Association of lipoprotein-associated phospholipase A(2) and risk of incident atrial fibrillation: Findings from 3 cohorts

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Association of Lipoprotein-associated Phospholipase A₂ and risk of incident atrial fibrillation: Findings from three cohorts


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Abstract

**Background**—Multiple prospective studies have established an association between inflammation and higher risk of atrial fibrillation (AF), but the association between lipoprotein-associated phospholipase A₂ (Lp-PLA₂) mass and activity and incident AF has not been extensively evaluated.

**Methods**—Using data from 10794 Atherosclerosis Risk In Communities (ARIC) study participants aged 53–75 years, 5181 Cardiovascular Health Study (CHS) participants aged 65 to 100 years, and 5425 Multi-Ethnic Study of Atherosclerosis (MESA) participants aged 45–84 years, we investigated the association between baseline Lp-PLA₂ levels and the risk of developing AF. Incident AF was identified in each cohort by follow-up visit electrocardiograms, hospital discharge coding of AF, or Medicare claims data.

**Results**—Over a mean of 13.1, 11.5, and 10.0 years of follow-up, 1439 (13%), 2084 (40%), and 615 (11%) incident AF events occurred in ARIC, CHS, and MESA respectively. In adjusted analyses, each standard deviation increment in Lp-PLA₂ activity was associated with incident AF in both ARIC (hazard ratio (HR) 1.13; 95% confidence interval (CI) 1.06, 1.20) and MESA (HR 1.24; 95% CI 1.05, 1.46). Each standard deviation increment in Lp-PLA₂ mass was also associated with incident AF in MESA (HR 1.25; 95% CI 1.11, 1.41). No significant associations were observed among CHS participants.

**Conclusions**—While higher Lp-PLA₂ mass and activity were associated with development of AF in ARIC and MESA, this relationship was not observed in CHS, a cohort of older individuals.

Keywords

Inflammation; Epidemiology; Atrial Fibrillation; Lipoprotein-associated Phospholipase A₂

Introduction

Atrial fibrillation (AF) is the most commonly presenting cardiac arrhythmia in clinical practice, with an estimated prevalence of over 6–12 million people in the United States by 2050.¹,² AF is a major source of morbidity and rising health care costs.³,⁴ Although the pathophysiology of AF is complex and incompletely understood, inflammation is thought to play a role in this process. At the atrial tissue level, inflammatory activity has been shown to be elevated in manifest AF, suggesting a link between inflammation and structural atrial remodeling.⁵

Although the associations between many serum markers of inflammation and incident AF are well established, the association between lipoprotein-associated phospholipase A₂ (Lp-PLA₂) levels and incident AF has not been extensively evaluated.⁶–⁹ Lp-PLA₂ is an enzyme highly expressed by macrophages in atherosclerotic lesions, particularly within the necrotic core and fibrotic cap of rupture-prone plaques.¹⁰–¹²
Considering the specificity of Lp-PLA₂ for vascular inflammation, a question of interest is whether Lp-PLA₂ levels are associated with incident AF independent of traditional, more general biomarkers of inflammation.\textsuperscript{13} Existing data on the association of Lp-PLA₂ levels and incident AF come from a single prospective study which reported a borderline significant association between higher Lp-PLA₂ mass and incident AF.\textsuperscript{14} The Cardiovascular Health Study (CHS), the Multi-Ethnic Study of Atherosclerosis (MESA), and the Atherosclerosis Risk in Communities (ARIC) prospective cohort studies offer an opportunity to prospectively examine the relationship between Lp-PLA₂ levels and the development of AF in multiple large, well-defined populations with long-term follow-up and very different baseline demographic characteristics.

**Methods**

**Study Participants**

ARIC, CHS, and MESA are National Heart, Lung, and Blood Institute–funded multicenter longitudinal community-based studies designed to assess risk factors for cardiovascular disease. Participants were followed longitudinally for incident CVD events and cause-specific mortality. Institutional review boards at each site approved the study, and all participants gave informed consent. Details of each cohort are published and summarized briefly below.

ARIC included 15792 men and women aged 45–64 years sampled from four U.S. communities (Forsyth County, NC; Jackson, MS; Minneapolis suburbs, MN; and Washington County, MD) who underwent baseline examination between 1987 and 1989.\textsuperscript{15} Participants were re-examined in 1990–92 (93\% response), 1993–95 (86\%), 1996–98 (80\%), and 2011–13 (65\%). Due to the availability of Lp-PLA₂ activity, ARIC Visit 4 (1996–98) provided the eligible cohort and served as the baseline visit for the present analysis.

CHS included 5888 adults aged 65 and older at baseline. An original cohort of 5201 community-dwelling individuals was recruited between 1989 and 1990, and a supplemental cohort of 687 African Americans was recruited between 1992 and 1993. Participants completed annual clinic exams through 1989–1999 as well as semi-annual telephone calls throughout follow-up. The primary objectives and design of the study have been reported previously.\textsuperscript{16, 17} Potential participants were randomly sampled from Medicare eligibility lists in four U.S. communities (Sacramento, California; Forsyth County, North Carolina; Washington County, Maryland; and Allegheny County, Pennsylvania). Eligibility also required an expectation to remain in the area for 3 years after recruitment, no active cancer treatment, and the ability to provide consent.

MESA included 6814 adults aged 45–84 years and free of clinically recognized cardiovascular disease who were recruited at six field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St Paul, Minnesota) and underwent baseline examination between 2000 and 2002.\textsuperscript{18} The study participants self-identified with one of four race/ethnic groups: non-Hispanic white (38\%), African (28\%), Hispanic (22\%), and Chinese-Americans (12\%). MESA conducted four subsequent examinations of the cohort between 2002 and 2012.
**Plasma Lp-PLA₂ Measurement**

For ARIC, Lp-PLA₂ activity was assessed from stored plasma at Visit 4 by an automated Colorimetric Activity Method assay (diaDexus Inc., South San Francisco, CA) using a Beckman Coulter (Olympus) AU400e autoanalyzer. The Lp-PLA₂ activity assay had an inter-assay variation coefficient of 4.4% and a reliability coefficient (R) of 0.92, based on 419 blinded replicate samples.

For CHS, Lp-PLA₂ mass and activity were measured in 2005 in EDTA plasma from stored baseline specimens (1989–90 for the original cohort, and 1992–93 for the supplemental cohort) that were not previously thawed. Lp-PLA₂ mass was measured at the University of Vermont using a commercially available ELISA (2nd generation PLAC Test; diaDexus Inc, South San Francisco, CA). Lp-PLA₂ activity was measured at GlaxoSmithKline (Research Triangle Park, NC) by high-throughput radiometric assay using a tritium-labeled form of platelet activating factor as substrate in a 96-well microplate. The interassay coefficients of variation were 6% for Lp-PLA₂ mass and 8% for Lp-PLA₂ activity.

For MESA, Lp-PLA₂ mass and activity were measured in stored baseline plasma samples (from 2000–2002). Lp-PLA₂ mass was measured using a sandwich enzyme immunoassay (2nd generation PLAC Test; diaDexus Inc, South San Francisco, CA). Lp-PLA₂ activity was measured by an enzymatic assay using a tritium-labeled platelet activating factor (PAF) analog as the substrate (diaDexus Inc., South San Francisco, CA). The interassay coefficients of variation were 6.0% for Lp-PLA₂ mass and 5.0% for Lp-PLA₂ activity. Lp-PLA₂ values were not available in 1328 MESA participants, mostly due to lack of consent for research involving a commercial entity.

**Atrial Fibrillation**

Criteria for AF identification were similar in the three cohorts.¹⁹,²⁰ In ARIC, measures included cardiologist-confirmed electrocardiogram (ECG) recordings automatically coded as AF at baseline and at each follow-up exam, ICD-9-CM discharge diagnoses consistent with AF (427.31 or 427.32) from each participant’s hospitalizations reported in the annual follow-up interview, and death certificates with AF listed as a cause of death. In CHS, measures included annual study ECGs performed through 1998–1999 and verified for AF, ICD-9-CM hospital discharge diagnoses consistent with AF (427.31, 427.32), and, for participants enrolled in fee-for-service Medicare, inpatient and outpatient AF claims data. In MESA, measures included study ECGs verified for AF at baseline and exam 5, ICD-9-CM hospital discharge diagnoses consistent with AF (427.31 or 427.32), and for participants enrolled in fee-for-service Medicare, inpatient and outpatient AF claims data. ECGs in ARIC, CHS and MESA were read at a centralized ECG reading center, EPICARE, at Wake Forest University. In all three cohorts, the date of incident AF was defined as the first date AF was noted by any of the measures used by each study. AF hospitalization diagnoses occurring simultaneously with heart revascularization surgery or other cardiac surgery were not counted as incident AF events, but a subsequent episode of AF not in the setting of cardiac surgery could be counted as incident AF.
Covariates

All covariates were ascertained at the time of Lp-PLA$_2$ measurement. Age (years), gender, race, smoking status (current, former, or never), alcohol consumption (drinks/week), and medication use (anti-diabetic, anti-hypertensive, and statin) were obtained by self-report. Field center staff directly measured weight and standing height, and body mass index was calculated as measured weight in kilograms divided by standing height in meters squared. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated based on the average of the two measurements. Fasting blood was collected and stored at −70°F or colder until needed for the appropriate assays, including total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, C-reactive protein (CRP), and Lp-PLA$_2$. Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald equation in those with triglycerides <400 mg/dL. Each cohort defined diabetes by some combination of the following criteria: physician-reported diagnosis, anti-diabetic medication use, fasting blood glucose ≥126 mg/dL, or non-fasting glucose ≥200 mg/dL.

Coronary heart disease (CHD) in ARIC was based on a review of a self-reported history of physician diagnosed myocardial infarction, prior coronary revascularization, a previous myocardial infarction by electrocardiogram, or having developed incident CHD from the prior visit (Visit 2, 3, and 4). Heart failure (HF) was defined at each visit as the presence of HF according to the Gothenburg criteria (Visit 1 only) or having developed incident HF from the previous visit (Visit 2, 3, and 4). Methods of ascertainment for incident CHD and incident HF in ARIC have been described previously.$^{21, 22}$

CHD and HF were both self-reported in CHS and validated by information obtained from the baseline examination, medical records, and physician questionnaires.$^{23}$ CHD was defined as having a history of one or more of the following at baseline: myocardial infarction, angina, coronary artery bypass surgery or angioplasty. Self-reported HF was confirmed by the baseline use of a diuretic and either digitalis or a vasodilator. For self-reported HF unconfirmed at the baseline examination, confirmation was sought from treating physicians or hospital discharge summaries. All MESA participants were free of a history of clinically recognized CHD and HF at baseline.

Statistical Analysis

Participants with baseline measures of either Lp-PLA$_2$ mass or activity, no evidence of baseline AF, and with follow-up data were included in the analysis. Since each individual cohort was powered adequately and significant heterogeneity existed across cohorts for baseline Lp-PLA$_2$ levels, analysis was performed separately in ARIC, CHS, and MESA. Comparison of baseline characteristics between those who developed AF and those who did not was performed using $\chi^2$ tests for categorical measures and t-tests for continuous measures.

Cox proportional hazards models were used to investigate the association of baseline Lp-PLA$_2$ mass and activity with incident AF. Lp-PLA$_2$ was modeled continuously per standard deviation (SD) increment. Distributions of Lp-PLA$_2$ across ARIC, CHS, and MESA were heterogeneous and we used cohort-specific standard deviations to allow for more accurate
comparisons of associations across cohorts. Models were initially adjusted for age, sex, race, and clinic site (Model 1). Additional adjustment included alcohol consumption, antihypertensive use, BMI, diabetes, HDL cholesterol, LDL cholesterol, smoking, SBP, and in ARIC and CHS, CHD and HF (Model 2). The final model included adjustment for CRP (Model 3). The analysis was repeated stratified by race/ethnicity and gender. In sensitivity analyses, (1) we limited analysis to individuals with no history of CHD or HF at baseline (ARIC & CHS only), to better resemble the MESA cohort, and (2) we limited analysis to participants 65 years of age or older (ARIC and MESA only) to better resemble the CHS cohort. Finally, (3) we performed an analysis with CHD and CHF modeled as time-dependent covariates when the main analysis was significant, to determine if any observed associations between Lp-PLA$_2$ and incident AF were impacted by the interim development of CHD or CHF.

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Results

Participant characteristics

There were 10794, 5181, and 5425 participants included in the analyses from the ARIC, CHS, and MESA cohorts respectively. In ARIC, the mean age of participants was 62.7 years, 56.6% were women, and 78.1% were white. In CHS, the mean age of participants was 72.6 years, 59.0% were women, and 84.3% were white. In MESA the mean age of participants was 62.1 years, 53.5% were women, and 38.5% were white.

Over a mean of 13.1, 11.5, and 10.0 years of follow-up, 1439 (13%), 2084 (40%), and 615 (11%) incident AF events occurred in ARIC, CHS, and MESA respectively. Table 1
compares baseline characteristics in participants who did and did not develop incident AF. Participants in ARIC and MESA who developed AF were older and more likely to be male, be white, have a higher SBP, have a lower LDL cholesterol, smoke, have diabetes, and be on anti-hypertensive and statin medications compared to those who did not. Participants in ARIC who developed AF were also more likely to have a higher BMI, have a lower HDL cholesterol, have CHD, have HF, and have a higher CRP compared to those who did not. Baseline characteristics were more similar between those who did and who did not develop AF in CHS with exception of race, BMI, anti-hypertensive use, CHD, and CHF. Additionally, participants in CHS who developed AF were less likely to smoke compared to those who did not.

Lp-PLA$_2$ mass and activity distribution levels and incident AF

Mean levels of Lp-PLA$_2$ activity were 228.8 nmol/min/mL, 40 nmol/min/mL, and 149.1 nmol/min/mL for ARIC, CHS, and MESA respectively. Mean levels of Lp-PLA$_2$ mass were 344 ng/mL and 177.6 ng/mL for CHS and MESA respectively. Distributions for Lp-PLA$_2$ mass and activity in each cohort are displayed in Supplemental Figure 1. Among participants who developed AF compared with those who did not, Lp-PLA$_2$ activity levels were higher in ARIC and Lp-PLA$_2$ mass levels were higher in MESA (Table 1), but there was little difference in CHS.

Lp-PLA$_2$ levels and incident AF

Table 2 shows the hazard ratios for developing AF across all cohorts according to Lp-PLA$_2$ levels. Adjusting for age, sex, race, clinic site, smoking, alcohol consumption, diabetes, systolic blood pressure, HDL cholesterol, LDL cholesterol, BMI, anti-hypertensive use, CHD, and HF, each standard deviation increment in Lp-PLA$_2$ activity was associated with incident AF in ARIC (hazard ratio (HR) 1.13; 95% confidence interval (CI) 1.05, 1.20). Each standard deviation increment in Lp-PLA$_2$ activity and mass were also associated with incident AF in MESA (HR: 1.22; 95% CI: 1.03, 1.45 for activity, and HR 1.25; 95% CI 1.11, 1.41 for mass). Addition of CRP to Model 2 covariates did not significantly change associations (Table 2). Adjustment for interim CHD or HF events in addition to Model 2 covariates also did not change associations in ARIC (HR: 1.13; 95% CI: 1.06, 1.21) or MESA (HR: 1.22; 95% CI: 1.03, 1.45 for activity, and HR 1.24; 95% CI 1.10, 1.40 for mass). No significant adjusted associations between Lp-PLA$_2$ measures and incident AF were observed among CHS participants and adjusting for CRP did not meaningfully change the results.

Stratified analyses and sensitivity analyses for the association of Lp-PLA$_2$ levels with incident AF

The adjusted association of Lp-PLA2 levels with incident AF did not differ in any of the cohorts in subgroups defined by gender (Supplemental Table 1) or race/ethnicity (Supplemental Table 2). In sensitivity analyses limited to participants with no history at baseline of CHD or HF in ARIC and CHS or participants aged 65 years or older in ARIC and MESA, associations between Lp-PLA$_2$ levels and incident AF were similar in each cohort to those in the overall analyses (Supplemental Table 3).
Discussion

In 3 large community-based cohort studies, we found that higher baseline Lp-PLA₂ mass and activity levels were associated with a higher risk of incident AF in ARIC and MESA; however, no significant associations were observed in CHS. Adjustment for interim development of CHD or HF did not affect observed associations. Additionally, there were no significant interactions found by race or gender/ethnicity. Hazard ratios for either Lp-PLA₂ mass or activity were similar across ARIC and MESA with widely overlapping confidence intervals.

Lp-PLA₂ is a proinflammatory enzyme bound primarily to LDL, with levels increasing particularly in the presence of small, dense LDL, and is positively correlated with serum LDL levels. Lp-PLA₂ hydrolyzes oxidized phospholipids found on the LDL particle in plaques, resulting in proinflammatory and proatherogenic products. Higher Lp-PLA₂ mass and activity levels have also been shown to be associated with the development of cardiovascular disease.

Inflammation is implicated in the development of AF based on studies showing an increased incidence of AF following cardiac surgery and histological findings of atrial myocarditis in individuals with lone AF versus those in sinus rhythm. Considering the relationship between systemic inflammatory biomarkers, namely CRP, and incident AF has been already been established in multiple prospective studies, it was important that associations between baseline Lp-PLA₂ levels and incident AF relationship in ARIC and MESA remained significant even after adjustment for CRP. Evidence of a relationship between Lp-PLA₂, a marker related to vascular inflammation, and incident AF, however, is limited to a single prospective study of Framingham Offspring participants. In that study each higher SD of Lp-PLA₂ mass was associated with a 22% higher risk of incident AF that was of borderline significance. Baseline characteristics in the Framingham study such as age, BMI, SBP, and cardiac disease were similar to those of the ARIC and MESA cohorts. Mean follow-up time (6 years) and rates of incident AF (5.5%) in the Framingham study were both considerably lower than in the ARIC and MESA cohorts, limiting study power.

Results with other inflammatory markers that can also affect the vasculature have been mixed. Associations of osteoprotegerin, a biomarker indicative of vascular stiffness, with incident AF lost significance after adjustment for interim development of myocardial infarction and heart failure in Framingham Offspring participants. In the Women’s Health Study, however, soluble intercellular adhesion molecule-1, a marker of endothelial dysfunction, remained significantly associated with incident AF after exclusion of participants who experienced a cardiovascular event prior to developing AF. Considering it is already known that pharmacologic Lp-PLA₂ inhibitors do not improve cardiovascular outcomes and that we found no evidence of attenuation after adjustment for CHD or HF, there is no indication that the enzyme’s vascular inflammation properties play any mechanistic role in the development of AF. Our results, therefore, build upon prior research and substantiate Lp-PLA₂ only as a risk marker, not a risk factor, for AF.
In contrast to findings in the ARIC and MESA cohorts, we found no significant association of either Lp-PLA₂ mass or activity with incident AF in CHS. CHS is a much older population and mean age at baseline was 10 years higher than either ARIC or MESA. The atrium undergo both structural and electrical remodeling with age, including increased fibrotic tissue between myocytes, modifications to the cardiac action potential shape, and enhanced dispersion of cardiac repolarization, that can specifically increase the risk in the elderly to AF. AF prevalence markedly increases between the ages of 60 and 65 years. We observed that the AF rate in CHS was over 3 times higher than either ARIC or MESA over similar follow-up periods. Presentation of AF and associated comorbidities also differ according to age. Older patients more often have persistent or permanent AF compared with younger patients. We found that many risk factors for AF, including age, BMI, diabetes, cholesterol, and SBP, did not significantly differ between those who did and did not develop AF in CHS but did differ in ARIC and MESA. Although subgroup analyses of individuals 65 years and over showed that the associations between Lp-PLA₂ activity and incident AF in ARIC and Lp-PLA₂ mass and incident AF in MESA remained significant, these cohorts did not include participants older than 75 or 84 years of age at baseline. Taken together, these findings suggest that Lp-PLA₂ is of lesser importance as a risk marker for AF late in life, a time when this measure of lipid-induced arterial inflammation may be rendered less relevant by accumulated heart and vascular damage or other aging-related processes. Further study in additional cohorts would be required to better understand the differences in associations seen in this study.

Our study has limitations. Measurement of Lp-PLA₂ mass and activity was performed using different techniques and, as a result, we observed very different distributions of the biomarker across the cohorts. Although individual cohort distributions seen for Lp-PLA₂ mass and activity in our study were consistent when comparing them to other cohorts using the same type and generation of assay, we attempted to mitigate the impact of this heterogeneity by evaluating associations with incident AF in each cohort per study-specific SD increment of Lp-PLA₂. Due to the significant heterogeneity, however, we did not meta-analyze associations. We relied only on a baseline measurement of Lp-PLA₂ to study associations with incident AF. Use of a single measure without accounting for change in levels over such an extended follow-up may have been inadequate to capture the association of elevated circulating Lp-PLA₂ with AF development, potentially either weakening reported associations or failing to detect significant ones. Lp-PLA₂ is relatively stable over time and exhibits little biovariability.

Ascertainment of AF relied primarily on hospital diagnosis in all three cohorts and the ability to identify asymptomatic paroxysmal AF was significantly impaired. Patients with persistent AF are more likely to have had undetected asymptomatic paroxysmal AF, which, in turn, might cause an increase in inflammation levels. We cannot exclude the possibility that increased Lp-PLA₂ may actually be a consequence of AF. Medicare claims data was not used for AF ascertainment in ARIC due to many participating sites’ participants not having fee-for-service programs, the younger age of the participants at baseline, and a lack of validity data on AF claims. Although AF incidence was underestimated, prior study in this cohort demonstrated that associations of risk factors with AF were not altered with the addition of Medicare claims data.
In conclusion, these results demonstrate that higher Lp-PLA₂ mass and activity were associated with development of AF in middle-aged to older cohorts, but these relationships were not detected in a third cohort of individuals late in life. More studies in other observational cohorts can help to further define which populations Lp-PLA₂ may offer predictive value in development of AF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References


Table 1

Baseline characteristics of study participants in ARIC, CHS, and MESA according to presence of absence of incident atrial fibrillation (AF)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ARIC (n=1439)</th>
<th>No AF (n=9355)</th>
<th>p-value †</th>
<th>CHS (n=2084)</th>
<th>No AF (n=3097)</th>
<th>p-value †</th>
<th>MESA (n=615)</th>
<th>No AF (n=4810)</th>
<th>p-value †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.3 (5.4)</td>
<td>62.3 (5.6)</td>
<td>&lt;0.01</td>
<td>72.7 (5.4)</td>
<td>72.6 (5.5)</td>
<td>0.23</td>
<td>70.0 (7.8)</td>
<td>61.1 (10.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Female, %</td>
<td>706 (49%)</td>
<td>5408 (58%)</td>
<td>&lt;0.01</td>
<td>1204 (58%)</td>
<td>1853 (60%)</td>
<td>0.14</td>
<td>277 (46%)</td>
<td>2615 (53%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>White</td>
<td>1211 (84%)</td>
<td>7220 (77%)</td>
<td>&lt;0.01</td>
<td>1828 (88%)</td>
<td>2538 (82%)</td>
<td>&lt;0.01</td>
<td>291 (47%)</td>
<td>1800 (37%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chinese</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>80 (13%)</td>
<td>636 (13%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>228 (16%)</td>
<td>2135 (23%)</td>
<td>&lt;0.01</td>
<td>256 (12%)</td>
<td>559 (18%)</td>
<td></td>
<td>123 (20%)</td>
<td>1268 (26%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>121 (20%)</td>
<td>1106 (23%)</td>
<td></td>
</tr>
<tr>
<td>Smoker status, %</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Never</td>
<td>532 (37%)</td>
<td>3980 (42%)</td>
<td>&lt;0.01</td>
<td>986 (47%)</td>
<td>1412 (46%)</td>
<td>&lt;0.01</td>
<td>287 (47%)</td>
<td>2462 (51%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Former</td>
<td>670 (47%)</td>
<td>4007 (43%)</td>
<td></td>
<td>885 (43%)</td>
<td>1268 (41%)</td>
<td></td>
<td>269 (44%)</td>
<td>1717 (36%)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>237 (16%)</td>
<td>1368 (15%)</td>
<td>&lt;0.01</td>
<td>213 (10%)</td>
<td>417 (13%)</td>
<td></td>
<td>57 (9%)</td>
<td>615 (13%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol, #drinks/week</td>
<td>2.7 (7.1)</td>
<td>2.4 (5.7)</td>
<td>0.25</td>
<td>2.87 (15.3)</td>
<td>2.45 (7.4)</td>
<td>0.19</td>
<td>4.4 (6.8)</td>
<td>3.7 (6.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>CHD, %</td>
<td>216 (15%)</td>
<td>625 (7%)</td>
<td>&lt;0.01</td>
<td>485 (23%)</td>
<td>532 (17%)</td>
<td>&lt;0.01</td>
<td>N/A</td>
<td>N/A</td>
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</tr>
<tr>
<td>HF, %</td>
<td>135 (9%)</td>
<td>625 (7%)</td>
<td>&lt;0.01</td>
<td>108 (5%)</td>
<td>109 (4%)</td>
<td>&lt;0.01</td>
<td>N/A</td>
<td>N/A</td>
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</tr>
<tr>
<td>Diabetes, %</td>
<td>333 (23%)</td>
<td>1422 (15%)</td>
<td>&lt;0.01</td>
<td>318 (15%)</td>
<td>468 (15%)</td>
<td>0.89</td>
<td>101 (16%)</td>
<td>571 (12%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>29.7 (5.9)</td>
<td>28.6 (5.5)</td>
<td>&lt;0.01</td>
<td>26.82 (4.7)</td>
<td>26.53 (4.7)</td>
<td>0.03</td>
<td>28.5 (5.6)</td>
<td>28.2 (5.5)</td>
<td>0.18</td>
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<tr>
<td>SBP, mmHg</td>
<td>132.1 (21.0)</td>
<td>126.8 (18.6)</td>
<td>&lt;0.01</td>
<td>136.64 (22.0)</td>
<td>135.47 (21.5)</td>
<td>0.06</td>
<td>133.3 (22.2)</td>
<td>125.3 (21.3)</td>
<td>&lt;0.01</td>
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<tr>
<td>Cholesterol, mg/dl</td>
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<tr>
<td>LDL</td>
<td>119.7 (32.8)</td>
<td>123.4 (33.2)</td>
<td>&lt;0.01</td>
<td>129.5 (34.9)</td>
<td>131.1 (35.9)</td>
<td>0.11</td>
<td>114.0 (31.7)</td>
<td>117.6 (31.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL</td>
<td>47.3 (15.7)</td>
<td>50.6 (16.6)</td>
<td>&lt;0.01</td>
<td>54.3 (15.4)</td>
<td>54.9 (15.8)</td>
<td>0.15</td>
<td>51.5 (15.2)</td>
<td>51.0 (14.9)</td>
<td>0.52</td>
</tr>
<tr>
<td>Characteristic</td>
<td>ARIC</td>
<td>CHS</td>
<td>MESA</td>
<td></td>
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<tr>
<td></td>
<td>Incident AF (n=1439)</td>
<td>No AF (n=9355)</td>
<td>Incident AF (n=2084)</td>
<td>No AF (n=3097)</td>
<td>p-value†</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lp-PLA₂ activity, nmol/min/mL</td>
<td>238.5 (60.8)</td>
<td>227.3 (62.3)</td>
<td>39.9 (13.0)</td>
<td>39.3 (13.0)</td>
<td>0.10</td>
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<tr>
<td>Lp-PLA₂ mass, ng/mL</td>
<td>N/A</td>
<td>N/A</td>
<td>345.7 (119.1)</td>
<td>343.2 (118.0)</td>
<td>0.47</td>
<td></td>
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</tr>
<tr>
<td>Anti-hypertensive use, %</td>
<td>820 (57%)</td>
<td>3775 (40%)</td>
<td>1049 (50%)</td>
<td>1353 (44%)</td>
<td>&lt;0.01</td>
<td></td>
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</tr>
<tr>
<td>Statin use, %</td>
<td>223 (15%)</td>
<td>995 (11%)</td>
<td>50 (2%)</td>
<td>74 (2%)</td>
<td>0.98</td>
<td></td>
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</tr>
</tbody>
</table>

ARIC=Atherosclerosis Risk in Communities Study, CHS=Cardiovascular Health Study, MESA=Multi-Ethnic Study of Atherosclerosis, CHD=coronary heart disease, HF=Heart failure, SBP=systolic blood pressure, DBP=diastolic blood pressure, LDL=low-density lipoprotein, HDL=high-density lipoprotein, Lp-PLA₂=Lipoprotein-associated phospholipase A₂

* Continuous variables are expressed as mean (SD). Categorical variables are N (percent).

† Comparisons were made between cases and noncases.
### Table 2

Associations between Lp-PLA₂ and incident atrial fibrillation *

<table>
<thead>
<tr>
<th></th>
<th>Model 1†</th>
<th>Model 2‡</th>
<th>Model 3§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>ARIC (mean follow-up=13.1 years)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lp-PLA₂ activity (n=10794)</td>
<td>1.06 (1.00, 1.13) p=0.04</td>
<td>1.13 (1.05, 1.20) p&lt;0.001</td>
<td>1.13 (1.06, 1.20) p&lt;0.001</td>
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<tr>
<td>CHS (mean follow-up=11.5 years)</td>
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<tr>
<td>Lp-PLA₂ activity (n=5170)</td>
<td>1.02 (0.97, 1.06) p=0.44</td>
<td>1.04 (0.99, 1.09) p=0.13</td>
<td>1.04 (0.99, 1.10) p=0.10</td>
</tr>
<tr>
<td>Lp-PLA₂ mass (n=5179)</td>
<td>1.02 (0.98, 1.07) p=0.33</td>
<td>1.04 (0.99, 1.09) p=0.08</td>
<td>1.04 (0.99, 1.09) p=0.10</td>
</tr>
<tr>
<td>MESA (mean follow-up=10.0 years)</td>
<td></td>
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<tr>
<td>Lp-PLA₂ activity (n=5425)</td>
<td>1.00 (0.91, 1.10) p=0.96</td>
<td>1.22 (1.03, 1.45) p=0.02</td>
<td>1.24 (1.05, 1.46) p=0.01</td>
</tr>
<tr>
<td>Lp-PLA₂ mass (n=5425)</td>
<td>1.13 (1.04, 1.24) p&lt;0.01</td>
<td>1.25 (1.11, 1.41) p&lt;0.001</td>
<td>1.25 (1.11, 1.41) p&lt;0.001</td>
</tr>
</tbody>
</table>

ARIC=Atherosclerosis Risk in Communities Study, CHS=Cardiovascular Health Study, MESA=Multi-Ethnic Study of Atherosclerosis, Lp-PLA₂=Lipoprotein-associated phospholipase A2

* Results of Cox proportional hazards regression models are shown for both Lp-PLA₂ mass and activity per 1 SD increment—ARIC: 62 nmol/min/mL for activity; CHS: 13 nmol/min/mL for activity and 118 ng/mL for mass; MESA: 36 nmol/min/mL for activity and 42 ng/mL for mass.

† Model 1 adjusted for age (years), sex, race, clinic site

‡ Model 2 adjusted for Model 1 + BMI, smoking, diabetes, HDL, LDL, SBP, hypertension medication, alcohol consumption, CHD (ARIC & CHS), HF (ARIC & CHS)

§ Model 3 adjusted for Model 2 + CRP

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