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Lipoprotein-Associated Phospholipase A2 and Risk of Congestive Heart Failure in Older Adults: the Cardiovascular Health Study

Suzuki

Brief Title: Lp-PLA2 and Congestive Heart Failure

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Abstract

**Background:** Inflammation may be an etiologic factor in congestive heart failure (CHF). Lipoprotein associated phospholipase A2 (Lp-PLA2) is an inflammation marker associated with vascular risk. One previous study showed an association of Lp-PLA2 activity with CHF risk, but there were only 94 CHF cases and Lp-PLA2 antigen, which is available clinically in the US, was not measured.

**Methods and Results:** We measured baseline Lp-PLA2 antigen and activity in 3991 men and women without baseline CHF or cardiovascular disease, participating in the Cardiovascular Health Study, a prospective observational study of adults ≥65 years old. Cox proportional hazards models adjusted for age, sex, clinic site, race, LDL and HDL cholesterol, body-mass index, systolic and diastolic blood pressure, hypertension, smoking status, pack-years and diabetes were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident CHF. Further models adjusted for coronary disease events during follow up and C-reactive protein (CRP). 829 participants developed CHF over 12.1 years. Adjusted HRs for CHF with Lp-PLA2 in the fourth compared to first quartile, were 1.44 (CI 1.16-1.79) for Lp-PLA2 antigen and 1.06 (CI 0.84-1.32) for activity. Adjustment for incident coronary disease attenuated the HR for Lp-PLA2 antigen to 1.26 (CI 1.02-1.57), adjustment for CRP had minimal impact.

**Conclusions:** Lp-PLA2 antigen was associated with risk of future CHF in older people, independent of CHF and coronary risk factors, and partly mediated by coronary disease events. Further clinical and basic research is needed to better understand the role of Lp-PLA2 in CHF.


Introduction

Congestive heart failure (CHF) is a major public health problem in the United States. Approximately 5 million patients have CHF and 550,000 are newly diagnosed each year.\(^1\) Accumulating evidence supports that inflammation is an underlying pathophysiology of CHF.\(^2\),\(^3\) Various inflammation markers such as C-reactive protein (CRP) and interleukin (IL)-6 are increased in patients with CHF.\(^4\)-\(^6\) CRP and IL-6 have been shown to be associated with incident CHF.\(^7\)-\(^9\)

Lipoprotein-associated phospholipase A\(_2\) (Lp-PLA\(_2\)), also known as platelet-activating factor acetylhydrolase (PAF-AH), is an inflammation marker used for cardiovascular risk assessment.\(^10\) It is synthesized by monocytes and macrophages, and, in the circulation, is bound to LDL.\(^11\),\(^12\) Lp-PLA\(_2\) has proinflammatory properties through hydrolyzing oxidized phospholipids generating lysophosphatidylcholine and oxidized fatty acids.\(^13\),\(^14\) Lp-PLA\(_2\) is strongly expressed in advanced coronary plaques suggesting a potential role in promoting plaque instability.\(^15\) However, Lp-PLA\(_2\) may also play an anti-inflammatory role through inhibition of PAF.\(^16\) Lp-PLA\(_2\) can be measured using an activity assay or a commercially available antigenic (mass) assay\(^17\) and the antigen and activity were measured in previous epidemiological studies.\(^18\),\(^19\) In a previous study from the Cardiovascular Health Study (CHS), Lp-PLA\(_2\) activity and antigen were not correlated \(r = 0.51\), but this modest association points out the importance of considering both measures.\(^20\) Recently, a U.S. expert panel published a document on the clinical use of Lp-PLA\(_2\) in cardiovascular disease.\(^21\)
Several epidemiological studies reported that higher Lp-PLA$_2$ is a risk marker for coronary heart disease (CHD)$^{22-28}$ and ischemic stroke.$^{22, 26}$ One study is available which reported an association of Lp-PLA$_2$ activity with risk of CHF$^{29}$, but there were less than 100 cases and Lp-PLA$_2$ antigen, which is available clinically in the U.S., was not measured. Thus, whether Lp-PLA$_2$ antigen or activity are a risk factor for CHF is not clear. We examined the association of both Lp-PLA$_2$ antigen and activity with risk of future CHF in the CHS.

**Methods**

**Subjects**

The Cardiovascular Health Study (CHS) is a prospective population-based observational study of older adults ≥65 years old at baseline to evaluate risk factors for the development and progression of cardiovascular disease (CVD). The design, rationale and examination details have been described elsewhere.$^{30}$ Briefly, participants were randomly selected from Medicare eligibility lists in four field centers: Forsyth County, North Carolina; Sacramento County, California, Allegheny County, Pennsylvania, and Washington County, Maryland. An initial primarily white cohort of 5201 was recruited between 1989 and 1990 and an additional 687 African-Americans (minority cohort) were recruited in 1992 and 1993. Persons were ineligible for participation if they were receiving active treatment for cancer, were wheelchair-bound or institutionalized, or were unable to participate in the examination. Comprehensive examinations and interviews were performed annually. The study was approved by institutional review boards at each site. Informed consent was obtained from all subjects.
Takeki Suzuki, MD, MPH

Self-reported health behaviors, medical history, anthropometric measures, current medication use, seated blood-pressure readings, electrocardiography recordings, and fasting blood chemistry measures were obtained at baseline for both cohorts. Common carotid intima-media thickness (IMT) was measured at baseline in a standard manner as previously described. In previous CHS reports, IMT was an independent predictor of CHF and Lp-PLA₂ was significantly higher in participants with higher IMT. Echocardiograms were obtained at baseline for the original cohort and again for members of both cohorts in 1994 to 1995. All participants in the original and minority cohorts were included in the primary analysis, except for 80 participants with baseline history of CHF, 115 with valvular heart disease by echocardiography (92 with aortic stenosis and 23 with severe mitral regurgitation), and 1190 with baseline CVD. Baseline CVD was defined as having one of the following at baseline: history of myocardial infarction, angina, stroke, transient ischemic attack, claudication, coronary artery bypass surgery, leg artery bypass, carotid endarterectomy, coronary angioplasty, or lower extremity angioplasty. Baseline CVD and CHF were adjudicated by a combination of self report of physician diagnosis as well as review of medical records. Secondary analysis was performed among participants with baseline CVD.

**Laboratory Methods**

Phlebotomy was performed on the morning of enrollment after 8-12 hours fast. Fibrinogen, total and HDL cholesterol, triglyceride, glucose and creatinine were measured at the central laboratory as previously reported. LDL cholesterol was calculated for those with triglycerides <400 mg/dL. CRP was measured by an in-house validated high-sensitivity enzyme-linked immunosorbent assay (ELISA). Interleukin-6 (IL-6) was measured by high-sensitivity ELISA (R&D Systems, Minneapolis, MN, USA). The interassay coefficients of variation were 6% for
CRP and 7% for IL-6. Elevated CRP was defined as >3.0 mg/L corresponding to the “high risk category” in the American Heart Association/Centers for Disease Control (AHA/CDC) consensus statement. Elevated IL-6 and fibrinogen were defined as values in the top tertile of the distribution (≥2.04 pg/mL and >338 mg/dL, respectively).

Plasma Lp-PLA₂ antigen (or “mass”) was determined at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT) using a commercially available enzyme-linked immunosorbant assay (ELISA) kit (second generation PLACTM Test; diaDexus Inc., South San Francisco, CA, USA). Plasma 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 [3H PAF] as substrate in a 96-well microplate, as previously described. The interassay coefficients of variation were 6.3 % for Lp-PLA₂ antigen and 7.5 % for Lp-PLA₂ activity.

Adjudication of Incident Congestive Heart Failure Events

Our outcome was incident CHF, which was assessed and validated as previously reported. Subjects were interviewed every 6 months and follow-up examinations were conducted annually at each study center until May 31, 1998, after which telephone follow up continued. Self-report of a physician diagnosis of CHF was confirmed by review of medical records, with validation requiring a constellation of symptoms (shortness of breath, fatigue, orthopnea, paroxysmal nocturnal dyspnea), physical signs (edema, pulmonary rales, gallop rhythm, displaced left ventricular apical impulse), chest X-ray results (cardiomegaly and pulmonary edema), and treatment of CHF using diuretic agents, digitalis, or vasodilators (nitroglycerin, hydralazine, or
Takeki Suzuki, MD, MPH

angiotensin-converting enzyme inhibitors). The CHS Events Committee adjudicated the index event of congestive heart failure by reviewing all pertinent data on hospitalization or outpatient visits, including history, physical examination, report of chest X-ray, and medication use. This analysis includes validated events through June 30, 2003.

Statistical Analysis

Baseline characteristics were compared between those who developed CHF and those who didn’t by using chi square tests for discrete values and t tests for continuous data. Lp-PLA₂ antigen or activity was divided into quartiles (Quartile1-4, 1 being the lowest, 4 being the highest values) based on sex (men and women) and race (African American and non-African American).

Kaplan-Meier curves with the endpoint of CHF were constructed based on Lp-PLA₂ antigen or activity quartiles. A log-rank test was performed to examine differences among the four groups. The associations of these categories of Lp-PLA₂ antigen or activity level with incident CHF were assessed using Cox proportional hazards models. Hazard ratios (HRs) and 95% confidence intervals (CIs) for incident CHF were calculated for each Lp-PLA₂ quartile compared to the 1st quartile. Models were first adjusted for age, sex, clinic site and race. Additional adjustments included LDL and HDL cholesterol, body-mass index, systolic and diastolic blood pressure, hypertension status, smoking status and pack-years, and diabetes status. Incident validated CHD was added to the model as a time-dependent covariate to assess mediation. Incident CHD was defined as incident MI, angina, angioplasty, coronary artery bypass surgery, or CHD death. Additional variables were added individually to evaluate potential biological pathways of Lp-PLA₂ and incident CHF: baseline serum creatinine, statin and aspirin use, CRP, IL-6, left
ventricular (LV) mass by electrocardiography\(^{39}\), and common carotid IMT. In secondary analysis, we replicated the above models among participants with baseline CVD. We did not adjust for incident CHD in secondary analysis since these participants had already had baseline CHD.

Stratified analyses were subsequently performed on the basis of sex and race (African American and non-African American). In addition, since it has been reported that Lp-PLA\(_2\) was more strongly associated with vascular events in those with low LDL cholesterol and in those subjects, those with both elevated Lp-PLA\(_2\) and CRP were at the greatest risk for CHD\(^{22}\), we evaluated incident CHF stratified by the levels of LDL (above or below median), HDL (above or below median), and CRP (above or below 3 mg/L).

To evaluate the combined predictive value of Lp-PLA\(_2\) and other inflammation markers for incident CHF, participants were cross-classified by Lp-PLA\(_2\) and inflammation markers (CRP >3 mg/L, and IL-6 and fibrinogen in tertiles) and interactions between Lp-PLA\(_2\) and these inflammation markers were assessed by calculating the relative excess risk due to interaction (RERI)\(^{40, 41}\), as well as the RERI\(\%\), defined as the proportion of disease related to Lp-PLA\(_2\) and the inflammation marker, either singly or in combination, attributable to their interaction. The Delta method was used to calculate P-values and 95% confidence intervals used to assess significance of the RERI.

Statistical analyses were performed at the Cardiovascular Health Study Coordinating Center using Stata, Release 10 (Stata Co, College Station, Texas).
Results

Baseline characteristics of the 3991 participants are shown in Table 1. There were 829 incident CHF cases over 12.1 years of follow-up (incidence rate of 19.1 per 1000 person-years). Those who developed CHF were older, more likely to be male, and to have diabetes, hypertension and greater LV mass. Smoking was relatively uncommon and was similar between the two groups. Baseline Lp-PLA₂ antigen and activity, along with other inflammation markers, were higher in those who developed CHF. There were 1190 participants with baseline CVD evaluated in secondary analyses. Patterns of association of baseline risk factors with CHF were similar to those without baseline CVD (data not shown).

Associations between Lp-PLA₂ Antigen/Activity and Incident CHF

Kaplan-Meier curves for time to CHF by Lp-PLA₂ antigen or activity quartiles are shown in Figure 1. Those with the highest Lp-PLA₂ antigen were more likely to develop CHF during follow-up, with the 10-year cumulative incidence rate ranging from 11.7 per 1000 person-years in the first quartile to 19.5 per 1000 person-years in the 4th quartile ($P=0.0001$) for difference among groups. There were no significant differences in CHF incidence among the quartiles of Lp-PLA₂ activity.

The HRs of CHF for each quartile of Lp-PLA₂ antigen and activity, compared with the first quartile, are shown in Table 2. Lp-PLA₂ antigen in the top three quartiles, but not activity, were associated with increased risk of CHF, with gradually increasing risk by quartile for Lp-PLA₂ antigen. The HR for Lp-PLA₂ antigen in the top quartile was 1.44 (95% CI 1.16-1.79) and that
Takeki Suzuki, MD, MPH

for Lp-PLA₂ activity was 1.06 (0.84-1.32) after adjustment for LDL and HDL cholesterol, body mass index, systolic and diastolic blood pressure, hypertension status, smoking status and pack-years, and diabetes status. When incident CHD was added to the model as a time-dependent covariate, the HRs for Lp-PLA₂ antigen in the top three quartiles were reduced, but remained significant with about a 25% increased risk for values above the median. Additional adjustment for other covariates, including common carotid IMT, had minimal impact on associations except IL-6 or LV mass, which slightly accentuated the HRs for Lp-PLA₂ (Table 2).

**Stratified Analyses**

Figure 2 shows results of stratified analyses for Lp-PLA₂ antigen and risk of CHF. Lp-PLA₂ antigen in the top quartile was associated with incident CHF in women (HR 1.46, 95% CI 1.10-1.94) but not men (HR 1.08, 95% CI 0.77-1.51). The association between Lp-PLA₂ antigen and incident CHF was slightly larger in non-African Americans (HR 1.30, 95% CI 1.03-1.65) than African-Americans (HR 1.20, 95% CI 0.68-2.14). Associations between Lp-PLA₂ antigen and CHF were stronger in those with LDL below median and with HDL above median. The association was stronger in those with elevated CRP. However, none of these associations were significantly different between strata.

**Interaction between Lp-PLA₂ and Other Inflammation Markers**

The joint associations of Lp-PLA₂ antigen and inflammation markers, adjusted for risk factors and interval incident CHD, are shown in Table 3. In general the inflammation markers had larger associations than Lp-PLA₂ with incident CHF. The relative excess risks due to interaction (RERI) between Lp-PLA₂ antigen and inflammation markers were calculated. Considered
Takeki Suzuki, MD, MPH

jointly, the risk of CHF was 13 to 16% higher than expected by the separate additive effects of Lp-PLA_2 antigen and other inflammation markers. For example, those with high Lp-PLA_2 antigen (top tertile) and high CRP (≥ 3mg/L) had a higher risk of CHF compared to those without either risk factor (HR 2.05, 95% CI 1.68-2.51). When considering interaction additively, a significant proportion of CHF risk, 13.9% (95% CI 6.3%-21.6%), was related to the combination of high levels of CRP and Lp-PLA_2 antigen.

**Secondary Analysis in Participants with Baseline CVD**

There were 440 incident CHF cases among 1190 participants with baseline CVD and no baseline CHF over 12.1 years of follow-up (incidence rate of 44.1 per 100 person-years). In these participants, the association of Lp-PLA_2 antigen with incident CHF was similar to the association in those without baseline CVD after adjustment for risk factors (HR 1.36, 95% CI 1.02-1.83, Table 4). After adjustment for individually for serum creatinine, CRP, IL-6, or LV mass, the association between Lp-PLA_2 antigen and incident CHF was modestly smaller and no longer statistically significant. The HR of incident CHF for Lp-PLA_2 activity was similar to that of Lp-PLA_2 antigen, with adjustment for age, sex, clinic site, and race.

**Discussion**

The main finding of this study was that Lp-PLA_2 antigen, but not activity, was associated with increased 12-year risk of CHF in older people without CVD or CHF at baseline, even after adjustment for interval development of CHD, which appeared to mediate part of this association. Adjustment for other CHF risk factors, including CVD risk factors, creatinine, common carotid IMT, or other inflammation markers had minimal impact on this association. In contrast, Lp-
PLA₂ activity was not associated with risk of incident CHF, except in participants with baseline CVD. There was modest complementary information in CHF risk prediction using combinations of elevated Lp-PLA₂ and other inflammation risk markers CRP, IL-6 and fibrinogen.

Previous epidemiologic studies have demonstrated associations between Lp-PLA₂ and risk of CVD. For CHF, the Rotterdam Study reported a hazard ratio of 2.33 for Lp-PLA₂ activity in the 4th versus 1st quartile with risk of CHF over 6.7 years (95% CI 1.21-4.49), but there were less than 100 CHF cases and Lp-PLA₂ antigen, which is available clinically in the U.S., was not measured. In our study Lp-PLA₂ antigen, but not activity, was associated with incident CHF, in an analysis involving 829 cases. The different findings between the studies could be due to differences in population characteristics and study design. Our cohort was older, had a higher CHF incidence rate, and a larger sample size and number of incident cases compared with the Rotterdam Study. Prior analyses in CHS showed that Lp-PLA₂ antigen and activity were associated with risk of myocardial infarction, while antigen but not activity was associated with stroke risk (Jenny et al, manuscript submitted). Disparate findings for antigen and activity assays may reflect assay design issues, pre-analytical factors such as differences in biovariability, complex biology of Lp-PLA₂, and heterogeneity of congestive heart failure and stroke as clinical syndromes. These findings may also relate to the modest, not high, correlation between antigen and activity or non-linear relationship between the two. In the CARDIA study, Lp-PLA₂ antigen was independently associated with calcified coronary plaque, while Lp-PLA₂ activity was not. Along with our findings, these results suggest Lp-PLA₂ antigen might be more associated with atherosclerosis than activity is. In contrast to our primary analysis involving participants without baseline CVD, analyses in those with baseline CVD showed associations of
both Lp-PLA₂ antigen and activity with incident CHF. This is compatible with our prior observations of associations of both analytes with MI and suggests that both analytes reflect biologies related to CHF associated with atherosclerosis. This may suggest that both analytes represent biologies reflecting a similar role in those with baseline atherosclerosis.

In stratified analyses, associations between Lp-PLA₂ antigen and CHF were stronger in non-African Americans, with LDL below median, and HDL above median. Our results agree with a previous study which showed that the association between Lp-PLA₂ and coronary heart disease risk was stronger in those with LDL below median\(^2\), but this was not observed in CHS for vascular outcomes (Jenny et al, manuscript submitted). This difference could be due to differing results with different outcomes, different population characteristics or that it is a chance finding. Inconsistent subgroup findings across studies require further evaluation and may be pursued using individual-level meta-analysis.\(^4\)

The pathophysiology explaining an association of Lp-PLA₂ with CHF may relate to Lp-PLA₂ as an inflammation marker.\(^2,3\) Lp-PLA₂, along with LDL particles, is proinflammatory by releasing lysophosphatidylcholine and oxidized nonesterified fatty acids. Our models evaluating biological pathways of Lp-PLA₂ and development of CHF suggested that adjustment for kidney function and other inflammation markers had minimal impact on the association between Lp-PLA₂ and CHF, consistent with the weak correlations of Lp-PLA₂ with renal function and inflammation markers.\(^20\) In previous studies, Lp-PLA₂ was related to different aspects of inflammation than CRP or IL-6.\(^18,27\) Our findings suggest a hypothesis that Lp-PLA₂ may represent a novel inflammatory pathway in the development of CHF. Further, our study suggests that the
association between Lp-PLA₂ antigen and incident CHF is minimally mediated by interval changes of coronary heart disease or baseline common carotid IMT. This could be because atherosclerotic burden was not fully accounted for by adjustment for these factors. However, this may mean that an inflammation pathway involving Lp-PLA₂ plays an important role in cardiac function independent of atherosclerosis. This may be supported by recent findings that Lp-PLA₂ was associated with mortality in a community-based cohort of CHF patients. Lastly, there is a Lp-PLA₂ inhibitor under investigation. Given the current findings, a Lp-PLA₂ inhibitor could be studied in relation to CHF as well as vascular outcomes.

The strengths of our study include measurement of both Lp-PLA₂ antigen and activity, its prospective population-based design, bi-ethnic sample, large sample size, long follow-up, and large number of incident CHF cases. Limitations of the study need to be considered. First, institutionalized individuals and those with short life expectancy were excluded. Thus, the sample was a relatively healthy community-dwelling elderly one and our results cannot be extrapolated to others. Second, the relatively low numbers of African Americans resulted in less power for ethnic-specific analyses. Third, adjustment of interval development of coronary heart disease may not account fully for role of atherosclerosis in CHF etiology. We added common carotid IMT to the model and it did not change the association. Residual confounding could be invoked to suggest that the associations of Lp-PLA₂ with CHF are not independent of subclinical or clinical vascular disease. Lastly, instability of proteins in long-term storage may lead to underestimates of risk in epidemiology studies, but we anticipate this to play a small role of this issue given the documented stability of other proteins in stored samples.
In conclusion, Lp-PLA$_2$ antigen was a risk factor for future CHF in older people, independent of CHF risk factors, other inflammation markers, and atherosclerosis measures. The association was partly mediated by occurrence of coronary vascular events. Further clinical and basic research is needed to better understand the pathophysiological role of Lp-PLA$_2$ in the development of CHF.

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Disclosures

Dr. Jeanenne J Nelson is an employee of GlaxoSmithKline. Dr. Mary Cushman has received modest research support and consulting fees from GSK. All other authors have no conflict of interest.
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Takeki Suzuki, MD, MPH


Takeki Suzuki, MD, MPH

Figure 1. Kaplan-Meier curves for time to CHF by Lp-PLA₂ antigen (1A) or activity (1B) quartiles

Figure 2. Hazard Ratios for Lp-PLA₂ Antigen in the Fourth versus First Quartile Stratified by Other Risk Factors*
Table 1. Baseline Characteristics by Incident CHF Status, Cardiovascular Health Study*

<table>
<thead>
<tr>
<th></th>
<th>No CHF</th>
<th>Incident CHF</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>3162</td>
<td>829</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.8 (5.1)</td>
<td>73.8 (5.6)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1156 (36.6)</td>
<td>338 (40.8)</td>
<td>0.026</td>
</tr>
<tr>
<td>Race (African American)</td>
<td>486 (15.4)</td>
<td>122 (14.7)</td>
<td>0.64</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.4 (4.5)</td>
<td>27.5 (5.2)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>1149 (36.4)</td>
<td>426 (51.4)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>134 (21)</td>
<td>142 (22)</td>
<td>&lt;0.0005</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>71 (11)</td>
<td>71 (12)</td>
<td>0.90</td>
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<tr>
<td>Current smoking (%)</td>
<td>385 (12.2)</td>
<td>99 (12.0)</td>
<td>0.88</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>365 (11.6)</td>
<td>174 (21.0)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LV mass (ECG)</td>
<td>148 (30)</td>
<td>158 (34)</td>
<td>&lt;0.0005</td>
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<tr>
<td>Cholesterol (mg/dL)</td>
<td>213 (39)</td>
<td>210 (38)</td>
<td>0.015</td>
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<td>Triglyceride (mg/dL)</td>
<td>135 (73)</td>
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<td>HDL (mg/dL)</td>
<td>57 (16)</td>
<td>53 (15)</td>
<td>&lt;0.0005</td>
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<td>LDL (mg/dL)</td>
<td>131 (36)</td>
<td>129 (35)</td>
<td>0.24</td>
</tr>
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<td>CRP (mg/L)†</td>
<td>2.30 [1.18,4.00]</td>
<td>2.90 [1.43,6.05]</td>
<td>&lt;0.0005</td>
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<tr>
<td>IL-6 (pg/ml)†</td>
<td>1.55 [1.09,2.29]</td>
<td>1.84 [1.27,2.79]</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)†</td>
<td>311 [274,358]</td>
<td>326 [285,362]</td>
<td>&lt;0.0005</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td>1.00 (0.26)</td>
<td>1.07 (0.46)</td>
<td>&lt;0.0005</td>
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<tr>
<td>Common Carotid IMT (mm)†</td>
<td>1.00 [0.90,1.12]</td>
<td>1.05 [0.96,1.20]</td>
<td>&lt;0.0005</td>
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<tr>
<td>Lp-PLA₂ Antigen (ng/mL)</td>
<td>337.8 (117.3)</td>
<td>351.6 (113.7)</td>
<td>0.003</td>
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<td>Lp-PLA₂ Activity (nmol/min/mL)</td>
<td>38.6 (12.8)</td>
<td>39.6 (12.5)</td>
<td>0.06</td>
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BMI indicates body-mass index; HDL high-density lipoprotein; LDL, low-density lipoprotein; LV, Left ventricular; ECG, electrocardiography; CRP, C-reactive protein; IL-6, interleukin-6; IMT, intima-media thickness.
Takeki Suzuki, MD, MPH

*for continuous variables mean (SD) is shown. For categorical variables percent is shown.

†median [IQR]
Table 2. Hazard Ratios and 95% CIs for Lp-PLA₂ Antigen/Activity Quartiles and Incident CHF. Quartile 1 is the reference group.

<table>
<thead>
<tr>
<th>Model</th>
<th>Lp-PLA₂ Antigen</th>
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<th>Lp-PLA₂ Activity</th>
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<td>Quartile 2</td>
<td>Quartile 3</td>
<td>Quartile 4</td>
<td>Quartile 2</td>
<td>Quartile 3</td>
<td>Quartile 4</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.38 (1.13, 1.69)</td>
<td>1.35 (1.11, 1.66)</td>
<td>1.58 (1.29, 1.92)</td>
<td>1.20 (0.99, 1.45)</td>
<td>1.12 (0.92, 1.36)</td>
<td>1.14 (0.94, 1.39)</td>
</tr>
<tr>
<td>+ Age, sex, clinic site, and race</td>
<td>1.31 (1.07, 1.61)</td>
<td>1.30 (1.06, 1.60)</td>
<td>1.47 (1.20, 1.79)</td>
<td>1.24 (1.02, 1.50)</td>
<td>1.13 (0.93, 1.38)</td>
<td>1.18 (0.97, 1.43)</td>
</tr>
<tr>
<td>+ Risk factors*</td>
<td>1.27 (1.03, 1.57)</td>
<td>1.34 (1.09, 1.66)</td>
<td>1.44 (1.16, 1.79)</td>
<td>1.18 (0.96, 1.44)</td>
<td>1.04 (0.83, 1.29)</td>
<td>1.06 (0.85, 1.34)</td>
</tr>
<tr>
<td>+ Incident CHD (Model A)</td>
<td>1.21 (0.98, 1.50)</td>
<td>1.30 (1.06, 1.61)</td>
<td>1.26 (1.02, 1.57)</td>
<td>1.19 (0.97, 1.46)</td>
<td>1.03 (0.83, 1.28)</td>
<td>1.02 (0.81, 1.28)</td>
</tr>
<tr>
<td>Following parameters added to Model A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.20 (0.97, 1.49)</td>
<td>1.29 (1.04, 1.59)</td>
<td>1.25 (1.01, 1.56)</td>
<td>1.19 (0.96, 1.46)</td>
<td>1.03 (0.83, 1.28)</td>
<td>1.02 (0.81, 1.28)</td>
</tr>
<tr>
<td>Statin and aspirin use</td>
<td>1.21 (0.98, 1.49)</td>
<td>1.30 (1.05, 1.61)</td>
<td>1.27 (1.02, 1.57)</td>
<td>1.19 (0.97, 1.46)</td>
<td>1.03 (0.85, 1.32)</td>
<td>1.03 (0.82, 1.29)</td>
</tr>
<tr>
<td>CRP</td>
<td>1.24 (1.00, 1.54)</td>
<td>1.33 (1.08, 1.64)</td>
<td>1.29 (1.04, 1.60)</td>
<td>1.23 (1.00, 1.52)</td>
<td>1.06 (0.85, 1.32)</td>
<td>1.07 (0.85, 1.35)</td>
</tr>
<tr>
<td>IL-6</td>
<td>1.28 (1.02, 1.60)</td>
<td>1.36 (1.08, 1.71)</td>
<td>1.34 (1.07, 1.69)</td>
<td>1.15 (0.93, 1.44)</td>
<td>1.01 (0.80, 1.28)</td>
<td>1.00 (0.79, 1.28)</td>
</tr>
<tr>
<td>LV mass by ECG</td>
<td>1.26 (1.01, 1.56)</td>
<td>1.34 (1.08, 1.67)</td>
<td>1.33 (1.06, 1.66)</td>
<td>1.19 (0.96, 1.46)</td>
<td>1.03 (0.82, 1.29)</td>
<td>1.02 (0.81, 1.29)</td>
</tr>
<tr>
<td>Common Carotid IMT</td>
<td>1.20 (0.97, 1.48)</td>
<td>1.29 (1.04, 1.60)</td>
<td>1.26 (1.01, 1.56)</td>
<td>1.20 (0.97, 1.47)</td>
<td>1.05 (0.84, 1.31)</td>
<td>1.01 (0.81, 1.28)</td>
</tr>
</tbody>
</table>

*LDL and HDL cholesterol, body-mass index, systolic and diastolic blood pressure, hypertension status, smoking status and pack-years, and diabetes status

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; LV, Left ventricle; ECG, electrocardiography; CRP, C-reactive protein; IL-6, interleukin-6; IMT, intima-media thickness.
Table 3. Combined Association of Lp-PLA₂ Antigen and Inflammation markers on Risk of CHF

<table>
<thead>
<tr>
<th>Lp-PLA₂ antigen in top tertile (316&gt;ng/mL)</th>
<th>Elevated Inflammation Marker</th>
<th>CRP &gt;3 mg/L</th>
<th>IL-6 &gt;2.04 pg/ml</th>
<th>Fibrinogen &gt;338 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)</td>
<td>(-)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>(+)</td>
<td>(-)</td>
<td>1.26 (1.04, 1.54)</td>
<td>1.35 (1.11, 1.64)</td>
<td>1.30 (1.09, 1.55)</td>
</tr>
<tr>
<td>(-)</td>
<td>(+)</td>
<td>1.78 (1.49, 2.12)</td>
<td>1.74 (1.44, 2.09)</td>
<td>1.47 (1.22, 1.76)</td>
</tr>
<tr>
<td>(+)</td>
<td>(+)</td>
<td>2.05 (1.68, 2.51)</td>
<td>2.05 (1.64, 2.56)</td>
<td>1.65 (1.33, 2.05)</td>
</tr>
</tbody>
</table>

RERI% (95% CI) 13.9 (6.3, 21.6) 16.4 (9.7, 23.0) 12.7 (7.2, 18.3)

Adjusted for LDL and HDL cholesterol, body-mass index, systolic and diastolic blood pressure, hypertension status, smoking status and pack-years, and diabetes status. Incident CHD is not included in this model.
Table 4. Hazard Ratios and 95% CIs for Incident CHF by Lp-PLA₂ Quartiles in Subjects with baseline CVD and no CHF.

Quartile 1 is the reference group.

<table>
<thead>
<tr>
<th>Lp-PLA₂ Antigen</th>
<th>Lp-PLA₂ Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quartile 2</td>
</tr>
<tr>
<td>Model</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.21 (0.91,1.62)</td>
</tr>
<tr>
<td>+ Age, sex, clinic site, and race</td>
<td>1.24 (0.93,1.65)</td>
</tr>
<tr>
<td>+ Risk factors*</td>
<td>1.20 (0.90,1.61)</td>
</tr>
<tr>
<td>+ Incident CHD (Model B)</td>
<td>1.20 (0.90,1.61)</td>
</tr>
<tr>
<td>Following parameters added to Model B</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.18 (0.88,1.58)</td>
</tr>
<tr>
<td>statin and aspirin use</td>
<td>1.19 (0.89,1.60)</td>
</tr>
<tr>
<td>CRP</td>
<td>1.19 (0.89,1.59)</td>
</tr>
<tr>
<td>IL-6</td>
<td>1.07 (0.79,1.46)</td>
</tr>
<tr>
<td>LV mass by ECG</td>
<td>1.14 (0.85,1.54)</td>
</tr>
<tr>
<td>Common Carotid IMT</td>
<td>1.18 (0.89,1.60)</td>
</tr>
</tbody>
</table>

* LDL and HDL cholesterol, body mass index, systolic and diastolic blood pressure, hypertension status, smoking status and pack-years, and diabetes status

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; LV, Left ventricle; ECG, electrocardiography; CRP, C-reactive protein; IL-6, interleukin-6; IMT, intima-media thickness.
Figure 2

*Adjusted for age, race, gender, clinic, LDL and HDL cholesterol, body-mass index, systolic and diastolic blood pressure, hypertension status, smoking status and pack-years, diabetes status, and incident CHD as a time-dependent covariate.

Non-AA indicates non-African American; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein.

Low LDL indicates LDL below median (128.7 mg/dL); Low HDL, HDL below median (53 mg/dL); High CRP, ≥ 3mg/L.
Lipoprotein-Associated Phospholipase A₂ and Risk of Congestive Heart Failure in Older Adults: the Cardiovascular Health Study
Takeki Suzuki, Cam Solomon, Nancy Swords Jenny, Russell Tracy, Jeanenne J. Nelson, Bruce M. Psaty, Curt Furberg and Mary Cushman

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