N-Terminal Pro-B-Type Natriuretic Peptide and Inducible Ischemia in the Heart and Soul Study

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Abstract

**Background**—B-type natriuretic peptide (BNP) is predictive of inducible ischemia in patients with coronary heart disease (CHD). Whether N-terminal pro-B-type natriuretic peptide (NT-proBNP) has a comparable strength of association with ischemia is uncertain.

**Hypothesis**—Resting NT-proBNP levels are associated with inducible ischemia in patients with stable CHD.

**Methods**—We performed a cross-sectional study of 901 outpatients with stable CHD. NT-proBNP was measured in all patients prior to exercise treadmill testing and stress echocardiography. In addition, plasma BNP was measured in a subset of 355 participants. Logistic regression was used to examine the association of NT-proBNP and BNP quartiles with inducible ischemia.

**Results**—Inducible ischemia was found in 216 (24%) patients. The proportion with inducible ischemia ranged from 42% (95/225) in the highest quartile of NT-proBNP levels (>410 pg/ml) to 9% (21/226) in the lowest quartile (0–72 pg/ml). The highest quartile had a 7-fold greater odds of inducible ischemia than the lowest quartile (odds ratio [OR]: 7.1, 95% confidence interval [CI]: 4.2–12; \( P < 0.0001 \)). This association remained robust after adjustment for traditional cardiovascular risk factors, left ventricular ejection fraction, and diastolic dysfunction (OR: 3.6, 95% CI: 1.4–9.1; \( P = 0.009 \)). In the subgroup with measurements of both NT-proBNP and BNP, both natriuretic peptides were predictive of ischemia. The multivariable-adjusted c-statistics for inducible ischemia were 0.71 for NT-proBNP and 0.62 for BNP (entered as continuous variables).

**Conclusions**—Resting NT-proBNP levels are independently associated with inducible ischemia in outpatients with stable CHD. Baseline elevations of natriuretic peptide may indicate subclinical inducible ischemia in high risk patients with CHD.

Introduction

Pro-B-type natriuretic peptide (proBNP) is principally released by cardiac myocytes in the ventricles in response to myocardial wall stress.1 The pro-protein form is cleaved by the enzyme corin into its active form B-type natriuretic peptide (BNP) and an inactive N-terminal fragment (NT-proBNP).2 Both BNP and NT-proBNP are detectable in the blood by several commercially available assays3 and have been found to have prognostic and diagnostic utility

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in relation to systolic and diastolic heart failure,\textsuperscript{4–6} acute coronary syndromes,\textsuperscript{7–9} and stable coronary heart disease (CHD).\textsuperscript{10,11}

Due to differing rates of renal clearance and protein degradation, NT-proBNP has a longer half-life than BNP, and blood levels are up to 2-fold greater on a molar basis.\textsuperscript{12} We and others have previously demonstrated an association between BNP and inducible ischemia in patients with CHD.\textsuperscript{10,13} Several studies have also found that elevated NT-proBNP levels are associated with inducible ischemia in patients referred for cardiac stress imaging.\textsuperscript{13–16} However, the association of NT-proBNP with inducible ischemia has not been evaluated in patients with known stable CHD.

We evaluated the relationship between resting levels of NT-proBNP and the presence of inducible ischemia by treadmill exercise testing with stress echocardiography in a cross-sectional study of 901 outpatients with stable CHD. We also compared the strength of association between BNP and NT-proBNP with inducible ischemia in a subsample of 355 participants.

Methods

Study Population

Between September 2000 and December 2002, we recruited 1024 outpatients with stable CHD from 2 VA medical centers, 1 university medical center, and 9 public health clinics to participate in the Heart and Soul Study, a prospective cohort study examining the influence of psychosocial factors on cardiovascular outcomes. Eligible patients had at least 1 of the following: (1) history of myocardial infarction, (2) angiographic evidence of $\geq 50\%$ stenosis in 1 or more coronary vessels, (3) exercise-induced ischemia by treadmill electrocardiogram or stress nuclear perfusion imaging, and/or (4) history of coronary revascularization. Patients who had an acute coronary syndrome within the prior 6 months and those who could not walk more than 1 block were excluded. The study protocol was approved by the institutional review boards of all sites, and written informed consent was obtained from all enrolled patients. For this analysis, we excluded 86 participants who were unable to complete the treadmill test, and 37 participants who were unable to provide blood samples, leaving 901 participants. NT-proBNP testing was performed on all 901 patients. BNP levels were available from only the first 355 participants, as detailed previously.\textsuperscript{10}

Measurement of Natriuretic Peptides

Prior to their study appointment, subjects completed an overnight fast, with the exception of taking their prescribed medications. Blood samples were collected in ethylenediaminetetraacetic (EDTA) acid tubes, centrifuged, aliquoted, and then stored at $-70\ ^\circ\mathrm{C}$. We measured NT-proBNP using the Elecsys 2010 proBNP electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN). 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\%. Triage B-type natriuretic fluorescence immunoassay (Biosite Diagnostics, San Diego, CA) was used to measure BNP levels with minimal detectable threshold of 5 pg/ml. The inter-assay coefficient of variation was 10.1\% for 28.8 pg/ml, 12.4\% for 586 pg/ml, and 16.2\% for 1180 pg/ml. The technicians performing the NT-proBNP and BNP assays were at a different site and blinded to echocardiography results.

Inducible Ischemia

We assessed for inducible cardiac ischemia using exercise treadmill testing with stress echocardiography. A symptom-limited, graded exercise treadmill test was performed
according to the standard Bruce protocol. We defined inducible ischemia as the presence of 1 or more new echocardiographic wall motion abnormalities at peak exercise that were not present at rest. To account for both fixed and exercise-induced wall motion defects, we also calculated a wall motion score index immediately following exercise. Results from the stress echocardiogram were interpreted by a single expert cardiologist who was blinded to NT-proBNP levels and clinical history.

Other Participant Characteristics
Age, sex, ethnicity, medical history, smoking status, and alcohol use were determined by a questionnaire. Weight and height were used to calculate body mass index (kg/m²). Fasting serum samples were obtained for total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Cardiac troponin T (cTnT) was measured using the Elecsys cTnT third generation assay (Roche Diagnostics, Inc, Indianapolis, IN) by an independent laboratory blinded to echocardiography results. The lowest measurable cTnT concentration was 0.01 μg/ml, with a 99th percentile reference limit of < 0.01 μg/ml. Creatinine clearance was estimated using a 24-hour urine collection. Participants were instructed to bring their medications, and study personnel recorded all current medications.

From the resting echocardiogram, we measured left ventricular ejection fraction (LVEF) and assessed for diastolic dysfunction using 4 categories of diastolic function: (1) normal = systolic dominant pulmonary vein flow and 0.75 < E/A < 1.5; (2) impaired relaxation = systolic dominant pulmonary vein flow and E/A ratio ≤ 0.75; (3) pseudonormal = diastolic dominant pulmonary vein flow and 0.75 < E/A < 1.5; and (4) restrictive filling = diastolic dominant pulmonary vein flow and E/A ≥ 1.5. Left ventricular hypertrophy was defined as left ventricular mass index>90 grams/meter².

Analysis
The cohort was divided a priori into quartiles of NT-proBNP levels. Participant characteristics across quartiles were compared using analysis of variance (ANOVA; or nonparametric equivalent) for continuous variables and χ² tests for dichotomous variables. We compared median NT-proBNP levels in patients with and without inducible ischemia using the Wilcoxon test. To determine the independent association between NT-proBNP and inducible ischemia, we used logistic regression analyses with quartiles of NT-proBNP as the primary predictor and inducible ischemia as the outcome.

To obtain adjusted risk estimates, we entered all variables including quartiles of NT-proBNP into a backwards stepwise elimination model. Variables associated with inducible ischemia at P <0.1 were retained in the final model. Since NT-proBNP is known to be associated with systolic and diastolic dysfunction, we also examined the association of NT-proBNP quartiles with inducible ischemia after adjustment for LVEF and diastolic dysfunction.

We tested for interactions of NT-proBNP (highest quartile compared with lowest) with age, sex, race, history of myocardial infarction, diabetes, revascularization, left ventricular hypertrophy, LVEF, and diastolic dysfunction. To determine whether the association of NT-proBNP with ischemia was similar to BNP, we calculated odds ratios (OR) and areas under receiver operating characteristic curves (ROC-curves) or c-statistics for unadjusted and adjusted models of log NT-proBNP and log BNP in the subgroup of participants who had both measures. All analyses were performed using Statistical Analysis Software (version 9.1, SAS Institute Inc., Cary, NC).
Results

Characteristics of participants are shown in Table 1. Among 901 participants with stable CHD, 216 (24%) had inducible ischemia by stress echocardiography. Median NT-proBNP levels were higher in patients with inducible ischemia than in those without inducible ischemia (326 vs 133 pg/ml; \(P<0.0001\)). The proportion of participants with inducible ischemia ranged from 42% (95/225) in the highest quartile of NT-proBNP to 9% (21/225) in the lowest quartile of NT-proBNP. After adjusting for other patient characteristics, participants in the highest quartile of NT-proBNP had a 5-fold greater odds of inducible ischemia than those in the lowest quartile (\(P<0.0001\); Table 2).

The association of NT-proBNP with ischemia did not vary by age, sex, history of myocardial infarction, diabetes, revascularization, or left ventricle (LV) hypertrophy (all \(P\) values for interaction>0.10). However, the association of NT-proBNP with ischemia differed by race (\(P\) for interaction = 0.06), systolic function (\(P\) for interaction = 0.05), and diastolic function (\(P\) for interaction = 0.01; Table 3). NT-proBNP was more strongly associated with ischemia in Caucasian than non-Caucasian participants. Likewise, NT-proBNP was strongly associated with ischemia in patients with normal systolic function (LVEF>50%) and in patients with normal diastolic function, but we did not observe a significant association between NT-proBNP and ischemia in participants with systolic dysfunction (LVEF \(\leq\) 50%) or in those with pseudonormal or restrictive diastolic dysfunction (Table 3). Each progressive quartile of NT-proBNP had a higher average wall motion scores index (Table 4), ranging from 1.06 ± 0.02 in the lowest quartile to 1.30 ± 0.02 in the highest quartile of NT-proBNP (\(P<0.0001\)).

Among the 355 study participants who had BNP and NT-proBNP levels available, both biomarkers were predictive of inducible ischemia (Figure 1) even after accounting for systolic and diastolic dysfunction (Table 5). When entered as continuous variables, the c-statistics for inducible ischemia were 0.71 for NT-proBNP and 0.62 for BNP, when adjusted for the variables in Table 1.

Discussion

We found that elevated NT-proBNP levels are associated with an increased risk of inducible ischemia in patients with stable CHD, independent of systolic dysfunction, diastolic dysfunction, and other measures of cardiovascular disease severity. The association between NT-proBNP and ischemia was most pronounced in patients with normal systolic and diastolic function. In addition, quartiles of NT-proBNP correlate with increasing severity of inducible ischemia, as measured by the post-exercise wall motion score index. These findings support the hypothesis that elevations of natriuretic peptides may signify subclinical ischemia and identify patients with increased ischemic burden on stress testing.\(^{19}\)

Prior studies have reported elevated levels of NT-proBNP to be associated with ischemia in patients referred for stress imaging.\(^{13,15}\) Our study extends these findings by demonstrating an association between NT-proBNP and ischemia in a large number of patients with stable coronary disease. It is possible that subdetectable abnormalities of ventricular dysfunction may be a consequence of microischemia, thereby leading to elevations in NT-proBNP that are not detectable by standard measures.\(^{13,14}\) In our study, only 48 patients (5%) had baseline detectable levels of cTnT which was not a significant covariate in multivariate analysis. Similarly, there was no association between the reported frequency of angina and NT-proBNP levels, which is consistent with our previously reported findings.\(^{20}\) Baseline NT-proBNP levels may represent an earlier, more sensitive means to detect subclinical ischemia than angina frequency or resting elevated troponin levels. Alternatively, studies have indicated that the rise of natriuretic peptides in acute ischemia may be independent of ventricular wall stress.\(^{21}\) Other
potential mechanisms for increase in BNP and NT-proBNP among patients with baseline low-level ischemia include decrease in stores of cellular energy and changes in vascular smooth muscle proliferation or contractility.19,22

In the subset of 355 patients for whom both NT-proBNP and BNP were measured, each biomarker was independently predictive of inducible ischemia. However, calculated c-statistics for models of log NT-proBNP and log BNP suggested better predictive test characteristics with NT-proBNP. While a large portion of the literature to date has considered NT-proBNP and BNP to be roughly equivalent tests, several other studies have found a preference for NT-proBNP in predicting left ventricular dysfunction and cardiovascular mortality.23,24 NT-proBNP is the biologically inactive N-terminal fragment of the prehormone, proBNP, and has a longer half-life (~ 120 minutes) than BNP (~ 20 minutes).25 NT-proBNP remains stable at room temperature for 72 hours in comparison to BNP that requires EDTA for stability up to ~ 24 hours.12,26,27 While both natriuretic peptides remain predictive of inducible ischemia, perhaps the increased in vivo and in vitro stability of NT-proBNP leads to its slightly better test characteristics as extrapolated by ROC-curves. There may be practical utility in measuring NT-proBNP in the assessment of “basal levels” of natriuretic peptide in patients with stable CHD.

While this is the largest study of NT-proBNP and inducible ischemia published to date, there are limitations to be considered. Our sample was predominantly male and thus the results may not be applicable to women. In addition, our cross-sectional study design does not enable us to determine causal mechanisms by which ischemia is related to elevations in NT-proBNP. This association between NT-proBNP and BNP with inducible ischemia is provocative, but without further prospective studies, NT-proBNP cannot be used on an individual basis to predict CHD. Though NT-proBNP levels have been shown to provide prognostic information for patients undergoing nonurgent percutaneous interventions,28 a recent post-hoc analysis did not find any additional benefit with NT-proBNP predicting CHD severity compared with traditional risk factors alone.29

In conclusion, we found that resting NT-proBNP levels were independently associated with inducible ischemia in outpatients with stable coronary disease, with better test characteristics than BNP. Greater underlying ischemia may be one reason why elevated NT-proBNP levels predict adverse cardiovascular outcomes in patients with stable CHD.

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Figure 1.
Proportion of study participants with inducible ischemia by quartile of NT-proBNP or BNP in 355 participants with stable CHD. Abbreviations: CHD, coronary heart disease; NT-proBNP, NT-pro-B-type natriuretic peptide.
Table 1

Characteristics of 901 Outpatients with Stable Coronary Disease, by Quartile of NT-proBNP

<table>
<thead>
<tr>
<th>Quartile of NT-pro-B-type Natriuretic Peptide (pg/ml)</th>
<th>I n = 226</th>
<th>II n = 225</th>
<th>III n = 225</th>
<th>IV n = 225</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;72</td>
<td>60.5 ± 9.8</td>
<td>66.7 ± 10.6</td>
<td>67.7 ± 10.5</td>
<td>71.7 ± 9.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>72–165</td>
<td>185 (82%)</td>
<td>190 (84%)</td>
<td>174 (77%)</td>
<td>196 (87%)</td>
<td>0.04</td>
</tr>
<tr>
<td>166–410</td>
<td>124 (55%)</td>
<td>130 (58%)</td>
<td>141 (63%)</td>
<td>154 (68%)</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;410</td>
<td>79 (35%)</td>
<td>71 (32%)</td>
<td>59 (26%)</td>
<td>59 (27%)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Demographics

- Age (years ± SD): 60.5 ± 9.8, 66.7 ± 10.6, 67.7 ± 10.5, 71.7 ± 9.8, P < 0.0001
- Male sex (%): 185 (82%), 190 (84%), 174 (77%), 196 (87%), P = 0.04
- Caucasian race (%): 124 (55%), 130 (58%), 141 (63%), 154 (68%), P = 0.02
- Current smoking (%): 59 (26%), 41 (18%), 42 (19%), 37 (16%), P = 0.05
- Regular alcohol consumption (%): 79 (35%), 71 (32%), 59 (26%), 59 (27%), P = 0.12

Medical history

- Hypertension (%): 140 (62%), 160 (71%), 162 (72%), 166 (74%), P < 0.0001
- Diabetes (%): 53 (24%), 48 (21%), 59 (26%), 67 (30%), P = 0.19
- Myocardial infarction (%): 103 (46%), 106 (47%), 123 (55%), 144 (65%), P = 0.0002
- Stroke (%): 20 (9%), 23 (10%), 38 (17%), 38 (17%), P = 0.01
- Revascularization (%): 113 (50%), 137 (61%), 132 (59%), 156 (70%), P = 0.0005
- Chronic lung disease (%): 33 (15%), 41 (18%), 37 (16%), 29 (13%), P = 0.44
- Weekly angina (%): 40 (18%), 51 (23%), 31 (14%), 40 (18%), P = 0.11

Current medication use

- β-Blocker (%): 91 (40%), 132 (59%), 149 (66%), 147 (66%), P < 0.0001
- Renin-angiotensin inhibitor (%): 86 (38%), 103 (46%), 126 (56%), 149 (66%), P < 0.0001
- Diuretic (%): 46 (20%), 52 (23%), 67 (30%), 93 (41%), P < 0.0001
- Aspirin (%): 176 (78%), 188 (84%), 184 (82%), 160 (71%), P = 0.007
- Statin (%): 129 (57%), 159 (71%), 159 (71%), 142 (63%), P = 0.004

Cardiac function

- LV hypertrophy (%): 80 (36%), 108 (48%), 125 (56%), 172 (77%), P < 0.0001
- LV ejection fraction: 0.65 ± 0.06, 0.65 ± 0.07, 0.62 ± 0.10, 0.57 ± 0.11, P < 0.0001

Diastolic dysfunction (%)

- Impaired relaxation: 36 (17%), 55 (26%), 57 (29%), 56 (32%), P = 0.005
- Pseudonormalization: 6 (3%), 11 (5%), 14 (7%), 24 (14%), P = 0.003
- Restrictive: 2 (1%), 4 (2%), 11 (6%), 25 (14%), P < 0.0001
- Cardiac troponin T (% detectable): 3 (1%), 2 (1%), 8 (4%), 35 (16%), P < 0.0001

Other measurements

- Body mass index (kg/m²): 29.4 ± 5.2, 28.5 ± 5.1, 28.1 ± 5.5, 27.4 ± 5.1, P = 0.007
- Exercise capacity (METs): 8.9 ± 3.6, 7.9 ± 3, 6.9 ± 3.1, 5.6 ± 2.7, P < 0.0001
- Total cholesterol (mg/dL): 184.6 ± 43, 176.3 ± 40, 175.6 ± 39, 170.3 ± 44, P = 0.005
- LDL cholesterol (mg/dL): 110 ± 32.6, 103 ± 33, 100.4 ± 30, 100.4 ± 37, P = 0.006
- HDL cholesterol (mg/dL): 45.6 ± 13, 45.4 ± 12, 46.7 ± 15, 45.2 ± 15, P = 0.66
- Creatinine clearance (ml/min): 99.7 ± 26.6, 87.5 ± 25.2, 77.9 ± 24.4, 63.1 ± 23.1, P < 0.0001

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular.
Table 2

Association Between Quartile of NT-proBNP and Inducible Ischemia in 901 Participants with Stable Coronary Disease

<table>
<thead>
<tr>
<th>NT-proBNP (pg/ml)</th>
<th>Proportion with Inducible Ischemia</th>
<th>Unadjusted OR (95% CI)</th>
<th>P Value</th>
<th>Adjusted OR (95% CI)(^a)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile I</td>
<td>9% (21/226)</td>
<td>1.0</td>
<td>–</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>Quartile II</td>
<td>17% (39/225)</td>
<td>2.0 (1.2–3.6)</td>
<td>0.01</td>
<td>1.8 (1.0–3.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Quartile III</td>
<td>27% (61/225)</td>
<td>3.6 (2.1–6.2)</td>
<td>&lt;0.0001</td>
<td>2.9 (1.7–5.1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Quartile IV</td>
<td>42% (95/225)</td>
<td>7.1 (4.2–12)</td>
<td>&lt;0.0001</td>
<td>5.1 (2.9–8.9)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(^a\) All variables from Table 1 (except LVEF and diastolic dysfunction) were entered into a logistic regression model that included NT-proBNP. Variables associated with ischemia at \(P<0.1\) were then entered into a second model that included NT-proBNP. Other variables included in the final model were age, ethnicity, and history of myocardial infarction. Abbreviations: CI, confidence interval; LVEF, left ventricular ejection fraction; NT-proBNP, NT-pro-B-type Natriuretic Peptide; OR, odds ratio.
Table 3
Association of NT-proBNP with Inducible Ischemia, Stratified by Race, Systolic Dysfunction, and Diastolic Dysfunction in 901 Outpatients with CHD

<table>
<thead>
<tr>
<th>NT-proBNP Quartile</th>
<th>Proportion with Ischemia</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>I, II, III</td>
<td>18% (51/284)</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>IV</td>
<td>30% (20/67)</td>
<td>1.5 (0.81–2.9)</td>
<td>0.19</td>
</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, II, III</td>
<td>20% (79/400)</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>IV</td>
<td>50% (75/149)</td>
<td>3.3 (2.2–5.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>B. Diastolic Function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudonormal or restrictive filling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, II, III</td>
<td>45% (28/62)</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>IV</td>
<td>60% (21/35)</td>
<td>1.2 (0.44–3.5)</td>
<td>0.68</td>
</tr>
<tr>
<td>Normal or impaired relaxation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, II, III</td>
<td>13% (69/547)</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>IV</td>
<td>37% (57/156)</td>
<td>3.2 (2.1–4.9)</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>C. Systolic Function</strong></td>
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<tr>
<td>LVEF ≤ 50%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>I, II, III</td>
<td>53% (28/53)</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>IV</td>
<td>56% (24/43)</td>
<td>1.1 (0.43–2.5)</td>
<td>0.91</td>
</tr>
<tr>
<td>LVEF &gt; 50%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>I, II, III</td>
<td>16% (102/632)</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>IV</td>
<td>41% (71/173)</td>
<td>2.7 (1.9–4.1)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Adjusted for age, Caucasian race, and history of myocardial infarction. Abbreviations: CHD, coronary heart disease; CI, confidence interval; LVEF, left ventricular ejection fraction; NT-proBNP, NT-pro-B-type natriuretic peptide; OR, odds ratio.*
<table>
<thead>
<tr>
<th>Quartile of NT-proBNP (pg/ml)</th>
<th>I (n = 226)</th>
<th>II (n = 225)</th>
<th>III (n = 225)</th>
<th>IV (n = 225)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;72</td>
<td>1.04 ± 0.16</td>
<td>1.07 ± 0.19</td>
<td>1.20 ± 0.38</td>
<td>1.30 ± 0.48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>72–165</td>
<td></td>
<td>1.07 ± 0.02</td>
<td>1.20 ± 0.02</td>
<td>1.30 ± 0.02</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>166–410</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;410</td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviation: NT-proBNP, NT-pro-B-type natriuretic peptide.
<table>
<thead>
<tr>
<th>Model</th>
<th>Odds Ratio (95% CI) NT-proBNP</th>
<th>P Value</th>
<th>Odds Ratio (95% CI) BNP</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for age, ethnicity, and myocardial infarction</td>
<td>3.1 (1.3–7.0)</td>
<td>0.008</td>
<td>2.8 (1.3–6.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjusted for above(^a) plus LVEF</td>
<td>3.2 (1.4–7.7)</td>
<td>0.007</td>
<td>3.1 (1.4–7.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Adjusted for above(^b) plus diastolic dysfunction(^a)</td>
<td>3.6 (1.4–9.1)</td>
<td>0.008</td>
<td>2.8 (1.1–6.9)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

\(^a\) Age, ethnicity, and myocardial infarction.

\(^b\) Age, ethnicity, myocardial infarction, and LVEF. Abbreviation: CHD, coronary heart disease; CI, confidence interval; LVEF, left ventricular ejection fraction; NT-proBNP, NT-pro-B-type naturetic peptide; OR, odds ratio.