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Association of N-terminal pro B-type natriuretic peptide (NT-proBNP) change with the risk of atrial fibrillation in the ARIC cohort

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Abstract

Background—Circulating N-terminal pro B-type natriuretic peptide (NT-proBNP) predicts incidence of atrial fibrillation (AF), but the association of longitudinal changes in NT-proBNP concentrations with incident AF has not been explored.

Methods—We studied 9,705 individuals without prevalent AF in 1996–1998 and with available NT-proBNP measurements obtained in samples collected during two visits in 1990–1992 (visit 2) and 1996–1998 (visit 4) in the Atherosclerosis Risk in Communities (ARIC) Study. Participants were followed through the end of 2013. AF was ascertained from electrocardiograms, hospital discharge codes, and death certificates. Multivariable Cox regression was used to evaluate the association of absolute change in log-transformed NT-proBNP [ln(NT-proBNP)] with incident AF.

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We also assessed the impact of adding ln(NT-proBNP) change as a predictor of AF by difference in the C-statistic and net reclassification improvement (NRI).

Results—Over a median follow up of 16 years, there were 1,503 incident cases of AF. The means (SD) ln(NT-proBNP) at visit 2 and visit 4 were 3.83 (1.01) and 4.35 (0.94), respectively. There was a 0.52 (0.79) increase in ln(NT-proBNP) over the 6-year period. Greater increases in ln(NT-proBNP) were associated with higher risk of AF [hazard ratio, 2.82 (95% confidence interval 2.34, 3.39), comparing top to bottom quintiles, and 1.74 (1.61, 1.87) per 1-unit increase in ln(NT-proBNP)]. Adding ln(NT-proBNP) change to a model with multiple predictors including baseline NT-proBNP had relatively limited impact in the C-statistic (increase from 0.748, 95%CI 0.736–0.761, to 0.762, 95%CI 0.750, 0.774). Adding ln(NT-proBNP) change to initial predictive models resulted in a categorical NRI of 0.062 (95% CI 0.033, 0.092) and a continuous NRI of 0.092 (95%CI, 0.017, 0.182).

Conclusion—Positive NT-proBNP change is associated with an increased incidence rate of AF. Adding NT-proBNP change into the prediction model modestly improved incident AF prediction. Future studies should assess the value of monitoring NT-proBNP concentration among individuals at high risk of developing AF.

Introduction

Atrial fibrillation (AF) is a common chronic cardiac arrhythmia responsible for increased cardiovascular and cerebrovascular morbidity and mortality. It is associated with a 5-fold increase in the risk of ischemic stroke, accounting for approximately 15% of all strokes nationally.[1] In the United States, the prevalence of AF, which rises exponentially with age, is likely to increase 2.5-fold during the next 50 years. AF is commonly asymptomatic and paroxysmal, likely resulting in an underestimate of its prevalence, and reducing opportunities for the prevention of AF-related complications, such as stroke.[2] To address this concern, risk scores for predicting AF have been developed, with the hope that they can contribute to identifying high-risk individuals that may benefit from AF screening.[3–5]

Biomarkers can potentially be used, in addition to established clinical AF risk factors, to characterize the risk of developing AF. N-terminal pro B-type natriuretic peptide (NT-proBNP) is an established biomarker of volume overload and myocardial stretch. NT-proBNP plays an important role in cardiovascular remodeling, volume homeostasis and response to ischemia.[6, 7] Prior studies have described the association between circulating NT-proBNP and the risk of developing AF, and provided evidence of the value of NT-proBNP measurements to predict AF. We have demonstrated previously in several prospective cohorts that circulating NT-proBNP concentration improved the ability to predict AF beyond information provided by clinical factors.[8, 9]

To our knowledge, prior studies have not specifically assessed whether changes in circulating NT-proBNP over time are associated with the risk of AF. Therefore, taking advantage of two repeated measurements of circulating NT-proBNP obtained approximately six years apart in the Atherosclerosis Risk in Communities (ARIC) Study, we sought to evaluate the association of change of circulating NT-proBNP concentrations with incident AF and the value of NT-proBNP changes in the prediction of AF in this population. We

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hypothesized that an increase in circulating NT-proBNP concentration would be associated with and would predict higher risk of AF beyond information traditional risk factors and single NT-proBNP measurements.

Methods

Study Population

The ARIC Study is a prospective epidemiologic study conducted in four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; selected Minneapolis Suburbs, Minnesota; and Washington County, Maryland. It aims at identifying the risk factors and investigating the etiology and natural history for cardiovascular diseases. Our data comes from the Cohort Component of ARIC, which began in 1987. Each ARIC field center randomly selected and recruited a cohort sample of approximately 4,000 individuals aged 45–64 from a defined population in their community. In total, 15,792 individuals (55% women, 27% blacks) participated and completed an extensive baseline examination. These participants had clinic visits at 3-year intervals through 1998, with the first exam (baseline, visit 1) occurring in 1987–89, the second (visit 2) in 1990–92, the third (visit 3) in 1993–95, and the fourth (visit 4) in 1996–98. Surviving participants underwent a fifth exam (visit 5) in 2011–13. A detailed description of the design and objectives of the ARIC cohort study has been published.[10] For this analysis, of the 15,792 participants, we included those who came to both visit 2 and visit 4, and had available circulating NT-proBNP concentrations at both visits (N=10,558). Of these, we excluded participants who had developed AF by visit 4 (N=237) or had missing information on AF incidence (N=346), as well as non-whites from the Minneapolis and Washington county field center and individuals other than white or African American in the Forsyth county field center (N=69). We also excluded participants who had missing values in any of the covariates (N=201), leaving a study sample of 9,705 individuals (Figure 1). The ARIC study has been approved by Institutional Review Boards at the participant institutions. Study participants provided written informed consent at baseline and each following visit.

Assessment of NT-proBNP

Assays of NT-proBNP were conducted at the University of Minnesota using stored serum from visit 2 in 2011–2013, and at Baylor College of Medicine using stored plasma from visit 4 in 2010. Samples were collected and then stored at −70°C until laboratory analysis. NT-proBNP was measured in visit 2 samples with a Roche sandwich immunoassay in a Roche Elecsys 2010 analyzer, while a Roche ECLIA for proBNP II assay in a Cobas e411 analyzer was used for visit 4 samples. Based on a recalibration study in ARIC, NT-proBNP showed excellent correlation between the visit 2 and visit 4 measurements, but a systematic bias was present. Specifically, serum values of NT-proBNP at visit 4 were on average 9 pg/mL higher than visit 4 plasma values.[11] Therefore, to align the measurements in visit 2 serum and visit 4 plasma samples, we added 9 pg/mL to the visit 4 plasma measurements.

Determination of incident AF

We used three methods to determine AF cases in the ARIC cohort. First, 12-lead electrocardiograms (ECGs) were obtained during study exams, and data were transmitted

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electronically to the ARIC ECG reading center at EPICARE (Wake Forest School of Medicine, Winston-Salem, NC), using the GE Marquette 12-SL program (GE Marquette, Milwaukee, WI) for processing. A computer algorithm identified the presence of AF or atrial flutter in the ECG. A cardiologist would confirm the computer diagnosis and overread any rhythm disorder other than AF in electrocardiograms to reduce the possibility of missed or misreading episodes of AF. Second, trained abstractors collected information from participants' hospitalization identified by follow-up phone calls and surveillance of local hospitals, including all discharge codes. If the ICD-9-CM codes 427.31 (AF) or 427.32 (atrial flutter) were listed in any given hospitalization, then AF was deemed as present. We excluded AF cases related to open cardiac surgery. Last, AF was identified from death certificates if ICD-9 427.3 or ICD-10 I48 were listed as any reason of death. A detailed description and validity of this approach has been previously published.[12]

Ascertainment of other covariates

We considered as covariates the following variables, which were measured both in visit 2 and visit 4: sex, age, race, study center, height, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking status, alcohol drinking status, diabetes history, heart failure history (HF), myocardial infarction history (MI), use of antihypertensive medications, use of aspirin medications, use of statin medications, and ECG p wave terminal force in V1. At visit 2, SBP and DBP were measured 3 times respectively and the mean of the last 2 measurements was used for our analysis. At visit 4, SBP and DBP were measured twice and the average of those two measurements was used. Diagnosis of diabetes was defined as fasting blood glucose ≥126mg/dl, non-fasting blood glucose >200 mg/dL, use of antidiabetic medication, or a self-reported physician diagnosis of diabetes. Sex, race, age, smoking and alcohol information, and use of medications were self-reported. HF was defined based on the Gothenburg criteria at visit 1 and from HF-related hospitalizations during follow-up.[13] MI was defined based on baseline self-reported physician diagnosis of MI or ECG evidence of old MI and adjudicated events during the follow-up.[14]

Statistical Analysis

Plasma NT-proBNP concentrations were natural logarithm-transformed (ln-transformed) and analyzed both as a continuous variable and as categorized into quintiles. The main independent variable was the difference between ln-transformed NT-proBNP levels of visit 2 and visit 4, which corresponds to the logarithm of the ratio $[\ \ln(\frac{NT-proBNP4}{NT-proBNP2})]$. A one unit difference in this variable corresponds to a relative increment of approximately 2.72 (e) times in NT-proBNP between the two visits. After exploring the distribution of this independent variable, we winsorized outliers that were below the 1st or above the 99th percentiles, equal to $\ln(\frac{NT-proBNP4}{NT-proBNP2}) < -1.3005$ and $\ln(\frac{NT-proBNP4}{NT-proBNP2}) > 3.0214$ respectively (N=196), to avoid undue influence of extreme values. We used Cox proportional hazards regression to calculate hazard ratios of developing AF and their 95% confidence intervals by change of NT-proBNP and ln-transformed NT-proBNP concentrations among those without AF at start of follow-up (defined as the date of visit 4 for this analysis). In addition to categorizing NT-proBNP change in quintiles, we also dichotomized participants at each visit

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as low or high NT-proBNP using 100 pg/mL as cutoff point, and explored the association of change in this category with AF incidence. To explore whether the association of change in NT-proBNP with AF incidence varied across baseline levels of NT-proBNP, we conducted additional analyses across quartiles of NT-proBNP at visit 2. The time of follow-up was defined as days from visit 4 to AF incidence, death, lost to follow up, or December 31, 2013 whichever occurred earlier. We used the following three models with incremental adjustments to analyze the association of NT-proBNP change and atrial fibrillation: (1) Model 1: adjustment for age, sex, race, ARIC study center and ln-transformed visit 2 NT-proBNP level; (2) Model 2: Model 1 + clinical variables (BMI, height, SBP, DBP, ECG p wave terminal force 1 in V1, HF history before visit 4, MI history and diabetes history); and (3) Model 3: Model 2 + lifestyles variables (smoking status, alcohol-using status, use of antihypertensive medications, aspirin and statin medications).

We conducted two secondary analysis. First, we excluded participants with prevalent HF at visit 4 to evaluate NT-proBNP changes outside the context of clinical HF. Second, we used inverse probability weighting to adjust for losses to follow-up between visits 2 and 4.[15] Specifically, we ran weighted Cox models using a robust variance estimator, with the weights calculated as the inverse of the probability of participating in visit 4 conditional on visit 2 participation and given visit 2 covariates (sex, race, age, age^2, diabetes, BMI, BMI^2, smoking status, drinker status, use of antihypertensive medications, height, prevalent heart failure, systolic blood pressure, diastolic blood pressure, NT-proBNP, NT-proBNP^2, and NT-proBNP^3). Weights were calculated from logistic models and stabilized using the probability of visit 4 participation given race, sex, age, and age^2 as the numerator.

In a second set of analyses, we evaluated the impact that information on NT-proBNP change had in models for the prediction of AF including clinical variables and baseline measures of NT-proBNP. For these models, the time horizon of prediction was 10 years. Model discrimination was assessed with a C-statistic test for survival analysis, while model calibration was evaluated with a modified Hosmer-Lemeshow χ^2 statistic.[16, 17] We calculated the difference in the C-statistic between models before and after adding difference in ln-transformed NT-proBNP change to the predictive ability of adding it and tested the statistical significance of the difference using the method proposed by DeLong et al.[18] We also computed the categorical net reclassification improvement (NRI) and continuous NRI as an alternative approach to assess improvement in prediction.[19] For this analysis, we used the following 10-year risk categories <5%, 5–10%, >10% risk based on the cutoffs used in a previously published 5-year risk prediction model.[5]

Results

The demographic and clinical characteristics of 9,705 participants at both visit 2 and visit 4 are presented in table 1. Characteristics of participants who died between visit 2 and visit 4 (N= 433) and those who did not participate in visit 4 (N=2,556) are showed in the Supplemental Table 1. Overall, mean age at visit 4 was 63, with women accounting for 57%. African Americans made up 21% of the analyzed sample. The median (Q1, Q3) of the absolute change of NT-proBNP and the mean (SD) of ln-transformed NT-proBNP change between visit 2 and visit 4 were 21.8 (0.6, 59.5) and 0.52 (0.79), respectively.

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Visits 2 and 4 characteristics according to the quintile of the ln-transformed NT-proBNP concentration between visit 2 and visit 4 can be found in Table 2. Increasing values of NT-proBNP change were associated with male sex, higher SBP, and a higher prevalence of MI and use of antihypertensive medication. The quintile-specific means (SD) in ln-transformed NT-proBNP change between visit 2 and visit 4 ranged from −0.49 (0.33) in the bottom quintile to 1.71 (0.53) in the top one.

Association of NT-proBNP and ln-transformed NT-proBNP change with AF

During a mean follow-up of 14 years, we identified 1,503 cases of newly-diagnosed AF. NT-proBNP concentration change was associated with the risk of AF (Table 3). The AF incidence rate in each quintile increased from 9 per 1,000 person-years in Q1 and Q2, to 15 per 1,000 person-years in Q5. There was evidence of dose-response in all three models. In model 1, 2 and 3, the HRs for atrial fibrillation in the highest quintile was 3.34 (95% CI, 2.80, 3.99), 3.02 (95% CI, 2.51, 3.63) and 2.82 (95%CI, 2.34, 3.39), respectively, compared to the lowest quintile. Similar associations were found when ln-transformed NT-proBNP change was modeled as a continuous variable. Hazard ratios and 95% CIs associated with one unit increase in the difference of ln-transformed NT-proBNP were 1.91 (95% CI, 1.77, 2.05), 1.81 (95% CI, 1.67, 1.95) and 1.74 (95% CI, 1.61, 1.87) in models 1, 2 and 3, respectively. As shown in Figure 2, the association between change in NT-proBNP and AF risk was approximately linear. The results were essentially unchanged when we restricted the analysis to participants without prevalent HF at visit 4 (n = 9,570, Supplemental Table 2) or when we adjusted for losses to follow-up between visits 2 and 4 using inverse probability weighting (Supplemental Table 3).

Increases in circulating NT-proBNP were related to higher risk of AF incidence (Table 4). Among those with NT-proBNP <100 pg/mL at visit 2, the AF incidence rate was 7 per 1000 person-years if NT-proBNP remained <100 pg/mL at visit 4, but 16 per 1000 person-years if NT-proBNP was ≥100 pg/mL at visit 4. The corresponding AF incidence rates among those with NT-proBNP 100 pg/mL or higher at visit 2 were 10 per 1000 person-years and 21 per 1000 person-years. Compared to the group with consistently low NT-proBNP (<100 pg/mL at visits 2 4), the HRs in the group with increased circulating NT-proBNP at visit 4 were 1.68 (1.47, 1.93) (model 3). Multivariable HR (95%CI) in the group with consistently high NT-proBNP 100 pg/mL or higher NT-proBNP was 1.70 (1.40, 2.06). AF incidence was similar among those who went from high to low NT-proBNP and those who remained at low concentrations in both visits. Dichotomizing NT-proBNP change as increased or decreased between both visits showed increased rates of AF among those with increasing versus those with decreasing concentrations those having HR 1.63 (95%CI 1.43, 1.87) (Table 4). In an additional analysis, the association of change in NT-proBNP with AF incidence was of similar magnitude across quartiles of visit 2 NT-proBNP, with HR (95%CI) for 1 unit difference in NT-proBNP change ranging between 1.86 (1.53, 2.27) for the bottom quartile to 1.63 (1.43, 1.85) for the top quartile (p for interaction 0.35, Supplemental Table 4).

Improvement of atrial fibrillation risk prediction with ln(NT-proBNP) change

The C-statistics of models without and with change in ln(NT-proBNP) and net reclassification improvement are presented in Table 5. Adding NT-proBNP change to the

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initial multivariable model modestly increased C-statistics: 0.031 in model 1, 0.018 in model 2 and 0.015 in model 3 (p-value for the improvement in C-statistic < 0.001 in all models). In a model including all covariates and NT-proBNP change, the C-statistic was 0.762 (95% CI, 0.750, 0.774). The user-defined NRI results from adding NT-proBNP change to initial predictive models were 0.133 (95%CI, 0.094, 0.170), 0.094 (95% CI, 0.060, 0.127) and 0.086 (95% CI 0.054, 0.116) in the three models respectively, while the continuous NRI after adding NT-proBNP change were 0.183 (95%CI, 0.103, 0.258), 0.157 (95%CI, 0.078, 0.230) and 0.114 (95%CI, 0.035, 0.190), respectively.

Discussion

Our study demonstrated that greater change in NT-proBNP concentrations over an approximately 6-year time period was associated with higher incidence of AF among ARIC cohort participants followed for 15 years. This association was independent of other risk factors for AF and present after adjustment for baseline NT-proBNP. Additionally, individuals with increasing NT-proBNP concentrations were at higher risk of AF incidence, compared to individuals with decreased NT-proBNP concentration. Also, our findings suggest that inclusion of change in circulating NT-proBNP into multivariable models marginally improved the ability to predict AF risk as measured by improvement in the C-statistic and measures of reclassification. The magnitude of this improvement is similar to that observed by adding genetic risk scores to the prediction of AF.[20]

Previous research has consistently reported associations of circulating NT-proBNP with AF incidence. In the Cardiovascular Health Study (CHS), a community-based population of older adults, NT-proBNP was identified as a remarkably strong predictor of both prevalent and incident AF independent of other known risk factors for AF.[21] Similarly, in the Multi-Ethic Study of Atherosclerosis (MESA), investigators found that circulating NT-proBNP was a robust predictor of incident AF, with differences in the prognosis and predictive value of this biomarker across age and racial/ethnic groups.[22] Using a multimarker approach, NT-proBNP showed powerful prediction in two cohorts, when adjusting for other four biomarkers and cardiovascular risk factors, such as gender and smoking status.[23] Moreover, in the MESA and ARIC cohorts, we have previously demonstrated that NT-proBNP is an independent predictor of 5-year AF risk beyond clinical variables.[8, 9] Notably, despite that important risk factors for AF, such as hypertension and prior history of cardiovascular disease,[24] could affect circulating NT-proBNP, all prior studies were able to adjust for these variables, supporting an independent association of this biomarker with AF risk.

To our knowledge, however, little is known regarding the association of change in circulating NT-proBNP with AF risk. Investigators from the Heart and Soul Study have reported that among patients with stable CVD, an increase of NT-proBNP was an independent predictor of subsequent HF and CV death over a long period of time.[25] These previous results are consistent with our findings, given the known association between HF and AF, through common risk factors and as causes of each other.[26, 27] Though not directly relevant, repeated measurements of NT-proBNP might provide predictive information on the risk of cardiovascular mortality among persons with AF.[28]

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The pathophysiologic mechanisms linking circulating NT-proBNP and AF incidence are not completely elucidated. NT-proBNP is secreted by both atria and ventricles and released into plasma due to increases in cardiac wall tension. NT-proBNP concentrations are usually elevated in patients with asymptomatic or symptomatic left ventricular and atrial dysfunction, and in patients with overt heart failure.[29] In addition, patients with right heart failure or pulmonary hypertension also have higher concentrations of NT-proBNP.[30, 31] In patients with heart failure, AF is a common finding. These findings suggest that increased NT-proBNP level might predict AF as a marker of asymptomatic heart failure first. In addition, elevations of NT-proBNP can also reflect renal dysfunction, which has been associated with AF,[32] or even the presence of asymptomatic AF.[33]

From a clinical perspective, our study suggests that individuals with increasing concentrations of NT-proBNP might benefit from screening for AF, such a routine ECG assessment or ambulatory ECG monitoring. Furthermore, in patients with heart failure, monitoring NT-proBNP might be useful for identifying those who have high risk of developing AF. In a public health context, the steadily increasing incidence and prevalence of AF underline the urgent need for primary prevention strategies against AF, such as predicting AF.[34] Individuals considered to be at higher risk of AF might be monitored more closely.

Our findings also highlight the importance of considering the dynamic nature of risk for the purpose of prediction. Recent studies in patients with AF demonstrate the value of incorporating changes in risk factors to established risk score for the prediction of stroke and bleeding. In large population-based databases in East Asia, changes in CHA2DS2-VASc and HAS-BLED, commonly used for prediction of stroke and bleeding among patients with AF, were better than single assessments at predicting these adverse endpoints.[35–37] Future work is needed to determine the optimal and most user-friendly approach to incorporate changes in biomarkers, as well as other risk factors, to established models for the prediction of AF, such as the CHARGE-AF score.[5]

Strengths and limitations

Our study has several strengths. First, the ARIC study includes a large and diverse population. Second, we were able to take advantage of repeated NT-proBNP measurements in samples obtained several years apart. Third, our study had extensive information on other biomarkers and clinical variables that allow adequate adjustments. Our study, however, also has important limitations. First, the study sample was limited to whites and African American from four communities in the United States, which may limit generalizability of our findings to other populations. Second, we were not able to differentiate between diverse patterns of AF, such as paroxysmal AF, persistent AF, or permanent AF, and between AF and atrial flutter. Third, our approach for AF ascertainment probably led to missing asymptomatic cases as well as those managed exclusively in the outpatient setting. Finally, being an observational study, we always have to recognize the potential for residual, uncontrolled confounding that may partly explain the associations.

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Conclusion

In conclusion, we have shown that increases in circulating NT-proBNP concentration is a strong predictor of future AF incidence in a community-based population. This prediction remains significant after adjusting for other known risk factors of AF. Adding the change of NT-proBNP to the prediction model offers modest improvement to our ability to identify individuals at higher risk of AF. Further studies of how NT-proBNP changes are involved in AF pathogenesis are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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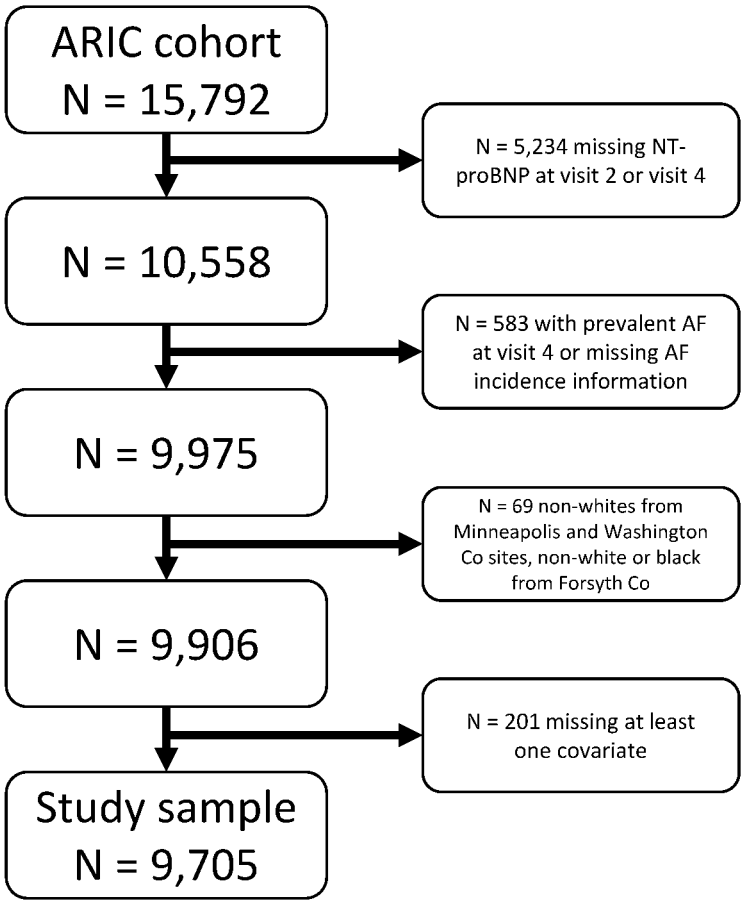

Figure 1.
Study sample inclusion flowchart

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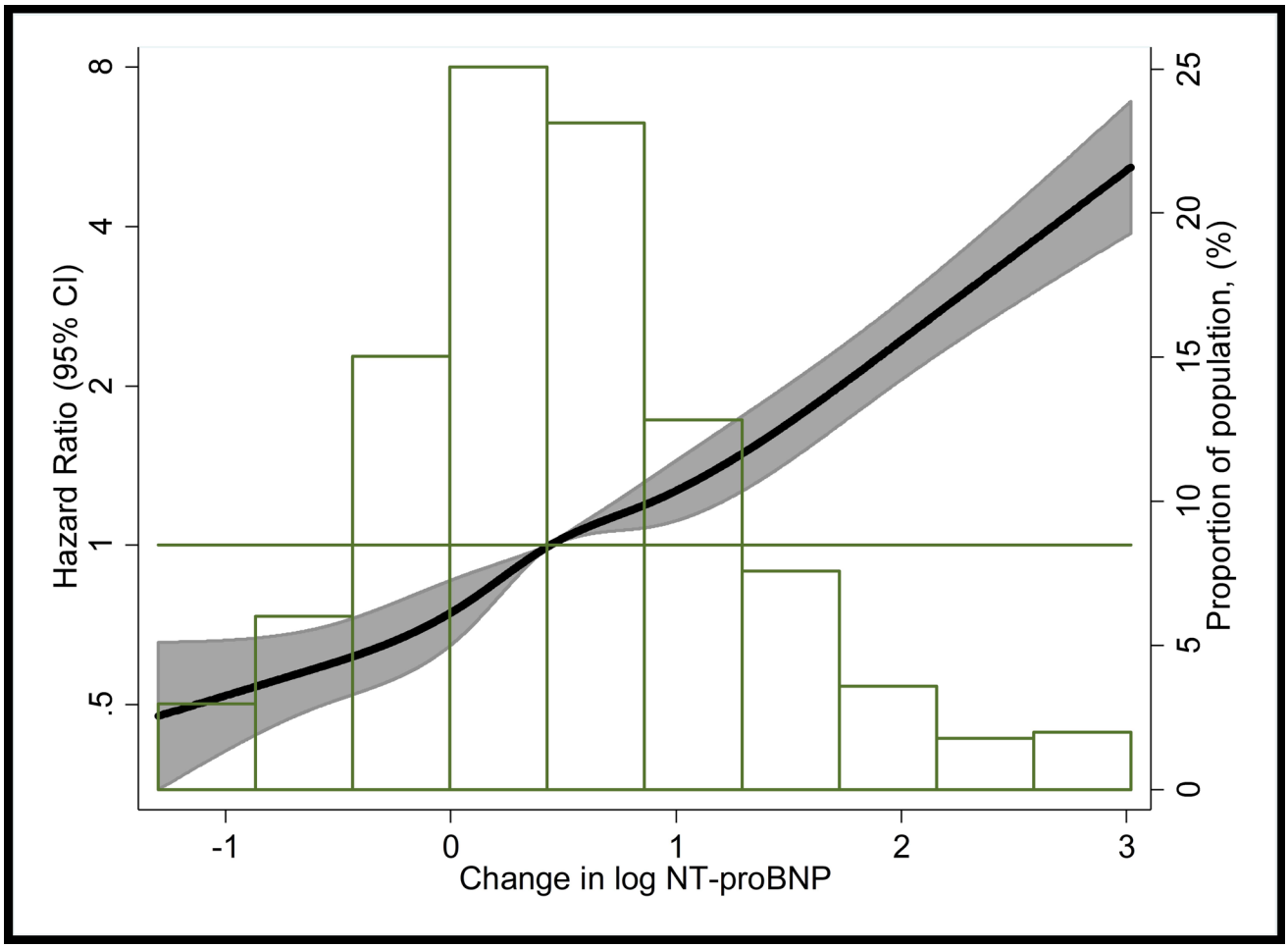

Figure 2.

Association of change in log NT-proBNP with incidence of atrial fibrillation presented as hazard ratio (solid line) and 95% confidence intervals (shaded area). The histogram represents the distribution of log NT-proBNP change in the study sample. Results from Cox proportional hazards model with change in log NT-proBNP modeled using a restricted cubic spline (knots at 5th, 27.5th, 50th, 72.5th, and 95th percentiles), adjusted for age, sex, race, ARIC study center, ln-transformed visit 2 NT-proBNP, BMI, height, SBP, DBP, ECG p wave terminal force in V1, HF history, MI history, diabetes history, smoking status, alcohol drinking status, use of antihypertensive medications, aspirin, and statin medications. ARIC 1996–2013

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Table 1.

Characteristics of study participants at Visit 2 (1990-1992) and Visit 4 (1996-1998), ARIC study

	Visit 2	Visit 4
Age, years	56.6 (5.6)	62.7 (5.6)
Sex, women	5,550 (57)	
Race, African American	2,048 (21)	
Height, cm		
Men	176 (7)	
Women	162 (6)	
Body mass index, kg/m^2		
Men	27.7 (4.1)	28.4 (4.5)
Women	28.0 (5.9)	29.0 (6.2)
Systolic blood pressure, mmHg	120 (18)	127 (19)
Diastolic blood pressure, mmHg	72 (10)	71 (10)
ECG p wave terminal force in V1, μV*ms	−1,979 (1,897)	−2,533 (2,211)
Smoking Status		
Current smoker	1,887 (19)	1,414 (15)
Former smoker	3,700 (38)	4,203 (43)
Never smoker	4,118 (42)	4,088 (42)
Drinking Status		
Current drinker	5,701 (59)	4,874 (50)
Former drinker	1,853 (19)	2,822 (29)
Never drinker	2,151 (22)	2,009 (21)
Hypertension treatment	2,858 (29)	4,116 (42)
Aspirin use	NA	5,461 (56)
Statin use	NA	1,104 (11)
Diabetes	1,208 (12)	1,543 (16)
Myocardial infarction history	378 (3.9)	577 (6.0)
Heart Failure at/before visit 4		135 (1.4)
NT-proBNP		
Median (Q1, Q3), pg/mL	49.7 (26.5, 88.4)	75.6 (41.9, 136)
Ln, mean(SD)	3.83 (1.01)	4.35 (0.94)
Difference between visits 2 and 4		
Absolute, pg/mL [median (Q1, Q3)]	21.8 (0.6, 59.5)	
Relative (difference in ln(NT-proBNP)	0.52 (0.79)	

Notes: Data are shown as frequency (percentage) or mean (SD) for continuous variables of the sample, unless otherwise stated. NA: Not available

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Table 2.

Participants' characteristic at visit 4 according to the quintile of the change of log-transformed NT-proBNP between visit 2 and visit 4, ARIC Study

	Quintile of the change of log-transformed NT-proBNP between visit 2 and visit 4				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
	(<−0.09)	**(−0.09-<0.28)**	**(0.28-<0.61)**	**(0.61-<1.09)**	**(≥1.09)**
N	1941	1941	1941	1941	1941
Clinical variables					
Age, years	61.8 (5.5)	62.5 (5.6)	63.0 (5.6)	63.1 (5.7)	62.9 (5.7)
Sex, women	1251 (64)	1218 (63)	1144 (59)	1081 (56)	856 (44.1)
Race, African American	498 (26)	362 (19)	350 (18)	326 (17)	512 (26)
Height, cm					
Men	177 (7)	177 (7)	177 (7)	176 (7)	176 (6)
Women	162 (6)	162 (6)	162 (6)	162 (6)	163 (6)
Body mass index, kg/m^2					
Men	28.8 (4.7)	28.2 (4.4)	28.2 (4.4)	28.2 (4.5)	28.7 (4.4)
Women	29.5 (6.4)	28.4 (6.2)	28.4 (6.2)	29.1 (6.1)	30.1 (6.3)
Systolic blood pressure, mmHg	125 (18)	125 (18)	126 (18)	129 (20)	131 (20)
Diastolic blood pressure, mmHg	71 (10)	71 (10)	71 (10)	71 (11)	72 (11)
ECG p wave terminal force in V1, μV*ms	−2456 (2098)	−2307 (2013)	−2523 (2110)	−2550 (2240)	−2828 (2527)
Smoking Status					
Current smoker	284 (15)	281 (14)	280 (14)	262 (14)	307 (16)
Former smoker	802 (41)	805 (41)	795 (41)	869 (48)	932 (48)
Never smoker	855 (44)	855 (44)	866 (45)	810 (42)	702 (36)
Drinking Status					
Current drinker	945 (49)	997 (51)	990 (51)	991 (51)	951 (49)
Former drinker	555 (28)	540 (28)	560 (29)	560 (29)	607 (31)
Never drinker	441 (22)	404 (21)	391 (20)	390 (20)	383 (20)
Hypertension treatment	857 (44)	726 (37)	718 (37)	799 (41)	1016 (52)
Aspirin use	1075 (55)	1094 (56)	1079 (56)	1106 (57)	1107 (57)
Statin use	211 (11)	200 (10)	193 (10)	222 (11)	278 (14)
Diabetes	280 (14)	241 (12)	261 (13)	308 (16)	453 (23)
Myocardial infarction history	98 (5.1)	76 (3.9)	93 (4.8)	115 (5.9)	195 (10.0)
Heart Failure before visit 4	27 (1.4)	11 (0.6)	19 (1.0)	24 (1.2)	54 (2.8)
NT-proBNP change between visit 2 and 4					
Median (IQR), pg/mL	−24.0 (−48.0, −11.9)	5.5 (0.6, 13.1)	27.5 (16.4, 46.4)	53.1 (31.0, 92.8)	86.3 (39.6, 183)
Ln, mean(SD)	−0.49 (0.33)	0.10 (0.11)	0.44 (0.09)	0.82 (0.14)	1.71 (0.53)

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Table 3.

Atrial fibrillation incidence after visit 4 by quintile of change of log-transformed NT-proBNP between visit 2 and visit 4, ARIC study

	Quintile of the change of log-transformed NT-proBNP between visit 2 and visit 4						
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**Continuous****	**P-value*****
N. AF cases	250	246	304	337	366	–	
AF incidence rate*	9	9	11	13	15	–	
HR (95%CI)							
Model 1	1 (ref)	1.14(0.95, 1.36)	1.56 (1.31, 1.85)	1.93 (1.63, 2.29)	3.34 (2.80, 3.99)	1.91 (1.77, 2.05)	<0.0001
Model 2	1 (ref)	1.18 (0.98, 1.41)	1.56 (1.31, 1.86)	1.86 (1.56, 2.21)	3.02 (2.51, 3.63)	1.81 (1.67, 1.95)	<0.0001
Model 3	1 (ref)	1.18 (0.99, 1.41)	1.56 (1.31, 1.85)	1.83 (1.53, 2.17)	2.82 (2.34, 3.39)	1.74 (1.61, 1.87)	<0.0001

*Rate in events per 1,000 person-years.

**Per 1 unit difference in $\ln\left(\frac{NT-proBNP4}{NT-proBNP2}\right)$, which corresponds to a relative increment of approximately 2.72 (e) times in NT-proBNP between the two visits.

***P-value for continuous trend.

Model 1: Cox regression model adjusting for age, sex, race, ARIC study center and ln-transformed visit 2 NT-proBNP level;

Model 2: Model 1 + clinical variables (BMI, height, SBP, DBP, ECG p wave terminal force 1 in V1, HF history, MI history and diabetes history);

Model 3: Model 2 + lifestyles variables (smoking status, alcohol-using status, use of antihypertensive medications, aspirin and statin medications).

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Table 4.

Atrial fibrillation incidence after visit 4 by NT-proBNP concentration categories and change between visit 2 and visit 4, ARIC Study

visit 2 NT-proBNP level	**<100 pg/mL**		**≥100 pg/mL**			
visit 4 NT-proBNP level	**<100 pg/mL**	**≥100 pg/mL**	**<100 pg/mL**	**≥100 pg/mL**		
NT-proBNP change					**Decrease**	**Increase**
N	5672	2055	397	1581	2353	7352
AF cases	591	443	59	410	294	1209
AF incidence rate *	7	16	10	21	9	12
Hazard Ratio (95% CI)						
Model 1	1(ref)	1.90 (1.66, 2.17)	1.09 (0.81, 1.47)	1.89 (1.56, 2.29)	1(ref)	1.74 (1.52, 1.98)
Model 2	1(ref)	1.75 (1.53, 2.00)	1.00 (0.75, 1.35)	1.79 (1.47, 2.16)	1(ref)	1.65 (1.44, 1.90)
Model 3	1(ref)	1.68 (1.47, 1.93)	0.93 (0.69, 1.25)	1.70 (1.40, 2.06)	1(ref)	1.63 (1.43, 1.87)

* Rate in events per 1,000 person-years.

Model 1: Cox regression model adjusting for age, sex, race, ARIC study center and ln-transformed visit 2 NT-proBNP level;

Model 2: Model 1 + clinical variables (BMI, height, SBP, DBP, ECG p wave terminal force 1 in V1, HF history, MI history and diabetes history);

Model 3: Model 2 + lifestyles variables (smoking status, alcohol-using status, use of antihypertensive medications, aspirin and statin medications).

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Table 5.

Additional predictive ability of NT-proBNP change added to risk factors for AF, ARIC Study

C-Statistic	before	95%CI	after	95%CI	ΔC*	Categorical NRI (0.05,0.10)	95%CI	Continuous NRI	95%CI
Model 1	0.693	(0.679, 0.707)	0.724	(0.711, 0.737)	0.031	0.133	(0.094, 0.170)	0.183	(0.103, 0.258)
Model 2	0.737	(0.724, 0.749)	0.755	(0.743, 0.767)	0.018	0.094	(0.060, 0.127)	0.157	(0.078, 0.230)
Model 3	0.747	(0.734, 0.759)	0.762	(0.750, 0.774)	0.015	0.086	(0.054, 0.116)	0.114	(0.035, 0.190)

*P-value for the comparison of the C-statistic before and after inclusion of NT-proBNP change < 0.001 in all three models, using the approach by DeLong, et al.[18]

Model 1: adjusting for age, sex, race, ARIC study center and ln-transformed visit 2 NT-proBNP level;

Model 2: Model 1 + clinical variables (BMI, height, SBP, DBP, ECG p wave terminal force 1 in V1, HF history, MI history and diabetes history);

Model 3: Model 2 + lifestyles variables (smoking status, alcohol-using status, use of antihypertensive medications, aspirin and statin medications).

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