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Amino-Terminal Pro-B-Type Natriuretic Peptide and High-Sensitivity C-Reactive Protein as Predictors of Sudden Cardiac Death Among Women

Ethan C. Korngold, MD; James L. Januzzi, Jr, MD; Mary Lou Gantzer, PhD; M.V. Moorthy, PhD; Nancy R. Cook, SCD; Christine M. Albert, MD, MPH

Background—Plasma concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) have been found to predict risk of sudden cardiac death (SCD) in patients with known cardiac disease, and C-reactive protein levels have been found to predict risk among apparently healthy men. However, there are no data on SCD risk prediction for either of these markers in a population of women unselected on the basis of cardiovascular disease.

Methods and Results—In a prospective, nested, case-control analysis within the 121 700-participant Nurses’ Health Study, 99 cases of definite or probable SCD were identified and matched to 294 controls. In multivariable models that adjusted for coronary heart disease risk factors, glomerular filtration rate, and other biomarkers, the trend across quartiles approached significance for NT-proBNP (rate ratio=2.37 for comparison of the highest and lowest quartile; \( P \) for trend=0.05) but not for high-sensitivity C-reactive protein (\( P \) for trend=0.60). When examined continuously, both NT-proBNP and high-sensitivity C-reactive protein were significantly associated with SCD risk in age- and fasting-adjusted models (\( P \) for linear trend=0.04 and 0.03). Adjustment for coronary heart disease risk factors and other biomarkers strengthened the relationship with NT-proBNP and SCD (relative risk for 1-SD increment=1.49; 95% confidence interval, 1.09 to 2.05; \( P=0.01 \)) but eliminated the relationship with high-sensitivity C-reactive protein (\( P=0.34 \)). Women with NT-proBNP levels above the prespecified cut point of 389 pg/mL were at a markedly increased risk of SCD in both models (rate ratio=5.68; 95% confidence interval, 1.78 to 18.2; \( P=0.003 \)).

Conclusions—In this population of women, baseline levels of NT-proBNP were associated with subsequent risk of SCD. If this association is confirmed in larger prospectively studied populations, these findings might provide another useful marker contributing to efforts to screen and prevent SCD among women. (Circulation. 2009;119:2868-2876.)

Key Words: death, sudden ■ epidemiology ■ natriuretic peptides ■ risk factors ■ women

Sudden cardiac death (SCD) is one of the most common causes of death in developed countries. Estimates approach 450 000 deaths per year,\(^1\) and these deaths account for >50% of coronary heart disease (CHD) deaths and 15% to 20% of all deaths.\(^2\) The vast majority of patients who suffer SCD do not fit into high-risk subsets, and >50% have no known history of heart disease at the time of death.\(^3\) In women, this percentage appears even higher, with estimates as high as 69%.\(^3,4\) Despite this, \( \approx90\% \) of women who suffer a cardiac arrest or die suddenly will have some sort of structural heart disease documented on evaluation or autopsy.\(^5,6\) Because SCD is often the first manifestation of clinically undetected structural heart disease, improved methods to detect structural heart disease may better identify women who are at risk.
healthy men, possibly through the detection of clinically unrecognized atherosclerosis. Several small studies also suggest that both NT-proBNP and CRP may specifically predict ventricular arrhythmias in patients with implantable cardioverter-defibrillators. To address the hypothesis that these markers of subclinical cardiovascular disease (CVD) might predict the risk of sudden arrhythmic death among women, we performed a prospective nested case-control analysis within the Nurses’ Health Study.

Methods

Study Population

The Nurses’ Health Study is a prospective cohort investigation among 121,700 female US registered nurses who were 30 to 55 years of age at baseline in 1976. Information about medical history, lifestyle choices, and incident disease is assessed biennially by self-administered questionnaires. The validity and reproducibility of the data collected have been reported in detail previously. Between 1989 and 1990, 32,826 women provided a blood sample, and these women served as a source population for this case-control analysis. Participants who provided blood samples were similar to those who did not. Blood samples were collected in tubes treated with liquid sodium heparin, placed on ice packs, stored in Styrofoam containers, and returned to our laboratory by overnight courier. The majority of blood samples (97%) arrived within 24 hours of phlebotomy. Immediately on arrival, samples were centrifuged (1200 × g at 15 minutes at room temperature) and divided into aliquots of plasma, and returned to our laboratory by overnight courier. The majority of blood samples (97%) arrived within 24 hours of phlebotomy. Immediately on arrival, samples were centrifuged (1200 × g for 15 minutes at room temperature) and divided into aliquots of plasma, erythrocytes, and buffy-coat fractions, which were then placed in liquid nitrogen freezers at −130 °C or colder until analysis. Informed consent was obtained from all subjects, and the research protocol was approved by the institutional review board at Brigham and Women’s Hospital.

End-Point Confirmation and Selection of Controls

The study end points included incident cases of sudden arrhythmic cardiac death that occurred after return of the blood sample and before June 1, 2006. The specific details on the classification of sudden and arrhythmic cardiac death in this cohort have been described in detail elsewhere. A cardiac death was considered a definite SCD if the death or cardiac arrest that precipitated death occurred within 1 hour of symptom onset as documented by medical records or next-of-kin reports. Deaths also were classified as arrhythmic or nonarrhythmic on the basis of the definition of Hinkle and Thaler. An arrhythmic death was defined as an abrupt spontaneous collapse of the circulation (pulsed disappeared) without evidence of prior circulatory impairment (shock, congestive heart failure) or neurological dysfunction (change in mental status, loss of consciousness, or seizure). Deaths in which the pulse gradually disappeared and/or those preceded by circulatory or neurological impairment were considered nonarrhythmic deaths and were excluded from the SCD end point. Unwitnessed deaths or deaths that occurred during sleep in participants documented to be symptom free when last observed within the preceding 24 hours in circumstances that suggested that the death could have been arrhythmic were considered probable SCDs (n = 36).

Using risk-set sampling, we randomly selected 3 controls for each case matched for age (±1 year), ethnicity, smoking status (current, never, past), time and date of blood sampling, fasting status, and presence or absence of reported CVD (myocardial infarction, angina, coronary artery bypass graft surgery, or stroke) at the time of blood draw. For cases who reported developing CVD after the blood draw, a second set of 3 controls who reported CVD after the blood draw were obtained to further control for the development of CVD before SCD.

Measurement of Biochemical Variables

All testing was done on the Dimension Vista 1500 System from Dade Behring (now Siemens Healthcare Diagnostics Inc, Deerfield, IL). The total cholesterol, high-density lipoprotein (HDL), and directly obtained low-density lipoprotein (LDL) cholesterol and triglycerides were measured with spectrophotometric assays. NT-proBNP was measured with a 1-step sandwich chemiluminescent immunoassay based on LOCI technology; CRP was measured with using the CardioPhase high-sensitivity CRP (hsCRP) assay, a nephelometric assay that uses monoclonal antibodies specific to human CRP. Typical coefficients of variation (20-day ANOVA) for the lipid assays are <5%. Study samples were sent to the laboratory for analysis in randomly ordered batches, and laboratory personnel were unaware of the case-control status of the samples. Within-run coefficients of variation were assessed by repeatedly analyzing quality control samples. The coefficients of variation were 6.33% for the NT-proBNP assay and 7.71% for the hsCRP assay.

Assessment of Other Factors

Data on anthropometric, lifestyle, and cardiac risk factor status were self-reported on questionnaires administered in 1990, with missing information substituted from previous questionnaires. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Physical activity was expressed in terms of metabolic equivalent hours. The validity and reproducibility of these measurements have been described previously. Glomerular filtration rate was estimated with the Modification of Diet in Renal Disease formula.

Statistical Analysis

Means or proportions for baseline cardiac risk factors were calculated for cases and controls. The significance of associations between cases and controls was tested with the generalized estimating equations for categorical variables and with repeated-measures analysis using Proc Mixed in SAS for continuous variables after natural logarithmic transformation to normalize their distribution. The raw values for continuous variables also were compared between case and control groups using conditional logistic regression. We analyzed the association between biomarker levels and the risk of sudden cardiac arrhythmic death using conditional logistic regression. With risk-set analysis, the odds ratio derived from the conditional logistic regression directly estimates the hazard ratio and thus the rate ratio (RR) or relative risk.

To determine whether a gradient of risk was present across plasma values, subjects were first divided into quartiles based on the distribution of control values. To test for a linear trend across quartiles, the median value was assigned to each quartile and then modeled as a continuous variable in separate conditional regression models. Plasma biomarker levels were analyzed as continuous variables and as categorical values. To minimize the influence of outliers and to encourage linearity, biomarkers not normally distributed were log transformed to improve the normality of their distributions.

For categorical analyses, we used prespecified cut points for each biomarker. For NT-proBNP and hsCRP, we used a cut point corresponding to the 80th percentile of the study population to facilitate comparisons with previous studies. In addition, we analyzed proposed clinical cut points for hsCRP (>3.0 mg/L) and NT-proBNP (≥389 pg/mL). We also examined clinical cut points for lipid values (LDL ≥160 mg/dL, HDL <40 mg/dL, triglycerides >200 mg/dL, total cholesterol ≥240 mg/dL). For each analysis, 3 multivariable conditional logistic regression models were performed. The first adjusted for age and fasting status (imperfectly matched variables). Fasting status was discordant from the case for 32 controls, and the maximum age difference between a case and control was 2.08 years, with 95% matched within 1 year. The second multivariable model further adjusted for body mass index (25.25 to 30, ≥30 kg/m²); history of diabetes, hypertension, or hyperlipidemia; parental history of premature myocardial infarction before 60 years of age; alcohol intake (<0.1, 0.1 to 15, 15 to 29.9, or at least 30 g/d); physical activity (quintiles from lowest to highest level); and use of postmenopausal hormone therapy (yes, no) and aspirin (<22 or ≥22 d/mo). The third model also simultaneously...
adjusted for other plasma biomarker levels (hsCRP, NT-proBNP, triglycerides, and ratio of total to HDL cholesterol).

Three sensitivity analyses were performed. The first sensitivity analysis used an alternative set of 3 controls matched for the development of CVD after the blood draw (n = 10 SCD cases) to explore the sensitivity of our results to the development of interim CVD. The second excluded women who reported CVD events before or at the time of the blood draw. The third excluded probable SCDs (n = 36) and matched controls from the analysis to determine the sensitivity of the result to the expanded definition of SCD. All analyses were carried out with SAS version 9.1 (SAS Institute Inc, Cary, NC). A 2-tailed value of P < 0.05 was considered to indicate statistical significance.

Drs Albert and Moorthy had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics and Traditional Risk Factors

Table 1 shows baseline characteristics at the time of blood draw for the 99 study subjects who died suddenly (63 definite and 36 probable) and the 294 matched controls. The mean time from study enrollment to SCD was 120.5 months. Risk factors significantly associated with SCD in this data set include parental history of myocardial infarction before 60 years of age, history of hypertension, and history of diabetes mellitus. Women who died suddenly also more frequently had aspirin. There were no significant associations between body mass index, hormone replacement therapy use, alcohol intake, or physical activity.

Table 1. Baseline Characteristics of the Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SCD Cases (n=99)</th>
<th>Controls (n=294)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>60.6±6.2</td>
<td>60.5±6.1</td>
<td></td>
</tr>
<tr>
<td>White, n (%)</td>
<td>99 (100)</td>
<td>294 (100)</td>
<td></td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>23 (23.2)</td>
<td>69 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, mean±SD, kg/m²</td>
<td>27.1±5.5</td>
<td>26.4±4.9</td>
<td>0.24</td>
</tr>
<tr>
<td>Parental history of MI &lt;60 y of age, n (%)</td>
<td>28 (28.3)</td>
<td>52 (17.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>HRT use, n (%)</td>
<td>32 (32.3)</td>
<td>102 (34.7)</td>
<td>0.64</td>
</tr>
<tr>
<td>Aspirin use ≥22 d/mo, n (%)</td>
<td>25 (25.3)</td>
<td>49 (16.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>History of hypertension, n (%)*</td>
<td>60 (60.6)</td>
<td>128 (43.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>History of diabetes mellitus, n (%)</td>
<td>21 (21.2)</td>
<td>21 (7.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol, median (IQR), g/d</td>
<td>1.10 (0–7.60)</td>
<td>1.0 (0–6.60)</td>
<td>0.70</td>
</tr>
<tr>
<td>Physical activity, median (IQR), MET h/wk</td>
<td>10.9 (3.2–24.0)</td>
<td>9.3 (3.5–24.9)</td>
<td>0.94</td>
</tr>
<tr>
<td>History of CVD, n (%)†</td>
<td>30 (30.3)</td>
<td>89 (30.3)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>234.3±39.9</td>
<td>229.2±41.3</td>
<td>0.27</td>
</tr>
<tr>
<td>LDL</td>
<td>155.8±37.1</td>
<td>150.4±37.8</td>
<td>0.20</td>
</tr>
<tr>
<td>HDL</td>
<td>64.6±16.8</td>
<td>65.2±15.3</td>
<td>0.76</td>
</tr>
<tr>
<td>Ratio of total to HDL</td>
<td>3.81±0.98</td>
<td>3.66±0.87</td>
<td>0.14</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>177.6±95.1</td>
<td>158.8±81.3</td>
<td>0.06</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>94.0 (47.0–194.0)</td>
<td>79.0 (45.0–148.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>3.62 (1.50–7.60)</td>
<td>3.08 (1.22–6.62)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Self-reported systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication.
†CVD includes a history of MI, angina, coronary artery bypass graft surgery, or stroke.

Serum Biomarker and Lipid Levels

The median levels of hsCRP and NT-proBNP were 3.36 mg/L and 82.0 pg/mL, respectively, in this population. The distribution of unadjusted hsCRP and NT-proBNP levels among cases and controls is demonstrated in Figure 1. Median levels of hsCRP and NT-proBNP tended to be slightly higher in cases than in controls, but the unadjusted continuous values did not achieve significance (P = 0.09 and P = 0.08, respectively). When the logarithmically transformed means of hsCRP and NT-proBNP were compared, these differences were significant (P = 0.03 and P = 0.04, respectively). Of the lipid parameters, only the logarithmically transformed triglyceride levels were marginally higher in SCD cases than in the matched controls (P = 0.06).

Table 2 displays the relationship between quartiles of plasma lipid, NT-proBNP, and hsCRP levels with the combined primary end point of probable and definite SCD. Baseline levels of hsCRP, LDL, HDL, triglycerides, and ratio of total to HDL cholesterol were not significantly associated with SCD in age- and fasting-adjusted or multivariable-adjusted models in the quartile analysis. In multivariable models that adjusted for CHD risk factors, glomerular filtration rate, and other biomarkers (hsCRP, triglyceride, and ratio of total to HDL cholesterol; Table 2, model 3), the trend across quartiles approached significance for NT-proBNP (P = 0.05). Compared with women in the lowest quartile, those in the highest quartile of NT-proBNP had an RR of 2.37 (95% confidence interval [CI], 0.97 to 5.80; P = 0.06). As demonstrated in Figure 2, the percentage of cases and...
controls reporting a history of prior CVD was highest in the top quartile for both NT-proBNP and hsCRP.

When examined continuously, logarithmically transformed NT-proBNP levels and hsCRP levels were significantly associated with SCD risk in age- and fasting-adjusted models ($P=0.04$ and $0.03$, respectively; Table 3). Further adjustment for CHD risk factors and glomerular filtration rate (model 2) as well as simultaneous control for other biomarkers (hsCRP, triglyceride, and ratio of total to HDL cholesterol; model 3) strengthened the relationship with NT-proBNP and SCD (RR for 1-SD increment in log NT-proBNP level = 1.49; 95% CI, 1.09 to 2.05; $P=0.01$), whereas the relationship for hsCRP was attenuated and no longer significant (RR for 1-SD increment in log hsCRP (RR = 1.17; 95% CI, 1.05 to 1.30; $P=0.34$)). Results were similar when the nontransformed continuous biomarker levels were entered into the above multivariable models (RR for 1-SD increment in NT-proBNP level = 1.34; 95% CI, 1.02 to 1.74; $P=0.03$). None of the lipid levels were significantly associated with SCD in the continuous analysis in either age-adjusted or multivariable models (data not shown).

When prespecified cutoffs were examined (Table 3), there was a trend toward a higher risk among those with NT-proBNP levels above the 80th percentile ($\geq 187$ pg/mL) in the fully adjusted multivariable model (RR=1.99; 95% CI, 0.97 to 4.12; $P=0.06$). Women with NT-proBNP levels above the proposed clinical cut point of 389 pg/mL ($n=24$, 6.1%) were at a markedly increased risk of SCD in both age-adjusted and multivariable-adjusted models (RR=5.68; 95% CI, 1.78 to 18.2; $P=0.003$) compared with women with NT-proBNP levels below this cut point. The proportion of cases with NT-proBNP levels >389 pg/mL was 12.6%, and the two thirds of cases and controls above this cut point had a history of prior CVD. The corresponding categorical analyses for hsCRP using the 80th percentile or a clinical cut point of >3.0 mg/L were not significant in either the age- and fasting-adjusted or the multivariable-adjusted models. Similarly, lipid levels above the 80th percentile and/or above accepted clinical cut points were not significantly associated with SCD risk in the age- and fasting-adjusted or multivariable-adjusted model (data not shown).

**Sensitivity Analyses**

When analyses were further adjusted for the development of CVD after the blood draw by the use of the alternate set of controls, relationships for NT-proBNP were attenuated slightly (Table 4). The RR was 1.35 (95% CI, 1.00 to 1.95; $P=0.05$) for 1-SD increment in log NT-proBNP level and 4.35 (95% CI, 1.49 to 12.6; $P=0.01$) for NT-proBNP levels above the 389 pg/mL cut point in the fully adjusted model. When analyses were limited to the 68 women without reported CVD at baseline, relationships for NT-proBNP were not materially altered (RR=1.54; 95% CI, 1.02 to 2.33; $P=0.04$ for 1-SD increment in log NT-proBNP level); however, only 8 women had NT-proBNP levels above the 389-pg/mL cut point (RR=4.51; 95% CI, 0.77 to 26.3; $P=0.09$). In contrast, relationships for hsCRP were attenuated further.

When analyses were limited to the definite SCDs ($n=63$), results for NT-proBNP and hsCRP were stronger. For each 1-SD increment in log NT-proBNP level, the RR for definite SCD was 1.71 (95% CI, 1.12 to 2.63; $P=0.01$) in the fully adjusted multivariable model, and women above the 389-pg/mL cut point were at a markedly elevated risk (RR=19.9; 95% CI, 2.67 to 149; $P=0.004$). For hsCRP, the multivariable continuous relationship between log-transformed hsCRP and definite SCD was strengthened but remained nonsignificant (RR=1.48; 95% CI, 0.94 to 2.33 for 1-SD increment in log hsCRP; $P=0.09$).

**Discussion**

In this prospective nested case-control study of women, baseline blood levels of NT-proBNP were associated with SCD risk over the 16 years of follow-up. These relationships were significant in the primary analyses when analyzed as continuous variables or when prespecified cutoffs were used. Relationships were strengthened when adjusted for CHD risk factors and in analyses limited to definite SCDs; the continuous relationship remained significant even after patients who reported CVD at baseline were excluded from analysis. In the primary multivariable analyses including definite and probable SCD events, each 1-SD increment in log NT-
proBNP was associated with an $\approx 50\%$ increase in the risk of SCD, and levels above the prespecified cut point of 389 pg/mL, where women with a history of CVD predominated, were associated with a 5-fold increased risk of SCD. In contrast to the findings for NT-proBNP, log hsCRP levels were not significantly associated with SCD risk after multivariable adjustment. No significant associations were observed between any of the lipid values and SCD among women in any of the primary or secondary analyses.

Previously elevated levels of natriuretic peptides, including NT-proBNP, have been shown to be associated with risk of SCD or ventricular arrhythmias in high-risk patient popula-
tions. In a study of 452 ambulatory patients with chronic heart failure and left ventricular ejection fraction <35%, elevated BNP levels were shown to be a strong independent predictor of SCD.9 In another series of 521 patients after acute myocardial infarction, elevated BNP (hazard ratio = 3.9; 95% CI, 1.2 to 12.3; \( P = 0.02 \)) remained a significant predictor of SCD risk even after adjustment for clinical variables and left ventricular ejection fraction.10 In addition, several small studies suggest that these markers may predict appropriate shocks for ventricular tachycardia/fibrillation in implantable cardioverter-defibrillator patients.12,13 In population-based studies, BNP and NT-proBNP levels have been associated with total cardiovascular events and overall mortality.21,22,25 This study extends these findings by establishing a relationship between NT-proBNP levels and the specific end point of SCD in an unselected population of women with and without CVD.

These data offer potential insights into the pathophysiology underlying SCD in women. Elevated natriuretic peptide levels are thought to be reflective of increased myocardial wall stress and filling pressures, and chronic exposure to these hemodynamic stressors may result in significant left ventricular dilation, hypertrophy, and/or fibrosis, altering the electrophysiological substrate and increasing cardiac vulnerability to malignant arrhythmias.26–28 Alternatively, increased ventricular filling pressures resulting from already established but as-yet unrecognized structural heart disease might be responsible for the elevated SCD risk associated with high levels of NT-proBNP. Consistent with this possibility, relationships were attenuated slightly with further control for the development of CVD detected after the NT-proBNP measurement.

The consistently observed association between NT-proBNP and SCD in all analyses compared with the relative
lack of an association between the other well-established CHD risk factors, namely HDL cholesterol, LDL cholesterol, triglycerides, ratio of total to HDL cholesterol, hsCRP, and SCD, suggests that elevated filling pressures and associated mechanical-electrical disturbances may play a greater role than occult CHD in SCD risk among women. In support of this hypothesis, women who suffer SCD appear to have a lower prevalence of underlying CHD compared with men in several series.5,6

This potential sex difference in the underlying prevalence of CHD may account for the relative lack of prediction of hsCRP compared with that previously observed among apparently healthy men.11 In the previous study, the CRP level was significantly associated with SCD risk even after controlling for lipid levels over 17 years of follow-up. An alternative explanation for these apparent sex differences may be the expanded definition of SCD. Because women are more likely to be unwitnessed at the time of their SCD,29 we included unwitnessed deaths in patients known to be alive and well without symptoms in the preceding 24 hours, similar to other epidemiological studies.16,17 The inclusion of unwitnessed deaths increases the sensitivity for arrhythmic death15 but also reduces the proportion of all sudden natural deaths that are due to cardiac causes.30 In support of this possible explanation for the discrepant results, associations were stronger for hsCRP in analyses excluding these unwitnessed deaths. However, the smaller number of events limits our ability to assess effects on short-term risk.

The positive relationships observed here for NT-proBNP also may have potential clinical implications. Marked elevations in NT-proBNP levels may be useful in identifying women at higher risk for SCD many years before the fatal event. However, the relationship observed here in the small subgroup with high NT-proBNP levels needs to be confirmed in a much larger population of women with high levels of NT-proBNP. If confirmed, documentation of high NT-proBNP levels may provide the impetus to screen for structural heart disease and to initiate specific therapy such as β-blockade to prevent SCD.

Several limitations of the present study warrant consideration. First, our analysis was based on a single baseline determination of each plasma marker. Therefore, we were unable to account for changes in these markers over time and are limited in our ability to assess effects on short-term risk. This limitation could account for the relatively null results observed for lipid parameters and hsCRP if the majority of their effects are on short-term risk or if levels changed significantly over the course of the study as a result of changes in dietary habits and/or lipid-lowering agents. Second, the selective nature of the cohort, white US female registered nurses, may limit the generalizability of the findings to other groups of women, ethnicities, or men. The healthy nature of this cohort is demonstrated by the low SCD rate, and the population effect observed here may or may not prove to have clinical applicability for individual subjects.

Although this study is the largest we know of to examine the association between these plasma markers and risk of SCD in women, our power to detect small to moderate effects is still limited by the small number of cases, especially for analyses limited to definite SCD cases and among women without CVD. Therefore, it is possible that associations for the other markers would have emerged in a larger sample size. Finally, although the primary and secondary analyses were prespecified, concern for multiple comparisons resulting in spurious significant results is warranted given the large number of comparisons. However, the consistency of the association between NT-proBNP and SCD across analyses supports the validity of the results.

**Conclusions**

In this population of women, higher baseline blood levels of NT-proBNP were associated with the subsequent development of SCD, and this relationship was independent of established risk factors for CHD and/or SCD. NT-proBNP,
when used in combination with other cardiac risk factors, may be a useful indicator of long-term SCD risk among women.

Acknowledgments
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Disclosures
Dr Januzzi reports receiving grant support, speaker’s fees, and/or consulting income from Roche Diagnostics, Siemens Healthcare Diagnostics, Ortho Clinical Diagnostics, Inverness Medical Innovations, BG Medicine, and Critical Diagnostics. Dr Gantzer is employed by the study sponsor, Siemens Healthcare Diagnostics. Dr Albert reports receiving grant support from Siemens Healthcare Diagnostics. The assays used in this study were paid for and manufactured by Siemens Healthcare Diagnostics, the study sponsor. In addition to Siemens Healthcare Diagnostics, the following companies that Dr Januzzi consults for also make assays for natriuretic peptides and/or hsCRP: Roche Diagnostics, Ortho Clinical Diagnostics, and Inverness Medical Innovations. The other authors report no conflicts.

References
17. de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, van Ree 50% Circulation June 9, 2009

**CLINICAL PERSPECTIVE**

Plasma concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) predict risk of sudden cardiac death (SCD) in patients with known cardiac disease, but currently there are no data for SCD risk prediction in populations unselected on the basis of cardiac disease. In this nested case-control analysis within the 121 700-person Nurses’ Health Study, 99 cases of definite or probable SCD were identified and matched to 294 controls on the basis of age, smoking, and prior cardiovascular disease. Baseline plasma NT-proBNP levels, but not C-reactive protein or lipid levels, were significantly associated with SCD using a multivariable model adjusted for coronary heart disease risk factors and other biomarkers. After multivariable adjustment, each 1-SD increment in log NT-proBNP was associated with an ≈50% increase in the risk of SCD, and levels above the prespecified cut point of 389 pg/mL were associated with a 5-fold increased risk of SCD. These findings offer potential insights into the pathophysiology underlying SCD in women. Specifically, they point to increased myocardial wall stress, along with associated left ventricular dilatation, hypertrophy, and/or fibrosis, as potential mediators of electrical instability leading to SCD in women. The lack of association of other well-established coronary heart disease risk factors (including high-sensitivity C-reactive protein) suggests that mechanical-electrical disturbances might play a greater role than undetected atherosclerosis in SCD risk among women. If confirmed in larger studies, marked elevations in NT-proBNP levels might also be useful in identifying women at higher risk for SCD many years before the fatal event.