Role of Lipoprotein-Associated Phospholipase A2 in Predicting Risk of Cardiovascular Disease

To the Editor: In their editorial accompanying the meta-analysis of lipoprotein-associated phospholipase A2 (Lp-PLA2) by Garza et al, Steinberg and Mayer brought up important points regarding the use of markers to predict risk of cardiovascular disease (CVD) before solid evidence is available to support such use. Although Lp-PLA2 is indeed considered a “novel risk factor,” I believe the authors made an incomplete and inaccurate statement about the role that Lp-PLA2 may play in the prediction of myocardial infarction and stroke, both of which are major components of CVD.

The Atherosclerosis Risk in Communities (ARIC) study suggested that Lp-PLA2 is a moderately strong predictor of risk of stroke and that the association between Lp-PLA2 and stroke is statistically independent of traditional risk factors. This study, as well as several others examining Lp-PLA2, and stroke, was neither mentioned in the editorial nor included in the meta-analysis. In fact, Garza et al did not include the term stroke in their literature search; an omission that would undoubtedly affect the authors’ findings. Of note, the US Food and Drug Administration has approved the PLAC test for measurement of Lp-PLA2, to predict stroke.

Interestingly, Steinberg and Mayer used high-sensitivity C-reactive protein as a comparator to Lp-PLA2. C-reactive protein is an acute phase reactant and inflammatory marker that has been shown to be a predictor of CVD risk. However, C-reactive protein elevation is not specific for CVD and may be present in other disorders as well. Lipoprotein-associated phospholipase A2, is an enzyme (platelet-activating factor acetylhydrolase) that is bound to low-density lipoprotein cholesterol. Although the precise mechanisms by which Lp-PLA2 confers risk have not been completely delineated, it appears to be relatively specific for CVD risk.

Finally, while I agree that the Framingham Risk Score has certainly held its own over the years, I disagree with the authors’ assertion that busy clinicians should use this tool for risk stratification. Many other factors can add to the predictive value of the Framingham score. Risk prediction is currently a very good, but not perfect, science. Undoubtedly, refinement of currently available methods will ultimately allow physicians to better determine who is at low or high risk for a CVD event. As novel factors emerge, we need to carefully evaluate all the evidence to support clinical applications. In their editorial, Steinberg and Mayer unfortunately took an incomplete look at Lp-PLA2.

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In reply: We thank Dr Myerson for his interest in our systematic review. However, we would like to address some of his comments on the relevance of stroke in our article.

First, we did search for stroke using many different terms but listed only a few examples, as explained by the abbreviation eg. Of the 14 studies selected for analysis, 4 included stroke as a separate outcome. When we tested subgroup interaction of studies that listed stroke as a separate outcome vs studies without stroke, no significant difference was noted (P=92). We chose a priori CVD as the outcome of interest and decided not to analyze different manifestations separately.

Second, the studies we identified that tested the association between Lp-PLA2 and stroke, including the article mentioned by Dr Myerson, had also reported the association between Lp-PLA2 and a more inclusive definition of CVD, either in the same report or in a previous one. Therefore, we decided to include the reports with a wider definition of CVD. Because meta-analytical techniques assume that pooled odds ratios are derived from independent samples, including 2 values of association from the same study population would be inappropriate.

Concerning C-reactive protein, we completely agree with Dr Myerson’s comments, as we stated in the Discussion part of our article that C-reactive protein is nonspecific and that Lp-PLA2 seems to be a specific marker of vascular inflammation. However, we still believe that clinicians should use the Framingham Risk Score for risk stratification first and consider using novel markers of risk in patients with intermediate risk, as recommended in the American Heart Association guidelines for primary prevention of CVD.

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