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High-Sensitivity Cardiac Troponin T and the Risk of Incident Atrial Fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Introduction—Structural changes in the heart are known risk factors for atrial fibrillation (AF). An association between cardiac troponin T (hs-cTnT), a marker of myocardial cell damage

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DISCLOSURES

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measured with a high sensitivity assay, and the risk of AF could have implications for AF risk stratification.

Objective—To estimate the association between hs-cTnT and the risk of incident AF in the Atherosclerosis Risk in Communities (ARIC) Study, a prospective cohort of middle-aged adults from 4 U.S. communities.

Methods—Study included 10,584 participants (mean age 62.7 years) free of AF in 1996-98 and followed through 2008. AF was defined using ICD codes from hospitalizations and death certificates. Participants with undetectable hs-cTnT levels (58%) were assigned the lower limit of measurement (5 ng/L). Net reclassification improvement (NRI) was used to examine the discriminative ability of hs-cTnT for 10-year AF risk prediction (categories: <5%, 5-15%, and >15%).

Results—A total of 920 incident AF cases were observed over 109,227 person-years. After adjustment, a 1-standard deviation difference in ln(hs-cTnT) was associated with a hazard ratio (HR) of 1.16 (95% CI=1.10-1.23). Compared with those with undetectable levels, participants with hs-cTnT 14 ng/L had a HR of 1.78 (95% CI=1.43-2.24). Addition of hs-cTnT to known AF predictors did not increase the c-statistic appreciably (0.756 vs 0.758) or improve risk stratification (NRI=0.4%, 95% CI=-1.4%-2.3%).

Conclusions—Hs-cTnT level is associated with an increased incidence rate of AF but did not improve risk stratification.

INTRODUCTION

Although substantial information exists regarding risk factors for atrial fibrillation (AF)(1), the predictive ability of these risk factors is modest (2;3). With recent evidence suggesting that myocardial ischemia may play a mechanistic role in AF development (4), and our established understanding of the role of processes associated with myocardial damage such as myocardial infarction (MI) or heart failure (HF) in its development, the assessment of subclinical myocardial damage may facilitate risk stratification for AF.

Previous clinical and population-based studies have found that high-sensitivity cardiac troponin T (hs-cTnT), a marker of subclinical myocardial damage, is associated with an increased risk of structural heart disease (5), incident HF (6), cardiovascular mortality (6), silent brain infarcts (7), and all-cause mortality (5). However, the association between hs-cTnT and the risk of incident AF remains unknown, as does the role of hs-cTnT in risk prediction and stratification for incident AF. Our primary objective was therefore to estimate the association between hs-cTnT and the risk of incident AF in participants of the Atherosclerosis Risk in Communities (ARIC) study. Our secondary objectives were to determine if this association differs by sex or race and to examine the predictive ability of hs-cTnT for incident AF.

METHODS

Study Design

The association between hs-cTnT and the risk of incident AF was examined using a longitudinal analysis of ARIC, a prospective study of the etiology of atherosclerosis in 4 U.S. communities (Forsyth County, North Carolina; Jackson, Mississippi; Washington County, Maryland; and Minneapolis, Minnesota)(8). ARIC involved 15,792 participants aged 45-64 years at the time of enrollment (1987-1989). Hs-cTnT levels were assayed in 2009-2010 from plasma samples collected at ARIC visit 4, conducted in 1996-98 and stored at -70°C ; this visit served as the baseline for the present study.

Exclusion criteria included evidence of a history of AF at visit 4 (from study ECGs or prior hospital discharge codes from baseline up to visit 4)(n=298), a missing or unreadable visit 4 electrocardiogram (n=174), and missing data for hs-cTnT (n=378) or covariates (n=153). Few participants from Minneapolis, MN or Washington County reported a race other than Caucasian and few from all sites reported a race other than Caucasian or African American (n=69). These individuals were excluded to avoid sparse strata and to appropriately adjust/stratify by race and study center. Thus, the final study population consisted of 10,584 participants.

Exposure Assessment

The hs-cTnT assays used in ARIC have been described previously (9). Briefly, using plasma samples from ARIC visit 4, hs-cTnT levels were measured using Elecsys Troponin T (lot number 154102, Roche Diagnostics, Indianapolis, IN), a high-sensitivity assay implemented on an automated Cobas e411 analyzer. All samples with undetectable hs-cTnT levels were assigned a value of 5 ng/L, the lower limit of detection. Analysis of 418 masked duplicate ARIC samples revealed a reliability coefficient of 0.98 (10). Participants were classified into one of four hscTnT categories: 5 ng/L (i.e., undetectable levels), 6-8 ng/L, 9-13 ng/L, and >14 ng/L. Similar categorization has been used previously in studies of hs-cTnT and other cardiovascular endpoints (9).

Outcome Measurement

Incident AF was defined using previously described methods (11;12). Briefly, possible hospitalizations were assessed during annual telephone follow-ups and review of local hospital discharge lists. Hospital discharge ICD codes and dates were abstracted, as previously described (13). Participants were considered to have AF if they had an ICD-9 code for AF (ICD-9 code 427.31) or atrial flutter (ICD-9 code 427.32) or if AF was listed on the death certificate (ICD-9 code 427.3 or ICD-10 code 148). Hospitalizations with an ICD code indicating that the AF occurred in hospital and those with ICD codes for cardiac procedures, including heart revascularization surgery or other cardiac surgery involving valves or septa were not considered events. The date of incident AF was defined as the date of the first evidence of its occurrence, and only 1 event was considered per participant. A previous ARIC sub-study has shown that the positive predictive value of ICD-9 codes for AF is $\sim 90\%$ (12).

Statistical Analysis

First, the dose-effect association between hs-cTnT and incident AF was explored modeling the natural log of hs-cTnT with a restricted cubic spline. There was some mild nonlinearity in the top 2.5% of the distribution, and sensitivity analyses were conducted excluding these individuals to obtain conservative estimates. These analyses removed this non-linearity; both analyses resulted in similar effect estimates and only those using the entire $\ln(\text{hs-cTnT})/\text{SD}$ distribution are reported here. Using Poisson regression, crude and age-, sex-, and race-adjusted incidence rates of AF were calculated for each hs-cTnT category.

Our primary analysis involved 3 Cox proportional hazards models to examine the association between hs-cTnT categories and the time to incident AF with varying degree of covariate adjustment. The first model was minimally adjusted, including only age, sex, and race. The second model also adjusted for AF risk factors included in the augmented Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) AF consortium risk score (2), including height, body mass index, systolic blood pressure, diastolic blood pressure, current smoking, diabetes, prevalent HF, previous MI, ECG-derived left ventricular hypertrophy, PR interval <120 ms, PR interval >199 ms, and use of anti-hypertensive medications. The third model included further adjustment for study center, education high school graduate, current alcohol intake, creatinine level, high-sensitivity C-reactive protein (hsCRP) level, and N-terminal pro b-type natriuretic peptide (NT-proBNP) level. In sensitivity analyses, analyses were restricted to participants free of prevalent coronary heart disease (CHD) and HF at baseline, with CHD and HF defined using previously published criteria (13;14). In additional analyses, time-dependent adjustment for incident MI and HF using hospitalization data collected during annual follow-ups was included to examine its role as a potential mediator; incident MIs included only those reviewed and adjudicated by the Endpoints Committee. Sex and race were examined as potential effect modifiers. In sensitivity analyses, hs-cTnT was modeled continuously as a one standard deviation change on the $\ln(\text{hs-cTnT})$ scale ($\text{SD}=0.47$).

The predictive ability of hs-cTnT for incident AF was examined in a two-step procedure. First, the c-statistic for the Cox proportional hazards models (15) was computed with and without the addition of hs-cTnT to traditional AF risk factors. Second, the net reclassification improvement (NRI)(16) was calculated and reclassification tables used (17) to examine the number of participants whose predicted 10-year AF risk was reclassified by adding hs-cTnT to previously-identified risk factors. NRI was examined with risk of AF treated categorically using cutoffs ($<5\%$, $5\text{--}15\%$, or $>15\%$)(3), and hs-cTnT treated log-linearly (16). In additional analyses, given the arbitrary nature of such categorization, NRI was examined using a continuous (or category-free) approach (16;18).

We conducted several sensitivity analyses. First, to examine the impact of death as a competing risk, we used the Fine and Gray method. Second, for illustrative purposes, we repeated our NRI analyses with NT-proBNP, a biomarker with higher granularity than hs-cTnT that has been shown to improve AF risk prediction in the CHARGE-AF Consortium of community-based cohort studies (including ARIC)(19), as the exposure variable.

Competing risk analyses were conducted using R version 3.0.2 (R Core Team, Vienna, Austria); all other analyses were conducted using SAS version 9.3 (The SAS Institute, Cary, NC).

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RESULTS

Demographic and Clinical Characteristics

There were a number of important differences in the demographic and clinical characteristics between hs-cTnT groups (Table 1). Participants with higher hs-cTnT levels were more likely to be older, more likely to be male, and more likely to be African American. Participants with higher hs-cTnT levels also had a higher prevalence of most cardiovascular risk factors, CVD, and current use of cardiac medications but lower prevalences of smoking and alcohol use.

Hs-cTnT and the Incidence Rate of AF

Overall, the crude incidence rate of AF was 8.4 per 1,000 person-years (95% CI=7.9-9.0). The rate ranged from 5.5 per 1,000 person-years (95% CI=4.9-6.1) among participants with undetectable hs-cTnT levels to 23.6 per 1,000 person-years (95% CI=20.4-27.3) among participants with hs-cTnT ≥ 14 ng/L (p for trend <0.0001)(Table 2). Similar trends were observed in both sex- and race-defined subgroups (Online Appendix 1).

After adjustment for known risk factors, a one-SD increase in ln(hs-cTnT) was associated with an increased rate of incident AF (HR=1.16, 95% CI=1.10-1.23)(Figure 1; Online Appendices 2-3). This association persisted after excluding participants with prevalent CHD or HF and following time-dependent adjustment for incident MI and HF.

The association between hs-cTnT as a categorical variable and the rate of incident AF was also estimated (Table 3). After adjusting for known risk factors, the rate of incident AF increased across hs-cTnT categories (p for trend <0.0001), with participants in the highest hscTnT category having a HR=1.78 (95% CI=1.43-2.24) compared with participants with undetectable levels. Similar results were obtained when restricting to participants free of CHD or HF at baseline. Although attenuated, a clinically important increased rate remained present after adjustment for incident MI and HF.

The association between hs-cTnT as a continuous variable and the rate of incident AF was present in both men and women, with a slightly stronger association in women (p for

interaction=0.03)(Online Appendix 3). This interaction persisted after restricting analyses to participants free of CHD and HF at baseline ($p=0.02$) but not after adjustment for incident MI and HF ($p=0.22$). This interaction with sex was not present when examining hs-cTnT categorically ($p=0.15$)(Figure 2). There was no evidence of interaction between hs-cTnT and race ($p=0.18$).

Discriminative Ability of hs-cTnT

The addition of $\ln(\text{hs-cTnT})$ as a continuous variable to a model containing known AF risk factors did not increase the c-statistic appreciably, both overall (0.756 vs 0.758) and in sex and race-defined subgroups (Online Appendix 4). Similar c-statistics were observed in men and women, and African Americans had a slightly higher c-statistic than Caucasians. Similar results were obtained when examining hs-cTnT categorically.

Risk Reclassification

The addition of hs-cTnT to previously-identified AF predictors did not improve risk classification (NRI =0.4%; 95% CI=-1.4-2.3%)(Table 4). When using the continuous approach, the inclusion of hs-cTnT did not result in significant reclassification (NRI=-7.3%, 95% CI=-14.5%-0.030%).

Sensitivity Analyses

Our sensitivity analyses that considered death as a competing risk produced results that were consistent with those of our primary analyses (HR for $\ln(\text{hs-cTnT})/\text{SD}=1.08$, 95% CI=1.01-1.15; categorical hs-cTnT: HR for 6-8 ng/L: 1.21 (95% CI=1.00-1.45), 9-13 ng/L: 1.39 (95% CI=1.14-1.69), 14 ng/L: 1.45 (95% CI=1.15-1.83). In addition, we found that unlike hs-cTnT, the addition of NT-proBNP to known risk factors improved risk classification (Online Appendix 5).

DISCUSSION

We aimed to examine the association between hs-cTnT level and the risk of incident AF. We found that the risk of AF increased with increasing hs-cTnT level and this association was consistent across different sex and race groups. However, the addition of hs-cTnT to traditional risk factors did not improve risk prediction, nor did it improve risk stratification. Similar results were obtained for both categorical and continuous NRI analyses. These results suggest that, although there is a strong and consistent association between hs-cTnT and incident AF, the clinical utility of hs-cTnT is modest at best. With no improvements in discrimination or prediction, findings are insufficient to recommend the use of hs-cTnT for AF risk stratification.

While hs-cTnT may not improve risk stratification for incident AF, its clinical relevance requires further investigation. If a biomarker such as hs-cTnT is related to a particular pathophysiology (e.g., ischemia or fibrosis), it may still be clinically useful to guide therapies that could prevent AF. Finally, biomarkers such as hs-cTnT may allow for the identification of groups which have a differential response to preventative therapies or may be altered by such therapies and thus be a surrogate for efficacy.

Previous studies have examined the association between troponin levels and clinical outcomes among patients with AF. These studies have shown that hs-cTnT level is associated with poorer outcomes in this population (20;21). Recently, investigators in the Heart and Soul Study showed that higher hs-cTnT levels are associated with a decreased left atrial function index in participants with stable CHD, which may have implications for the development of AF (22).

Previous studies have also found that hs-cTnT level is associated with prevalent AF. Using data from the Uppsala Longitudinal Study of Adult Men, Eggers and colleagues examined cross-sectionally the association between hs-cTnT and cardiovascular risk factor levels and prevalent cardiovascular diseases (23). Although the authors found that hs-cTnT level was associated with previous or prevalent AF, they did not examine incident AF as part of their longitudinal analysis.

To our knowledge, the association between hs-cTnT and incident AF has only been examined in one previous study. Anegawa and colleagues (24) examined this association among 220 individuals free of CVD who were enrolled during routine check-ups in Uku, Japan. A total of 12 incident AF cases were identified by electrocardiogram; these individuals had a substantially higher hs-cTnT level than those without AF (0.0115 ± 0.0052 ng/mL vs 0.0058 ± 0.0061 ng/mL, $p=0.002$). After adjustment for potential confounders, $\ln(\text{hs-cTnT})$ was associated with an increased rate of AF (HR=4.81, 95% CI=1.41-16.37). This observed association is consistent with the findings of the present study, though our larger sample size has allowed for the estimation of more precise estimates in a biracial cohort of men and women. Importantly, while similar results have been observed between troponin I and AF risk (25), to our knowledge, the predictive ability of hs-cTnT for incident AF has not been examined previously.

The strengths of our study merit a brief mention. First, detailed medical histories were obtained and cardiovascular risk factor levels were measured in ARIC, allowing for rigorous adjustment for known AF risk factors and minimizing residual confounding. Second, hs-cTnT level was measured using a validated assay that, in a sub-sample of ARIC participants, has been shown to have a reliability coefficient of 0.98 (9). Finally, the incorporation of risk reclassification analyses allows for the evaluation of the clinical utility of hs-cTnT for AF risk prediction.

Our study also has some potential limitations. First, since the baseline for this study was ARIC visit 4, follow-up was restricted to 1996-98 to 2008. With 920 incident AF cases, the study has ample power to address its primary objective but the power to examine interactions may be modest. Second, although events were assessed using a previously-validated definition (12), asymptomatic cases and those managed in outpatient settings were not included as events. This misclassification is not expected to be associated with participants' hs-cTnT level and thus should be non-differential and bias towards the null hypothesis. Third, despite rigorous statistical adjustment, some residual confounding due to unmeasured variables (e.g., sleep apnea, physical activity) remains possible. Finally, ARIC is a cohort of middle age Caucasian and African American participants from only a few

geographic regions, and the generalizability of our results outside this demographic is not known.

CONCLUSIONS

Higher hs-cTnT level is strongly associated with an increased rate of incident AF. This association is independent of previously-identified AF risk factors and incident MI and HF. However, hs-cTnT did not improve our predictive ability or risk stratification for AF relative to previously-identified AF risk factors. These results do not support the use of hs-cTnT for risk stratification as part of routine clinical practice.

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Figure 1.

Age-, sex-, and race-adjusted Cox proportional hazards model with restricted cubic splines examining the association between $\ln(\text{high-sensitivity cardiac troponin T})$ and the risk of incident atrial fibrillation. Knots were placed at the 75th, 90th, and 95th percentiles. Hazard ratios were estimated for a 1-standard deviation change ($SD=0.47$) in $\ln(\text{high-sensitivity cardiac troponin T})$. The top 2.5% of the high-sensitivity cardiac troponin T distribution was excluded from this analysis due to some mild non-linearity. Abbreviation: SD=standard deviation.

Figure 2.

Adjusted hazards ratios and corresponding 95% confidence intervals for sex- and race-specific models examining the association between high-sensitivity cardiac troponin T and the risk of incident atrial fibrillation. Models were adjusted for variables included in Model 3 (see Table 3).

Table 1

Baseline Characteristics by High-Sensitivity Cardiac Troponin T Group Among Participants of the ARIC Study (1996-1998).

Characteristic *	5 ng/L	6-8 ng/L	9-13 ng/L	14 ng/L
Number of Participants	6,099	2,152	1,424	909
<u>Demographic Characteristics:</u>				
Age, Years	61 (57.0, 65.0)	64.0 (59.0, 68.0)	65.0 (61.0, 70.0)	66.0 (61.0, 70.0)
Men, %	29.5	54.5	65.5	76.5
African-American, %	20.2	21.4	22.6	29.5
High School Diploma, %	83.6	80.8	76.6	72.1
<u>Lifestyle Variables:</u>				
Current Smoking Status, %		10.8	11.0	12.7
Current Alcohol Use, %	52.1	48.7	45.7	42.2
<u>Clinical Measurements:</u>				
<u>Blood Pressure, mmHg</u>				
Systolic	123.0 (112.0, 136.0)	126.0 (116.0, 139.0)	129.0 (118.0, 145.0)	131.0 (118.0, 145.0)
Diastolic	71.0 (64.0, 77.0)	71.0 (64.0, 78.0)	71.0 (65.0, 78.0)	71.0 (64.0, 78.0)
BMI, kg/m ²	27.5 (24.5, 31.2)	28.1 (25.1, 31.6)	29.0 (25.9, 32.3)	29.2 (26.2, 32.8)
Creatinine, mg/dL	0.88 (0.78, 0.98)	0.88 (0.78, 1.08)	0.98 (0.88, 1.08)	1.08 (0.88, 1.28)
Height, cm	164.0 (159.0, 172.0)	169.0 (162.0, 176.0)	171.0 (163.0, 177.0)	172.0 (166.0, 178.0)
hsCRP, µg/L	2.5 (1.1, 5.5)	2.1 (1.0, 5.0)	2.1 (1.0, 5.0)	3.0 (1.2, 6.5)
NT-proBNP, pg/mL	61.6 (31.5, 112.8)	66.3 (31.8, 127.6)	75.1 (37.9, 154.7)	113.5 (51.5, 308.3)
PR Interval, ms	162.0 (148.0, 180.0)	166.0 (150.0, 184.0)	168.0 (152.0, 186.0)	172.0 (154.0, 190.0)
<u>Medical History (%):</u>				
Congestive Heart Failure	0.5	1.0	2.3	7.4
Coronary Heart Disease	4.4	8.4	12.4	21.8
Coronary Revascularization	2.7	5.5	7.5	12.7
Diabetes	11.0	16.8	22.4	39.4
ECG-Derived Left	1.6	2.5	3.4	6.8
Ventricular Hypertrophy				
Hypertension	40.4	49.6	56.8	66.2

Characteristic *	High-Sensitivity Cardiac Troponin T			
	5 ng/L	6-8 ng/L	9-13 ng/L	14 ng/L
Myocardial Infarction	1.6	2.7	3.9	8.0
Stroke	1.4	2.0	2.3	6.1
<u>Current Medication Use (%)</u> :				
ACE Inhibitors/ARBs	10.0	15.7	18.0	27.6
Beta-Blockers	10.7	13.4	14.7	17.8
Calcium Channel Blockers	9.8	12.8	17.0	22.6
Class I Anti-Arrhythmics	0.03	0.3	0.4	0.9
Class III Anti-Arrhythmics	0	0	0	0.7
Other Anti-Hypertensive	16.7	19.3	22.0	27.1
Agents †				

Abbreviations: ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker; BMI: body mass index; ECG: electrocardiogram; hsCRP: high sensitivity C-reactive protein; NT-proBNP: N-terminal pro b-type natriuretic peptide.

* Data are presented as median (inter-quartile range) or percentage.

† Other anti-hypertensive agents include those other than ACE-Inhibitors, ARBs, and beta-blockers.

Table 2

Crude and Age-, Sex-, and Race-Adjusted Incidence Rate of Atrial Fibrillation by High-Sensitivity Cardiac Troponin T Level among Participants of the ARIC Study (1996-1998 to 2008).

	High-Sensitivity Cardiac Troponin T			
	5 ng/L	6-8 ng/L	9-13 ng/L	14 ng/L
Number of AF Events	359	196	186	179
Number of Participants	6,099	2,152	1,424	909
Total Person-Years	65,786	22,010	13,851	7,580
Crude IR (95% CI) *	5.5 (4.9-6.1)	8.9 (7.7-10.2)	13.4 (11.6-15.5)	23.6 (20.4-27.3)
Adjusted IR (95% CI) *†	8.6 (7.2-10.3)	9.8 (8.0-11.9)	12.6 (10.3-15.4)	24.1 (20.0-29.1)

Abbreviations: AF: Atrial Fibrillation; CI=Confidence Interval; IR=Incidence Rate; PY: Person-Years.

* Rates are expressed in cases per 1,000 person-years.

† Adjusted for age, sex, and race, and rates were estimated for a 65 year old, male Caucasian.

Adjusted Hazard Ratios (95% CI) for the Association of High-Sensitivity Cardiac Troponin T with the Risk of Incident Atrial Fibrillation among Participants of the ARIC Study (1996-1998 to 2008).

Table 3

Model #	High-Sensitivity Cardiac Troponin T*				P-value (trend)
	5 ng/L	6-8 ng/L	9-13 ng/L	14 ng/L	
1 [†]	1 (Reference)	1.41 (1.18-1.69)	1.96 (1.62-2.37)	3.64 (2.98-4.43)	<0.0001
2 [‡]	1 (Reference)	1.30 (1.08-1.56)	1.63 (1.34-1.97)	2.60 (2.11-3.21)	<0.0001
3 [§]	1 (Reference)	1.22 (1.02-1.47)	1.41 (1.16-1.72)	1.78 (1.43-2.22)	<0.0001
4	1 (Reference)	1.20 (0.99-1.46)	1.40 (1.13-1.72)	1.74 (1.35-2.24)	<0.0001
5 [¶]	1 (Reference)	1.16 (0.97-1.39)	1.19 (0.98-1.45)	1.30 (1.04-1.62)	0.02

* Data are presented as hazard ratios with corresponding 95% confidence intervals.

[†] Model 1 is adjusted for age, sex, and race.

[‡] Model 2 is adjusted for variables included in the augmented CHARGE risk score (2), including age, sex, race, height, body mass index, systolic blood pressure, diastolic blood pressure, current smoking, diabetes, prevalent heart failure, previous myocardial infarction, ECG-derived left ventricular hypertrophy, PR interval <120 ms, PR interval >199 ms, and use of anti-hypertensive medications. Height was modeled as one standard deviation changes on the log scale.

[§] Model 3=Model 2 + further adjustment for study center, education high school graduate, current alcohol intake, creatinine, high-sensitivity C-reactive protein, and N-terminal pro b-type natriuretic peptide. Creatinine, C-reactive protein, and N-terminal pro b-type natriuretic peptide were modeled as one standard deviation changes on the log scale.

^{||} Model 4=Model 3 but restricted to participants free of prevalent coronary heart disease or heart failure at baseline.

[¶] Model 5=Model 3 + time-dependent adjustment for incident myocardial infarction and incident congestive heart failure.

Table 4

Predicted 10-Year Risk of Incident Atrial Fibrillation with and without High-Sensitivity Cardiac Troponin T among Participants of the ARIC Study (1996-1998 to 2008)^{*,†}.

Traditional Risk Factors + High-Sensitivity Cardiac Troponin T				
Traditional Risk Factors Only	< 5%	5% to 15%	>15%	Total
Participants with AF, n (%)				
<5%	132 (91.7)	12 (8.3)	0 (0)	144 (18.7)
5% to 15%	6 (1.9)	294 (94.2)	12 (3.9)	312 (40.5)
>15%	0 (0)	19 (6.0)	296 (94.0)	315 (40.8)
Total, n (%)	138 (17.8)	325 (42.2)	308 (40.0)	771 (100)
Participants without AF, n (%)				
<5%	4,723 (96.6)	164 (3.4)	0 (0)	4,887 (49.8)
5% to 15%	163 (4.3)	3,545 (93.5)	84 (2.2)	3,792 (38.6)
>15%	0 (0)	129 (11.4)	1,005 (88.6)	1,134 (11.6)
Total, n (%)	4,886 (49.8)	3,838 (39.1)	1,089 (11.1)	9,813 (100)

Abbreviations: AF: Atrial fibrillation

* Percentages sum to 100 across rows except the marginal cells, which represent the percentage of all participants with and without AF. Risks were estimated using Kaplan-Meier methods to account for observations that were censored within 10 years.

† See model 3 in Table 3 for a list of traditional risk factors for atrial fibrillation included in this analysis. Atrial fibrillation risk cutoffs were developed in the Framingham Heart Study (3).