

N-Terminal Pro-B-Type Natriuretic Peptide as a Diagnostic Test for Ventricular Dysfunction in Patients With Coronary Disease

Data From the Heart and Soul Study

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Background: N-terminal pro-B-type natriuretic peptide (NT-proBNP) testing is useful for diagnosing acute decompensated heart failure. Whether NT-proBNP can be used to detect ventricular dysfunction in patients with stable coronary heart disease (CHD) and no history of heart failure is unknown.

Methods: We measured NT-proBNP levels and performed transthoracic echocardiography in 815 participants from the Heart and Soul Study, who had stable CHD and no history of heart failure. We hypothesized that NT-proBNP concentrations lower than 100 pg/mL would rule out ventricular dysfunction and concentrations higher than 500 pg/mL would identify ventricular dysfunction. We calculated sensitivities, specificities, likelihood ratios, and areas under the receiver operating characteristic curves for NT-proBNP as a case-finding instrument for systolic and diastolic dysfunction.

Results: Of the 815 participants with no history of heart failure, 68 (8%) had systolic dysfunction defined as a left ventricular ejection fraction of 50% or lower. Of the 730 participants for whom the presence or absence of dia-

stolic dysfunction could be determined, 78 (11%) had diastolic dysfunction defined as a pseudonormal or restrictive filling pattern. The overall area under the receiver operating characteristic curve for detecting systolic or diastolic dysfunction was 0.78 (95% confidence interval, 0.74-0.82). Likelihood ratios were 0.28 for NT-proBNP concentrations lower than 100 pg/mL, 0.95 for concentrations between 100 and 500 pg/mL, and 4.1 for concentrations higher than 500 pg/mL. A test result lower than 100 pg/mL reduced the probability of ventricular dysfunction from a pretest probability of 18% to a posttest probability of 6%. A test result higher than 500 pg/mL increased the probability of ventricular dysfunction from a pretest probability of 18% to a posttest probability of 47%. A test result between 100 and 500 pg/mL did not change the probability of ventricular dysfunction.

Conclusion: In patients with stable CHD and no history of heart failure, NT-proBNP levels lower than 100 pg/mL effectively rule out ventricular dysfunction, with a negative likelihood ratio of 0.28.

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PRO-B-TYPE NATRIURETIC PEPTIDE (proBNP) is secreted by myocardial cells in response to increased volume and pressure. This precursor molecule is cleaved to form the active BNP and the inactive N-terminal fragment of proBNP (NT-proBNP).¹ Comparisons of BNP and NT-proBNP have shown that both molecules are effective in diagnosing left ventricular dysfunction in the acute care/emergency setting.²⁻⁹ Additional studies have established NT-proBNP level as a predictor of future cardiac events and mortality following acute coronary syndromes.^{5,10-15} Given the increasing usefulness of this assay, some studies have evaluated the potential for NT-proBNP to be used as a screening tool for left ventricular dysfunction in the general population.^{9,16,17} Little is known, however, about the association of

NT-proBNP with ventricular dysfunction in patients with stable coronary heart disease (CHD).

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Since patients with CHD are at high risk for the development of heart failure, this group represents a relevant target population in which an NT-proBNP testing strategy might reasonably be adopted. We sought to evaluate the characteristics of NT-proBNP as a diagnostic test for systolic or diastolic dysfunction in 815 patients with stable CHD and no history of heart failure. We hypothesized that NT-proBNP levels lower than 100 pg/mL would rule out ventricular dysfunction and levels higher than 500 pg/mL would identify ventricular dysfunction.

PARTICIPANTS

The Heart and Soul Study is a prospective cohort study that was designed to examine the mechanisms of association between psychosocial factors and health outcomes. The methods of the Heart and Sound Study have been described previously.¹⁸ We recruited outpatients with established CHD from 2 Department of Veterans Affairs Medical Centers (San Francisco and Palo Alto, Calif), 1 university medical center (University of California, San Francisco), and 9 public health clinics in the Community Health Network of San Francisco. Patients were eligible to participate if they had 1 or more of the following: a history of coronary revascularization; angiographic evidence of at least 50% stenosis in 1 or more coronary vessels; previous evidence of exercise-induced ischemia by treadmill electrocardiographic or stress nuclear perfusion imaging; a history of myocardial infarction; or a diagnosis of CHD listed in the medical record by an internist or cardiologist. Patients were excluded if they were unable to walk 1 block or were planning to move from the local area within 3 years. The institutional review board at each of the sites approved this protocol, and all participants provided written informed consent.

Between September 2000 and December 2002, a total of 1024 participants enrolled and completed a full-day study appointment at the San Francisco VA Medical Center. Of these, we excluded 39 who were unable to provide serum samples and 171 who reported a history of congestive heart failure (as indicated by a yes answer to the question, "Has a doctor or nurse ever told you that you have congestive heart failure?"), leaving 815 participants for the analysis. Of these 815, there were 85 participants for whom diastolic function could not be determined for technical reasons (eg, presence of atrial fibrillation or significant valve disease). Of the 85 participants for whom diastolic function could not be determined, 10 had systolic dysfunction. Therefore, we evaluated the association of NT-proBNP with systolic dysfunction in 815 participants, the association of NT-proBNP with diastolic dysfunction in 730 participants, and the association of NT-proBNP with either systolic or diastolic dysfunction in 740 participants.

MEASUREMENTS

N-Terminal Pro-B-Type Natriuretic Peptide

Prior to the study appointment, subjects completed an overnight fast, except for taking their regularly prescribed medications. After blood samples were drawn into chilled EDTA tubes, aliquots of plasma were prepared and stored at -70°C until January 2005. We measured NT-proBNP levels using the Roche Diagnostics Elecsys proBNP electrochemiluminescence immunoassay (Elecsys proBNP; Roche Diagnostics, Indianapolis, Ind). The assay range is 5 to 35 000 pg/mL. The within-run coefficient of variation ranges from 1.8% to 2.7%, and the between-run coefficient of variation ranges from 2.3% to 3.2%. The technician performing the NT-proBNP assays was blinded to the echocardiography results. According to the package insert, the normal range for NT-proBNP is lower than 125 pg/mL for adults younger than 75 years and lower than 450 pg/mL for adults 75 years or older.¹ For ease of interpretation, we evaluated NT-proBNP level cutpoints of lower than 100, between 100 and 500, and higher than 500 pg/mL.

A complete echocardiogram was obtained using an Acuson Sequoia Ultrasound System (Mountain View, Calif) with a 3.5-MHz transducer. Resting 2-dimensional echocardiography including Doppler imaging was performed in all standard views. Standard 2-dimensional parasternal short-axis and apical 2- and 4-chamber views were obtained during held inspiration; a computerized digitization system (Tom Tec Corporation, Boulder, Colo) was used to planimeter these views and to measure end-diastolic and end-systolic left ventricular volume. We calculated left ventricular ejection fraction (LVEF) as:

$$\frac{(\text{End-Diastolic Volume} - \text{End-Systolic Volume})}{(\text{End-Diastolic Volume})}$$

An experienced echocardiographer (N.B.S.) interpreted all of the echocardiograms, blinded to the NT-proBNP test results.

We defined systolic dysfunction as an LVEF of 50% or lower. We also examined the association of NT-proBNP with systolic dysfunction using a lower ejection fraction definition of 40% or lower. We assessed diastolic function using peak early diastolic filling velocity (E velocity) and peak filling velocity at atrial contraction (A velocity). We categorized diastolic function as follows: (1) normal (E/A ratio >0.75 and systolic dominant pulmonary vein flow), (2) impaired relaxation (E/A ratio ≤ 0.75 and systolic-dominant pulmonary venous flow), (3) pseudonormal (E/A ratio >0.75 and <1.5 and diastolic-dominant pulmonary venous flow), or (4) restrictive filling (E/A ratio ≥ 1.5 and diastolic-dominant pulmonary venous flow), according to published criteria.¹⁹

Other Measurements

Self-reported age, sex, ethnicity, marital status, smoking status, alcohol use, physical activity, and medical history were determined by questionnaire. Participants were instructed to bring all medications to the study appointment, where study personnel recorded them. Participants were considered to be physically active if they answered fairly, quite, very, or extremely active (vs not at all or a little active) to the following multiple-choice question: "Which of the following statements best describes how physically active you have been during the last month, that is, done activities such as 15 to 20 minutes of brisk walking, swimming, general conditioning, or recreational sports?"

Total, high-density lipoprotein, and low-density lipoprotein cholesterol levels were measured after an overnight fast. Study personnel measured weight and height and calculated body mass index. Creatinine clearance was assessed by 24-hour urine collection.²⁰ Systolic and diastolic blood pressures were measured with a standard sphygmomanometer. The presence or absence of inducible ischemia was determined by stress echocardiography. Participants performed a symptom-limited graded exercise treadmill test according to the standard Bruce protocol. We defined inducible ischemia as the presence of new echocardiographic wall motion abnormalities not visualized on the baseline rest echocardiogram.

STATISTICAL ANALYSIS

We sought to examine the association of NT-proBNP with ventricular function and to evaluate the test characteristics for NT-proBNP as a diagnostic test for ventricular dysfunction. Differences in participant characteristics by category of NT-proBNP levels were compared using analysis of variance for continuous variables and χ^2 tests for dichotomous variables.

Table 1. Characteristics of 815 Outpatients With Coronary Disease and No History of Heart Failure*

Characteristic	NT-proBNP, pg/mL			P Value
	<100 (n = 297)	100-500 (n = 367)	>500 (n = 151)	
Age, y	62 ± 10	68 ± 10	73 ± 10	<.001
Male	241 (81)	290 (79)	134 (89)	.03
White race	160 (54)	229 (63)	100 (66)	.02
Medical history				
Hypertension	187 (63)	258 (70)	113 (75)	.02
Diabetes	63 (21)	85 (23)	45 (30)	.13
Myocardial infarction	132 (45)	184 (50)	92 (62)	.003
Stroke	28 (10)	51 (14)	21 (14)	.19
Percutaneous revascularization	110 (37)	132 (36)	63 (42)	.40
Coronary artery bypass graft	64 (22)	134 (37)	65 (44)	<.001
Current angina	57 (19)	54 (15)	28 (19)	.27
Current smoking	70 (24)	62 (17)	23 (15)	.04
Regular alcohol consumption	99 (34)	109 (30)	40 (27)	.31
Physical inactivity	104 (35)	118 (32)	68 (45)	.02
Other measurements				
BMI	29 ± 5	28 ± 5	28 ± 5	.10
Inducible ischemia	32 (11)	81 (24)	51 (39)	<.001
Total cholesterol, mg/dL	183 ± 42	178 ± 42	173 ± 44	.04
LDL-C, mg/dL	108 ± 32	104 ± 34	101 ± 33	.07
HDL-C, mg/dL	46 ± 13	46 ± 14	46 ± 17	.79
Creatinine clearance, mL/min	96.0 ± 26.7	80.4 ± 24.4	59.9 ± 23.6	<.001
Medications				
β-Blocker	133 (45)	218 (59)	103 (68)	<.001
Renin-angiotensin inhibitor	107 (36)	180 (49)	97 (64)	<.001
Aspirin	233 (78)	297 (81)	103 (68)	.006
Diuretic	58 (20)	80 (22)	56 (37)	<.001
Statin	171 (58)	246 (67)	91 (60)	.04

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

*Data are given as mean ± SD value or number (percentage) of patients unless otherwise specified.

Because NT-proBNP levels were not normally distributed, we log-transformed NT-proBNP and used logistic regression to examine the association of log NT-proBNP as a continuous predictor variable (per standard deviation increase) with systolic and diastolic dysfunction, adjusted for all variables in **Table 1**. For these logistic regression analyses, we report odds ratios (ORs) with 95% confidence intervals (CIs). We then calculated sensitivity, specificity, and likelihood ratios using standard formulas. We used continuous NT-proBNP measurements to generate receiver operating characteristic (ROC) curves and calculated areas under the ROC curves as the C statistic from logistic regression. We tested for interactions of NT-proBNP with age and sex in these logistic regression models. All statistical analyses were performed using SAS software (version 9; SAS Institute Inc, Cary, NC).

RESULTS

Compared with participants who had lower NT-proBNP levels, those with higher levels were older, more likely to be white or male, and more likely to have a history of hypertension, myocardial infarction, or coronary artery bypass grafting (Table 1). Participants with higher NT-proBNP levels were less likely to smoke and were less physically active. Higher NT-proBNP levels were associated with inducible ischemia, renal insufficiency, and the use of cardioprotective medications.

Among our 815 study participants with no history of heart failure, 68 had an LVEF of 50% or lower (including 22 with an LVEF of 40% or lower). Of the 730 participants for whom diastolic dysfunction could be determined, 465 (64%) had normal diastolic function, 187 (26%) had impaired relaxation, and 78 (11%) had pseudo-normal or restrictive filling pattern.

Overall, of the 740 participants for whom either systolic or diastolic dysfunction could be determined, 133 (18%) had either systolic or diastolic dysfunction (pseudo-normal or restrictive filling), including 13 (2%) who had both systolic and diastolic dysfunction. After adjustment for all variables in Table 1, each 1.3-point SD increase in log NT-proBNP level was associated with a 3.8-fold odds of having systolic dysfunction (OR, 3.8; 95% CI, 2.4-6.0; $P < .001$), a 2.9-fold odds of having pseudo-normal or restrictive filling (adjusted OR, 2.9; 95% CI, 1.9-4.6; $P < .001$), and a 5.1-fold odds of having either systolic or diastolic dysfunction (adjusted OR, 5.1; 95% CI, 3.4-7.6; $P < .001$).

At a cutpoint of 100 pg/mL, NT-proBNP was 88% sensitive for ventricular dysfunction, with a negative likelihood ratio of 0.28 (**Table 2**). A negative test result (<100 pg/mL) reduced the probability of ventricular dysfunction from a pretest probability of 18% (133/740) to a posttest probability of 6% in our sample. Levels of NT-

Table 2. Test Characteristics of NT-proBNP for Identifying Ventricular Dysfunction in 815 Study Participants With Known Coronary Disease and No History of Heart Failure

Ventricular Dysfunction	% (No./Total No.)		% (No./Total No.)		Likelihood Ratio	Pretest Probability of Disease in This Sample, %	Posttest Probability of Disease in This Sample, %
	Sensitivity	Specificity	Proportion With Disease Who Had This Test Result	Proportion Without Disease Who Had This Test Result			
NT-proBNP <100 pg/mL							
LVEF ≤50%	91 (62/68)	39 (291/747)	9 (6/68)	39 (291/747)	0.23	8	2
LVEF ≤40%	95 (21/22)	37 (296/793)	5 (1/22)	37 (296/793)	0.12	3	0
Diastolic dysfunction*	85 (66/78)	41 (265/652)	15 (12/78)	41 (265/652)	0.38	11	4
LVEF ≤50% or diastolic dysfunction	88 (117/133)	43 (261/607)	12 (16/133)	43 (261/607)	0.28	18	6
NT-proBNP 100-500 pg/mL							
LVEF ≤50%	46 (31/68)	55 (411/747)	46 (31/68)	45 (336/747)	1.01	8	8
LVEF ≤40%	45 (10/22)	55 (436/793)	45 (10/22)	45 (357/793)	1.01	3	3
Diastolic dysfunction*	40 (31/78)	53 (348/652)	40 (31/78)	47 (304/652)	0.85	11	9
LVEF ≤50% or diastolic dysfunction	44 (58/133)	54 (327/607)	44 (58/133)	46 (280/607)	0.95	18	17
NT-proBNP >500 pg/mL							
LVEF ≤50%	46 (31/68)	84 (627/747)	46 (31/68)	16 (120/747)	2.8	8	21
LVEF ≤40%	50 (11/22)	82 (653/793)	50 (11/22)	18 (140/793)	2.8	3	07
Diastolic dysfunction*	45 (35/78)	87 (569/652)	45 (35/78)	13 (83/652)	3.5	11	30
LVEF ≤50% or diastolic dysfunction	44 (59/133)	89 (541/607)	44 (59/133)	11 (66/607)	4.1	18	47

Abbreviations: LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Diastolic dysfunction defined as pseudonormal or restrictive filling.

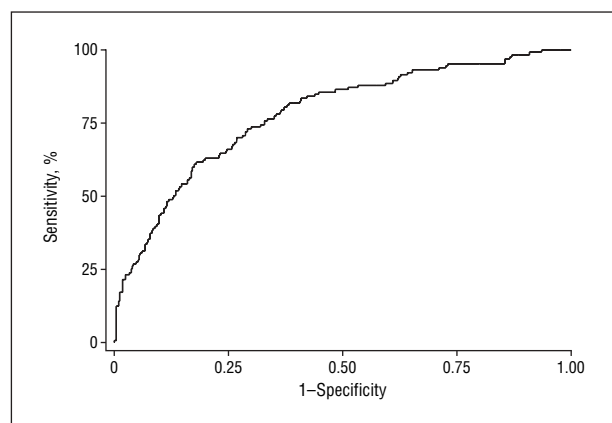


Figure. Receiver operating characteristic curve for N-terminal pro-B-type natriuretic peptide as a case-finding instrument for ventricular dysfunction (left ventricular ejection fraction ≤50% or diastolic dysfunction). The area under the receiver operating characteristic curve is 0.78 (95% confidence interval, 0.74-0.82).

proBNP higher than 500 pg/mL were 89% specific for ventricular dysfunction, with a positive likelihood ratio of 4.1 and a 47% posterior probability of disease. Levels of NT-proBNP between 100 and 500 pg/mL did not affect the probability of ventricular dysfunction (likelihood ratio, 0.95).

Areas under the ROC curve (95% CIs) were 0.77 (0.71-0.82) for an LVEF of 50% or lower, 0.80 (0.71-0.89) for an LVEF of 40% or lower, and 0.76 (0.69-0.82) for pseudonormal or restrictive diastolic function. For detecting the presence of systolic or diastolic dysfunction, the area under the ROC curve (95% CI) was 0.78 (0.74-0.82) (**Figure**). The overall test characteristics of NT-proBNP appeared to vary somewhat by sex (*P* value for

interaction, .02) and by age (*P* value for interaction, .01). Areas under the ROC curve (95% CIs) for detecting the presence of systolic or diastolic dysfunction were 0.83 (0.70-0.97) in women, 0.78 (0.73-0.82) in men, 0.80 (0.72-0.88) in participants 75 years or older, and 0.77 (0.72-0.83) in participants younger than 75 years. However, the posterior probability of ventricular dysfunction with a negative test result (<100 pg/mL) was low regardless of sex (**Table 3**) or age (**Table 4**).

COMMENT

We evaluated the association of NT-proBNP with ventricular dysfunction and the characteristics of NT-proBNP as a diagnostic test for systolic and diastolic dysfunction in 815 patients with stable CHD and no history of heart failure. A cutpoint of 100 pg/mL had 88% sensitivity for ventricular dysfunction, with a likelihood ratio of 0.28 and a 6% posterior probability of disease. Levels of NT-proBNP higher than 500 pg/mL were 89% specific for ventricular dysfunction, with a likelihood ratio of 4.1 and a 47% posterior probability of disease. Likelihood ratios for NT-proBNP concentrations in the intermediate range were not of sufficient strength to rule in or out ventricular dysfunction. These results indicate that NT-proBNP levels lower than 100 pg/mL effectively rule out the presence of ventricular dysfunction in patients with stable CHD.

Both NT-proBNP and BNP accurately detect the presence of left ventricular dysfunction in patients with symptoms of acute decompensated heart failure, for whom the prevalence of disease is high.²⁻⁹ Whether NT-proBNP case finding functions as an accurate diagnostic test in pa-

Table 3. Test Characteristics of NT-proBNP for Identifying Ventricular Dysfunction, Stratified by Sex

Ventricular Function	NT-proBNP <100 pg/mL				NT-proBNP >500 pg/mL			
	Proportion With Disease Who Had This Test Result, % (No./Total No.)	Proportion Without Disease Who Had This Test Result, % (No./Total No.)	Likelihood Ratio	Posttest Probability of Disease in This Sample, %	Proportion With Disease Who Had This Test Result, % (No./Total No.)	Proportion Without Disease Who Had This Test Result, % (No./Total No.)	Likelihood Ratio	Posttest Probability of Disease in This Sample, %
Men (n = 665)								
LVEF ≤50%	8 (5/65)	39 (236/600)	0.20	2	46 (30/65)	17 (104/600)	2.7	22
Diastolic dysfunction	16 (11/67)	41 (215/528)	0.40	5	43 (29/67)	14 (74/528)	3.1	28
LVEF ≤50% or diastolic dysfunction	13 (15/120)	44 (211/485)	0.29	7	43 (52/120)	12 (58/485)	3.6	47
Women (n = 150)								
LVEF ≤50%	33 (1/3)	37 (55/147)	0.89	2	33 (1/3)	11 (16/147)	3.1	6
Diastolic dysfunction	9 (1/11)	40 (50/124)	0.23	2	55 (6/11)	7 (9/124)	7.5	40
LVEF ≤50% or diastolic dysfunction	8 (1/13)	41 (50/122)	0.19	2	54 (7/13)	7 (8/122)	8.2	47

Abbreviations: See Table 2.

Table 4. Test Characteristics of NT-proBNP for Identifying Ventricular Dysfunction, Stratified by Age

Ventricular Function	NT-proBNP <100 pg/mL				NT-proBNP >500 pg/mL			
	Proportion With Disease Who Had This Test Result, % (No./Total No.)	Proportion Without Disease Who Had This Test Result, % (No./Total No.)	Likelihood Ratio	Posttest Probability of Disease in This Sample, %	Proportion With Disease Who Had This Test Result, % (No./Total No.)	Proportion Without Disease Who Had This Test Result, % (No./Total No.)	Likelihood Ratio	Posttest Probability of Disease in This Sample, %
Age <75 y (n = 598)								
LVEF ≤50%	7 (3/44)	47 (258/554)	0.15	1	41 (18/44)	11 (59/554)	3.8	23
Diastolic dysfunction	24 (12/50)	47 (229/484)	0.51	5	28 (14/50)	10 (47/484)	2.9	23
LVEF ≤50% or diastolic dysfunction	15 (13/84)	50 (228/455)	0.31	5	33 (28/84)	8 (36/455)	4.2	44
Age ≥75 y (n = 217)								
LVEF ≤50%	13 (3/24)	17 (33/193)	0.73	8	54 (13/24)	32 (61/193)	1.7	18
Diastolic dysfunction	0 (0/28)	21 (36/168)	0.00	0	75 (21/28)	21 (36/168)	3.5	37
LVEF ≤50% or diastolic dysfunction	6 (3/49)	22 (33/152)	0.28	8	63 (31/49)	20 (30/152)	3.2	51

Abbreviations: See Table 2.

tients without symptoms of heart failure is less clear. We previously evaluated BNP for detecting systolic or diastolic dysfunction in 293 outpatients with stable CHD, who were free of heart failure.²¹ Areas under the ROC curve for NT-proBNP were 0.75 for systolic dysfunction and 0.79 for diastolic dysfunction. Similarly, Vasan et al²² examined the test characteristics of BNP for detecting systolic dysfunction among 213 participants with prevalent cardiovascular disease in the Framingham Heart Study cohort. Areas under the ROC curve for detecting systolic dysfunction in this group were 0.70 in men and 0.75 in women.²² Our present findings demonstrate that NT-proBNP has a utility similar to BNP as a diagnostic test for ventricular dysfunction, with an area under the ROC curve of 0.78 in patients with stable CHD and no symptoms of heart failure.

In our sample of patients without a history of heart failure, those who had NT-proBNP levels higher than 500 pg/mL were 4 times more likely to have ventricular dysfunction than patients who had NT-proBNP levels of 500

pg/mL or lower. Although NT-proBNP levels higher than 500 pg/mL were specific (89%) for ventricular dysfunction, high specificity is not associated with high posterior probability (or positive predictive value) when the prevalence of disease is low. Because the prevalence of ventricular dysfunction in patients without symptoms of heart failure is by definition low (18% in our sample), the positive predictive value was only 47%, meaning that more than half of patients with NT-proBNP levels higher than 500 pg/mL did not have ventricular dysfunction. Thus, although NT-proBNP case finding may be an effective test for ruling out the presence of ventricular dysfunction, our results indicate that elevated NT-proBNP levels do not necessarily identify the presence of ventricular dysfunction in patients without symptoms of heart failure.

Heart failure represents a significant burden on the US health care system. Over 5 million patients in the United States have heart failure, and an additional 500 000 patients are diagnosed as having heart failure each year. Heart failure is the underlying reason for 12 to 15 mil-

lion office visits and 6.5 million hospital days each year.^{23,24} Given this burden, having an accurate diagnostic test for high-risk patients is important. The American College of Cardiology/American Heart Association guidelines for the evaluation and management of chronic heart failure define 4 stages in the evolution of heart failure.²⁵ In adults at high risk for heart failure but without structural heart disease or symptoms of heart failure (stage A), the guidelines recommend aggressive risk factor reduction. In patients with structural heart disease (eg, ventricular dysfunction) but without symptoms of heart failure (stage B), the guidelines recommend therapy with angiotensin-converting enzyme inhibitors and β -blockers.

In the present study, of 740 participants for whom either systolic or diastolic dysfunction could be determined, 607 (82%) had no evidence of ventricular dysfunction, and of these, 261 (43%) had NT-proBNP levels lower than 100 pg/mL. Overall, NT-proBNP levels lower than 100 pg/mL accurately identified stage A heart failure (at risk but without structural heart disease) in 261 (35%) of the 740 study participants. Since current guidelines recommend echocardiography or radionuclide angiography to assess left ventricular function in patients with known CHD,²⁶ it is possible that NT-proBNP case finding could reduce overall costs by avoiding echocardiography in one third of patients with CHD. Although the positive predictive value of NT-proBNP case finding was too low to be of diagnostic value, 44% of patients with NT-proBNP levels higher than 500 pg/mL had stage B heart failure (ventricular dysfunction in the absence of symptoms) by echocardiography. Therefore, NT-proBNP levels higher than 500 pg/mL may identify a subgroup of patients who might benefit from more aggressive management of risk factors. Although patients with CHD should already be taking angiotensin-converting enzyme inhibitors and β -blockers, NT-proBNP levels higher than 500 pg/mL would provide further impetus to prescribe and encourage compliance with these medications.

Our study has several strengths, including a large number of study participants, comprehensive echocardiographic evaluation of systolic and diastolic dysfunction, and examination of NT-proBNP levels in patients without heart failure. However, a number of limitations must be considered when interpreting our results. First, we used self-reported heart failure as an exclusion criterion, and self-report is not always an accurate measure of heart failure. Incorrectly excluding patients without heart failure would have increased sensitivity and negative predictive value, while decreasing specificity and positive predictive value of NT-proBNP testing. However, all participants completed an intensive daylong examination that included an exercise treadmill test, and none of the study participants had overt symptoms of heart failure. Alternatively, incorrectly including patients with heart failure would have decreased sensitivity and negative predictive value, while increasing specificity and positive predictive value. Second, our study participants were predominantly older men, and few women had ventricular dysfunction. Thus, our results may not generalize to other patient populations.

In summary, our findings indicate that NT-proBNP levels lower than 100 pg/mL effectively rule out ven-

tricular dysfunction in patients with CHD. Although elevated NT-proBNP levels do not necessarily identify ventricular dysfunction, NT-proBNP levels higher than 500 pg/mL identify a subgroup of patients with CHD who have a 47% probability of ventricular dysfunction. Whether use of NT-proBNP can reduce the burden of heart failure in high-risk patients deserves further study.

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