.42 (0.99)	5.33 (1.07)	<0.001
HDL-C	1.41 (0.41)	1.37 (0.39)	1.42 (0.40)	1.43 (0.41)	1.44 (0.43)	1.38 (0.41)	0.4
Medications							
ACEI	6.6%	6.2%	6.9%	6.0%	6.0%	7.8%	0.40
BB	13.2%	6.5%	9.7%	11.1%	16.1%	22.7%	<0.001
Diuretic	24.9%	20.7%	23.3%	23.3%	27.1%	30.4%	<0.001
Aspirin	33.8%	31.8%	33.9%	33.4%	34.2%	35.7%	0.10
Major ECG abnormality	28.7%	18.4%	18.9%	22.7%	30.2%	53.7%	<0.001
Systolic function							
Borderline	5.2%	4.4%	2.7%	4.5%	5.0%	9.3%	<0.001
Abnormal	2.7%	0.2%	0.7%	0.8%	2.0%	9.7%	
LV mass (g) by echocardiography (n = 2,792)							
Women	140.2 (49.0)	133.5 (35.4)	130.7 (32.4)	131.6 (35.4)	135.0 (43.6)	145.5 (49.2)	<0.001
Men	179.8 (54.1)	165.9 (44.1)	158.2 (41.3)	170.1 (46.5)	187.0 (56.2)	201.8 (65.5)	<0.001
Left atrial diameter (cm)	3.78 (0.6)	3.79 (0.61)	3.77 (0.59)	3.83 (0.61)	3.88 (0.65)	4.14 (0.78)	<0.001

ACEI = angiotensin-converting enzyme inhibitor; ASA = aspirin; BB = beta-blocker; BMI = body mass index; CHD = coronary heart disease; DBP = diastolic blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; NT-proBNP = N-terminal pro–B-type natriuretic peptide; Q = quintile; SBP = systolic blood pressure.

were examined using residual change scores, by regressing the follow-up NT-proBNP measures on the baseline measures after logarithmic transformation, thereby correcting change in NT-proBNP for correlation between baseline and follow-up levels (20); this change score was then entered as the predictor variable in Cox survival models. For both categorical and continuous forms of change in NT-proBNP, Cox regression models were adjusted for the elapsed time between NT-proBNP measurements, the covariates described above, and interval change in cardiovascular medications and diagnosis of coronary disease. For all Cox models, graphical and formal methods were used to test the assumption of proportional hazards.

Effect modification by coronary heart disease was examined by testing multiplicative interaction terms (6). To examine model discrimination, the C-statistic was computed for survival regression models with and without baseline NT-proBNP and interval change (21). The improvement in risk classification by addition of the change in NT-proBNP to risk-factor–adjusted models with only baseline NT-proBNP was examined using the net reclassification improvement, which represents the net percentage of subjects correctly reclassified to risk categories (22). We categorized individuals according to model-based risk of 10-year HF or cardiovascular death of <10%, 10% to 20%, or >20%. Statistical analysis was performed with Stata version 10 (Statacorp, College Station, Texas); time-dependent C-statistics were generated using R version 2.7.0 (23).

Results

Subject characteristics. The median NT-proBNP was 111.7 pg/ml. Participants were divided into quintiles based on initial NT-proBNP levels (Table 1). Higher levels were associated with older age, female sex, Caucasian race, known coronary heart disease, a lower estimated glomerular filtration rate, a greater prevalence of major ECG abnormalities, increased LV mass, and decreased LVEF. However, even in the highest quintile of NT-proBNP (>267.5 pg/ml), more than 80% had a normal LVEF.

Outcomes based on the initial NT-proBNP level. Over a median follow-up time of 11.9 years, the rates of incident HF and cardiovascular death were 2.6 (95% confidence interval [CI]: 2.5 to 2.8) and 2.1 (95% CI: 1.9 to 2.2) per 100 person-years, respectively. Time to incident HF and cardiovascular death by NT-proBNP quintile is shown in Figures 3A and 3B, respectively. Differentiation of risk appeared within the first year and continued throughout follow-up for both end points. As shown in Table 2, the

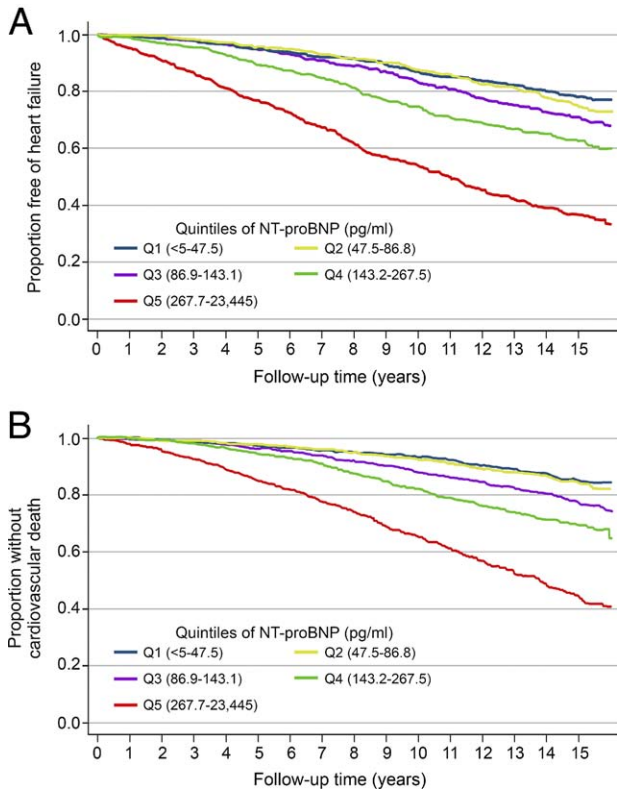

Figure 3 Kaplan-Meier Plots Based on Quintile of NT-proBNP

Unadjusted Kaplan-Meier plots for **(A)** time to new-onset HF diagnosis and **(B)** time to cardiovascular death based on the quintile (Q) of the baseline visit NT-proBNP level. Abbreviations as in Figure 1.

unadjusted risk of incident HF was approximately 4.5-fold higher and the risk of cardiovascular death was 5.4-fold higher for subjects in the highest quintile versus the lowest quintile of NT-proBNP. After adjustment for routinely available clinical factors, the risk remained increased approximately 3-fold for both end points between the first and fifth quintile. With further adjustment for LV mass, left atrial diameter, and LVEF, hazard ratios comparing the highest and lowest quintile of NT-proBNP were 2.62 (95% CI: 2.02 to 3.30) for incident HF and 2.53 (95% CI: 1.92 to 3.33) for cardiovascular death. No significant or clinically important differences were observed for the effect of NT-proBNP on incident HF ($p = 0.1$) or cardiovascular death ($p = 0.7$) between those with and without prevalent coronary disease.

An inflection for increased risk of incident HF based on the adjusted hazard ratios by NT-proBNP decile was identified between the seventh and eighth deciles (Fig. 2). Therefore, the NT-proBNP value at the 70th percentile (190 pg/ml) was used as a cut-point to separate subjects into lower- and higher-risk groups. A similar inflection was seen for cardiovascular death. The associated sensitivity, specificity, and positive and negative predictive values for incident HF during follow-up for this cut-point were 47.6%, 75.6%, 38.4%, and 81.9%, respectively.

Prognosis based on change in NT-proBNP level over time. Follow-up NT-proBNP samples were available in 2,975 subjects, representing 85.8% of the study population that was alive, returned for an in-person follow-up visit, and was without a diagnosis of HF in the interim (Fig. 1). Subjects with available samples were younger, more often male, and less often diabetic (15.6% vs. 20.7%), and had slightly better renal function and a lower rate of incident HF and cardiovascular death (Online Appendix Table 1).

Table 2 Association of NT-proBNP and Incident Heart Failure and Cardiovascular Mortality

	Unadjusted	Risk-Factor Adjusted*	Adjusted for Clinically Available Factors†
Incident heart failure, n	4,312	4,292	4,129
1 log-unit increment	1.78 (1.68–1.88)	1.61 (1.52–1.71)	1.52 (1.43–1.62)
Quintiles (pg/ml)			
1 (<5.0–47.5)	Referent	Referent	Referent
2 (47.5–86.8)	1.12 (0.91–1.39)	1.13 (0.91–1.40)	1.10 (0.89–1.37)
3 (86.9–143.1)	1.38 (1.13–1.70)	1.34 (1.08–1.65)	1.30 (1.05–1.61)
4 (143.2–267.5)	2.01 (1.65–2.45)	1.83 (1.48–2.24)	1.81 (1.46–2.23)
5 (267.7–23,445)	4.53 (3.77–5.46)	3.41 (2.80–4.18)	3.05 (2.46–3.78)
Cardiovascular mortality			
1 log-unit increment	1.87 (1.77–1.98)	1.71 (1.61–1.82)	1.46 (1.36–1.57)
Quintiles			
1	Referent	Referent	Referent
2	1.11 (0.85–1.44)	1.03 (0.77–1.39)	1.05 (0.80–1.36)
3	1.63 (1.28–2.08)	1.52 (1.16–2.00)	1.40 (1.09–1.80)
4	2.39 (1.90–3.01)	2.16 (1.65–2.81)	1.91 (1.50–2.44)
5	5.44 (4.38–6.76)	3.77 (2.91–4.87)	3.02 (2.36–3.86)

Values are presented as hazard ratio (95% confidence interval). *Adjusted for age, sex, race, smoking, total cholesterol and HDL-C, SBP, and hypertension. †Additionally adjusted for diabetes, BMI, CHD, renal function, any major ECG abnormality, use of ACEIs/angiotensin receptor blockers, BBs, and diuretics; models predicting cardiovascular mortality additionally adjusted for prior stroke.

Abbreviations as in Table 1.

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Table 3 Characteristics of Participants at Follow-Up NT-proBNP Measurement by Interval Change in NT-proBNP

Baseline <190 pg/ml (n = 2,243)	>25% Decrease n = 357 (16%)	No Significant Increase n = 1,418 (63%)	Increase >25% and >190 pg/ml n = 468 (21%)	Test for Trend
Age (yrs)	73.1 (4.0)	73.6 (4.3)	75.7 (5.0)	<0.001
Male	141 (39.5%)	552 (38.9%)	184 (39.2%)	0.98
African American	70 (19.6%)	263 (18.6%)	42 (9.0%)	<0.001
Diabetes	74 (20.7%)	237 (16.7%)	56 (12.0%)	<0.001
CHD	41 (11.5%)	198 (14.0%)	124 (26.5%)	<0.001
Hypertension	158 (44.4%)	767 (54.2%)	288 (61.5%)	<0.001
Major ECG abnormality	55 (21.0%)	241 (22.8%)	152 (42.7%)	<0.001
BMI (kg/m^2)	27.7 (4.6)	27.1 (4.5)	26.3 (4.7)	<0.001
eGFR (ml/min/1.73 m^2)	71.0 (15.9)	70.1 (15.3)	65.7 (16.0)	<0.001
Baseline NT-proBNP	89.1 (59.6–127.6)	60.8 (33.1–93.9)	116.1 (75.9–148.6)	<0.001
ACEI/ARB	43 (12.0%)	113 (8.0%)	52 (11.1%)	0.9
BB	23 (6.4%)	133 (9.4%)	85 (18.2%)	<0.001
Baseline ≥190 pg/ml (n = 732)	**Decrease >25% and <190 pg/ml n = 112 (15%)**	**No Significant Decrease n = 327 (45%)**	**>25% Increase n = 293 (40%)**	
Age (yrs)	75.1 (5.0)	76.6 (5.6)	78.4 (6.1)	<0.001
Male	32 (28.6%)	101 (30.9%)	122 (41.6%)	0.003
African American	23 (20.5%)	36 (11.0%)	27 (9.2%)	0.005
Diabetes	18 (16.1%)	32 (9.8%)	46 (15.7%)	0.51
CHD	24 (21.4%)	86 (26.3%)	107 (36.5%)	<0.001
Hypertension	78 (69.6%)	215 (65.8%)	193 (66.1%)	0.6
Major ECG abnormality	25 (28.1%)	98 (40.0%)	100 (53.5%)	<0.001
BMI (kg/m^2)	27.7 (5.6)	25.8 (4.6%)	25.9 (4.6)	0.007
eGFR (ml/min/1.73 m^2)	66.3 (15.0)	63.0 (16.7)	58.7 (17.0)	<0.001
Baseline NT-proBNP	251.7 (216.6–302.4)	366.5 (247.7–595.3)	300.6 (237.5–474.5)	0.007
ACEI/ARB	15 (13.4%)	38 (11.6%)	31 (10.6%)	0.4
BB	18 (16.1%)	51 (15.6%)	65 (22.2%)	0.06

Values in parentheses are SD or percent.
ARB = angiotensin receptor blocker; other abbreviations as in Table 1.

Substantial individual differences in changes of NT-proBNP were observed during follow-up. Of subjects with baseline NT-proBNP levels <190 pg/ml, 468 (21%) had a change of >25% and to a level ≥190 pg/ml and 357 (16%) had a >25% decrease on the second sample measurement. For subjects with initial levels ≥190 pg/ml at baseline, 112 (15%) had a >25% decrease to <190 pg/ml and 293 (40%) had a >25% increase on the second sample measurement. Characteristics of participants with respect to change in NT-proBNP levels are shown in Table 3.

Incident rates for new-onset HF and cardiovascular death based on change from baseline levels are shown in Figures 4A and 4B. Subjects with initially low levels of NT-proBNP whose level increased at follow-up had higher rates of incident HF and cardiovascular death compared with subjects whose NT-proBNP level remained low and unchanged ($p < 0.001$). In contrast, subjects with initially low levels of NT-proBNP whose level decreased >25% had no significant difference in outcomes compared with subjects whose NT-proBNP level remained low (Fig. 4, Table 4). Subjects with initial NT-proBNP levels ≥190 pg/ml and who displayed a >25% increase had a higher incidence of HF and cardiovascular death during follow-up compared with subjects with initially high levels that remained high but unchanged. In contrast, subjects with initial levels of NT-proBNP ≥190 pg/ml whose levels decreased >25% had a significantly lower incidence of both outcomes compared with subjects whose NT-proBNP levels remained high and unchanged (Fig. 4, Table 4). Furthermore, a signal for increased risk of incident HF with a >25% increase in NT-proBNP level could be seen in subjects with baseline values as low as the second quintile (median baseline concentration 59.2 pg/ml, median increase 70.5 pg/ml, unadjusted hazard ratio: 2.70; 95% CI: 1.52 to 4.83). Tests of effect modification by prevalent coronary heart disease revealed no significant interactions ($p > 0.1$). Using residual change scores, baseline-corrected changes in NT-proBNP remained significantly predictive for incident HF and cardiovascular death after adjusting for covariates (Online Appendix Table 2).

Improvement in prognostic accuracy and reclassification. The areas under the ROC curves were calculated adjusting for demographic and cardiovascular risk factors (Table 5). Demographic and cardiovascular risk factors were highly predictive of incident HF and cardiovascular death. Addition of baseline and follow-up NT-proBNP increased predictive accuracy significantly ($p < 0.05$) for both outcomes (HF area under the curve 0.80; cardiovascular death area

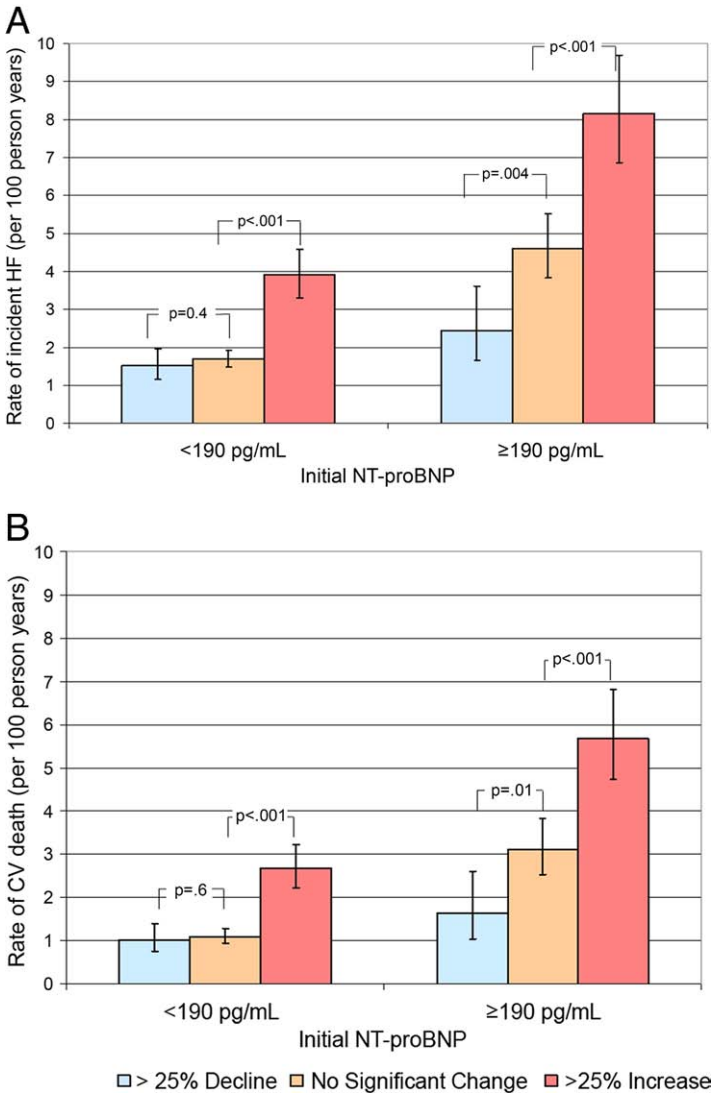

Figure 4 **Incident Rates for CV Outcomes Based on Change in NT-proBNP Level**

Incident rates for **(A)** new-onset HF and **(B)** cardiovascular (CV) death based on change or absence of change between baseline and follow-up NT-proBNP levels. Change in NT-proBNP level is defined among those with a baseline NT-proBNP <190 pg/ml as either a decrease in NT-proBNP of at least 25% or an increase of at least 25% to a level ≥190 pg/ml. Change in NT-proBNP level is defined among those with a baseline NT-proBNP ≥190 pg/ml as either a decline of at least 25% to a level <190 pg/ml or an increase of >25%. Abbreviations as in Figure 1.

under the curve 0.81). Model discrimination as measured by net reclassification improvement was also improved 4.5% to 7.9% by the addition of change in NT-proBNP (Online Appendix Table 3) compared with traditional risk-factor–adjusted models containing baseline NT-proBNP only.

Discussion

Independent of age, traditional cardiovascular risk factors, ECG, and echocardiographic abnormalities, an elevated NT-proBNP level is a long-term predictor of new-onset HF and cardiovascular death in community-dwelling individuals age 65 years and older. Furthermore, NT-proBNP levels frequently are dynamic over time, conferring a change in risk for subsequent cardiac events concordant with the direction of change of the biomarker. The NT-proBNP measurement may be particularly well suited to an elderly population with highly prevalent cardiovascular risk factors.

Assessment of risk for cardiovascular events can be particularly challenging in elderly people, with less accuracy associated with composite risk scores of traditional cardiovascular risk factors, including the Framingham risk score, and absent or attenuated risk prediction with the use of established biomarkers such as lipid levels and C-reactive protein, compared with the general population (3,6,24,25). In contrast, a natriuretic peptide level may reflect the contributions of multiple cardiac pathologies, including

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Table 4 Association of Significant Changes in NT-proBNP and Outcomes Among Those Free of HF and With Baseline NT-proBNP <190 pg/ml and ≥190 pg/ml

	Interval Change in NT-proBNP	Unadjusted	Traditional Risk Factors*	Clinically Available Risk Factors†
NT-proBNP <190 pg/ml				
Incident HF (439 events)	>25% decrease	0.89 (0.67–1.19)	1.00 (0.74–1.35)	0.83 (0.60–1.13)
	<25% change	Reference	Reference	Reference
	>25% increase to ≥190 pg/ml	2.41 (1.96–2.96)	2.10 (1.69–2.62)	2.13 (1.68–2.71)
CV death (315 events)	>25% decrease	0.92 (0.65–1.30)	0.99 (0.69–1.40)	0.86 (0.59–1.24)
	<25% change	Reference	Reference	Reference
	>25% increase to ≥190 pg/ml	2.55 (2.01–3.23)	2.06 (1.60–2.66)	1.91 (1.43–2.53)
NT-proBNP ≥190 pg/ml				
Incident HF (271 events)	>25% decrease to <190 pg/ml	0.53 (0.34–0.81)	0.51 (0.32–0.79)	0.58 (0.36–0.93)
	<25% change	Reference	Reference	Reference
	>25% increase	1.83 (1.42–2.36)	1.68 (1.30–2.17)	2.06 (1.56–2.72)
CV death (224 events)	>25% decrease to <190 pg/ml	0.51 (0.31–0.85)	0.49 (0.29–0.84)	0.57 (0.32–1.01)
	<25% change	Reference	Reference	Reference
	>25% increase	1.94 (1.47–2.55)	1.77 (1.33–2.35)	1.88 (1.37–2.57)

Values are presented as hazard ratio (95% confidence interval). *Age, sex, race, smoking, hypertension, SBP, total cholesterol, and HDL-C. †Additionally adjusted for baseline NT-proBNP, renal function, BMI, diabetes, CHD (none, prevalent at baseline, or incident during interval between NT-proBNP measurements), and for use of ACE inhibitor/ARB and BBs (both prevalent and interval use). Models predicting CV mortality additionally adjusted for prior stroke.

CV = cardiovascular; HF = heart failure; other abbreviations as in Tables 1 and 3.

ischemia, fibrosis, and hypertrophy, in addition to hemodynamic stress, such that these biomarkers reflect the overall burden of clinical and subclinical cardiovascular disease (26).

Two prior studies have shown single measurements of NT-proBNP to independently predict outcomes in elderly people (6,9). In the first study, NT-proBNP was a significant prognostic factor of cardiovascular events only in subjects with known coronary heart disease (6). In contrast, NT-proBNP predicted cardiovascular-related mortality among older Swedish men of similar age, including those without coronary heart disease, when combined with markers of inflammation, renal function, and myocardial necrosis (9). The present results expand on these prior reports by demonstrating the ability of NT-proBNP to predict both incident HF and cardiovascular death in a geographically and racially diverse cohort of men and women regardless of comorbidity and independent of age, as well as echocardiographic and ECG measures of subclinical heart disease.

We also identify for the first time in a community-dwelling general population that NT-proBNP levels are dynamic and that fluctuation reflects a change in risk for subsequent cardiovascular events independent of baseline level and comorbidity. The concept that fluctuations in natriuretic peptide levels outside acute hospitalizations reflect a change in the level of risk has been studied previously in 2 symptomatic patient populations, including those with acute coronary syndrome presentations and those with chronic stable HF (27,28). Progression of levels over time may reflect the trajectory of progression of subclinical cardiovascular disease. Even at levels within the normal range, an increased NT-proBNP level corresponds with increased risk. We also observed that decreases in levels are common, and in participants with initial levels ≥190 pg/ml this reflects a significant decrease in risk of incident HF or cardiovascular death. This may reflect differences in cardiac pathology leading to the initial elevation.

Table 5 AUC of Consecutively More Complex Models Predicting HF and CV Death

	AUC	
Model	Incident HF	CV Death
Demographic	0.66	0.71
+ comorbidity*	0.75†	0.77†
+ baseline NT-proBNP	0.78†	0.79
+ follow-up NT-proBNP	0.80†	0.81†

*Similar variables to second model in Table 2. †$p < 0.05$ comparing AUC with more simple nested model in previous row.

AUC = area under the receiver-operator curve; other abbreviations as in Tables 1 and 4.

The present findings indicate the dynamic nature of cardiovascular risk in elderly people and raise the possibility that specific interventions could delay progression to symptomatic HF or cardiovascular death. Prior studies targeting hypertension and sedentary lifestyle have shown success in reducing cardiovascular mortality in elderly people (29,30). Strategies particularly targeting patients identified as higher risk with initially high levels or those that progressively increase may warrant testing. Early identification of risk in the subclinical phase of cardiovascular disease may be particularly critical in elderly people because progression to symptomatic HF with associated elevated NT-proBNP levels may be more resistant to therapy and to strategies designed to lower NT-proBNP compared with younger individuals (31). Our analyses suggest that in older adults free of HF, a strategy of serial NT-proBNP testing would correctly risk-stratify an additional 4.5% to 8% of individuals compared with a single NT-proBNP measurement alone.

Study limitations. Samples were available in approximately three-fourths of the cohort at baseline, with one-fourth of these having no available sera for follow-up

measures. Subjects with a blood sample at follow-up compared with those without a sample were younger and had a lower prevalence of clinical risk factors. The differential absence of NT-proBNP measures may have introduced bias into the estimates of associations with HF and cardiovascular death. The duration of follow-up is a strength of this study, but cardiovascular therapy has changed over time and it is possible that more ubiquitous use of medications such as statins could have blunted the predictive value of the NT-proBNP level. Because lipid levels were not independently predictive of outcome in this population, this effect is likely modest (25,32). These limitations are largely offset by the representative nature of the CHS trial cohort and the high levels of incident HF. The length of follow-up and high event rate allowed for a robust multivariate analysis and the ability to analyze the significance of change in NT-proBNP levels over longer periods of time than done previously in populations with symptomatic cardiovascular disease (27,28). Lastly, we measured NT-proBNP in samples nearly 20 years old. Given the relatively recent introduction of this assay, we cannot determine with certainty, through repeated measures, the stability of the samples. However, stability has been confirmed by repeated measures as far apart as 2 years, making sample stability less likely to be an important explanation for between-sample differences in NT-proBNP measurements (33). Our choice of a >25% change in NT-proBNP over time was initially based on short-term intraindividual variability in NT-proBNP in stable HF patients. One small study of stable HF patients confirms that 1-year intraindividual variability is also approximately 25% in HF patients with initially low NT-proBNP levels (34).

Conclusions

The NT-proBNP level is a long-term predictor of new-onset HF and cardiovascular death in community-dwelling elderly people. Furthermore, NT-proBNP levels frequently change substantially over 2 to 3 years. This change in level reflects a significant change in patient risk independent of cardiovascular risk factors, ejection fraction, or medication use. Ultimately, NT-proBNP levels may guide further diagnostic testing or potential preventive measures to reduce the risk of developing HF or dying of cardiovascular disease.

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Key Words: biomarkers ■ risk stratification ■ heart failure ■ elderly.

APPENDIX

For Appendix Tables 1 to 3, please see the online version of this article.