

Lipoprotein-Associated Phospholipase A₂: An Independent Predictor of Coronary Artery Disease Events in Primary and Secondary Prevention

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In recent years, atherosclerosis has become recognized as an inflammatory disease whose activity can be assessed by circulating biomarkers. Along with C-reactive protein (CRP), lipoprotein-associated phospholipase A₂ (Lp-PLA₂) may now be considered as a biomarker with sufficient accumulated evidence to support its application in clinical practice. Lp-PLA₂ is especially appealing because of its vascular specificity, which directly derives from its role in plaque pathophysiology. This article reviews the highlights of the >25 prospective epidemiologic studies now published on Lp-PLA₂ as a risk marker in primary or secondary prevention. These trials demonstrate generally consistent correlations between elevated Lp-PLA₂ levels and the increased risk for cardiovascular events, even after multivariable adjustment for traditional risk factors, with roughly a doubling of risk associated with upper quantile levels. Furthermore, Lp-PLA₂ as a risk predictor has been shown to be independent of and complementary to high-sensitivity CRP. These study results combined with recommendations from the American Heart Association/Centers for Disease Control (AHA/CDC) and the National Cholesterol Education Program III (NCEP III) suggest that Lp-PLA₂ might best be used in current clinical practice to refine risk prediction in those at intermediate cardiovascular risk. An increasingly prevalent group at intermediate risk shown to benefit from Lp-PLA₂ risk modification is the population with the cardiovascular metabolic syndrome, clinically identified as overweight patients with features of mixed dyslipidemia, dysglycemia, and hypertension. An additional application supported by these studies is further risk stratification of high- (often secondary-) risk patients into a group at very high risk, for whom a more aggressive target for low-density lipoprotein of <70 mg/dL (1 mg/dL = 0.02586 mmol/L) is now recommended as a reasonable therapeutic goal. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101[suppl]:23F-33F)

Pioneering research into inflammatory biomarkers has opened up an exciting new era in the assessment of risk in patients with cardiovascular disease (CVD). Of the dozens of candidate biomarkers, there are 2—C-reactive protein (CRP) and lipoprotein-associated phospholipase A₂ (Lp-PLA₂)—that have enough accumulated study evidence to support their utility in clinical practice. Lp-PLA₂ is especially appealing in that it is produced in atherosclerotic plaque, and its biology is linked to the causal pathway of plaque inflammation and ultimate rupture. Elevated Lp-PLA₂ levels have been evaluated as a risk factor for cardiovascular events in >25 prospective epidemiologic studies.¹⁻²⁵

Lp-PLA₂ resides mainly on and travels with low-density lipoprotein (LDL) particles in plasma, although it is also

associated with high-density lipoprotein (HDL) particles, lipoprotein(a), and remnant lipoproteins. Because it is produced by macrophages and foam cells in the vascular intima, it is a more vascular-specific marker than CRP or other hepatic-produced inflammatory markers.²⁶ Lp-PLA₂ is highly upregulated in atherosclerotic plaque, and through hydrolysis of oxidized LDL particles, this enzyme generates 2 proinflammatory mediators: lysophosphatidylcholine and oxidized fatty acid. In preclinical animal studies, inhibition of the enzyme attenuates the inflammatory process and slows atherosclerotic disease progression, suggesting that it is not only a risk marker but also a candidate risk factor because it is intimately involved in the causal pathway of the intimal inflammatory cascade. Finally, Lp-PLA₂ has low biologic variability, which along with its high specificity for vascular inflammation, makes it a practical tool for assessing risk in both the primary and secondary prevention settings and for potentially allowing serial assessment over time. The purpose of this article is to review the evidence for Lp-PLA₂ as a risk marker additive to traditional risk factors for primary and secondary

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Statement of author disclosure: Please see the Author Disclosures section at the end of this article.

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