N-Terminal Pro-B-Type Natriuretic Peptide Is a Major Predictor of the Development of Atrial Fibrillation
The Cardiovascular Health Study

Kristen K. Patton, MD; Patrick T. Ellinor, MD, PhD; Susan R. Heckbert, MD, PhD; Robert H. Christenson, PhD; Christopher DeFilippi, MD; John S. Gottdiener, MD; Richard A. Kronmal, PhD

**Background**—Atrial fibrillation (AF), the most common cardiac rhythm abnormality, is associated with significant morbidity, mortality, and healthcare expenditures. Elevated B-type natriuretic peptide levels have been associated with the risk of heart failure, AF, and mortality.

**Methods and Results**—The relation between N-terminal pro-B-type natriuretic peptide (NT-proBNP) and AF was studied in 5445 Cardiovascular Health Study participants with the use of relative risk regression for predicting prevalent AF and Cox proportional hazards for predicting incident AF. NT-proBNP levels were strongly associated with prevalent AF, with an unadjusted prevalence ratio of 128 for the highest quintile (95% confidence interval, 17.9 to 913.3; \( P < 0.001 \)) and adjusted prevalence ratio of 147 for the highest quintile (95% confidence interval, 20.4 to 1064.3; \( P < 0.001 \)) compared with the lowest. After a median follow-up of 10 years (maximum of 16 years), there were 1126 cases of incident AF (a rate of 2.2 per 100 person-years). NT-proBNP was highly predictive of incident AF, with an unadjusted hazard ratio of 5.2 (95% confidence interval, 4.3 to 6.4; \( P < 0.001 \)) for the development of AF for the highest quintile compared with the lowest; for the same contrast, NT-proBNP remained the strongest predictor of incident AF after adjustment for an extensive number of covariates, including age, sex, medication use, blood pressure, echocardiographic parameters, diabetes mellitus, and heart failure, with an adjusted hazard ratio of 4.0 (95% confidence interval, 3.2 to 5.0; \( P < 0.001 \)).

**Conclusions**—In a community-based population of older adults, NT-proBNP was a remarkable predictor of incident AF, independent of any other previously described risk factor. (Circulation. 2009;120:1768-1774.)

**Key Words:** arrhythmia ■ atrial fibrillation ■ natriuretic peptides

Atrial fibrillation (AF) is the most common sustained arrhythmia. It is associated with increased mortality, and is a major risk factor for cardiovascular morbidity, including heart failure and stroke. The clinical presentation of AF is heterogeneous, and it is often associated with structural heart disease. Because AF is known to lead to electric and mechanical remodeling, differentiating factors predisposing to AF from the pathology created by the arrhythmia itself is difficult. Identification of markers that predate the development of AF may permit early treatment of those at risk and facilitate the development of therapeutic strategies aimed at preventing the disease.

The neurohormone B-type natriuretic peptide (BNP) is a regulator of cardiovascular function. BNP is produced chiefly in the ventricular myocardium, with additional production in the atrial myocardium and the brain. In the ventricles, production is stimulated by stretch receptors. The precursor protein pro-B-type natriuretic peptide is cleaved to form BNP and the amino terminal N-terminal pro-B-type natriuretic peptide (NT-proBNP), both of which circulate in the plasma. Although most widely used as a marker of heart failure, elevated BNP levels have been reported in patients with AF, even in the absence of heart failure or other cardiac pathology. Furthermore, in a population-based study from Framingham, a single determination of elevated BNP was found to be predictive of the future development of AF, cardiovascular outcomes, and death. However, only 68 of 3260 subjects developed AF during the time of the study, levels predictive of the outcome were often well within the normal range, and the generalizability of these results is unclear.

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1768
To address the potential value of NT-proBNP as an early marker of the development of AF, we examined the association between baseline NT-proBNP levels and prevalent and incident AF in the Cardiovascular Health Study (CHS), a large, population-based, longitudinal study of older adults.

**Methods**

**Study Population**
The design and objectives of CHS have been described previously. In brief, CHS is a longitudinal study of 5888 men and women aged ≥65 years, randomly selected from 4 communities in the United States and enrolled during 2 time periods: 1989–1990 for the “original” cohort (n = 5201) and 1992–1993 for the “minority” cohort (n = 687 [blacks]). The institutional review board at each center approved the study, and each participant gave informed consent. The baseline examination included a standardized questionnaire assessing a variety of risk factors, including smoking, alcohol intake, history of diabetes mellitus, stroke, coronary heart disease, heart failure, self-reported health status, medication use, and history of prior cardiovascular disease. The physical examination included measurements of height, weight, and seated blood pressure measured with a random-zero sphygmomanometer. Other evaluation included a resting 12-lead ECG and an echocardiogram that assessed left ventricular dimensions, ventricular septal thickness, posterior wall thickness, aortic root dimension, left atrial dimension, percent fractional shortening, left ventricular mass, and end-systolic stress.

Laboratory examinations included measurement of total cholesterol, high-density lipoprotein cholesterol, fasting glucose, C-reactive protein, and serum creatinine. Participants were contacted every 6 months for follow-up, alternating between a telephone interview and a clinic visit for the first 10 years and by telephone interview only after that. An annual resting ECG was obtained yearly through the ninth year of follow-up. Discharge diagnoses for all hospitalizations were entered into the database. Adjudication of cardiovascular events was performed by a centralized events committee. The maximum follow-up was 16 years (median, 10 years).

NT-proBNP levels were determined in 5447 participants. From the original cohort of 5201 subjects, 3979 participants had NT-proBNP measured at baseline, and 832 had a NT-proBNP measurement at year 3 only, for a total of 4811. From the 687 participants in the original cohort of 5201 subjects, 3979 participants had NT-proBNP measured at baseline and 193, or if the participant had a self-report of AF and was taking medications for AF (n = 193), or if the participant had a pacemaker (n = 67). Thus, the analyses for incident AF included a total of 5021 participants.

**Natriuretic Hormone Assays**
Frozen serum was utilized for determination of NT-proBNP. Serum samples were maintained at −70°C until testing. All measurements were performed in a Clinical Laboratory Improvement Amendments–certified laboratory accredited by the College of American Pathologists. Measurement of NT-proBNP was performed with the use of a Food and Drug Administration–approved commercially available immunoassay from Roche Diagnostics Corporation (Roche Diagnostics Elescsys proBNP Assay, Indianapolis, Ind) on the Elescys 2010 instrument. The core laboratory was blinded as to patient outcome and reported certified data to the central data repository.

**Determination of Incident AF**
For the analyses of prevalent AF, only AF present on ECG at the examination at which NT-proBNP was measured was included as a prevalent case. Incident cases of AF were identified by 2 methods.

**Annual study ECGs were interpreted by the CHS centralized reading center, and the diagnoses of AF or atrial flutter were verified.**

When hospital discharge diagnosis International Classification of Diseases, Ninth Revision code identified AF or atrial flutter, AF was considered to be present as of the date of hospital admission. (A prior study determined the positive predictive value of hospital discharge diagnosis to be 98.6% for diagnosis of AF in CHS, and a Holter substudy identified that only 1 in 819 subjects [0.1%] had persistent or intermittent AF not identified by the above measures.)

**Statistical Analysis**
NT-proBNP levels were analyzed both as a continuous variable, for which the natural log of NT-proBNP was used, and as categorized into quintiles. In initial analyses, we compared the prevalence of AF on ECG at baseline across quintiles of NT-proBNP levels. We used relative risk regression to estimate the prevalence ratios for prevalent AF associated with the quintiles of NT-proBNP and for the log of NT-proBNP. Initially, the prevalence of AF was modeled as a function of NT-proBNP with a generalized linear model with log link and binomial error distribution. Because the model failed to converge when covariates were included, we used instead the log link with gaussian error distribution for this analysis with robust standard errors to correct the standard errors for the misspecification of the error distribution.

We then examined the risk of incident AF associated with baseline NT-proBNP among the 5021 subjects without AF at baseline. We present unadjusted Kaplan-Meier survival curves comparing cumulative risk of developing AF across quintiles of baseline NT-proBNP. We used covariate-adjusted Cox model regressions to estimate the hazard ratios of developing AF by quintile of baseline NT-proBNP among those with no AF at baseline and using the log of NT-proBNP as a continuous predictor. Failure time for the Cox models for those who developed AF was the earliest of the following: the date of first occurrence of AF on an ECG or the date of the first hospitalization with an AF diagnosis code. For those who did not develop AF, failure time was the date of last known follow-up or the date of death.

Relative risk regression and Cox models were adjusted for the following covariates measured at baseline: age, sex, race, body mass index, height, smoking (never, former, and present), hypertension, diabetes mellitus, total cholesterol, high density lipoprotein cholesterol, C-reactive protein, creatinine, systolic and diastolic blood pressure, history of stroke, history of coronary heart disease, and history of heart failure. Stratified analyses were performed for age, race, baseline heart failure, hypertension, overweight or obesity (body mass index >25), and sex.

In supplementary analyses, the echocardiographic variables left atrial size, left ventricular dimension, ventricular septal thickness, posterior wall thickness, aortic root dimension, percent fractional shortening, left ventricular mass, ratio of early to late atrial mitral Doppler peak flow velocity, and end-systolic stress were examined. For NT-proBNP measures at examinations other than the baseline examination, the covariate values were taken from the same examination if the variable was measured at that examination or from the nearest examination in time before the NT-proBNP determination if not available at that examination.

We report prevalence ratios and hazard ratios from the relative risk regressions and Cox models, respectively, along with 95% confidence intervals (CIs) and P values. All analyses were conducted with STATA 10.0.

**Results**
The demographic and medical characteristics of the CHS participants according to AF status are compared in Table 1. Those with prevalent AF compared with those without prevalent or incident AF were older, more frequently male, white, diabetic, hypertensive, had a history of cardiovascular disease (stroke, coronary heart disease, or heart failure), had
Table 1. Selected Baseline Characteristics of the CHS Participants According to AF Status (Prevalent or Incident)

<table>
<thead>
<tr>
<th>Quintile of NT-proBNP</th>
<th>Quintile Range, pg/dL</th>
<th>No. of Participants</th>
<th>Prevalent AF, n (%)</th>
<th>Prevalent AF (n=148)</th>
<th>Incident AF (n=1126)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unadjusted</td>
<td>Adjusted†</td>
<td>Unadjusted†</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prevalence Ratio</td>
<td>95% CI</td>
<td>P</td>
<td>Prevalence Ratio</td>
</tr>
<tr>
<td>1</td>
<td>5.00–50.81</td>
<td>1088</td>
<td>1 (0.10)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>50.82–91.78</td>
<td>1090</td>
<td>3 (0.28)</td>
<td>3.0</td>
<td>0.3–28.7</td>
<td>3.3</td>
</tr>
<tr>
<td>3</td>
<td>91.79–156.09</td>
<td>1089</td>
<td>7 (0.64)</td>
<td>7.0</td>
<td>0.9–56.8</td>
<td>7.9</td>
</tr>
<tr>
<td>4</td>
<td>156.1–290.3</td>
<td>1089</td>
<td>9 (0.83)</td>
<td>9.5</td>
<td>1.1–70.1</td>
<td>9.7</td>
</tr>
<tr>
<td>5</td>
<td>&gt;290.3</td>
<td>1089</td>
<td>128 (11.75)</td>
<td>127.9</td>
<td>17.9–913.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data presented in the table are mean and SD for continuous variables and number of cases with percentage in parentheses for categorical variables. HDL indicates high-density lipoprotein; ACE, angiotensin-converting enzyme; and HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

NT-proBNP was strongly associated with the ECG diagnosis of AF at baseline enrollment (Table 2); with increasing risk according to quintile of NT-proBNP. The adjusted prevalence ratio for those in the highest quintile was 147.3 (95% CI, 20.4 to 1064.3; P<0.001) compared with the first quintile. Similarly, there was a highly statistically significant association of the log of NT-proBNP with prevalent AF (adjusted prevalence ratio for a 1-SD unit change in log of NT-proBNP of 3.44; 95% CI, 2.79 to 4.24; P<0.0001).

elevated total cholesterol and lower high-density lipoprotein cholesterol, had higher C-reactive protein and creatinine levels, and had substantially increased left atrial size and NT-proBNP levels. In general, similar results held for those with incident AF, except in most instances the difference compared with those without prevalent or incident AF was much smaller. The use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and angiotensin-converting enzyme inhibitors was infrequent in this cohort at baseline.
strong gradation of prevalence is shown by the breakdown of the prevalence by quintiles of NT-proBNP, with only 1 participant with AF in the first quintile compared with 128 in the fifth quintile with an adjusted prevalence ratio of 147.3 (95% CI, 20.4 to 1064.3; \( P < 0.001 \)) for the fifth quintile compared with the first quintile. Because of the small number of events in the first quintile, the prevalence ratios have wide CIs and thus are not estimated with precision and should be interpreted with caution; however, this is not the case for log(NT-proBNP).

Among subjects without AF at baseline, 1126 developed AF during the follow-up period. The incidence rate of AF per 100 person-years of follow-up was 1.2 for participants in the lowest quintile compared with 5.1 for participants in the highest quintile. By 16 years of follow-up, the estimated cumulative incidence of AF in the highest quintile was \( \approx 64\% \) compared with 20% for those in the lowest quintile (Figure). The hazard ratio for incident AF increased in a dose-dependent fashion with each quintile of baseline NT-proBNP (Table 3). The unadjusted hazard ratio associated with the highest quintile was 5.2 (95% CI, 4.3 to 6.4; \( P < 0.001 \)) compared with the lowest quintile. This association remained strong even after adjustment for an extensive number of relevant covariates. Because this is a cross-sectional relationship, it is impossible to know whether NT-proBNP is elevated before the AF episode or is a consequence of the AF or some other clinical variable; however, the association remained strong even after adjustment for clinically relevant covariates. This is a strong predictor of both prevalent and incident AF, which suggests that NT-proBNP is not mediated by these covariates.

Almost all of the subjects who were in AF at enrollment had elevated NT-proBNP levels at baseline, an association that remained strong even after adjustment for clinically relevant covariates. Because this is a cross-sectional relationship, it is impossible to know whether NT-proBNP is elevated before the AF episode or is a consequence of the AF or some combination of both. The analysis of incident AF revealed a linear risk gradient, with significantly increased risk in each quintile. The estimated cumulative incidence of AF over 16 years of follow-up. Adjustment for covariates associated with AF had little influence on the association of NT-proBNP with either prevalent or incident AF, which suggests that NT-proBNP is not mediated by these covariates.

Our results indicate a compelling, graded association between NT-proBNP levels and AF in a large, diverse cohort with extensive follow-up. There was a robust relationship between AF and NT-proBNP was by far the strongest predictor of incident AF over 16 years of follow-up. Adjustment for covariates associated with AF had little influence on the association of NT-proBNP with either prevalent or incident AF, which suggests that NT-proBNP is not mediated by these covariates.

Discussion

Our results indicate a compelling, graded association between NT-proBNP levels and AF in a large, diverse cohort with extensive follow-up. There was a robust relationship between AF and NT-proBNP was by far the strongest predictor of incident AF over 16 years of follow-up. Adjustment for covariates associated with AF had little influence on the association of NT-proBNP with either prevalent or incident AF, which suggests that NT-proBNP is not mediated by these covariates.

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The analysis of incident AF revealed a linear risk gradient, with significantly increased risk in each quintile. The estimated cumulative incidence of AF over 16 years of follow-up, based on almost 822 participants in the highest quintile of NT-proBNP, was 64% compared with 20% for those in the lowest quintile. The baseline level of NT-proBNP was a considerably stronger predictor of the development of AF than any other clinical covariate, including age, sex, race, height, body mass index, current smoking, hypertension medication use, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, C-reactive protein, creatinine, systolic and diastolic blood pressure, history of stroke, history of coronary heart disease, and history of congestive heart failure.

Table 3. Cox Proportional Hazards Regression Results for NT-proBNP as a Predictor of Incident AF*

<table>
<thead>
<tr>
<th>Quintile of NT-proBNP Range, pg/dL</th>
<th>No. With Incident AF (Rate per 100 Person-Years)</th>
<th>Hazard Ratio 95% CI</th>
<th>( P )</th>
<th>Hazard Ratio 95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 5.00–50.81</td>
<td>146 (1.2)</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>2 50.82–91.78</td>
<td>191 (1.6)</td>
<td>1.4</td>
<td>1.1–1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 91.79–156.09</td>
<td>233 (2.2)</td>
<td>1.9</td>
<td>1.6–2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 156.1–298.3</td>
<td>273 (2.8)</td>
<td>2.6</td>
<td>2.1–3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 ≥290.3</td>
<td>283 (5.1)</td>
<td>5.2</td>
<td>4.3–6.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>log(NT-proBNP)</td>
<td>in SD units</td>
<td>1.88</td>
<td>1.59–1.78</td>
<td>0.001</td>
<td>1.66</td>
</tr>
</tbody>
</table>

*Includes 5021 participants with no history of AF before or at the examination at which NT-proBNP was measured.
†Adjusted for age, sex, race, body mass index, height, current smoking, hypertension medication use, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, C-reactive protein, creatinine, systolic and diastolic blood pressure, history of stroke, history of coronary heart disease, and history of congestive heart failure.
comorbidities previously associated with increased levels of BNP, and all echocardiographic parameters.

These findings add substantially to our previous knowledge about the relation between increased level of NT-proBNP and AF. Although the Framingham Heart study also explored goal. Measurement of NT-proBNP levels may ultimately provide a reasonable way of risk stratifying individuals who may benefit from more careful monitoring or aggressive preventative medical therapy.

Little is known about potential electrophysiological effects of BNP on cardiac myocytes, the conduction system, or ion channels. Atrial natriuretic peptide has been shown to alter channels. Atrial natriuretic peptide has been shown to alter calcium handling, or activation of the sympathetic nervous system. This finding has been attributed to alterations in left ventricular filling patterns due to lack of mechanical atrial synchrony, myocardial ischemia, alterations in calcium handling, or activation of the sympathetic nervous system or is indicative of concealed ventricular dysfunction. However, the underlying process is not well understood.

Plasma NT-proBNP levels were noted to be elevated in our study before the onset of clinical disease, suggesting that elevated NT-proBNP may be a marker of underlying disease predisposition, play an unknown role in pathogenesis, or represent the presence of undiagnosed, paroxysmal AF. Given the medical and financial burden of AF, primary prevention of the disease is a worthy yet relatively unexplored goal. Measurement of NT-proBNP levels may ultimately provide a reasonable way of risk stratifying individuals who may benefit from more careful monitoring or aggressive preventative medical therapy.

Little is known about potential electrophysiological effects of BNP on cardiac myocytes, the conduction system, or ion channels. Atrial natriuretic peptide has been shown to alter
the permeability of the sodium channel, modulate the L-type calcium channel current, decrease the outward potassium current, and increase the cardiac pacemaker current, all perturbations that may predispose to the generation and maintenance of AF. 20–22 Infusion of atrial natriuretic peptide in human subjects reduces intra-atrial conduction time and atrial refractory periods without affecting heart rate or blood pressure. 23 Indeed, a mutant form of atrial natriuretic peptide has been demonstrated recently to lead to AF in one family. 24 Given the sequence homology between atrial natriuretic peptide and BNP, it is possible that they may have similar electrophysiological actions, although this hypothesis will require further experimental study.

The strengths of this study include the large sample size and high incidence of AF, with long-term follow-up. The mechanism underlying this association is unclear, given that the source of NT-proBNP is largely the ventricle, although 2 physiological studies have demonstrated increased BNP production in the atria of subjects with AF. 25,26 The strong associations of NT-proBNP with prevalent AF and with incident AF over a decade later make it likely that it is either in the causal pathway or that it is strongly associated with a cause of AF. This raises the question of the role of NT-proBNP in the pathogenesis of AF, and future studies to elucidate this connection are clearly of interest.

We have shown that elevated NT-proBNP is a marker of substantial risk for AF in a community-based population of older adults, to a degree not shown for any other known risk factor. This association remains remarkably predictive, even after adjustment for other known risk factors for AF. Further studies are needed to assess whether NT-proBNP is simply a marker of underlying atrial disease or is more directly involved in pathogenesis.

Acknowledgments
A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm.

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Disclosures
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References


**CLINICAL PERSPECTIVE**

Atrial fibrillation (AF) is a ubiquitous cardiac arrhythmia and is associated with significant morbidity, mortality, and economic burden. In the United States, ~5% of the population is affected by age 65 years; therefore, efforts to prevent AF are vital. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is associated with many of these conditions, as well as AF. In this analysis of 5445 participants in the Cardiovascular Health Study, elevated NT-proBNP levels were found to be highly associated with prevalent AF (hazard ratio of 147 for the highest quintile compared with the lowest after adjustment for associated risk factors). Over the median follow-up period of 10 years, there were 1126 incident cases of AF. Elevated levels of NT-proBNP were robustly predictive of the development of AF; the hazard ratio for the highest quintile was 4 compared with the lowest, after adjustment for a comprehensive number of clinical and echocardiographic covariates. Elevated levels of NT-proBNP were by far the most powerful predictor of incident AF. These findings suggest that NT-proBNP might be useful in identifying patients at risk for AF many years before its occurrence. This provides a way to target future therapeutic research aimed at preventing AF to a group at particularly high risk. In the future, this simple test might allow an early initiation of therapies designed to prevent the development of AF. In addition, these findings offer insight into the pathophysiology underlying AF.
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