

# Lipoprotein-Associated Phospholipase A<sub>2</sub>: A Risk Marker or a Risk Factor?

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**Multiple cardiovascular biomarkers are associated with increased cardiovascular disease (CVD) risk. Lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>) appears to be relatively unique in its high specificity for and the causal pathway of plaque inflammation. In both primary and secondary prevention study populations, Lp-PLA<sub>2</sub> was consistently associated with higher cardiovascular risk, and the risk estimate appears to be relatively unaffected by adjustment for conventional CVD risk factors. Risk ratios were similar, whether the mass concentration or activity of the enzyme was measured. The purpose of this article is to review the evidence for the clinical utility of Lp-PLA<sub>2</sub>, both as a risk marker and as a risk factor involved in the causal pathway of plaque inflammation and the formation of rupture-prone plaque. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101[suppl]: 11F–22F)**

Lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>) is among the multiple cardiovascular biomarkers that have been associated with increased cardiovascular disease (CVD) risk. Lp-PLA<sub>2</sub> appears, however, to be relatively unique in its high specificity for vascular inflammation as opposed to systemic inflammation, its low biologic variability, and its direct role in the causal pathway of plaque inflammation. In a recent meta-analysis by Garza et al,<sup>1</sup> 14 prospective epidemiologic studies of > 20,000 patients were pooled in an examination of Lp-PLA<sub>2</sub> as an independent risk factor for cardiovascular events. For quantile-based (upper quantile vs bottom quantile) comparisons, the risk ratios were 1.86 (95% confidence interval [CI], 1.47-2.34) and for risk per 1 change in standard of deviation in the marker, the relative risk was 1.21 (95% CI, 1.11-1.32). In both primary and secondary prevention study populations, Lp-PLA<sub>2</sub> was consistently associated with a higher cardiovascular risk, and as stated by the investigators, “the risk estimate appears to be relatively unaffected by adjustment for conventional CVD risk factors.” Risk ratios were similar, whether the mass concentration or activity of the enzyme was measured. They found that Lp-PLA<sub>2</sub> levels may be useful to further stratify patients with an intermediate probability of developing cardiovascular events by the Framingham score. The purpose of this article is to review the evidence for the clinical utility of Lp-PLA<sub>2</sub> both as a risk

marker and as a risk factor involved in the causal pathway of plaque inflammation and the formation of rupture-prone plaque. Thus, it may be speculated that specific therapies after Lp-PLA<sub>2</sub> measurement may be of beneficial effect to decrease cardiovascular risk.

## Pathophysiology of Lipoprotein-Associated Phospholipase A<sub>2</sub> and Mechanism of Action

A cardiovascular biomarker should be directly involved in the causal pathway of plaque formation and inflammation. Lp-PLA<sub>2</sub> is a member of a family of intracellular and secretory phospholipase enzymes that are capable of hydrolyzing the sn-2 ester bond of phospholipids of cell membranes and lipoproteins.<sup>2</sup> In fact, Lp-PLA<sub>2</sub> attached to low-density lipoprotein (LDL) is the enzyme solely responsible for the hydrolysis of oxidized phospholipid (oxPL) on the LDL particle.<sup>3</sup> It differs from the other phospholipase enzymes in that its activity is calcium independent and it lacks activity against the naturally occurring phospholipids present on the cellular membrane.<sup>4,5</sup> Thus, Lp-PLA<sub>2</sub> hydrolyzes oxPL on the surface of lipoproteins but has weak activity against non-oxPL. In terms of location on apolipoprotein B-containing lipoproteins, Stafforini et al<sup>6</sup> demonstrated that Lp-PLA<sub>2</sub> interacts directly with apolipoprotein B-100, and that the carboxyl terminus of this apolipoprotein is required for such interaction.

Earlier reports found that approximately 80% of Lp-PLA<sub>2</sub> (a subtype of the PLA<sub>2</sub> family) circulates bound to LDL, whereas the other 20% is bound to high-density lipoprotein (HDL) and remnant lipoprotein particles. However, the distribution of Lp-PLA<sub>2</sub> between HDL and LDL particles may be more variable than previously reported.<sup>7</sup> It has been shown that the distribution of Lp-PLA<sub>2</sub> between LDL and HDL depends on the extent of its glycosylation,

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