Editorial

An evolving story of lipoprotein-associated phospholipase A2 in atherosclerosis and cardiovascular risk prediction

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Online publish-ahead-of-print 8 December 2004

This editorial refers to ‘Association of lipoprotein-associated phospholipase A2 levels with coronary artery disease risk factors, angiographic coronary artery disease, and major adverse events at follow-up’ by E.S. Brilakis et al., on page 137

Over the past 50 years, the age-adjusted mortality rate from cardiovascular disease has decreased substantially. Despite the improved mortality rate, there is evidence that actual cardiovascular event rates remain relatively unchanged (i.e. more people are surviving acute events), and heart disease and stroke continue to be leading causes of death in Western societies.1 Intensive research efforts are currently under way with the goal of further reducing the global burden of cardiovascular disease. An improved understanding of vascular biology and the pathogenesis of atherosclerosis—including the role of inflammatory processes—may prove helpful in achieving this goal.

Atherosclerosis is a condition involving numerous complex processes within the vessel wall that can be characterized as an inflammatory response to injury. The ‘injury’ is most likely attributable to oxidized low-density lipoprotein (LDL) cholesterol, and the inflammatory response is mediated predominantly by monocyte-derived macrophages and T-lymphocytes.2 Together, these cells, along with endothelial cells and vascular smooth muscle cells, express or enhance the expression of inflammatory mediators—cytokines, chemokines, adhesion molecules, growth factors, and other bioactive substances—that play an important role in each stage of atherosclerosis, from initial plaque formation to plaque (in)stability/rupture.

Improvements in the understanding of vascular biology have led investigators to evaluate whether certain components of the inflammatory processes may be helpful in identifying high-risk individuals with vulnerable plaques. Examples of inflammatory markers being evaluated for an association with prevalent or incident cardiovascular disease include interleukin-1, tumour necrosis factor-α, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, fibrinogen, interleukin-6, and C-reactive protein (CRP).

While a positive association between these or other inflammatory markers and cardiovascular risk may exist, the applicability to clinical practice is dependent on several factors. Such factors include: assay standardization, independence from established risk factors, association with cardiovascular events (e.g. myocardial infarction, stroke) in observational studies and clinical trials, well-defined distribution in the general population (i.e. population norms), predictive power beyond that of traditional risk factors, generalization to various patient populations, and acceptable assay cost.3

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a novel marker that has been studied only recently for an association with prevalent and incident cardiovascular events. The biology of Lp-PLA2 has been studied extensively, but was previously described as platelet activating factor acetylhydrolase (PAF-AH). Because of its ability to degrade PAF, this enzyme was historically considered to be atheroprotective. However, the enzyme has significantly broader substrate specificity than only PAF (various polar phosphatidylcholines), and recent studies evaluating the biology of this enzyme suggest it may play a key role in promoting atherosclerosis.

In humans, Lp-PLA2 is bound predominantly to LDL-cholesterol particles, and remains latent until the LDL-cholesterol particles undergo oxidative damage. Lp-PLA2 acts immediately following oxidization to
cleave the oxidized phosphatidylcholine into two bioactive compounds—lysophosphatidylcholine (Lyso-PC) and oxidized free fatty acids—that contribute significantly to the inflammatory processes involved in atherosclerosis.

Lp-PLA₂ was first shown to be an independent marker of incident coronary heart disease (CHD) in a nested case–control study involving individuals from the West of Scotland Coronary Prevention Study (WOSCOPS). In this study, there was a 60% increase in the risk of events (CHD death, non-fatal MI, need for revascularization) in the highest quintile of Lp-PLA₂ compared with the lowest, after adjusting for traditional risk factors, CRP, fibrinogen, and white blood cell count. Subsequent to WOSCOPS, Lp-PLA₂ has been evaluated in other epidemiology studies, with slightly discordant results observed. In the Women's Health Study, the relative risk between the highest and lowest quartile of Lp-PLA₂ did not achieve statistical significance in a multivariate model among 123 cases and 123 matched controls. In the population-based Atherosclerosis Risk in Communities (ARIC) study comprised of middle-aged men and women, there was a statistically significant difference in relative risk between the highest and lowest tertiles of Lp-PLA₂, but only for those with LDL-cholesterol levels below the median value (<130 mg/dL). In the most recent study, MONICA-men Augsburg, Lp-PLA₂ predicted incident CHD independent of traditional risk factors and hsCRP.

Brilakis et al. report the results from another study evaluating the association of Lp-PLA₂ with incident cardiovascular events (fatal CHD, non-fatal MI, need for revascularization, stroke). In this study, the risk of an event increased by 28% (95% CI 1.06–1.54) per standard deviation increase in Lp-PLA₂, independent of traditional risk factors and CRP. Another important finding of this study was the observation that Lp-PLA₂ was higher among participants with events than among those without an event. The results by Brilakis et al., along with those from recently presented studies, complement the observations from previously published studies (WOSCOPS, ARIC, MONICA), thereby contributing to the growing body of evidence that Lp-PLA₂ appears to be an independent marker of cardiovascular risk.

An important issue regarding Lp-PLA₂ stemming from previously published studies is whether there is effect modification by LDL-cholesterol on the association between Lp-PLA₂ and cardiovascular risk. In the present study, there was a similar association at all levels of LDL-cholesterol, which contrasts with the ARIC results. More recent studies may help clarify this issue.

Another important question is whether Lp-PLA₂ is predictive of future events in various populations at risk. The current study consisted almost entirely of Caucasians (97%), and based on the exclusion criteria (no persons with diabetes or prior coronary revascularizations, or heavy smokers) and clinical characteristics, the study population had a relatively low baseline risk for future events. This is reflected in the proportion of patients with no evidence of coronary artery disease (CAD) (24%) at baseline, and the relatively low incidence of events (13%) throughout the four-year follow-up period.

However, the clinical circumstances warranted coronary angiography in each study participant, which inherently suggests a higher-risk population. Diabetics and heavy smokers comprise high-risk groups for underlying inflammatory processes; understanding the association between Lp-PLA₂ and cardiovascular risk in these high-risk groups will be helpful in clarifying a causal role for the enzyme in atherogenesis.

It is important to note that in this study the association of Lp-PLA₂ with severity of CAD at baseline, as defined by angiographic evidence, did not persist after accounting for traditional risk factors; yet Lp-PLA₂ was an independent predictor of incident cardiovascular events. Whether this observation is a reflection of plaque vulnerability vs. arterial lumen narrowing requires further investigation. Another interesting finding in the present study is that Lp-PLA₂ did not differ significantly between patients with and without an acute coronary syndrome, though this may be a reflection of the metabolic changes experienced during acute phase ischemia.

Clearly, the role of Lp-PLA₂ in cardiovascular risk prediction is intriguing, and is further supported by the study by Brilakis et al., as well as by recent findings from other investigators. Despite the growing body of evidence, the current knowledge base regarding this enzyme is relatively limited. Important issues that require clarification include: predictive power in various populations at risk (to validate Lp-PLA₂ as an independent cardiovascular risk factor), inter- and intra-individual variability, the distribution and correlates of Lp-PLA₂ with demographic variables and conventional risk factors within general populations, and the influence of genetic polymorphisms on cardiovascular risk. As more pieces of information become available, the story will continue to unfold.

References


