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N-terminal pro-B-type Natriuretic Peptide is a Major Predictor of the Development of Atrial Fibrillation: The Cardiovascular Health Study

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Abstract

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

Methods and Results—The relation between N-terminal pro-B-type natriuretic peptide (NT-proBNP) and AF was studied in 5,445 Cardiovascular Health Study participants, using 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%CI 17.9, 913.3, $p< 0.001$); and adjusted prevalence ratio of 147 for the highest quintile (95% CI 20.4, 1064.3, $p<0.001$) compared to the lowest. After a median follow up of 10 years (maximum of 16 years), there were 1,126 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% CI 4.3, 6.4, $p < 0.001$) for the development of AF for the highest quintile compared to 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,

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sex, medication use, blood pressure, echocardiographic parameters, diabetes, and heart failure; with an adjusted hazard ratio of 4.0 (CI 3.2, 5.0, p< 0.001).

Conclusions—In a community based population of older adults, NT-pro BNP was a remarkable predictor of incident AF, independent of any other previously described risk factor.

Keywords

B-type natriuretic peptide; atrial fibrillation; BNP; NT-proBNP

Introduction

Atrial fibrillation is the most common sustained arrhythmia. It is associated with increased mortality[1, 2] and is a major risk factor for cardiovascular morbidity, including heart failure and stroke[3]. The clinical presentation of atrial fibrillation is heterogeneous, and it is often associated with structural heart disease. Since atrial fibrillation is known to lead to electrical and mechanical remodeling, differentiating factors predisposing to atrial fibrillation from the pathology created by the arrhythmia itself is difficult. Identification of markers that predate the development of atrial fibrillation 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 is a regulator of cardiovascular function[4]. B-type natriuretic peptide 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 B-type natriuretic peptide and the amino terminal N-terminal pro-B-type natriuretic peptide (NT-proBNP), both of which circulate in the plasma[4]. Although most widely used as a marker of heart failure, elevated B-type natriuretic peptide levels have been reported in patients with atrial fibrillation, even in the absence of heart failure or other cardiac pathology [5–7]. Furthermore, in a population based study from Framingham, a single determination of elevated B-type natriuretic peptide was found to be predictive of the future development of atrial fibrillation, cardiovascular outcomes, and death[8]. However, only 68 of 3260 subjects developed atrial fibrillation 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.

To address the potential value of NT-proBNP as an early marker of the development of atrial fibrillation, we examined the association between baseline NT-proBNP levels and prevalent and incident atrial fibrillation 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[9]. In brief, CHS is a longitudinal study of 5,888 men and women aged 65 and older, randomly selected from 4 communities in the United States and enrolled during two time periods; 1989–1990 for the

'original' cohort (N=5201) and 1992–1993 for the 'minority' cohort (N=687, African-Americans). 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, 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-zerosphygmomanometer[10]. Other evaluation included a resting 12-lead electrocardiogram (ECG) and an echocardiogram which 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[11]. Laboratory examinations included measurement of total cholesterol, high density lipoprotein, cholesterol, fasting glucose, C-reactive protein, and serum creatinine[12]. 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 electrocardiogram was obtained yearly through the 9th 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[13]. The maximum follow-up was 16 years (median 10 years).

NT-proBNP levels were determined in 5,447 participants. From the original cohort of 5,201 subjects, 3,979 participants had NT-proBNP measured at baseline, and 832 had a NT-proBNP measurement at year 3 only, for a total of 4,811. From the 687 participants in the minority cohort, 545 had NT-proBNP measured at baseline and 91 at year 2 only, for a total of 636. Two subjects were excluded because no baseline electrocardiogram was available. Participants were excluded from the incidence analysis if, at baseline or at an exam prior to the NT-proBNP measurement, atrial fibrillation was present (n=177), or if the participant had a self report of atrial fibrillation and was taking medications for atrial fibrillation (n=193), or if the participant had a pacemaker (n=67). Thus the analyses for incident atrial fibrillation included a total of 5,021participants.

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 CLIA certified laboratory accredited by the College of American Pathologists. Measurement of NT-proBNP was performed using an FDA approved commercially available immuno-assay from Roche Diagnostics Corporation (Roche Diagnostics Elescys® proBNP Assay, Indianapolis, Indiana) 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 atrial fibrillation

For the analyses of prevalent atrial fibrillation, only atrial fibrillation present on ECG at the exam at which NT-proBNP was measured was included as a prevalent case. Incident cases of atrial fibrillation were identified by two methods. Annual study electrocardiograms were interpreted by the CHS centralized reading center and the diagnoses of atrial fibrillation or

flutter were verified[14]. When hospital discharge diagnosis ICD-9 code identified atrial fibrillation or flutter, atrial fibrillation 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 atrial fibrillation in CHS[14]; and a holter substudy identified that only 1 in 819 subjects (0.1%) had persistent or intermittent atrial fibrillation not identified by the above measures[15]).

Statistical analysis

NT-proBNP levels were analyzed both as a continuous variable, where the natural log of NT-proBNP was used, and as categorized into quintiles. In initial analyses we compared the prevalence of atrial fibrillation on ECG at baseline across quintiles of NT-proBNP levels. We used relative risk regression[16] to estimate the prevalence ratios for prevalent atrial fibrillation associated with the quintiles of NT-proBNP and for the log of NT-proBNP. Initially, the prevalence of atrial fibrillation was modeled as a function of NT-proBNP using a generalized linear model with log link and binomial error distribution. As 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 atrial fibrillation associated with baseline NT-proBNP, among the 5,021 subjects without atrial fibrillation at baseline. We present unadjusted Kaplan-Meier survival curves comparing cumulative risk of developing atrial fibrillation across quintiles of baseline NT-proBNP. We used covariate-adjusted Cox model regressions to estimate the hazard ratios of developing atrial fibrillation by quintile of baseline NT-proBNP among those with no atrial fibrillation at baseline and using the log of NT-proBNP as a continuous predictor. Failure time for the Cox models for those who developed atrial fibrillation was the earliest of: the date of first occurrence of atrial fibrillation on an electrocardiogram, or the date of the first hospitalization with an atrial fibrillation diagnosis code. For those who did not develop atrial fibrillation, 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, total cholesterol, high density lipoprotein, C-reactive protein, creatinine, systolic and diastolic blood pressure, history of stroke, history of coronary heart disease, and a history of heart failure. Stratified analyses were performed for age, race, baseline heart failure, hypertension, overweight or obesity (body mass index > 25), and gender.

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, E/A ratio, and end systolic stress were examined.

For NT-proBNP measures at exams other than the baseline exam, the covariate values were taken from the same exam if the variable was measured at that exam or from the nearest exam in time prior to the NT-proBNP determination if not available at that exam.

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

Results

The demographic and medical characteristics of the CHS participants according to atrial fibrillation status are compared in Table 1. Those with prevalent atrial fibrillation compared to those without prevalent or incident atrial fibrillation were older, more frequently male, Caucasian, diabetic, hypertensive, had a history of cardiovascular disease (stroke, coronary heart disease or heart failure), had elevated total cholesterol and lower HDL cholesterol, had higher CRP and creatinine levels, and 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 to those without prevalent or incident AF was much smaller. The use of HMG-CoA reductase inhibitors, and angiotensin converting enzyme inhibitors was infrequent in this the cohort at baseline.

NT-proBNP was strongly associated with the electrocardiographic diagnosis of atrial fibrillation 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, 1064.3, $p<0.001$) compared to the first quintile. Similarly, there was a highly statistically significant association of the log of NT-proBNP with prevalent atrial fibrillation (adjusted prevalence ratio for a 1 standard deviation unit change in log of N-terminal pro-B-type natriuretic peptide of 3.44 (95% CI 2.79, 4.24, $p<0.0001$). The strong gradation of prevalence is shown by the breakdown of the prevalence by quintiles of NT-proBNP, with only 1 participant with atrial fibrillation in the first quintile compared to 128 in the 5th quintile with an adjusted prevalence ratio of 147.3 (95% CI 20.4, 1064.3, $p<0.001$) for the 5th quintile compared to the first quintile. Because of the small number of events in the 1st quintile, the prevalence ratios have wide confidence intervals and thus are not estimated with precision and should be interpreted with caution; however, this not the case for log (NT-proBNP).

Among subjects without atrial fibrillation at baseline, 1,126 developed atrial fibrillation during the follow-up period. The incidence rate of atrial fibrillation per 100 person years of follow-up was 1.2 for participants in the lowest quintile, compared to 5.1 for participants in the highest quintile. By 16 years of follow-up, the estimated cumulative incidence of atrial fibrillation in the highest quintile was approximately 64% compared to 20% for those in the lowest quintile (Figure 1). The hazard ratio for incident atrial fibrillation 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, 6.4, $p<0.001$) compared to the lowest quintile. This association remained strong even after adjustment for an extensive number of covariates; the adjusted hazard ratio for the highest versus the lowest

quintile was 4.0 (95% CI 3.2, 5.0 p<0.001). Similar results were obtained for NT-proBNP as a continuous predictor.

Subgroup analyses of variables associated with increased NT-proBNP revealed the risk of developing AF associated with NT-proBNP decreased with age, although it remained substantial and statistically significant at all ages (Table 4). Also, the risk associated with NT-proBNP was somewhat higher in those with prevalent cardiovascular disease than those without; however, NT-proBNP remained a strong predictor in both groups. Other clinical variables previously associated with increased NT-proBNP did not affect the predictive value of NT-proBNP (Table 4).

Of all the echocardiographic variables assessed, only left atrial size and left ventricular posterior wall thickness were significant predictors of atrial fibrillation. The hazard ratio of log (NT-proBNP) in the model including the echocardiographic variables was 1.67 (95% CI 1.50, 1.85, p < 0.001), and without was 1.74 (95% CI 1.57, 1.93, p < 0.001). There was no interaction of these variables with NT-proBNP.

Discussion

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

Almost all of the subjects who were in atrial fibrillation 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 if NT-proBNP is elevated prior to the AF episode or is a consequence of the AF or some combination of both.

The analysis of incident atrial fibrillation revealed a linear risk gradient, with significantly increased risk in each quintile. The estimated cumulative incidence of atrial fibrillation 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 atrial fibrillation than any other clinical covariate, including age, gender, race, comorbidities previously associated with increased levels of BNP and all echocardiographic parameters.

These findings add substantially to our previous knowledge regarding the relation between increased level of NT-proBNP and atrial fibrillation. Although the Framingham Heart study also reported an increased risk of atrial fibrillation associated with higher baseline levels of BNP, these findings were based on only 68 atrial fibrillation events over five years of follow-up, and BNP levels were largely in the normal range[8]. Atrial fibrillation was newly diagnosed in 1,126 Cardiovascular Health Study subjects during the course of this study;

and we found a 50% increase in the risk of developing atrial fibrillation per standard deviation increase in log peptide value (SD=1.2 log(pg/dl) after adjustment for comorbid conditions.

The Cardiovascular Health Study is characterized by an older patient population, with a large number of cardiovascular events and a long follow-up period. The long follow-up is especially valuable given the uncertainty regarding delays in diagnosis: the fact that elevated baseline NT-proBNP levels predicted a diagnosis of atrial fibrillation even sixteen years later strongly suggests that peptide elevations precede the onset of the arrhythmia. The high hazard ratio of 4 is all the more remarkable given the age of the population, and the high frequency of atrial fibrillation. Furthermore, we may have underestimated the true relationship between NT-proBNP and atrial fibrillation since the onset of atrial fibrillation may have been before the hospitalization at which it was noted or before the formal diagnosis by ECG at the yearly examination. Also, we may have missed some cases of paroxysmal atrial fibrillation not noted on a hospital discharge or detected during the yearly exam. The potential of underestimating the predictive value is also true of those who died before atrial fibrillation diagnosis, especially given that elevated B-type natriuretic peptide levels have been associated with death,[8] which would also tend to cause an underestimate of the association.

The NT-proBNP assay could only be performed in subjects with available blood samples, a potential source of bias. However, the subjects in whom blood samples were missing were those who had sustained early cardiac events, which is likely to have resulted in bias toward the null. To assess for the possibility of this bias, age and gender (variables associated with atrial fibrillation where no data were missing) were used to predict atrial fibrillation in the entire cohort and compared to the results using the subset of subjects where NT-proBNP was measured. The results were similar, indicating that selection bias is unlikely.

Our findings contrast with the study of Rossi et. al., which found NT-proBNP levels were unrelated to the presence of atrial fibrillation, and were most strongly related to left ventricular function in a case/control study matched for baseline characteristics, including echocardiographic parameters, comorbid conditions, and medical therapy[6]. This difference may be explained by the presence of persistent atrial fibrillation in the study group, as compared to incident atrial fibrillation in our population, or the presence of significant structural heart disease in the study group. Elevated B-type natriuretic peptide values have often been reported to be associated with diagnosed atrial fibrillation, in the presence or absence of left ventricular dysfunction [17–19]. 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, activation of the sympathetic nervous system or indicative of concealed ventricular dysfunction. However, the underlying process is not well understood.

Plasma NT-proBNP peptide levels were noted to be elevated in our study before the onset of clinical disease, suggesting elevated NT-proBNP may be a marker of underlying disease predisposition, play an unknown role in pathogenesis, or may represent the presence of undiagnosed, paroxysmal atrial fibrillation. 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 electrophysiologic effects of B-type natriuretic peptide on cardiac myocytes, the conduction system, or ion channels. Atrial natriuretic peptide (ANP) 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 atrial fibrillation [20–22]. Infusion of ANP 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 ANP has recently been demonstrated to lead to atrial fibrillation in one family[24]. Given the sequence homology between atrial and B-type natriuretic peptides, it is possible that they may have similar electrophysiologic actions, although this hypothesis will require further experimental study.

The strengths of this study include the large sample size and high incidence of atrial fibrillation, with long-term follow-up. The mechanism underlying this association is unclear, given that the source of NT-proBNP is largely the ventricle, although two physiologic studies have demonstrated increased B-type natriuretic peptide production in the atria of subjects with atrial fibrillation [25, 26]. The strong associations of NT-proBNP with prevalent atrial fibrillation and with incident atrial fibrillation 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 atrial fibrillation, and future studies to elucidate this connection are clearly of interest.

We have shown elevated NT-proBNP is a marker of substantial risk for atrial fibrillation 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 atrial fibrillation. Further studies are needed to assess whether NT-proBNP is simply a marker of underlying atrial disease, or is more directly involved in pathogenesis.

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Atrial fibrillation (AF) is a ubiquitous cardiac arrhythmia and it is associated with significant morbidity, mortality and economic burden. In the United States, approximately 5% of the population is affected by age 65; 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 with 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 to 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 to 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 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.

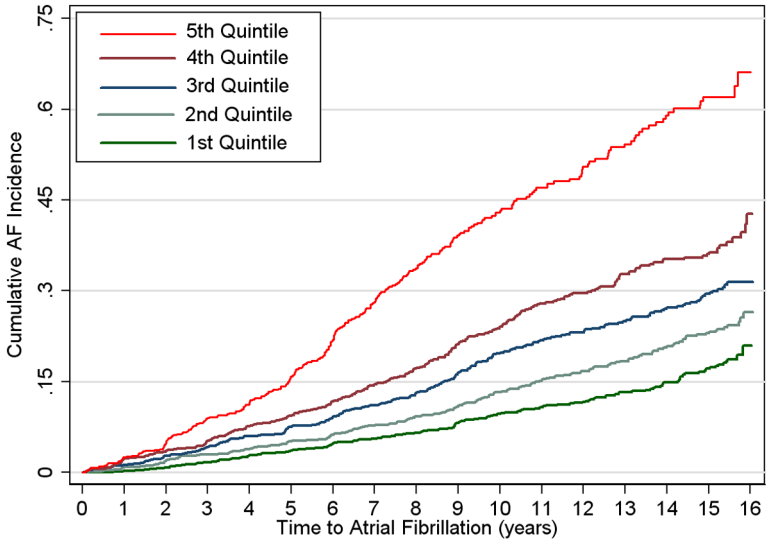

Figure 1.
Cumulative incidence of atrial fibrillation by quintile of NT-proBNP

Table I

Selected baseline characteristics of the CHS participants according to atrial fibrillation (AF) status (prevalent or incident)

Data presented in the table are mean and standard deviation for continuous variables, and number of cases with percentage in parenthesis for categorical variables.

				p-value	
	No Prevalent or Incident AF (n=3894)	**Prevalent AF (n=148)**	**Incident AF (n=1126)**	**Prevalent**	**Incident**
Age (y)	72.3 ± 5.4	75.2 ± 6.4	73.3 ± 5.5	< 0.001	< 0.001
Male	1502 (39)	87 (59)	516 (46)	< 0.001	< 0.001
African American	677 (17)	11 (7)	128 (11)	< 0.001	< 0.001
Body mass index (kg/m2)	26.6 ± 4.7	26.3 ± 4.8	27.0 ± 4.9	0.45	0.01
Standing height (cm)	164.1 ± 9.3	168.3 ± 10.6	165.9 ± 9.5	< 0.001	< 0.001
Current smoker	431 (11)	14 (9)	125 (11)	0.54	0.98
Diabetes	604 (16)	34 (23)	217 (19)	<0.05	<0.005
History of Stroke	139 (3.6)	18 (12.6)	47 (4.2)	<0.001	0.36
History of coronary heart disease	669 (17)	38 (26)	277 (25)	< 0.01	< 0.001
History of heart failure	125 (3.2)	35 (23.7)	64 (5.7)	< 0.001	< 0.001
Hypertension medication user	1752 (45)	102 (69)	579 (51)	< 0.001	< 0.001
Systolic blood pressure (mm Hg)	136.0 ± 21.4	136.9 ± 22.0	139.3 ± 22.6	0.62	<0.001
Diastolic blood pressure (mm Hg)	71.0 ± 11.1	71.8 ± 12.7	70.8 ± 11.3	0.42	0.46
Total cholesterol (mg/dl)	213.1 ± 38.8	189.6 ± 39.2	208.2 ± 37.0	< 0.001	<0.001
HDL cholesterol (mg/dl)	54.6 ± 15.7	49.6 ± 14.0	53.4 ± 15.2	< 0.001	< 0.05
C-reactive protein (mg/l)	3.41 ± 5.56	5.68 ± 11.76	3.93 ± 6.78	< 0.001	<0.05
Creatinine (mg/dl)	1.04 ± 0.37	1.12 ± 0.31	1.07 ± 0.43	< 0.01	< 0.05
Ace inhibitors	283 (7)	17 (11)	107 (7)	0.06	<0.05
HMG COA reductace inhibitors	89 (2)	3(2)	24(2)	0.83	0.75
Glucose (mg/dl)	109.9 ± 35.9	119.8 ± 46.0	113.8 ± 42.0	<0.005	<0.005
Left atrial size (cm)	3.82 ± 0.63	4.82 ± 0.98	3.97 ± 0.68	< 0.001	< 0.001
Natural log of NT-proBNP	4.63 ± 1.13	6.77 ± 1.01	5.05 ± 1.10	< 0.001	< 0.001

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Table 2

Relative Risk regression results for the association of baseline NT-proBNP with prevalent atrial fibrillation* at baseline.

				Unadjusted			Adjusted †		
Quintile of NT-proBNP	**Quintile range ‡**	**Number of Participants**	**Prevalent AF, N (%)**	**Prevalence Ratio**	**95% Confidence Interval**	**p-value**	**Prevalence Ratio**	**95% Confidence Interval**	**p-value**
1	5.00–50.81	1088	1 (0.10)	1.0			1.0		
2	50.82–91.78	1090	3 (0.28)	3.0	(0.3,28.7)		3.3	(0.3,31.5)	
3	91.79–156.09	1089	7 (0.64)	7.0	(0.9,56.8)		7.9	(1.0,64.6)	0.05
4	156.1–290.3	1089	9 (0.83)	9.5	(1.1,70.1)	<0.05	9.7	(1.2,78.4)	<0.05
5	>290.3	1089	128 (11.75)	127.9	(17.9,913.3)	<0.001	147.3	(20.4,1064.3)	<0.001
	log (NT-proBNP) in standard deviation units			2.12	(1.93,2.31)	<0.001	3.44	(2.79,4.24)	<0.001

* Includes all participants with a measured NT-proBNP and an electrocardiogram at the exam when NT-proBNP was measured (N=5,445)

† Adjusted for age, sex, race, body mass index, height, current smoking, hypertension medication use, diabetes, total cholesterol, HDL, CRP, creatinine, systolic and diastolic blood pressure, history of stroke, history of coronary heart disease and history of congestive heart failure.

‡ pg/dl

Table 3

Cox proportional hazards regression results for NT-proBNP as a predictor of incident atrial fibrillation*

			Unadjusted			Adjusted †		
Quintile of NT-proBNP	**Quintile range ‡**	**Number with incident AF (rate per 100 person years)**	**Hazard Ratio**	**95% Confidence Interval**	**p-value**	**Hazard Ratio**	**95% Confidence Interval**	**p-value**
1	5.00–50.81	146 (1.2)	1.0			1.0		
2	50.82–91.78	191 (1.6)	1.4	(1.1,1.7)	<0.005	1.4	(1.1,1.8)	<0.005
3	91.79–156.09	233 (2.2)	1.9	(1.6,2.4)	<0.001	1.8	(1.5,2.3)	<0.001
4	156.1–298.3	273 (2.8)	2.6	(2.1,3.1)	<0.001	2.4	(1.9,3.0)	<0.001
5	>290.3	283 (5.1)	5.2	(4.3,6.4)	<0.001	4.0	(3.2,5.0)	<0.001
	log (NT-proBNP) in standard deviation units		1.88	(1.59,1.78)	<0.001	1.66	(1.75,2.01)	<0.001

*Includes 5021 participants with no history of atrial fibrillation prior to or at the exam at which NT-proBNP was measured.

†Adjusted for age, sex, race, body mass index, height, current smoking, hypertension medication use, diabetes, total cholesterol, HDL, CRP, creatinine, systolic and diastolic blood pressure, history of stroke, history of coronary heart disease and history of congestive heart failure.

‡pg/dl

Table 4

Subgroup analyses of the association of BNP to AF risk adjusted for age, gender and race

Subgroup	Hazard Ratio per standard deviation of log(BNP)	95% Confidence Interval	p-value	Interaction p-value
Age				<0.01*
65–69	1.93	1.69–2.21	<0.00001	
70–74	1.81	1.60–2.05	<0.00001	
75–79	1.75	1.51–2.02	<0.00001	
80–84	1.61	1.31–1.97	<0.0001	
85–100	1.55	1.07–2.25	<0.05	
Gender				n.s.
Female	1.88	1.70–2.08	<0.00001	
Male	1.66	1.51–1.83	<0.00001	
African-American				n.s.
No	1.77	1.64–1.91	<0.00001	
Yes	1.75	1.46–2.10	<0.00001	
Prevalent CVD				<0.01
No	1.53	1.35–1.74	<0.00001	
Yes	1.80	1.65–1.97	<0.00001	
Hypertension				n.s.
No	1.73	1.56–1.92	<0.00001	
Yes	1.75	1.59–1.94	<0.00001	
Overweight or obese (BMI>25)				n.s.
No	1.73	1.54–1.95	<0.00001	
Yes	1.83	1.67–2.01	<0.00001	
Left Atrial Dimension †				n.s.
1st Quintile	1.64	1.36–1.99	<0.00001	
2nd Quintile	1.96	1.62–2.38	<0.00001	
3rd Quintile	1.59	1.33–1.89	<0.00001	
4th Quintile	1.91	1.62–2.26	<0.00001	
5th Quintile	1.61	1.40–1.85	<0.00001	

* Test for linear trend with age as a continuous variable

† Left Atrial Dimension was only available for the original cohort participants with a NT-BNP measurement at baseline because the echocardiogram was performed two years after enrollment of the minority cohort.