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Plasma Lipoprotein-Associated Phospholipase A2 Levels in Heart Failure: Association with Mortality in the Community

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Abstract

Objective—Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a useful inflammatory marker of cardiovascular risk, yet little is known of its prognostic role in heart failure (HF). We evaluated the association of Lp-PLA2 with mortality in subjects with HF and assessed its incremental value for risk discrimination over established risk factors and biomarkers.

Methods—Residents of Olmsted County, MN, diagnosed with HF between September 2003 and April 2007 (n=646; mean age 76 years; 51% women) were prospectively enrolled and followed-up. Plasma Lp-PLA2 levels were measured at baseline and evaluated along with known risk indicators.

Results—Lp-PLA2 was positively associated with male gender and low-density lipoprotein cholesterol and inversely associated with statin use and diabetes. During follow up (median 21 months), 213 deaths occurred. Elevated Lp-PLA2 was associated with an increased risk of mortality (hazard ratio [HR]=1.57; 95% confidence interval [CI]: 1.03 to 2.37; $P=0.035$, per 1-unit increase in the log-transformed values). The relationship differed markedly by age ($P_{\text{interaction}}=0.003$), with a strong association in patients under 80 years (covariate-adjusted HR=3.83; 95% CI: 1.93 to 7.61; $P<0.001$) and none in older ones (covariate-adjusted HR=0.82; 95% CI: 0.44 to 1.51; $P=0.55$). For the younger subjects, an improvement in the model's discriminatory power was obtained by adding Lp-PLA2 to established risk indicators and biomarkers (area under the receiver operating characteristic curve, 0.709 to 0.744, $P_{\text{difference}}=0.008$).

Conclusion—In this community-based cohort of patients with HF, Lp-PLA2 was strongly and independently associated with mortality and contributed incrementally to risk discrimination in patients under 80 years of age.

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Keywords

Age; Cardiovascular Diseases; Epidemiology; Heart failure; Inflammation; Lipoprotein-associated phospholipase A2; Risk factors; Secondary prevention

Introduction

Much of the recent focus in cardiovascular disease (CVD) research has revolved around the role of inflammatory biomarkers (1–5). The studies generally support a relationship with CVD risk, although the incremental discriminatory power conveyed by these markers over traditional risk factors is still a matter of debate (6–9). Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a novel inflammatory biomarker specific for vascular inflammation (10–13). Observational studies carried out in both primary and secondary prevention settings have found an association between elevated Lp-PLA2 levels and increased CVD risk (14,15). However, little is known of its relationship to heart failure (HF), a unique syndrome that shares some, but not all, characteristics of the other CVD states. Inflammatory mediators previously have been shown to adversely affect left ventricular remodeling, left ventricular function, pulmonary edema, and post-HF survival (16–19). Further, a single study suggested an independent association between Lp-PLA2 and HF incidence in a population-based cohort of healthy individuals (20). However, no data are available on the prognostic role of Lp-PLA2 in patients diagnosed with HF.

The present study was undertaken to evaluate the relationship between Lp-PLA2 and death after HF in contemporary patients from a geographically defined population and to determine its incremental predictive utility over established indicators of risk.

Methods

Study setting

The study was conducted in Olmsted County, MN, where Mayo Clinic and the Olmsted Medical Center provide medical care for all county residents. Each institution uses a unit medical record in which the details of care for a patient, regardless of setting, are available in one place. The records are easily retrievable because Mayo Clinic maintains extensive indices that, through the Rochester Epidemiology Project, are extended to the records of other health care providers in the county, resulting in the linkage of all medical records from all sources of care through a centralized system (21).

Olmsted County (2000 census population, 124,277) is 144 km southeast of Minneapolis and St Paul, with approximately 70% of its population residing in Rochester, the centrally located county seat. In 2000, about 90% of all residents were white and 11% were aged 65 years or older (22). With the exception of a higher proportion being employed in the health care industry, the population characteristics are similar to those of U.S. whites.

Patient enrollment

The parent study, which enabled the present analysis, consists of a prospective observational investigation aimed at characterizing patients diagnosed with HF from a geographically defined population, with emphasis on biomarker evaluation. The details of the enrollment procedures have been described previously (23). Briefly, the case finding and data collection involved a 2-step prospective approach. First, for case finding, we used natural language processing of the unstructured text of the electronic medical record to prospectively identify patients presenting with clinical findings compatible with HF (24). Because most clinical evaluations

are electronically transcribed within 24 hours, this method, which was applied to all care settings including outpatient visits, allows rapid identification by electronic search of the transcribed notes for a wide range of terms indicative of HF. The search was restricted to patients at least 20 years old residing in Olmsted County. This approach yielded 100% sensitivity compared with billing data, which is the desired methodology for case finding (24,25).

Second, the complete records (including inpatient and outpatient records) of potential cases were manually reviewed to validate the diagnosis of HF using Framingham criteria (26) and to collect clinical data. Patients were contacted directly and asked to participate in a study that involves Doppler echocardiography and venous blood draw. The feasibility and reliability of the Framingham criteria for the ascertainment of HF in Olmsted County have been previously published (27).

All participants provided written consent to participate in the study, which was approved by the Mayo Clinic Institutional Review Board.

Risk factor assessment

The characteristics of patients at the time of HF diagnosis were determined from the medical records. Measurements recorded at the index date or at the closest time before or after the index HF were used.

Smoking was classified into current vs. non-current smoking. Diabetes mellitus was defined according to the National Diabetes Data Group criteria (28). Hypertension was defined clinically. Low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were recorded. High-sensitivity C-reactive protein (hs-CRP) and brain natriuretic peptide (BNP) were measured in stored blood samples and were log-transformed for data analysis purposes. Ejection fraction was estimated echocardiographically (23). Medication use before, during and at the time of hospital discharge were recorded. For outpatients, medications prescribed within 7 days post-HF were considered “during” the event, whereas those prescribed after 7 days were considered “at discharge”.

Mortality follow-up

Follow-up was completed by surveillance of medical records. The comprehensive approach in place under the auspices of the Rochester Epidemiology Project ensures complete ascertainment of deaths as it incorporates several sources of information. First, all death certificates for Olmsted County residents are obtained every year from the county office. Second, the Mayo Clinic registration office monitors the obituaries and notices of death in the local newspapers to update the record. Finally, electronic files of death certificates are obtained from the State of Minnesota Department of Vital and Health Statistics (21).

Lp-PLA2 measurement

Blood samples were collected by venipuncture in EDTA tubes. After centrifugation, plasma was stored at -70°C . Lp-PLA2 mass was measured by enzyme-linked immunoassay (PLAC test, diaDexus, Inc., CA) (29). Samples were incubated in microtitre plate wells with an immobilized monoclonal antibody (2C10) against Lp-PLA2. A secondary monoclonal antibody (4B4) labeled with horseradish peroxidase was used to identify the enzyme, and recombinant Lp-PLA2 was used as the standard reference. The range of detection was 50–1000 ng/mL, and the inter-assay coefficients of variation were 7.8% at 276 ng/mL, 6.1% at 257 ng/mL, and 13.5% at 105 ng/mL. The 2C10 monoclonal antibody against Lp-PLA2 has been shown to have no cross-reactivity with other A2 phospholipases (29). Lp-PLA2 is stable in samples stored at 4°C for at least 7 days and repeated freeze thaw cycles (three cycles) do

not affect the measured Lp-PLA2 concentration. Long term stability of Lp-PLA2 has been demonstrated in frozen samples (30). All of the assays were performed by a single investigator who was blinded to the clinical characteristics and patients' outcome.

Statistical analyses

Trends in baseline characteristics across Lp-PLA2 tertiles (≤ 220 ; 221–279; and ≥ 280 ng/mL) were assessed with the Mantel-Haenszel χ^2 test (categorical variables) and linear regression (continuous variables). Survival was assessed by the Kaplan-Meier method with right-censoring at the time of last follow-up. Cox proportional hazards regression models were constructed to evaluate the unadjusted and covariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for death associated with Lp-PLA2. Because Lp-PLA2 displayed a skewed distribution, it was log-transformed and modeled as a continuous variable where appropriate. Variables adjusted for in the multivariable models were those identified earlier as prognostic factors in HF and those that differed between Lp-PLA2 tertiles at baseline. The proportional hazards assumption was tested using the Schoenfeld residuals, with no violations detected. Missing values for ejection fraction (11%), LDL-C (7%), and hs-CRP (23%) were imputed using multiple imputation (31). Given a sample size of 646 patients, an average probability of 45% of surviving to the end of follow-up, and a significance level of 5%, the statistical power to detect a HR of at least 1.40 was 80% in the upper Lp-PLA2 tertile compared with the lower tertiles. All first order interactions between Lp-PLA2 and baseline characteristics were examined. Because age and Lp-PLA2 significantly interacted, analyses were stratified by age (≤ 80 vs. >80 years).

The incremental value of Lp-PLA2 for risk discrimination was assessed by comparing the c-statistic, which represents the area under the receiver operating characteristic (ROC) curve, before and after the inclusion of Lp-PLA2. Calculating the c-statistic and its standard error from a Cox proportional hazards model was performed through a local SAS macro (Walter K. Kremers, 2006), and statistical significance was determined by a method previously described (32). All reported *P* values are two-tailed. SAS 9.1 (SAS Institute Inc., Cary, NC) was used for all statistical analyses.

Results

Between September 2, 2003 and April 1, 2007, 945 consenting patients were enrolled in the parent study. The consent rate during this time period was 69%. This study included 646 patients whose HF met Framingham criteria, who had a clinical diagnosis of HF, and who had Lp-PLA2 measured. The mean (standard deviation) age of the cohort was 76 (13) years and 51% were women. Functional status was impaired in many patients, with 34% and 40% classified as New York Heart Association (NYHA) class 3 and 4, respectively. A quarter of the patients had an ejection fraction below 35%. The baseline characteristics across Lp-PLA2 tertiles are presented in Table 1. Patients with higher levels of Lp-PLA2 were more likely to be men, had higher mean LDL-C levels, and included fewer diabetics. In addition, Lp-PLA2 was inversely associated with statin treatment. No additional differences were detected for other medications. Measured on a continuous scale, the natural logarithm of Lp-PLA2 was modestly correlated with LDL-C ($r=.12$, $P=0.004$), but not with age, body mass index, ejection fraction, HDL-C, hs-CRP, or BNP.

Association between Lp-PLA2 and mortality

Over a median (interquartile range) follow-up of 21 (7–28) months, 213 patients died. The overall survival estimates were 78% (standard error 2%) at 1 year and 56% (standard error 3%) at 3 years. In Cox proportional hazards regression analyses, the HRs for death associated with a 1-unit increase in the log-transformed Lp-PLA2 levels were 1.57 (95% CI: 1.03–2.37; $P=$

0.035) before adjustment, and 1.53 (95% CI: 1.00–2.34; $P=0.050$) after age and gender adjustment. However, assessment of 2-way interactions revealed a strong age-by-Lp-PLA2 interaction ($P=0.003$). The risk of death associated with increased Lp-PLA2 was substantial in patients under 80 years of age, but not in those over 80 years (Table 2; Figure 1). Multivariable adjustment for age, gender, diabetes, hypertension, prior myocardial infarction (MI), incident HF, cerebrovascular disease, peripheral vascular disease, renal disease, ejection fraction, NYHA class, LDL cholesterol, pre-admission statin use, hs-CRP, and BNP yielded HRs of 3.83 (95% CI: 1.93–7.61; $P<0.001$) in the younger group and 0.82 (95% CI: 0.44–1.51; $P=0.55$) in the older group. Similar results were obtained upon adjustment for statin use during hospitalization or at discharge or after controlling for other variables shown in Table 1. The above HR estimates were somewhat sensitive to the cut-off used for age. For example, applying an age cut-off of 75 years resulted in estimates of 3.49 (95% CI: 1.40–8.72; $P=0.008$) in the younger group and 1.05 (95% CI: 0.62–1.77; $P=0.86$) in the older group, whereas using an 85 year cut-off yielded estimates of 2.60 (95% CI: 1.53–4.39; $P<0.001$) and 0.43 (95% CI: 0.19–0.95; $P=0.036$), respectively. Thus, somewhere around 80 years old, elevated Lp-PLA2 was no longer a risk marker in this patient population. Notably, no gender differences were shown in the Lp-PLA2-mortality association ($P_{\text{interaction}}=0.70$).

Contribution of Lp-PLA2 to risk discrimination

For patients under 80 years of age, an improvement in the predictive accuracy of the multivariable model (described above) was observed upon inclusion of Lp-PLA2. The area under the ROC curve increased from 0.709 without Lp-PLA2 to 0.744 with Lp-PLA2 added ($P=0.008$ for the difference between the curves). The relative contribution of Lp-PLA2 measurement to the multivariable Cox regression model in this age group was also indicated by the change in the $-2 \log$ likelihood ($X^2=14.6$; $P<0.001$), which attests to the robustness of the data.

Discussion

In this prospective cohort study of community-dwelling patients with established HF, elevated Lp-PLA2 levels were predictive of mortality in patients under 80 years of age, but not in older ones. In patients under 80 years old, Lp-PLA2 contributed incrementally to the model's discriminatory power beyond established risk factors and biomarkers. Patients with HF may manifest some of the clinical features observed in chronic inflammatory conditions (33). The findings that several proinflammatory cytokines may be involved in the pathogenesis of ventricular dysfunction and may contribute to the cachexia of severe HF have led to a resurgence of interest in the role of inflammation and its markers in HF (17,19). While several biomarkers have been recently evaluated, many inflammatory molecules are involved in the atherothrombotic process and likely provide distinct information (12,18,34).

Lp-PLA2 (also known as platelet-activating factor acetylhydrolase) is an enzyme produced by inflammatory cells. It is thought to circulate bound primarily to small, dense LDL, and is responsible for the hydrolysis of oxidized LDL. Recent studies have focused on the proinflammatory role mediated by products of the Lp-PLA₂ reaction with lipids such as lysophosphatidyl-choline and oxidized free fatty acids (10,12). These bioactive lipid mediators, which are generated in lesion-prone vasculature and to a lesser extent in the circulation, are known to elicit several potentially adverse proinflammatory responses (35,36).

Epidemiological studies in general support the concept that elevated plasma Lp-PLA2 is a risk marker for cardiovascular disease in both primary and secondary prevention settings. Indeed, Garza et al. (15) have recently summarized the results of published studies showing an overall 60% increase in the adjusted risk of cardiovascular events associated with elevated Lp-PLA2 (i.e., highest vs. lowest quantile). However, far less is known about the potential association

of Lp-PLA2 with HF. A single follow-up study involving 1,820 healthy individuals has found a steep dose-response relationship between Lp-PLA2 and HF development (20). Subjects with prevalent and incident coronary artery disease were excluded from analysis, suggesting that the association between Lp-PLA2 and HF is independent of coronary artery disease. Indeed, in patients with no significant coronary artery disease, local production of Lp-PLA2 is associated with the development of endothelial dysfunction (13), and plasma Lp-PLA2 is an independent predictor of endothelial dysfunction (37). Further, endothelial dysfunction has been reported in patients with both ischemic and non-ischemic HF (38), and has been associated with adverse outcomes (39). Thus, Lp-PLA2, a valid marker of endothelial dysfunction, may confer adverse risk in HF patients, but had not been investigated until now.

This study provides novel information on the prognostic value of Lp-PLA2 after HF. First, we assessed the relationship between Lp-PLA2 and mortality and observed a strong independent association and an interaction with age. The attenuation of the association with increasing age is in accordance with previous observations of other lipid-related factors (40). For example, lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality has been reported in subjects older than 70 years (41), and an inverse association between LDL-C and fatal HF has been suggested in another prospective cohort study of elderly persons (42). Importantly, while most of the data pertain to biomarkers in HF are derived from clinical trials, there is under-representation of elderly patients in these trials (43), and consequently some important age-specific associations might have been overlooked. Our community-based design, where there is no exclusion on the basis of age, provides a unique opportunity to study such age-related modifications.

By ROC analysis, we found an incremental value for risk assessment conveyed by Lp-PLA2 over a variety of established risk indicators and biomarkers. This analytical step is essential for the assessment of a new risk marker (44,45).

Compared with other inflammatory markers currently in use, Lp-PLA2 has several potential advantages. Except for a moderate correlation with LDL-C, Lp-PLA2 is only minimally associated with other risk factors (11,46). Further, Lp-PLA2 is not correlated with markers of systemic inflammation (9,30), and is not elevated in unstable angina, non-ST-elevation MI, and ST-elevation MI (47). Our data may have therapeutic implications as well, as inhibitors of Lp-PLA2 have been developed (48) and are currently being assessed in clinical trials.

The following issues should be considered in the interpretation of these data. Although Olmsted County is becoming more diverse, as the study population consisted primarily of U.S. whites, the findings should be evaluated in different racial and ethnic groups. In addition, Lp-PLA2 levels were based on a single measurement, which may result in regression dilution bias (14) and thus conservative effect estimates. Finally, while participation rate for the study was reasonable compared to other community studies of CVD, a selection bias cannot be ruled out (49). However, an overall similarity in HF characteristics between participants and non-participants has been found in a previous report of this cohort (23). Moreover, it was previously demonstrated that in a prospective cohort design, initial non-response does not necessarily affect the risk ratio estimates. For example, participation may differ across exposure categories, but as long as each of these categories is unbiased with respect to outcome, no bias is introduced into the relative risk (50). Thus, we consider it unlikely that a different association between Lp-PLA2 and mortality would have been obtained among the non-respondents.

Conclusions

In this community-based cohort of subjects with HF followed-up for a median of 21 months, elevated Lp-PLA2 levels were associated with decreased survival. This association was

strongly modulated by age. For patients under 80 years, Lp-PLA2 contributed significantly to the predictive accuracy of known clinical indicators and biomarkers, demonstrating its potential for risk stratification after HF.

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Abbreviations

BNP	brain natriuretic peptide
CI	confidence interval
CVD	cardiovascular disease
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HR	hazard ratio
hs-CRP	high-sensitivity C-reactive protein
LDL-C	low-density lipoprotein cholesterol
Lp-PLA2	lipoprotein-associated phospholipase A2
NYHA	New York Heart Association
ROC	receiver operating characteristic

References

1. Biasucci LM. CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: clinical use of inflammatory markers in patients with cardiovascular diseases: a background paper. *Circulation* 2004;110:e560–7. [PubMed: 15611382]
2. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the

Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499–511. [PubMed: 12551878]

3. Berton G, Cordiano R, Palmieri R, Pianca S, Pagliara V, Palatini P. C-reactive protein in acute myocardial infarction: association with heart failure. *Am Heart J* 2003;145:1094–1101. [PubMed: 12796768]
4. Elkind MS, Tai W, Coates K, Paik MC, Sacco RL. High-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2, and outcome after ischemic stroke. *Arch Intern Med* 2006;166:2073–80. [PubMed: 17060536]
5. Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004;350:1387–97. [PubMed: 15070788]
6. Blankenberg S, Yusuf S. The inflammatory hypothesis: any progress in risk stratification and therapeutic targets? *Circulation* 2006;114:1557–60. [PubMed: 17030701]
7. Folsom AR, Chambless LE, Ballantyne CM, et al. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the atherosclerosis risk in communities study. *Arch Intern Med* 2006;166:1368–73. [PubMed: 16832001]
8. Chambless LE, Heiss G, Shahar E, Earp MJ, Toole J. Prediction of ischemic stroke risk in the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 2004;160:259–69. [PubMed: 15257999]
9. Gerber Y, McConnell JP, Jaffe AS, Weston SA, Killian JM, Roger VL. Lipoprotein-associated phospholipase A2 and prognosis after myocardial infarction in the community. *Arterioscler Thromb Vasc Biol* 2006;26:2517–22. [PubMed: 16902161]
10. Caslake MJ, Packard CJ. Lipoprotein-associated phospholipase A2 (platelet-activating factor acetylhydrolase) and cardiovascular disease. *Curr Opin Lipidol* 2003;14:347–52. [PubMed: 12865731]
11. Packard CJ, O'Reilly DS, Caslake MJ, et al. Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 2000;343:1148–55. [PubMed: 11036120]
12. Zalewski A, Macphee C. Role of lipoprotein-associated phospholipase A2 in atherosclerosis: biology, epidemiology, and possible therapeutic target. *Arterioscler Thromb Vasc Biol* 2005;25:923–31. [PubMed: 15731492]
13. Lavi S, McConnell JP, Rihal CS, et al. Local production of lipoprotein-associated phospholipase A2 and lysophosphatidylcholine in the coronary circulation: association with early coronary atherosclerosis and endothelial dysfunction in humans. *Circulation* 2007;115:2715–21. [PubMed: 17502572]
14. Ballantyne C, Cushman M, Psaty B, et al. Collaborative meta-analysis of individual participant data from observational studies of Lp-PLA2 and cardiovascular diseases. *Eur J Cardiovasc Prev Rehabil* 2007;14:3–11. [PubMed: 17301621]
15. Garza CA, Montori VM, McConnell JP, Somers VK, Kullo IJ, Lopez-Jimenez F. Association between lipoprotein-associated phospholipase A2 and cardiovascular disease: a systematic review. *Mayo Clin Proc* 2007;82:159–65. [PubMed: 17290721]
16. Anker SD, von Haehling S. Inflammatory mediators in chronic heart failure: an overview. *Heart* 2004;90:464–70. [PubMed: 15020532]
17. Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. *Circ Res* 2002;91:988–98. [PubMed: 12456484]
18. Vasan RS, Sullivan LM, Roubenoff R, et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation* 2003;107:1486–91. [PubMed: 12654604]
19. Anand IS, Latini R, Florea VG, et al. C-reactive protein in heart failure: prognostic value and the effect of valsartan. *Circulation* 2005;112:1428–34. [PubMed: 16129801]
20. van Vark LC, Kardys I, Bleumink GS, et al. Lipoprotein-associated phospholipase A2 activity and risk of heart failure: The Rotterdam study. *Eur Heart J* 2006;27:2346–52. [PubMed: 16952920]
21. Melton LJ 3rd. History of the Rochester Epidemiology Project. *Mayo Clin Proc* 1996;71:266–74. [PubMed: 8594285]
22. http://factfinder.census.gov/home/saff/main.html?_lang=en

23. Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. *JAMA* 2006;296:2209–16. [PubMed: 17090767]
24. Pakhomov SV, Buntrock J, Chute CG. Prospective recruitment of patients with congestive heart failure using an ad-hoc binary classifier. *J Biomed Inform* 2005;38:145–53. [PubMed: 15797003]
25. Pakhomov S, Weston SA, Jacobsen SJ, Chute CG, Meverden R, Roger VL. Electronic medical records for clinical research: application to the identification of heart failure. *Am J Manag Care* 2007;13:281–8. [PubMed: 17567225]
26. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993;22:6A–13A. [PubMed: 8509564]
27. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004;292:344–50. [PubMed: 15265849]
28. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 1979;28:1039–57. [PubMed: 510803]
29. Caslake MJ, Packard CJ, Suckling KE, Holmes SD, Chamberlain P, Macphee CH. Lipoprotein-associated phospholipase A(2), platelet-activating factor acetylhydrolase: a potential new risk factor for coronary artery disease. *Atherosclerosis* 2000;150:413–9. [PubMed: 10856534]
30. Brilakis ES, McConnell JP, Lennon RJ, Elesber AA, Meyer JG, Berger PB. Association of lipoprotein-associated phospholipase A2 levels with coronary artery disease risk factors, angiographic coronary artery disease, and major adverse events at follow-up. *Eur Heart J* 2005;26:137–44. [PubMed: 15618069]
31. Rubin, D. *Multiple Imputations for Nonresponse in Surveys*. New York: John Wiley & Sons, Inc; 1987.
32. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;148:839–43. [PubMed: 6878708]
33. Katz AM, Katz PB. Diseases of the heart in the works of Hippocrates. *Br Heart J* 1962;24:257–64. [PubMed: 14454369]
34. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;105:1135–43. [PubMed: 11877368]
35. Carpenter KL, Dennis IF, Challis IR, et al. Inhibition of lipoprotein-associated phospholipase A2 diminishes the death-inducing effects of oxidised LDL on human monocyte-macrophages. *FEBS Lett* 2001;505:357–63. [PubMed: 11576528]
36. Hakkinen T, Luoma JS, Hiltunen MO, et al. Lipoprotein-associated phospholipase A(2), platelet-activating factor acetylhydrolase, is expressed by macrophages in human and rabbit atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 1999;19:2909–17. [PubMed: 10591668]
37. Yang EH, McConnell JP, Lennon RJ, et al. Lipoprotein-associated phospholipase A2 is an independent marker for coronary endothelial dysfunction in humans. *Arterioscler Thromb Vasc Biol* 2006;26:106–11. [PubMed: 16239595]
38. Mathier MA, Rose GA, Fifer MA, et al. Coronary endothelial dysfunction in patients with acute-onset idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1998;32:216–24. [PubMed: 9669273]
39. Fischer D, Rossa S, Landmesser U, et al. Endothelial dysfunction in patients with chronic heart failure is independently associated with increased incidence of hospitalization, cardiac transplantation, or death. *Eur Heart J* 2005;26:65–9. [PubMed: 15615801]
40. Lewington S, Whitlock G, Clarke R, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 2007;370:1829–39. [PubMed: 18061058]
41. Krumholz HM, Seeman TE, Merrill SS, et al. Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. *JAMA* 1994;272:1335–40. [PubMed: 7772105]
42. Tikhonoff V, Casiglia E, Mazza A, et al. Low-density lipoprotein cholesterol and mortality in older people. *J Am Geriatr Soc* 2005;53:2159–64. [PubMed: 16398902]
43. Alexander KP, Biswas MS. Heart failure and the elderly: disease diversity, data, and delivery of care. *Am Heart J* 2003;146:194–6. [PubMed: 12891180]

44. Greenland P, O'Malley PG. When is a new prediction marker useful? A consideration of lipoprotein-associated phospholipase A2 and C-reactive protein for stroke risk. *Arch Intern Med* 2005;165:2454–6. [PubMed: 16314539]
45. Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. *Am J Epidemiol* 2004;159:882–90. [PubMed: 15105181]
46. Persson M, Nilsson JA, Nelson JJ, Hedblad B, Berglund G. The epidemiology of Lp-PLA(2): Distribution and correlation with cardiovascular risk factors in a population-based cohort. *Atherosclerosis* 2007;190:388–396. [PubMed: 16530769]
47. Winkler K, Winkelmann BR, Scharnagl H, et al. Platelet-activating factor acetylhydrolase activity indicates angiographic coronary artery disease independently of systemic inflammation and other risk factors: the Ludwigshafen Risk and Cardiovascular Health Study. *Circulation* 2005;111:980–7. [PubMed: 15710755]
48. Blackie JA, Bloomer JC, Brown MJ, et al. The identification of clinical candidate SB-480848: a potent inhibitor of lipoprotein-associated phospholipase A2. *Bioorg Med Chem Lett* 2003;13:1067–70. [PubMed: 12643913]
49. Gerber Y, Jacobsen SJ, Killian JM, Weston SA, Roger VL. Participation bias assessment in a community-based study of myocardial infarction, 2002–2005. *Mayo Clin Proc* 2007;82:933–8. [PubMed: 17673061]
50. Crijqui MH. Response bias and risk ratios in epidemiologic studies. *Am J Epidemiol* 1979;109:394–9. [PubMed: 443238]

Figure 1.

Covariate-Adjusted Survival by Lp-PLA2 Tertiles, Stratified by Age Groups

The curves represent the survival function by Lp-PLA2 tertiles and are derived from a multivariable Cox proportional hazards regression analysis (see Table 2's footnote).

Table 1
Baseline Characteristics by Lipoprotein-Associated Phospholipase A2 Tertiles

Characteristic	Lowest tertile (n=217)	Middle tertile (n=215)	Upper tertile (n=214)	<i>P</i> _{trend}
Lp-PLA2, median (interquartile range), ng/mL	192 (174–204)	247 (232–264)	347 (309–404)	
Age, mean (SD), yrs	76 (13)	76 (13)	77 (14)	0.56
Men, %	44	48	56	0.01
Prior MI, %	24	27	27	0.47
History of congestive HF, %	49	48	53	0.39
PVD, %	27	33	31	0.35
Cerebrovascular disease, %	32	28	35	0.43
Renal disease, %	16	17	16	0.86
Ejection fraction, %				0.77
≥50	52	53	57	
35–49	25	23	18	
<35	23	24	25	
NYHA class ≥3, %	71	74	76	0.26
Cardiovascular Risk Factors				
Hypertension, %	80	80	73	0.09
Diabetes, %	33	36	17	<0.001
Current Smoking, %	8	10	11	0.30
Log-transformed CRP, mean (SD)	0.37 (1.7)	0.29 (1.8)	0.62 (1.7)	0.21
Log-transformed BNP, mean (SD)	5.7 (1.1)	5.6 (1.1)	5.7 (1.1)	0.73
LDL-C [*] , mean (SD), mg/dl	85 (33)	95 (32)	96 (34)	0.001
HDL-C [*] , mean (SD), mg/dl	51 (17)	50 (18)	52 (17)	0.53

Characteristic	Lowest tertile (n=217)	Middle tertile (n=215)	Upper tertile (n=214)	<i>P</i> _{trend}
Statin use [†] , %	65	52	36	<0.001

BNP, brain natriuretic peptide; CRP, C-reactive protein; HF, heart failure; MI, myocardial infarction; PVD, peripheral vascular disease; SD, standard deviation.

* As measured during the index hospitalization or last measurement before admission.

[†] Prior to hospital admission.

Hazard Ratios for Mortality Associated with Lipoprotein-Associated Phospholipase A2

Table 2

	Age ≤ 80 Years (n=354; 88 deaths)			Age > 80 Years (n=292; 124 deaths)		
	HR [*]	95% CI	P	HR [*]	95% CI	P
Unadjusted	2.96	1.62–5.41	<0.001	0.91	0.52–1.60	0.74
Age- and gender-adjusted	3.53	1.90–6.56	<0.001	0.82	0.46–1.46	0.49
Multivariable adjustment [†]	3.83	1.93–7.61	<0.001	0.82	0.44–1.51	0.55

^{*} Per 1-unit increase in the log-transformed Lp-PLA2 levels;

[†] Adjusting for age, gender, diabetes, hypertension, prior MI, history of congestive HF, cerebrovascular disease, peripheral vascular disease, renal disease, ejection fraction, NYHA class, LDL cholesterol, pre-admission statin use, hs-CRP (log-transformed), and BNP (log-transformed).