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Lipoprotein-Associated Phospholipase A₂ and Risk Stratification for Cardiovascular Disease: Not Ready for “Prime Time”

Cardiovascular disease (CVD) was the underlying cause or contributing cause of death in 58% of all deaths in the United States in 2003. Since 1900, CVD has been the No. 1 killer in the United States every year except 1918, when the influenza pandemic took more lives.¹

With CVD being responsible for such staggering mortality, the discovery of a novel risk factor for this disease can surely be considered one of the “holy grails” of medicine. Discovering modifiable risk factors is of prime importance because they may hold the possibility of reducing morbidity and mortality. However, identifying factors that add only to risk stratification are also valuable. Treatment decisions for many important disease states, hyperlipidemia being a prime example, are now based more on baseline risk than on levels of physiologic markers.

Fueled by the discovery of inflammatory cells in the cap of atherosclerotic plaques², research has focused on whether markers of inflammation can aid in the prediction of CVD. Many novel markers of CVD, both inflammatory and noninflammatory, have been discovered and studied. A partial list includes C-reactive protein (CRP), lipoprotein-associated phospholipase A₂ (Lp-PLA₂), homocysteine, E-selectin, plasminogen, interleukin 6, and vitamin B₆.

In the first systematic review of the topic, Garza et al³ examined the association between Lp-PLA₂ and CVD. Lipoprotein-associated phospholipase A₂, also known as platelet-activating factor acetylhydrolase, is an enzyme that circulates bound to low-density lipoproteins, high-density lipoproteins, and very low-density lipoproteins. The role of Lp-PLA₂ is unclear. Both proatherogenic and antiatherogenic mechanisms have been proposed. Lipoprotein-associated phospholipase A₂ leads to formation of lysophosphatidylcholine, a mediator of inflammation that

is proatherogenic.⁴ On the other hand, Lp-PLA₂ could be protective by reducing inflammation and the propensity for thrombosis in blood through its hydrolysis of platelet-activating factor.⁵

Garza et al are to be commended for their rigorous methodology. They describe a clear and focused question and search strategy, conducted duplicate searching and source abstraction, resolved disagreements by consensus, and defined subgroups a priori. They acknowledge that publication bias may be present but made efforts to limit this by contacting experts in the field in a search for possible unpublished data and by including studies published only in abstract form. Follow-up for some studies in the review was as short as 3 to 4 years, although all studies (except those published in abstract form) were rated highly on the Newcastle-Ottawa Scale, a tool used for quality assessment of cohort and case-control studies. Overall, the systematic review is valid and represents the best available evidence on the subject. To our knowledge, it is the first article to provide a pooled estimate of the association between Lp-PLA₂ and the risk of CVD.

Garza et al report an unadjusted odds ratio of 1.51 (95% confidence interval [CI], 1.30-1.75) for the association between elevated Lp-PLA₂ and CVD. When adjusted for traditional CVD risk factors and CRP, the odds ratio was 1.60 (95% CI, 1.36-1.89). Moderate heterogeneity was found across the studies (I²=67.4%). Despite this, an association between elevated Lp-PLA₂ and CVD appears to exist.

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Although meta-analytic confirmation of this association is notable, clinicians must not “jump the gun.” Important questions should be answered before Lp-PLA₂ is incorporated into clinical practice, and the authors acknowledge this fully in their discussion.

The first of these questions is whether measurement of Lp-PLA₂ yields additional predictive power beyond that already provided by an assessment of traditional cardiovascular risk factors and by current scoring systems such as the Framingham Risk Score. Given the weak association between Lp-PLA₂ and CVD, this seems unlikely. If a patient’s baseline probability of CVD is 50%, plotting an odds ratio of 1.60 on a Bayesian nomogram results in a posterior probability of about 59%, a relatively small increase.⁶ Such small changes in probability rarely translate into changes in patient management or reclassification of patients into different risk groups.

The data on CRP can also serve as a rough guide in evaluating whether Lp-PLA₂ will make the leap from being a biomarker associated with CVD to one that helps predict CVD in clinical practice. Despite a clear association with CVD, and all the excitement in the literature that has accompanied this, the role of CRP in risk stratification for CVD remains questionable.

A recent meta-analysis of 22 prospective studies examined CRP as a predictor of cardiovascular events. For the highest compared with the lowest quartile of CRP, the authors report a multivariable adjusted odds ratio for coronary heart disease of 1.58 (95% CI, 1.48-1.68).⁷ A recent review examined the value of CRP measurement in the overall population and in patients judged to be at high (>20%) and low (<10%) risk for CVD by the Framingham Risk Score. Measurement of CRP did not add additional predictive value in any of these groups (CRP level >0.3 mg/dL was found to be possibly useful in intermediate groups, but further study was advised).⁸

Given that the odds ratio for the association between Lp-PLA₂ and CVD is *similar* to that of CRP, the contribution to risk stratification for CVD by Lp-PLA₂ may prove to be extremely small. An analysis of the Atherosclerosis Risk in Communities Study, which aimed to assess the association of 19 novel risk factors with coronary heart disease in a cohort of 15,792 adults, supports this view. The authors found that Lp-PLA₂ resulted in an extremely small increase in the area under the receiver operating curve of only 0.006. Measurement of Lp-PLA₂ (and CRP) in that population added virtually nothing to the 5-year predicted risk of a coronary heart disease event based on assessment of traditional risk factors.⁹

Is it really possible that novel risk factors such as Lp-PLA₂, CRP, and homocysteine, each having been met with such fanfare and excitement and each already ordered hun-

dreds of times in academic medical centers by the best of the best in medicine, add so little to risk stratification? The answer, at least at this point, seems to be a resounding (and for some a troubling) “yes.” As has happened time and again, enthusiasm has charged ahead of the evidence, only to be steadily deflated by thoughtful debate and subsequent research.

Of course, what systematic reviews or large studies of general populations gain in power, they lose in applicability and focus. It is certainly possible that further studies of Lp-PLA₂ in narrower patient populations, which target specific outcomes, might yield more promising results.

Clinicians have another reason to wait before incorporating Lp-PLA₂ into practice. The operating characteristics of the Food and Drug Administration–approved test for Lp-PLA₂, the PLAC test (diaDexus Inc, San Francisco, Calif), have not been adequately established, despite optimism on the company’s Web site (www.plactest.com). Decisions about the utility of a novel biomarker should not be based solely on measurements of association, such as odds ratios or relative risk. Instead, clinical decision making should be guided by the performance characteristics of the diagnostic test that measures the biomarker.⁸ Test characteristics can vary significantly between patient populations. The positive and negative likelihood ratios of the PLAC test for patients at low-, intermediate-, and high-risk of various cardiovascular outcomes need to be clarified if the test is to be used in these populations. Furthermore, prospective studies need to be performed to determine whether the use of the PLAC test, or any other test of Lp-PLA₂, leads to meaningful changes in patient management. As mentioned previously, the weak association between Lp-PLA₂ and CVD makes this unlikely.

Even if a novel biomarker does not contribute to risk stratification, it can still be a target for therapy and risk reduction. At the same time, the fact that Lp-PLA₂ is associated with CVD does not mean it can be relied on as a surrogate marker of morbidity or mortality. Clinical trials of drug therapy will surely track Lp-PLA₂ levels, but they must also measure clinical outcomes.

Do drugs that target Lp-PLA₂ even need to be developed? In the same way that novel risk factors must demonstrate additive predictive value, new medications should ideally improve outcomes above and beyond that accomplished by current treatments of CVD. The physiology of Lp-PLA₂ seems to be somehow linked to lipid metabolism and inflammation. Is it possible that widespread statin use, which has changed and grown considerably since many of the patients in the studies reviewed herein were enrolled, is already offsetting the small increased risk of CVD that elevated Lp-PLA₂ might confer? This question highlights a critical goal for researchers of

Lp-PLA₂ drug therapy—randomized controlled trials must be performed against background therapy that reflects current practice. Not until this work is done, likely many years and many debates from now, will we know if lowering Lp-PLA₂ with targeted drug therapy is good for patients.

In the meantime, what is a busy clinician to do? Risk stratification for CVD should continue to be based on well-established traditional risk factors and widely accepted tools such as the Framingham Risk Score. Neither Lp-PLA₂ nor CRP⁸ should be used for screening or risk stratification until further study. Regarding Lp-PLA₂ specific drug therapy, healthy skepticism is advised. Life can be good for pharmaceutical companies and industry-sponsored physicians before the benefits (or harms, see comments on Natrecor¹⁰) of a new drug become evident. Responsible clinicians will resist the temptation to prescribe on the basis of pharmaceutical claims and inadequate information and wait for solid data instead.

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