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Biomarkers

Left Ventricular Ejection Fraction Assessment in Older Adults

An Adjunct to Natriuretic Peptide Testing to Identify Risk of New-Onset Heart Failure and Cardiovascular Death?

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Objectives The goal of this paper was to determine whether assessment of left ventricular ejection fraction (LVEF) enhances prediction of new-onset heart failure (HF) and cardiovascular mortality over and above N-terminal pro–B-type natriuretic peptide (NT-proBNP) level in older adults.

Background Elevated NT-proBNP levels are common in older adults and are associated with increased risk of HF.

Methods NT-proBNP and LVEF were measured in 4,137 older adults free of HF. Repeat measures of NT-proBNP were performed 2 to 3 years later and echocardiography was repeated 5 years later (n = 2,375), with a median follow-up of 10.7 years. The addition of an abnormal (<55%) LVEF (n = 317 [7.7%]) to initially elevated or rising NT-proBNP levels was evaluated to determine risk of HF or cardiovascular mortality. Changes in NT-proBNP levels were also assessed for estimating the risk of conversion from a normal to abnormal LVEF.

Results For participants with a low baseline NT-proBNP level (<190 pg/ml; n = 2,918), addition of an abnormal LVEF did not improve the estimation of risk of HF and identified a moderate increase in adjusted risk for cardiovascular mortality (hazard ratio: 1.69 [95% confidence interval: 1.22 to 2.31]). Among those whose NT-proBNP subsequently increased ≥25% to ≥190 pg/ml, an abnormal LVEF was likewise associated with an increased risk of cardiovascular mortality but not HF. Participants with an initially high NT-proBNP level (≥190 pg/ml) were at greater risk overall for both outcomes, and those with an abnormal LVEF were at the highest risk. However, an abnormal LVEF did not improve model classification or risk stratification for either endpoint when added to demographic factors and change in NT-proBNP. An initially elevated NT-proBNP or rising level was associated with an increased risk of developing an abnormal LVEF.

Conclusions Assessment of LVEF in HF-free older adults based on NT-proBNP levels should be considered on an individual basis, as such assessments do not routinely improve prognostication. (J Am Coll Cardiol 2011;58:1497–506)

Detection of depressed left ventricular function may improve prevention and treatment of progression to symptomatic heart failure (1). In adults >50 years of age, the presence of even a mildly abnormal left ventricular ejection fraction (LVEF) (i.e., ≤55%) is associated with an approximately 3-fold increased risk of developing heart failure and a 2-fold increased risk of mortality compared with individuals with normal LVEF (2–4). Despite declines in the rates

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of cardiovascular deaths in the general population, more

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Abbreviations and Acronyms

AUC = area under the curve

CI = confidence interval

ECG = electrocardiogram

LVEF = left ventricular ejection fraction

NRI = net reclassification improvement

NT-proBNP = N-terminal pro–B-type natriuretic peptide

than 80% of cardiovascular deaths occur in older adults (5). However, with a relatively low prevalence (<8%) of an abnormal LVEF even in those age ≥65 years, it is difficult to advocate a routine imaging strategy in this population (3,6). Elevated natriuretic peptide levels are associated with depressed LVEF in the general population including older adults (7,8). Elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels are also associated with an increased risk of new-onset heart failure in general population studies (9,10). Currently, neither assessment of natriuretic peptides nor LVEF is recommended for general population screening (11). However, a combination of both measures would potentially refine risk stratification to identify subjects who could benefit from therapies to reduce the risk of progression to heart failure (12). Following recommendations from recent guidelines for biomarker assessment of risk, we sought to determine the additional prognostic impact of likely downstream testing with echocardiography based on NT-proBNP results in this population (13). Second, to establish if NT-proBNP levels are a biochemical precursor to left ventricular systolic dysfunction in older adults, we investigated whether an elevated or rising NT-proBNP level identifies individuals at risk of progression from a normal to an abnormal LVEF based on sequential echocardiography.

Methods

Study population. The CHS (Cardiovascular Health Study) is a multicenter, prospective observational cohort study of cardiovascular disease in independently living older adults (age ≥65 years) recruited from 4 communities. The study population consists of the original cohort recruited in 1989 to 1990 and those enrolled in 1992 to 1993 when the study was expanded to include more African Americans. A detailed description of the study methods has been published previously (14).

Of the 5,888 CHS participants, subjects were included if they had no prevalent heart failure, interpretable echocardiograms, and sufficient serum for NT-proBNP measurement. Ultimately, 4,188 (71.1%) participants were included in this analysis (Fig. 1). Participants with sufficient sera volumes and an initial LVEF assessment were modestly

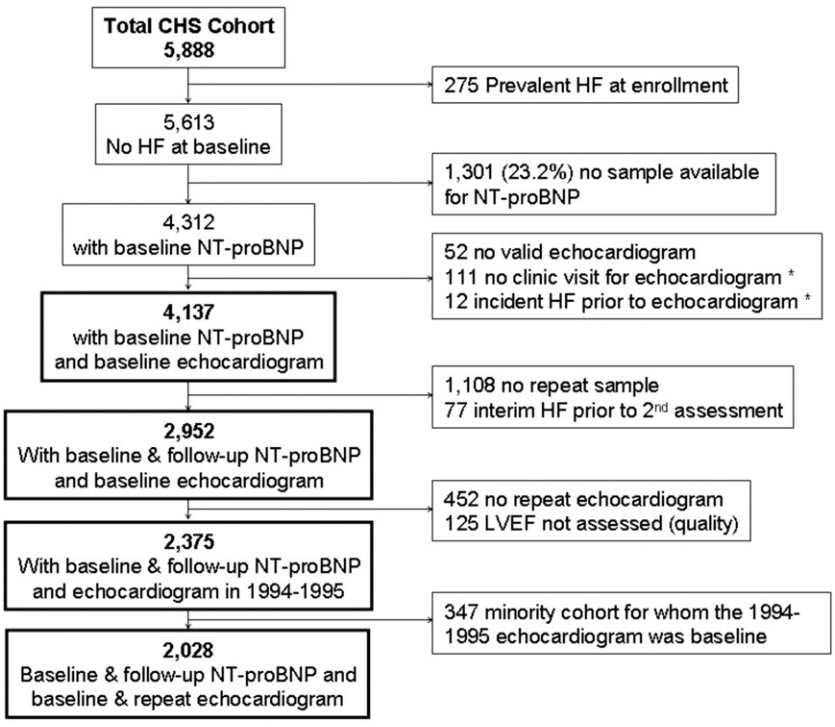

Figure 1 Flow Chart of CHS Participants Included in the Study Analysis

Flow chart of the CHS (Cardiovascular Health Study) participants with blood samples available for N-terminal pro–B-type natriuretic peptide (NT-proBNP) testing and echocardiography performed at baseline and again during follow-up. *Minority cohort only (2-year interval between enrollment and echocardiography). HF = heart failure; LVEF = left ventricular ejection fraction.

more likely to be female and less likely to be African American and diabetic than those without sufficient sera and/or initial ejection fraction measurement (Online Table 1), but other factors did not differ.

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

Echocardiography. The design for the echocardiographic evaluation of CHS participants has been described previously (15). In summary, 2-dimensional echocardiography was performed in 1989 to 1990 and again in 1994 to 1995. For the original cohort, this corresponded to the baseline visit and 5 years later. For the second cohort, this resulted in a single echocardiogram 2 years after the baseline visit. Global left ventricular systolic function was qualitatively assessed from the 2-dimensional echocardiogram as normal (LVEF ≥5%), borderline (LVEF ≥45% to <55%), or subnormal (LVEF <45%) ejection fraction. LVEF was qualitatively interpreted in 99% of the original CHS cohort, with inter-reader agreement of 94% and intrareader agreement of 98% of paired studies (16). For this analysis, subjects with a borderline or subnormal LVEF were grouped together and classified as having an "abnormal" LVEF. In addition, we report measures of Doppler mitral diastolic inflow peak E (early) and peak A (atrial) velocities and left atrial size measured by linear dimensions based on 2-dimensional directed M-mode imaging (17).

Assay methods. NT-proBNP was measured in serum collected at baseline in the main CHS cohort (1989 to 1990) and the second 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 second cohort (1994 to 1995).

All samples were stored at −70° to −80° C and were thawed before testing (maximum of 3 freeze–thaw cycles). NT-proBNP was measured using electrochemiluminescence immunoassay 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. Baseline NT-proBNP levels ≥190 pg/ml (the 70th percentile for the study population) were considered elevated on the basis of previously identified cutoff values best corresponding with increased risk of heart failure in this population (10).

Primary outcomes. Outcomes were incident heart failure and cardiovascular mortality. Incident heart failure events were ascertained through review of medical records, by participant interview at annual study visits, and semi-annual phone calls. An expert adjudication panel determined potential heart failure events and cause of mortality (18). Cardiovascular mortality was defined as mortality related to atherosclerotic heart disease, mortality after cerebrovascular disease, or mortality from other atherosclerotic and cardiovascular diseases as described in detail previously (18).

Clinical history and the electrocardiogram. Clinical characteristics and cardiovascular risk factors 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 (for the analysis of change in NT-proBNP and outcomes). The methods for assessing cardiovascular risk factors have been described previously (19).

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 mass was estimated from the ECG, and major ECG abnormalities, including atrial fibrillation and left ventricular hypertrophy, were defined according to previously described methods (20,21).

Statistical methods. Characteristics according to baseline NT-proBNP and left ventricular functional status were compared using chi-square tests or 1-way analysis of variance as appropriate. Cumulative incidence of heart failure and cardiovascular mortality were estimated using the Kaplan-Meier method. Multivariate analyses were performed using Cox proportional hazards models for new-onset heart failure and cardiovascular mortality outcomes, adjusting for demographic characteristics (age, sex, and race), cardiovascular disease history, cardiovascular risk factors (systolic blood pressure, diabetes, cholesterol, creatinine, and body mass index), use of antihypertensive medications, and major ECG abnormalities. Elevated NT-proBNP was defined using a previously validated cutoff value of ≥190 pg/ml (10).

Change in NT-proBNP was considered as a categorical predictor among those with an initial low NT-proBNP level of <190 pg/ml. Risk of heart failure and cardiovascular mortality were examined associated with: 1) a stable or decrease in NT-proBNP level (i.e., no increase >25%); and 2) an increase of at least 25% to a level ≥190 pg/ml. The 25% threshold for change was based on the reported intraindividual variability in NT-proBNP levels in patients with stable heart failure (22). We then evaluated whether baseline echocardiographic information about LVEF (≥55% vs. <55%) added to the predictive value of increases in NT-proBNP. Last, we evaluated the incremental value of LVEF as a semi-quantitative variable (<45%, 45% to 54% and ≥55%) and NT-proBNP as a continuous variable (after log-transformation) for both outcomes. The time-dependent C-statistic was used to examine the added predictive value of the LVEF assessment to: 1) a demographic model with and without baseline NT-proBNP levels; and 2) the combination of baseline and of follow-up NT-proBNP levels for incident heart failure and cardiovascular mortality. The improvement in risk classification by the addition of LVEF measurements to NT-proBNP levels in demographic adjusted models was examined using the net reclassification improvement (NRI), which represents the net percentage of subjects correctly reclassified to risk categories (23). We categorized individuals according to

Cox model–based risk of 10-year heart failure or cardiovascular mortality of <10%, 10% to 20%, or >20%. An exploratory analysis was also performed using echocardiographic measures of diastolic function, including Doppler mitral E/A ratio (categorized as <0.7, 0.8 to 1.5, and >1.5) and left atrial dimension added to LVEF, NT-proBNP, or both.

Association between changes in NT-proBNP and subsequent new-onset left ventricular dysfunction were evaluated using chi-square tests. Statistical analyses were performed with Stata version 10 (Stata Corp., College Station, Texas) and SPSS version 17.0 (SPSS Inc., Chicago, Illinois), and time-dependent C-statistics were generated using R version 2.7.0. (24).

Results

Participant characteristics. Of the 4,137 participants without prevalent heart failure and a baseline echocardiogram, 107 (2.6%) had subnormal LVEF (<45%) and 210 (5.1%) had a borderline reduced LVEF (45% to 54%). The area under the curve (AUC) for NT-proBNP to diagnose a subnormal LVEF (<45%) was 0.85, and for any abnormal LVEF (<55%), the AUC was 0.69. High-risk NT-proBNP levels (≥190 pg/ml) were observed in 29.5% (n = 1,219). Table 1 displays demographic, clinical, and echocardiographic diastolic information based on the presence of a high or low NT-proBNP value, further subdivided by the presence of a normal versus abnormal LVEF. The median age of the participants was 71 years (range 65 to 100 years). NT-proBNP status (high vs. low) differentiated patients with a higher prevalence of risk factors, ECG abnormalities, history of coronary heart disease, cardiovascular medication use, increased left atrial size, and diastolic abnormalities. An abnormal LVEF was further associated with male sex, diabetes, coronary heart disease, ECG abnormalities,

Table 1 Characteristics of Participants as Related to NT-proBNP and LVEF

Variable	Total (N = 4,137)	NT-proBNP <190 pg/ml		NT-proBNP ≥190 pg/ml		p Value
		LVEF ≥55% (n = 2,783)	LVEF <55% (n = 135)	LVEF ≥55% (n = 1,037)	LVEF <55% (n = 182)	
Demographics						
Age (yrs)	72.7 ± 5.5	71.6 ± 4.8	71.7 ± 4.8	75.2 ± 6.2	75.5 ± 6.0	<0.001
Female	2,462 (59.3%)	1,689 (60.8%)	44 (32.1%)	686 (64.4%)	63 (34.6%)	<0.001
Race (African American)	548 (13.2%)	411 (14.8%)	19 (14.1%)	129 (12.1%)	20 (10.9%)	0.037
Risk factors						
SBP (mm Hg)	136.6 ± 21.4	133.9 ± 19.9	132.0 ± 17.1	143.6 ± 23.5	141.5 ± 24.0	<0.001
DBP (mm Hg)	70.8 ± 11.1	70.7 ± 10.8	71.07 ± 11.2	70.9 ± 11.7	71.9 ± 13.2	0.403
Hypertension	1,823 (44.1%)	1,118 (40.2%)	61 (45.2%)	551 (53.2%)	93 (51.1%)	<0.001
Diabetes	715 (17.3%)	483 (17.4%)	34 (25.2%)	155 (14.9%)	43 (23.6%)	0.002
BMI (kg/m^2)	26.6 ± 4.6	26.8 ± 4.6	27.9 ± 4.5	25.9 ± 4.7	26.5 ± 4.34	<0.001
Current smoker	453 (11.0%)	311 (11.2%)	14 (10.4%)	113 (10.9%)	15 (8.2%)	0.668
Cardiovascular history						
CHD at baseline	727 (17.6%)	345 (12.4%)	40 (29.6%)	243 (23.4%)	99 (54.4%)	<0.001
ECG abnormalities						
LVH on ECG	172 (4.3%)	64 (2.4%)	5 (3.9%)	82 (8.3%)	21 (12.8%)	<0.001
Atrial fibrillation	89 (2.2%)	13 (0.5%)	1 (0.7%)	59 (5.9%)	16 (9.8%)	<0.001
Laboratory values						
NT-proBNP (pg/ml)	110.5 [56.4–218.8]	76.4 [43.3–117.5]	88.8 [43.4–124.5]	314.1 [236.0–522.5]	530.6 [299.8–1208.0]	NA*
eGFR (ml/min/1.73 m^2)	79.0 ± 23.2	81.8 ± 22.3	79.7 ± 23.1	73.1 ± 24.2	68.7 ± 23.4	<0.001
Cholesterol (mg/dl)	212.3 ± 39.0	214.6 ± 38.3	211.5 ± 40.2	208.2 ± 39.7	201.1 ± 42.1	<0.001
Medications at baseline visit						
ACE inhibitor	258 (6.2%)	169 (6.1%)	9 (6.7%)	64 (6.2%)	18 (8.8%)	0.516
Beta-blocker	554 (13.4%)	281 (10.1%)	20 (14.9%)	216 (20.8%)	37 (20.4%)	<0.001
Diuretic	1,015 (24.6%)	623 (22.4%)	36 (26.9%)	305 (29.4%)	51 (28.2%)	<0.001
Antihypertensive (any)	1,889 (45.7%)	1,149 (41.3%)	73 (54.5%)	558 (53.8%)	109 (60.29%)	<0.001
Digoxin	279 (6.8%)	121 (4.4%)	5 (3.7%)	119 (11.5%)	34 (18.8%)	<0.001
Lipid-lowering drugs	240 (5.8%)	170 (6.1%)	7 (5.2%)	51 (4.9%)	12 (6.6%)	0.515
Echocardiography measurements						
Left atrial diameter (cm)	3.9 (0.7)	3.8 (0.6)	4.0 (0.7)	4.0 (0.7)	4.3 (0.8)	<0.001
E/A <0.7	810 (20.1%)	499 (18.3%)	36 (27.3%)	209 (20.8%)	66 (38.4%)	<0.001
E/A 0.7–1.5	3,002 (74.5%)	2,147 (78.9%)	95 (72.0%)	685 (68.2%)	75 (43.6%)	
E/A >1.5	218 (5.4%)	76 (2.8%)	1 (0.8%)	110 (11.0%)	31 (18.0%)	

Values are mean ± SD, n (%), or median [interquartile range]. *p value not calculated (NA) because NT-proBNP was used to create the grouping variable.

ACE = angiotensin-converting enzyme; BMI = body mass index; CHD = cardiovascular heart disease; DBP = diastolic blood pressure; E/A = ratio of peak mitral diastolic E- and A-wave velocities; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro–B-type natriuretic peptide; SBP = systolic blood pressure.

cardiovascular medication use, increased left atrial size, and diastolic abnormalities.

Outcomes based on NT-proBNP levels and LVEF. The median follow-up was 10.7 years (range 0.1 to 14.1 years) from the time of the baseline measure. There were 1,112 participants who developed heart failure, and 893 who died of cardiovascular causes. The unadjusted hazard ratios for heart failure were 2.95 (95% confidence interval [CI]: 2.61 to 3.32) and 2.42 (95% CI: 2.03 to 2.90) for a baseline NT-proBNP level ≥190 pg/ml and LVEF <55%, respectively. Survival functions for heart failure and cardiovascular mortality based on the combination of baseline NT-proBNP level and LVEF assessment are shown in the Kaplan-Meier plots in Figures 2A and 2B. Differentiation of risk occurred within the first year and continued throughout follow-up. As shown in Table 2 in an unadjusted analysis, the increased risks of heart failure or cardiovascular mortality were of significant magnitude among participants with a low NT-proBNP and an abnormal LVEF (a 1.7- to 2.3-fold increased risk) compared with those with a normal LVEF. For participants with high baseline NT-proBNP, risks of heart failure and cardiovascular mortality were higher, and this finding was further stratified by LVEF assessment.

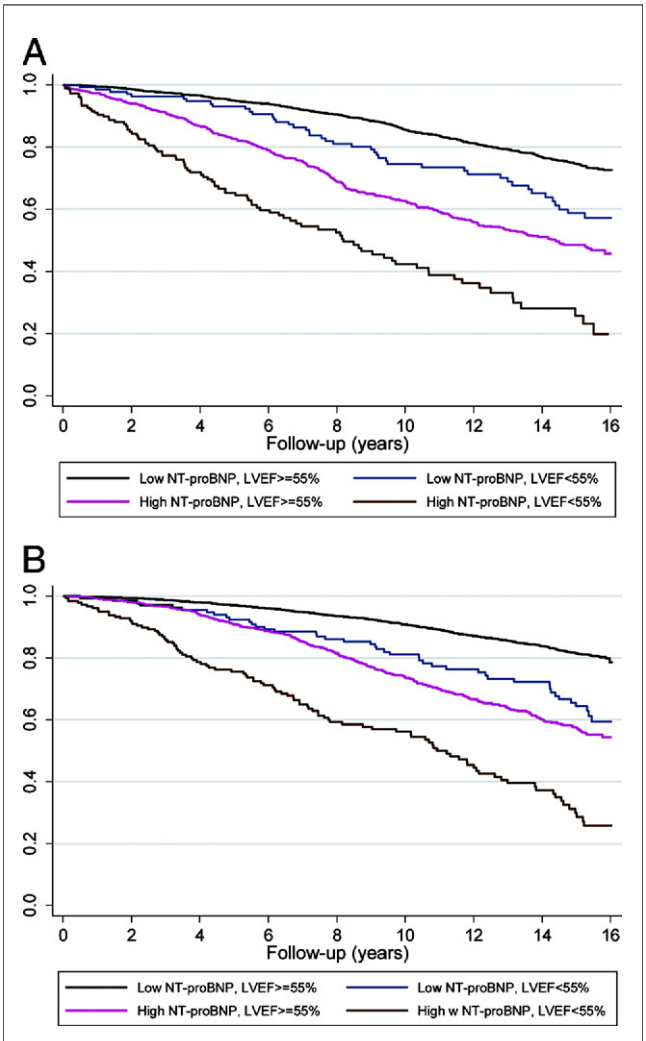

Figure 2 **Survival Plots for Outcomes Using Baseline LVEF and NT-proBNP Level**

Unadjusted Kaplan-Meier plots for **(A)** time to new-onset HF diagnosis and **(B)** time to cardiovascular mortality based on the combination of a baseline low (<190 pg/ml) or high (≥190 pg/ml) NT-proBNP and normal or abnormal LVEF. $p < 0.001$ for comparison of survival curves for both HF and cardiovascular mortality. Abbreviations as in Figure 1.

After adjustment for clinical risk factors, body mass index, ECG abnormalities, and cardiovascular medications in those with low or high NT-proBNP levels, the increased risk associated with the presence of an abnormal LVEF was markedly attenuated but remained significant for both outcomes among those with an initially high NT-proBNP level and for cardiovascular mortality among those with an initially low NT-proBNP level. An abnormal LVEF was no longer associated with risk of heart failure among those with an initially low NT-proBNP (Table 2). In contrast, in a statistical model using NT-proBNP as a continuous variable and LVEF as a semi-quantitative variable, LVEF continued to predict both outcomes after multivariate adjustment (Online Table 2). In a separate sex-based analysis, no differences in the combined effects of LVEF and NT-proBNP were observed between men and women (Online Table 3).

To complement the Cox regression analysis, the C-statistic and NRI were used to evaluate the incremental predictive value of LVEF assessment to NT-proBNP measurement for each outcome (Table 3). For both heart failure and cardiovascular death, the addition of LVEF improved prediction compared with demographic characteristics alone and resulted in a modest reclassification of risk. In contrast, the addition of LVEF assessment to demographic information and the NT-proBNP level resulted in minimal, but statistically significant, improvement in the C-statistic for only the outcome of heart failure and no reclassification of risk for either outcome by the NRI statistic. When restricting the analyses to individuals with an initially elevated NT-proBNP, LVEF assessment did not reclassify risk of heart failure or cardiovascular mortality beyond demographic information and NT-proBNP level (cardiovascular mortality: NRI, −0.006, $p = 0.7$; heart failure: NRI, 0.008; $p = 0.2$). Adding echocardiographic measures of diastolic function to LVEF resulted in a significant increase in the C-statistic and reclassification by NRI. However, the addition of NT-proBNP still significantly increased the C-statistic and improved reclassification even after accounting for both LVEF and diastolic measures along with demographic characteristics.

As part of a secondary analysis, we also determined the number of participants who would need to undergo echocardiography to detect either one subnormal (<45%) or abnormal (<55%) LVEF based on an initially high NT-proBNP (Online Table 4).

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Table 2 Cox Regression Analysis for Endpoints Based on the Initial NT-proBNP and LVEF Measurements

Measurement	Patients	Heart Failure			Cardiovascular Mortality		
		No. of Events	Unadjusted	Adjusted*	No. of Events	Unadjusted	Adjusted*
Low NT-proBNP/normal LVEF	2,783 (67.3%)	575	1.00	1.00	424	1.00	1.00
Low NT-proBNP/LVEF <55%	135 (3.3%)	44	1.75 (1.29–2.38)	1.26 (0.92–1.73)	43	2.34 (1.59–3.45)	1.68 (1.22–2.31)
High NT-proBNP/normal LVEF	1,037 (25.1%)	400	2.75 (2.42–3.13)	2.05 (1.78–2.36)	327	2.67 (2.22–3.22)	1.92 (1.63–2.26)
High NT-proBNP/LVEF <55%	162 (4.4%)	93	5.73 (4.60–7.15)	2.67 (2.07–3.44)†	99	5.45 (3.94–7.54)	2.95 (2.30–3.79)‡

Values are n (%) or HR (95% CI). *Hazard ratios adjusted for demographic characteristics (age, sex, and race), CHD history, cardiovascular risk factors (systolic blood pressure, diabetes, cholesterol, body mass index, and creatinine), use of antihypertensive medications, and major ECG abnormalities. †In participants with a high NT-proBNP level, there was a significant difference ($p = 0.03$) in the hazard ratios for new-onset heart failure comparing participants with a normal LVEF versus LVEF <55%. ‡In participants with a high NT-proBNP level, there was a significant difference ($p < 0.001$) in the hazard ratios for cardiovascular mortality comparing participants with a normal LVEF versus LVEF <55%.

Abbreviations as in Table 1.

Follow-up echocardiography with repeat NT-proBNP assessment. Echocardiography was available for 2,375 participants with repeat NT-proBNP levels who had not developed heart failure in the interim between measures (Fig. 1). LVEF <55% (n = 202 [8.5%]) was associated with increased risk of subsequent heart failure (n = 505 events; hazard ratio: 2.38 [95% CI: 1.80 to 3.13]) and cardiovascular mortality (n = 390 events; hazard ratio: 2.93 [95% CI: 2.18 to 3.98]).

We then investigated whether LVEF assessments would add to the risk of both outcomes over and above repeated NT-proBNP assessments in participants with initially low NT-proBNP levels (<190 pg/ml, n = 1,840). Participants were subdivided by comparing those whose NT-proBNP levels had increased >25% to ≥190 pg/ml versus those with stable or decreased NT-proBNP levels.

Among participants with initially low NT-proBNP levels, 361 (19.6%) had increased at follow-up. For these participants, the risk of heart failure was highest among those with an abnormal LVEF, with intermediate risk being present in participants with only one characteristic (i.e., either an increase in NT-proBNP or an abnormal LVEF) (Fig. 3A). For cardiovascular mortality, a persistently low NT-proBNP level indicated a low risk, irrespective of LVEF, whereas LVEF assessment further differentiated the risk of cardiovascular death in individuals with an increase in NT-proBNP level (Fig. 3B). By Cox regression analysis, after adjustment for covariates, LVEF only differentiated risk in the cohort of participants with a rising NT-proBNP level, and only for cardiovascular death (Table 4).

The C-statistic and NRI analysis confirmed the findings from the adjusted Cox regression models. The addition of LVEF assessment to demographic information and serial NT-proBNP measurements neither significantly increased the AUC for the C-statistic nor reclassified the risk of having either outcome using the NRI statistic (Table 5). Similar to models with a single measure of NT-proBNP, echocardiographic diastolic parameters provided additional prognostic and reclassification information to LVEF and serial NT-proBNP concentrations.

As part of a secondary analysis based on change in NT-proBNP level, we determined the number of participants who would need to undergo echocardiography to detect either one subnormal (<45%) or abnormal (<55%) LVEF based on an initial NT-proBNP level of <190 pg/ml that increased >25% to ≥190 pg/ml at follow-up (Online Table 4).

Predicting a decline in LVEF based on serial NT-proBNP levels. Participants in the main cohort with an NT-proBNP level <190 pg/ml and a normal LVEF had repeat echocardiograms 2 years after their second measure of NT-proBNP level (n = 1,486). An abnormal LVEF devel-

Table 3 Time-Dependent C-Statistic and NRI for Progressively More Complex Predictive Models of Outcomes Using LVEF and a Single Measure of NT-proBNP

Model	Compared With Model No.	Heart Failure				Cardiovascular Mortality			
		AUC	p Value	NRI	p Value	AUC	p Value	NRI	p Value
1. Demographics		0.667				0.715			
2. Demographics + LVEF	1	0.679	0.008	0.023	0.04	0.726	0.018	0.057	<0.001
3. Demographics + LVEF + diastolic measurements*	2	0.720	<0.001	0.102	<0.001	0.741	0.014	0.057	0.003
4. Demographics + LVEF + diastolic measurements* + baseline NT-proBNP	3	0.748	<0.001	0.082	<0.001	0.774	<0.001	0.079	<0.001
5. Demographics + NT-proBNP	1	0.719	<0.001	0.118	<0.001	0.759	<0.001	0.123	<0.001
6. Demographics + NT-proBNP + LVEF	5	0.723	0.024	0.011	0.14	0.761	0.28	0.015	0.25
7. Demographics + NT-proBNP + LVEF + diastolic measures*	6	0.748	<0.001	0.073	<0.001	0.774	0.004	0.042	0.01

*Diastolic measures: mitral inflow velocity E/A ratio (<0.7, 0.7–1.5, and >1.5), left atrial diameter.

AUC = area under the curve; NRI = net reclassification improvement; other abbreviations as in Table 1.

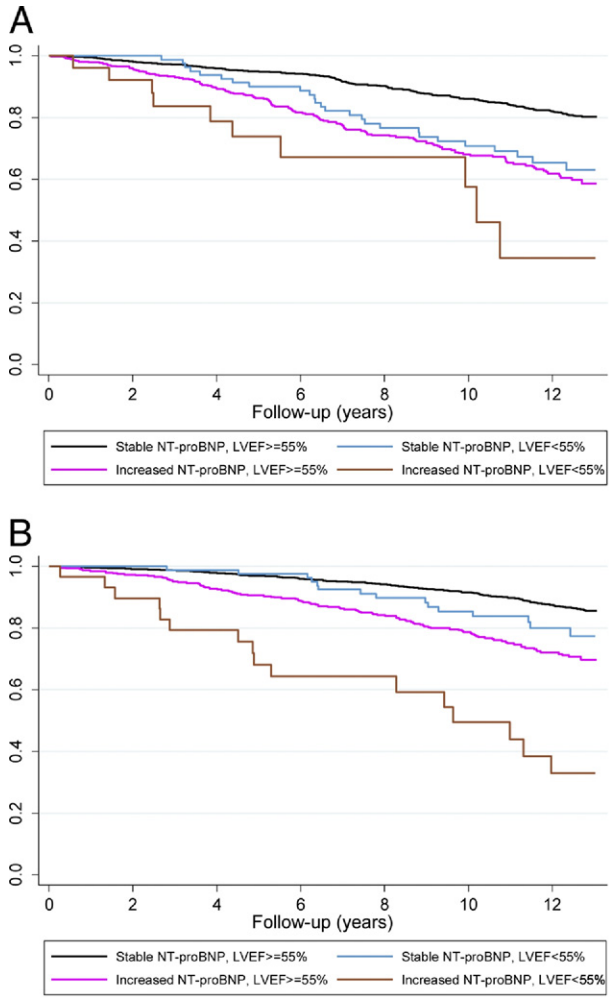

Figure 3 **Survival Plots for Outcomes Using Follow-Up LVEF and Change in NT-proBNP Level**

Unadjusted Kaplan-Meier plots for participants with baseline NT-proBNP <190 pg/ml **(A)** time to new-onset HF diagnosis and **(B)** time to cardiovascular mortality based on the increase or absence of an increase in NT-proBNP level at follow-up and a normal or abnormal LVEF at echocardiography at follow-up. $p < 0.001$ for comparison of survival curves for both HF and cardiovascular mortality. Abbreviations as in Figure 1.

oped in 95 patients (6.4%). Participants with an increase in NT-proBNP level were significantly more likely to have subsequent decline in their LVEF compared with participants with a stable low NT-proBNP level. Those who started with a high NT-proBNP and a normal LVEF (n = 426) had a similar proportion who developed an abnormal LVEF as those with an initially normal but rising NT-proBNP (Fig. 4).

Discussion

The results from this study demonstrate that, in ambulatory older adults without heart failure, the addition of LVEF assessment to either a single NT-proBNP assessment or sequential measures adds little to risk assessment for new-onset heart failure or cardiovascular mortality. Furthermore, in contrast to NT-proBNP levels, LVEF alone only modestly reclassifies risk when considering just demographic characteristics. Confirming the limited utility of a natriuretic peptide level to "screen" for subnormal (i.e., <45%) LVEF, 14 participants with a high baseline NT-proBNP level and 34 participants with rising NT-proBNP levels would need to be screened to detect one subnormal LVEF. Despite limited accuracy to detect a subnormal LVEF, a high baseline or an increasing NT-proBNP level identified individuals at greatest risk of developing a new abnormal LVEF on follow-up echocardiography. This latter finding is potentially intriguing because many CHS participants with initially normal LVEF who develop symptoms of heart failure are found to have an abnormal LVEF at the time of presentation (25).

In CHS and other community population studies, an abnormal LVEF is an independent predictor of both new heart failure hospitalizations and cardiovascular mortality (2–4,26). Yet in this analysis, once adjusted for comorbidities, LVEF assessment added little additional predictive benefit beyond the measurement of NT-proBNP. There are several potential reasons for this new finding. First, an abnormal LVEF is a relatively infrequent finding in community-dwelling older adults (<8%) compared with an elevated NT-proBNP level (approximately 30%) (3,6,10). The low prevalence accounts in part for the weak influence of LVEF in reclassifying risk of heart failure or cardiovascular death (Tables 3 and 5). The lack of specificity of natriuretic peptides for increased left ventricular volumes or

Table 4 **Risk of New-Onset Heart Failure and Cardiovascular Mortality Based on Follow-Up LVEF and Change in NT-proBNP in Patients With Low NT-proBNP at Baseline (N = 1,840)**

		Heart Failure		Cardiovascular Mortality	
Model	No. (%) of Patients	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Stable† NT-proBNP/normal LVEF	1,399 (58.9%)	1.00	1.00	1.00	1.00
Stable† NT-proBNP/LVEF <55%	80 (3.4%)	1.94 (1.17–3.23)	1.34 (0.80–2.24)	1.71 (0.90–3.22)	1.09 (0.57–2.11)
Increased NT-proBNP/normal LVEF	319 (13.3%)	2.77 (2.21–3.48)	2.15 (1.66–2.80)	2.24 (1.78–3.12)	1.83 (1.33–2.52)
Increased NT-proBNP/LVEF <55%	42 (1.8%)	5.90 (2.91–11.98)	3.19 (1.46–6.99)	8.89 (4.68–16.89)	4.73 (2.37–9.45)‡

Values are n (%) or HR (95% CI). *Adjusted for demographic characteristics (age, sex, and race), CHD history, cardiovascular risk factors (systolic blood pressure, diabetes, cholesterol, creatinine, and body mass index), use of antihypertensive medications, major ECG abnormalities, and baseline NT-proBNP level. †Stable includes participants with stable or decreased NT-proBNP levels at follow-up. ‡p value is <0.05 for comparison between a normal and abnormal baseline LVEF among participants with an NT-proBNP that increased between baseline and follow-up.
Abbreviations as in Table 1.

Table 5 Time-Dependent C-Statistic AUC and NRI for Progressively More Complex Predictive Models of Outcomes Using LVEF, Diastolic Measures, and Repeated Measures of NT-proBNP

Model	Compared With Model No.	Heart Failure				Cardiovascular Mortality			
		AUC	p Value	NRI	p Value	AUC	p Value	NRI	p Value
1. Demographics		0.661				0.700			
2. Demographics + LVEF	1	0.670	0.06	0.022	0.08	0.714	0.015	0.055	0.006
3. Demographics + LVEF + diastolic measures*	2	0.702	<0.001	0.079	<0.001	0.734	0.004	0.047	0.052
4. Demographics + LVEF + diastolic measures* + baseline and second NT-proBNP	3	0.771	<0.001	0.152	<0.001	0.779	<0.001	0.144	<0.001
5. Demographics + baseline and second NT-proBNP	1	0.755	<0.001	0.212	<0.001	0.762	<0.001	0.170	<0.001
6. Demographics + baseline and second NT-proBNP + LVEF	5	0.758	0.23	0.000	0.9	0.766	0.22	0.023	0.11
7. Demographics + baseline and second NT-proBNP + LVEF + diastolic measures*	6	0.771	0.009	0.034	0.04	0.779	0.003	0.046	<0.001

*Diastolic measures: mitral inflow velocity E/A ratio (<0.7, 0.7–1.5, and >1.5), left atrial diameter.
Abbreviations as in Tables 1 and 3.

pressure in asymptomatic subjects can explain the false positive results when using NT-proBNP as a screening tool for an abnormal LVEF in the general population (27–29).

Assessment of LVEF to refine prognostication in community-dwelling older adults on the basis of an elevated natriuretic peptide level should be approached cautiously. Despite a previous study suggesting that natriuretic peptide measurement could be cost-effective in select populations to screen for abnormal LVEF, recent guidelines do not recommend measuring either natriuretic peptides or LVEF as part of a screening strategy (11,12). It may be tempting to consider combining natriuretic peptide levels and LVEF to identify those at greatest risk, and by unadjusted analysis, this seems to be present. With introduction and dispersion of inexpensive handheld ultrasound imaging devices, rapid and less-expensive assessment of LVEF will become prevalent (30). However, once comorbidities are considered, the additional prognostication of LVEF to an NT-proBNP level is markedly attenuated. Furthermore, the addition of LVEF provides insignificant information to improve discrimination and reclassify individuals into lower- or high-risk groups even when considering only participants with initially high NT-proBNP. Our findings should be contrasted to earlier findings in the post-myocardial infarction setting in which natriuretic peptide levels and LVEF have prognostic synergism for both heart failure and death (31). However, reflective of the differences between a post-myocardial infarction population and screening "at-risk" community-based subjects, the prevalence of an abnormal LVEF was approximately 10 times higher in the post-myocardial infarction setting (31). In older adults without known heart failure, clinicians will need to individualize decision making with respect to echocardiography even in the presence of a high NT-proBNP level indicating an increased risk of developing heart failure symptoms, while also considering the importance of knowing diastolic filling patterns, left atrial size, or other cardiac pathologic conditions in specific cases.

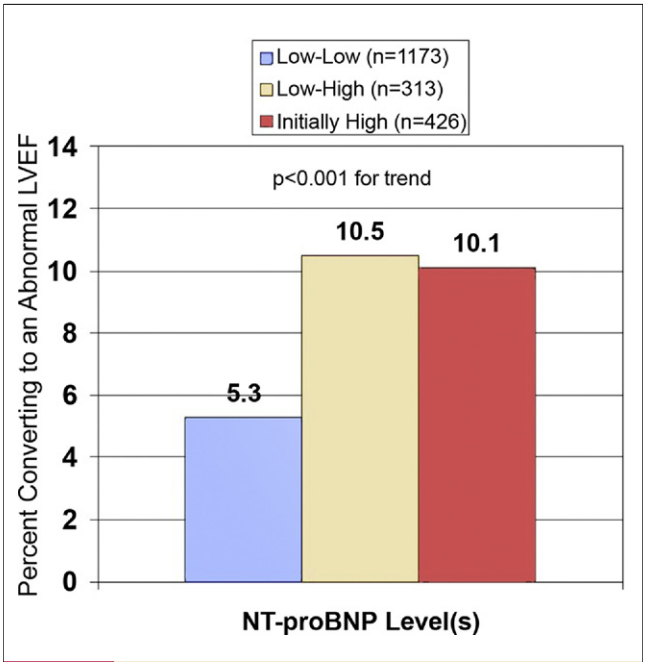

Figure 4 Participants Whose LVEF Changed From Normal to Abnormal as Predicted by NT-proBNP Levels

Participants whose LVEF changed from normal to abnormal (LVEF <55%) from baseline to follow-up echocardiogram as predicted by serial NT-proBNP levels or an initial high level. Low indicates NT-proBNP <190 pg/ml. High indicates an initial NT-proBNP level ≥190 pg/ml or an increase >25% to ≥190 pg/ml. Abbreviations as in Figure 1.

Study limitations. This was a large, well-characterized cohort of community-dwelling older adults with serial NT-proBNP levels and echocardiography. However, there are limitations to the study design. The addition of the second cohort of African-American older adults provides for a balanced demographic reflective of older adults in the United States. For this group, baseline NT-proBNP was measured 2 years before an echocardiogram. We have shown that LVEF will change over time but only in a minority of participants even in the presence of an abnormal NT-proBNP level.

In CHS, LVEF was not quantified as a percentage. Interpretation was performed in a semi-quantitative manner, with excellent intrareader and inter-reader reproduc-

ibility (16). It is noteworthy that poor outcomes have been associated with even a borderline LVEF (estimated at 45% to 55%) (3). Last, this study does not incorporate all echocardiographic measures of diastolic function, but we do show that diastolic measures can assist in reclassifying risk beyond LVEF and NT-proBNP levels. It remains complex as to how best to integrate diastolic measures into an individual's care.

Conclusions

Older adults comprise the majority of new cases of heart failure, yet most live many years without the diagnosis. Elevated NT-proBNP levels likely reflect an ongoing pathologic process that can initially manifest as progression to an abnormal LVEF before symptoms or as symptoms in the presence of preserved LVEF. Once adjusting for the multiple comorbidities often present in ambulatory older adults, we were unable to demonstrate that an assessment of LVEF could further stratify prognosis after measurement of NT-proBNP. In the presence of an elevated NT-proBNP level in this population, a tailored approach to cardiac imaging appears most appropriate.

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REFERENCES

1. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685–91.
2. Hobbs FD, Roalfe AK, Davis RC, Davies MK, Hare R. Prognosis of all-cause heart failure and borderline left ventricular systolic dysfunction: 5 year mortality follow-up of the Echocardiographic Heart of England Screening Study (ECHOES). Eur Heart J 2007;28:1128–34.
3. Gottdiener JS, McClelland RL, Marshall R, et al. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. Ann Intern Med 2002;137:631–9.
4. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation 2003;108:977–82.
5. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115:e69–171.
6. Redfield MM, Jacobsen SJ, Burnett JC Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.
7. Ewald B, Ewald D, Thakkinstian A, Attia J. Meta-analysis of B type natriuretic peptide and N-terminal pro B natriuretic peptide in the diagnosis of clinical heart failure and population screening for left ventricular systolic dysfunction. Intern Med J 2008;38:101–13.
8. Costello-Boerrigter LC, Boerrigter G, Redfield MM, et al. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community: determinants and detection of left ventricular dysfunction. J Am Coll Cardiol 2006;47:345–53.
9. Smith JG, Newton-Cheh C, Almgren P, et al. Assessment of conventional cardiovascular risk factors and multiple biomarkers for the prediction of incident heart failure and atrial fibrillation. J Am Coll Cardiol 2010;56:1712–9.
10. deFilippi CR, Christenson RH, Gottdiener JS, Kop WJ, Seliger SL. Dynamic cardiovascular risk assessment in elderly people. The role of repeated N-terminal pro-B-type natriuretic peptide testing. J Am Coll Cardiol 2010;55:441–50.
11. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010;56:2182–99.
12. Heidenreich PA, Gubens MA, Fonarow GC, Konstam MA, Stevenson LW, Shekelle PG. Cost-effectiveness of screening with B-type natriuretic peptide to identify patients with reduced left ventricular ejection fraction. J Am Coll Cardiol 2004;43:1019–26.
13. Hlatky MA, Greenland P, Arnett DK, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation 2009;119:2408–16.
14. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol 1991;1:263–76.
15. Gardin JM, Wong ND, Bommer W, et al. Echocardiographic design of a multicenter investigation of free-living elderly subjects: the Cardiovascular Health Study. J Am Soc Echocardiogr 1992;5:63–72.
16. Gardin JM, Siscovick D, Anton-Culver H, et al. Sex, age, and disease affect echocardiographic left ventricular mass and systolic function in the free-living elderly. The Cardiovascular Health Study. Circulation 1995;91:1739–48.
17. Gottdiener JS, Kitzman DW, Aurigemma GP, Arnold AM, Manolio TA. Left atrial volume, geometry, and function in systolic and diastolic heart failure of persons ≥65 years of age (The Cardiovascular Health Study). Am J Cardiol 2006;97:83–89.
18. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. Ann Epidemiol 1995;5:278–85.
19. Psaty BM, Kuller LH, Bild D, et al. Methods of assessing prevalent cardiovascular disease in the Cardiovascular Health Study. Ann Epidemiol 1995;5:270–7.
20. Furberg CD, Manolio TA, Psaty BM, et al., for the Cardiovascular Health Study Collaborative Research Group. Major electrocardiographic abnormalities in persons aged 65 years and older (the Cardiovascular Health Study). Am J Cardiol 1992;69:1329–35.
21. Rautaharju PM, Manolio TA, Siscovick D, et al., for the Cardiovascular Health Study Collaborative Research Group. Utility of new electrocardiographic models for left ventricular mass in older adults. Hypertension 1996;28:8–15.
22. Schou M, Gustafsson F, Kjaer A, Hildebrandt PR. Long-term clinical variation of NT-proBNP in stable chronic heart failure patients. Eur Heart J 2007;28:177–82.
23. Pencina MJ, D'Agostino RB Sr., D'Agostino RB Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72.
24. The R Project for Statistical Computing. Available at: http://www.r-project.org. Accessed August 15, 2011.
25. Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the Cardiovascular Health Study. J Am Coll Cardiol 2001;37:1042–8.
26. Di Angelantonio E, Chowdhury R, Sarwar N, et al. B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. Circulation 2009;120:2177–87.
27. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide to detect preclinical ventricular systolic or diastolic dysfunction: a community-based study. Circulation 2004;109:3176–81.

28. de Lemos JA, McGuire DK, Khera A, et al. Screening the population for left ventricular hypertrophy and left ventricular systolic dysfunction using natriuretic peptides: results from the Dallas Heart Study. Am Heart J 2009;157:746–753.
29. Eggers KM, Lindahl B, Venge P, Lind L. B-type natriuretic peptides and their relation to cardiovascular structure and function in a population-based sample of subjects aged 70 years. Am J Cardiol 2009;103:1032–8.
30. Atherton JJ. Screening for left ventricular systolic dysfunction: is imaging a solution? J Am Coll Cardiol Img 2010;3:421–8.
31. Richards AM, Nicholls MG, Espiner EA, et al. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. Circulation 2003;107:2786–92.

Key Words: echocardiography ■ elderly ■ heart failure ■ natriuretic peptides ■ outcomes.

APPENDIX

For supplemental tables, please see the online version of this article.