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Lipoprotein-Associated Phospholipase A_2 Bound on High-Density Lipoprotein Is Associated With Lower Risk for Cardiac Death in Stable Coronary Artery Disease Patients

A 3-Year Follow-Up

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Objectives The aim of this study was to examine the prognostic value of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) associated with high-density lipoprotein (HDL) (HDL-Lp-PLA_2) in patients with stable coronary artery disease (CAD).

Background Lp-PLA_2 is a novel risk factor for cardiovascular disease. It has been postulated that the role of Lp-PLA_2 in atherosclerosis may depend on the type of lipoprotein with which it is associated.

Methods Total plasma Lp-PLA_2 and HDL-Lp-PLA_2 mass and activity, lipids, and C-reactive protein were measured in 524 consecutive patients with stable CAD who were followed for a median of 34 months. The primary endpoint was cardiac death, and the secondary endpoint was hospitalization for acute coronary syndromes, myocardial revascularization, arrhythmic event, or stroke.

Results Follow-up data were obtained from 477 patients. One hundred twenty-three patients (25.8%) presented with cardiovascular events (24 cardiac deaths, 47 acute coronary syndromes, 28 revascularizations, 22 arrhythmic events, and 2 strokes). Total plasma Lp-PLA_2 mass and activity were predictors of cardiac death (hazard ratio [HR]: 1.013; 95% confidence interval [CI]: 1.005 to 1.021; $p = 0.002$; and HR: 1.040; 95% CI: 1.005 to 1.076; $p = 0.025$, respectively) after adjustment for traditional risk factors for CAD. In contrast, HDL-Lp-PLA_2 mass and activity were associated with lower risk for cardiac death (HR: 0.972; 95% CI: 0.952 to 0.993; $p = 0.010$; and HR: 0.689; 95% CI: 0.496 to 0.957; $p = 0.026$, respectively) after adjustment for traditional risk factors for CAD.

Conclusions Total plasma Lp-PLA_2 is a predictor of cardiac death, while HDL-Lp-PLA_2 is associated with lower risk for cardiac death in patients with stable CAD, independently of other traditional cardiovascular risk factors. (J Am Coll Cardiol 2012;60:2053–60) © 2012 by the American College of Cardiology Foundation

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2), also known as platelet-activating factor (PAF) acetylhydrolase, expresses a Ca^{2+}-independent phospholipase A_2 activity and catalyzes the hydrolysis of the ester bond at the sn-2 position of PAF and oxidized phospholipids (1,2). These phospholipids are formed during oxidative modification of low-density lipoprotein (LDL) in the arterial intima and may play important roles in atherogenesis (1,2). Lp-PLA_2 is produced by inflammatory cells such as macrophages, foam cells, T cells, hepatic Kupffer cells, and mast cells (3,4). Lp-PLA_2 circulates in plasma in active form bound to various lipoproteins, primarily to LDL, whereas a minor proportion of circulating enzyme is also associated with high-density lipoprotein (HDL), lipoprotein(a), and remnant lipoproteins (1,5). Lp-PLA_2 is located in advanced rupture-prone plaques, from which it can be released into the circulation (2,6).

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Abbreviations and Acronyms

ACS = acute coronary syndrome
apo = apolipoprotein
CAD = coronary artery disease
CI = confidence interval
HDL = high-density lipoprotein
HDL-Lp-PLA$_2$ = high-density lipoprotein–associated lipoprotein-associated phospholipase A$_2$
HR = hazard ratio
hsCRP = high-sensitivity C-reactive protein
IPAQ = International Physical Activity Questionnaire
LDL = low-density lipoprotein
Lp-PLA$_2$ = lipoprotein-associated phospholipase A$_2$
MET = metabolic equivalent
PAF = platelet-activating factor

Several epidemiologic studies suggest that plasma Lp-PLA$_2$ is an independent predictor of cardiovascular events in primary and secondary prevention (7–15). A recent meta-analysis (9), which included 79,036 participants with or without coronary artery disease (CAD) from 32 prospective studies, showed that Lp-PLA$_2$ activity and mass each had a continuous association with the risk for CAD. Particularly, in the setting of stable CAD, it has been shown that Lp-PLA$_2$ is a significant predictor of nonfatal adverse cardiovascular outcomes independent of traditional clinical risk factors (10).

It has been postulated that the role of Lp-PLA$_2$ in atherosclerosis may depend on the type of lipoprotein with which it is associated (16,17). In contrast to total Lp-PLA$_2$ plasma enzyme, which mainly represents the LDL-associated Lp-PLA$_2$, several lines of evidence suggest that HDL-associated Lp-PLA$_2$ (HDL-Lp-PLA$_2$) may substantially contribute to the antiatherogenic activities of HDL (16). However, the clinical value of HDL-Lp-PLA$_2$ as a potent inhibitor of the atherosclerotic process remains to be established. Thus, the aim of the present study was to explore whether HDL-Lp-PLA$_2$ can predict future cardiovascular events in patients with stable CAD.

Methods

Study population. All patients with stable CAD who attended the outpatient cardiologic department of 3 large hospitals in Athens between 2006 and 2009 were asked to participate in the study. All patients were participants of the LAERTES (Lipoprotein-Associated phospholipasE A2 in stable coronary aRTEry diSease Study), which is an ongoing prospective, hospital-based study investigating the prognostic impact of Lp-PLA$_2$ in stable CAD. We initially screened 620 patients, of whom 524 satisfied the selection criteria and made up the final sample. Subjects were included in the study if they had been previously hospitalized for acute coronary syndromes (ACS), had undergone myocardial revascularization intervention, or had undergone coronary angiography for chest pain and there was documentation of CAD. Coronary artery stenosis was defined as ≥50% reduction in luminal diameter of any of the 3 coronary arteries or their primary branches.

Exclusion criteria were ACS or coronary artery bypass grafting within the previous 6 months, clinical evidence of heart failure, chronic renal failure (creatinine level >2 mg/dl), age >75 years, and coexistent neoplasm or inflammatory disease.

All patients underwent clinical examination and blood testing. The following definitions were used: hypertension, blood pressure ≥140/90 mm Hg and/or antihypertensive treatment; hypercholesterolemia, total cholesterol >200 mg/dl (5.2 mmol/l); diabetes mellitus, fasting plasma glucose >125 mg/dl (6.94 mmol/l) and/or glucose-lowering treatment. Smoking habits were recorded, and body mass index (weight in kilograms divided by the square of height in meters) and waist circumference were also evaluated.

Dietary habits were evaluated using a validated diet score that assesses adherence to Mediterranean dietary patterns (18). The score is derived from a questionnaire that includes 9 major food groups (nonrefined cereals, fruit, vegetables, legumes, potatoes, fish, meat and meat products, poultry, and full-fat dairy products), as well as olive oil and alcohol intake. Each question is scored on a scale of 0 through 5 according to the frequency of food consumption per week, and the diet score ranges between 0 and 55. Higher values of this diet score indicate greater adherence to the Mediterranean diet.

Physical activity was also assessed using a translated short version of the International Physical Activity Questionnaire (IPAQ), an index of weekly energy expenditure using the frequency (times per week), duration (minutes per time), and intensity of physical activity. The IPAQ measures are expressed as metabolic equivalent (MET)–minutes per week. One MET is defined as 3.5 ml oxygen · kg^{-1} · min^{-1}. We used the following MET estimates of the IPAQ: vigorous physical activity = 8 METs, moderate activity = 4 METs, walking on average = 3.3 METs, and sitting = 0 METs. For calculating the overall METs of physical activity, each category was multiplied by its special MET estimate value. The IPAQ has reasonable measurement properties for monitoring population levels of physical activity (19).

Finally, all patients underwent echocardiography, and the ejection fraction of the left ventricle was measured using the biplane method of discs (modified Simpson's rule) (20).

Measurement of Lp-PLA$_2$ activity and mass in total plasma and on HDL. Peripheral blood samples were collected from patients after an overnight fast between 8 AM and 10 AM. Lp-PLA$_2$ activity in total plasma and in apolipoprotein (apo) B–depleted plasma, after the sedimentation of all apo B–containing lipoproteins with dextran sulfate-magnesium chloride (HDL-Lp-PLA$_2$ activity), was determined using the trichloroacetic acid precipitation procedure using [^{3}H]-PAF (100 μmol/l final concentration) as a substrate (21,22). Fifty microliters of total plasma diluted 1:50 v/v with 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid buffer (pH 7.4) or the apo B–depleted