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 prevention.
coronary events and to review commentary in recent guidelines relating to the use of inflammatory markers in clinical practice.

Assessment of Risk Using Lipoprotein–Associated Phospholipase A2 in Primary Prevention Studies

The key clinical trials that have evaluated the relative risk and the hazard or odds ratios for Lp-PLA2 in primary and secondary prevention studies are shown in Table 1 and Table 2.1–25 Hazard and odds ratios generally express the risk of a cardiovascular event based on being in the top quintile compared with the bottom quintile of the Lp-PLA2 level (eg, top tertile vs bottom tertile or top quartile vs bottom quartile). Relative risk in these trials is generally defined as the relative risk per 1 standard deviation increase in Lp-PLA2 level as a continuous variable. These trials demonstrate generally consistent and statistically significant correlations between elevated levels of Lp-PLA2 and increased risks for cardiovascular events. It should be noted that the results reflect a full multivariable adjustment for traditional risk factors, indicating the independent contribution of Lp-PLA2 beyond traditional risk factors in risk assessment. Overall, elevated Lp-PLA2 is associated with roughly a doubling of risk, with some attenuation in the elderly population.

Prospective Epidemiologic Studies of Elevated Lipoprotein-Associated Phospholipase A2 as a Predictor of Coronary Events in Primary Prevention

As listed in Table 1, there have been several studies of Lp-PLA2 elevation as a predictor of coronary events in primary prevention. The first major study evaluating Lp-PLA2 as a risk marker was the West of Scotland Coronary Prevention Study (WOSCOPS), a trial evaluating the role of pravastatin in the prevention of coronary events that was published in 2000.1 WOSCOPS provided the first evidence that Lp-PLA2 could be a potential biomarker for cardiovascular risk assessment. As shown in Figure 1, in WOSCOPS, both high-sensitivity CRP (hs-CRP) and Lp-PLA2 are correlated by quintiles with an increase in cardiovascular risk, with a statistically significant risk increase above the 40th percentile (2nd quintile). In the third, fourth, and fifth quintiles of Lp-PLA2 elevation, there is almost a doubling of risk for cardiovascular events. This risk was not confounded by traditional risk factors or hs-CRP or leukocyte count, as demonstrated by multivariable adjustment. Although there were weak-to-modest but significant associations of Lp-PLA2 levels with total and LDL cholesterol levels, the Lp-PLA2 level was independent of age, body mass index, systolic and diastolic blood pressure, and even smoking status. As the risk ratio within each quintile is adjusted for progressively more traditional risk factors, Lp-PLA2 continues to demonstrate a consistent relation with risk, whereas the risk associated with elevated hs-CRP is markedly attenuated as more traditional risk factors are added into the model.1

Another large prospective study, the Atherosclerosis Risk in Communities (ARIC) trial, found that Lp-PLA2 levels were higher in middle-aged US men and women who subsequently developed coronary artery disease (CAD) events than in those who remained free of CAD.4 Individuals with incident CAD had a significantly higher body mass index, systolic blood pressure, and levels of total cholesterol, triglycerides, and LDL cholesterol, and significantly lower HDL cholesterol levels than patients without incident CAD. Hypertension, diabetes mellitus, and current smoking were more prevalent in CAD cases. In addition to these differences in traditional risk factors, the weighted mean levels of both Lp-PLA2 and hs-CRP were higher in patients with CAD events than in those without events. Weak-to-modest correlations of Lp-PLA2 levels to lipids were noted, with positive correlations to LDL cholesterol and total cholesterol levels and a negative correlation to HDL cholesterol level, in both men and women. Lp-PLA2 levels also correlated weakly with triglycerides. Importantly, there was no significant correlation between Lp-PLA2 levels and body mass index. This observation suggests an advantage in specificity over CRP because persons with abdominal adiposity have been shown to release cytokines from their mesenteric fat that stimulate hepatic expression of CRP and several other inflammatory markers, potentially weakening the link between the serum levels of these other markers and vascular inflammation. In addition, Lp-PLA2 levels were independent of other traditional risk factors, such as systolic and diastolic blood pressure. Lp-PLA2 levels also were independent of CRP levels.

This is the only study where adjustment for LDL cholesterol attenuated the risk ratio for Lp-PLA2. However, when patients with LDL cholesterol levels below the median (130 mg/dL) (1 mg/dL = 0.02586 mmol/L) were considered separately, elevation of the Lp-PLA2 enzyme was again significantly associated with a doubling of risk for coronary events. Because current guidelines call for an LDL cholesterol level <130 mg/dL in intermediate-risk persons, the intermediate- or moderate-risk patient who has achieved this lipid goal may benefit from the use of Lp-PLA2 to further assess residual risk. The ARIC results support the proposal that Lp-PLA2 and hs-CRP may be useful to identify intermediate-risk patients with an LDL cholesterol target level <130 mg/dL to assess residual risk, which might warrant reclassifying their risk status from intermediate to high risk: a risk doubling of an intermediate-risk person with 10%–20% 10-year risk would put the person into the high-risk >20% 10-year risk category. Interestingly, in the ARIC study when both Lp-PLA2 and hs-CRP were elevated (top tertile), the risk for coronary events increased by 4-fold and for stroke by 11-fold compared with the bottom tertile for each marker.4,27 The Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA)–Augsburg study also found that risk
Elevated lipoprotein-associated phospholipase A2 (Lp-PLA2) as a predictor of incident cardiovascular (CV) events or severe coronary artery disease

Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>CV End Point</th>
<th>Year</th>
<th>Population</th>
<th>#Cases/#Controls</th>
<th>Relative Risk (95% CI)</th>
<th>Hazard/Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS1</td>
<td>Coronary events</td>
<td>2000</td>
<td>Men with hypercholesterolemia</td>
<td>580/1,160</td>
<td>1.18 (1.05–1.33)</td>
<td>1.80 (1.3–2.6)</td>
</tr>
<tr>
<td>WHS2</td>
<td>Coronary events</td>
<td>2001</td>
<td>Healthy women</td>
<td>123/123</td>
<td>1.17 (0.5–3.0)</td>
<td>—</td>
</tr>
<tr>
<td>ARIC4</td>
<td>Coronary events</td>
<td>2004</td>
<td>Healthy subjects</td>
<td>608/740</td>
<td>1.15 (0.8–1.6)</td>
<td>2.08 (1.2–3.6)</td>
</tr>
<tr>
<td>Winkler et al6</td>
<td>Severe CAD</td>
<td>2004</td>
<td>Patients with type 2 diabetes mellitus</td>
<td>23/66</td>
<td>—</td>
<td>2.09 (1.0–4.2)</td>
</tr>
<tr>
<td>MONICA8</td>
<td>Coronary events</td>
<td>2004</td>
<td>Men with moderate hypercholesterolemia</td>
<td>97/837</td>
<td>1.21 (1.01–1.5)</td>
<td>—</td>
</tr>
<tr>
<td>Rotterdam Study8</td>
<td>Coronary events</td>
<td>2005</td>
<td>Healthy subjects aged &gt;55 years</td>
<td>308/1,820</td>
<td>1.97 (1.13–3.0)</td>
<td>—</td>
</tr>
<tr>
<td>PROSPER13</td>
<td>Coronary events</td>
<td>2006</td>
<td>Elderly subjects</td>
<td>856/4,801</td>
<td>1.25 (1.02–1.5)</td>
<td>—</td>
</tr>
<tr>
<td>Cardiovascular Health Study14</td>
<td>MI</td>
<td>2006</td>
<td>Elderly subjects</td>
<td>504/4,318</td>
<td>1.26 (1.03–1.6)</td>
<td>—</td>
</tr>
<tr>
<td>Rancho Bernardo Study15</td>
<td>MI and stroke</td>
<td>2007</td>
<td>Subjects without diabetes</td>
<td>262/4,480</td>
<td>1.16 (1.01–1.33)</td>
<td>1.54 (1.1–2.2)</td>
</tr>
<tr>
<td>Malmo Study24</td>
<td>MI and stroke</td>
<td>2007</td>
<td>Healthy subjects</td>
<td>82/765</td>
<td>1.4 (1.1–1.4)</td>
<td>—</td>
</tr>
<tr>
<td>Bruneck Study21</td>
<td>MI</td>
<td>2007</td>
<td>Healthy subjects</td>
<td>431/858</td>
<td>1.76 (1.1–2.8)</td>
<td>—</td>
</tr>
</tbody>
</table>

ARIC = Atherosclerosis Risk in Communities; CAD = coronary artery disease; CI = confidence interval; CV = cardiovascular; LDL = low-density lipoprotein; MI = myocardial infarction; MONICA = Monitoring of Trends and Determinants in Cardiovascular Disease; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; WHS = Women’s Health Study; WOSCOPS = West of Scotland Coronary Prevention Study.

* All models were multivariate adjusted for all traditional risk factors, lipids and C-reactive protein, and sometimes for other inflammatory markers.

† Risk ratios and 95% CIs are expressed as relative risk per 1 standard deviation or as hazard/odds ratios based on levels in the highest versus lowest quantile (tertile, quartile, etc.) of the Lp-PLA2 biomarker.

‡ 1 mg/dL = 0.02586 mmol/L.

Table 2

Elevated lipoprotein-associated phospholipase A2 (Lp-PLA2) as a predictor of incident cardiovascular (CV) events or severe coronary artery disease (CAD) in 13 prospective secondary prevention studies*

<table>
<thead>
<tr>
<th>Study</th>
<th>CV End Point</th>
<th>Year</th>
<th>Population</th>
<th>#Cases/#Controls</th>
<th>Relative Risk (95% CI)</th>
<th>Hazard/Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AtheroGENE1</td>
<td>ACS and angina</td>
<td>2003</td>
<td>CAD</td>
<td>496/477</td>
<td>—</td>
<td>1.80 (1.01–3.20)</td>
</tr>
<tr>
<td>Mayo Heart Study7</td>
<td>Coronary events</td>
<td>2005</td>
<td>CAD</td>
<td>61/466</td>
<td>1.3 (1.06–1.59)</td>
<td>2.29 (1.12–4.68)</td>
</tr>
<tr>
<td>LURIC20</td>
<td>Severe CAD</td>
<td>2005</td>
<td>Angio patients</td>
<td>2,454/694</td>
<td>1.85 (1.23–2.78)</td>
<td>—</td>
</tr>
<tr>
<td>HELICOR10</td>
<td>Severe CAD</td>
<td>2005</td>
<td>Angio patients</td>
<td>312/479</td>
<td>1.91 (1.12–3.28)</td>
<td>—</td>
</tr>
<tr>
<td>KAROLA11</td>
<td>Recurrent CV</td>
<td>2005</td>
<td>S/P ACS or Revascularization</td>
<td>95/1,051</td>
<td>2.09 (1.10–3.96)</td>
<td>—</td>
</tr>
<tr>
<td>Intermountain Heart Study12</td>
<td>MI</td>
<td>2006</td>
<td>Angio patients</td>
<td>475/1,012</td>
<td>2.44 (1.58–3.79)</td>
<td>—</td>
</tr>
<tr>
<td>THROMBO17</td>
<td>Recurrent MI</td>
<td>2006</td>
<td>Post MI</td>
<td>766</td>
<td>1.90 (1.31–2.75)</td>
<td>—</td>
</tr>
<tr>
<td>Mayo (Olmsted) Study18</td>
<td>Death after MI</td>
<td>2006</td>
<td>Acute MI</td>
<td>42/229</td>
<td>4.93 (2.10–11.6)</td>
<td>—</td>
</tr>
<tr>
<td>PROVE-IT20</td>
<td>Recurrent CV events</td>
<td>2006</td>
<td>ACS</td>
<td>3,265</td>
<td>1.33 (1.01–1.74)</td>
<td>—</td>
</tr>
<tr>
<td>VA-HIT20</td>
<td>CV events</td>
<td>2006</td>
<td>Stable CAD</td>
<td>927</td>
<td>1.13 (p = 0.018)</td>
<td>—</td>
</tr>
<tr>
<td>GUSTO &amp; FRISC21</td>
<td>Recurrent CV events</td>
<td>2007</td>
<td>ACS</td>
<td>435/2,266</td>
<td>1.40 (0.77–2.5)</td>
<td>—</td>
</tr>
<tr>
<td>NOBIS-II15</td>
<td>Coronary events</td>
<td>2007</td>
<td>Chest pain</td>
<td>56/429</td>
<td>2.60 (1.1–6.6)</td>
<td>—</td>
</tr>
<tr>
<td>PEACE19</td>
<td>MI and stroke</td>
<td>2007</td>
<td>Stable CAD</td>
<td>1,108/3,766</td>
<td>1.41 (1.17–1.70)</td>
<td>—</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndromes; angio = angiography; CI = confidence interval; FRISC = Fragmin During Instability in Coronary Artery Disease; GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries; KAROLA = Langzeiterfolge der Kardiologischen Anschlussbehandlung; LURIC = Ludwigshafen Risk and Cardiovascular Health Study; MI = myocardial infarction; NOBIS-II = North Wuerttemberg and Berlin Infarction Study-II; PROVE-IT = Pravastatin or Atorvastatin and Recurrent Coronary Events; PEACE = Prevention of Events with Angiotensin-Inhibiting Enzyme Inhibition; S/P = status post; THROMBO = Thrombogenic Factors and Recurrent Coronary Events; VA-HIT = Veterans Affairs HDL Intervention Trial.

* All models were multivariate adjusted for all traditional risk factors, lipids and C-reactive protein, and sometimes for other inflammatory markers.

† Risk ratios and 95% CIs are expressed as relative risk per 1 standard deviation or as hazard/odds ratios based on levels in the top quantile to bottom quantile of the Lp-PLA2 biomarker. Major population studies evaluating Lp-PLA2 as an independent predictor of future CV events have shown that Lp-PLA2 generally indicates an approximate 2-fold increased risk.

related to high levels of Lp-PLA2 and CRP were additive for cardiovascular events.5 The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) was published in 2001.28 However, at that time, there was only 1 major published study—WOSCOPS—of Lp-PLA2 as a risk marker. Although the ATP III committee did not recommend the routine measurement of inflammatory markers for clinical risk assessment, they did state that proinflammatory markers collectively should be considered as “emerging risk
factors” for coronary heart disease (CHD) that “appear to contribute to CHD risk to varying degrees and can have utility in selected persons to guide intensity of risk-reduction therapy. Their presence can modulate clinical judgment when making therapeutic decisions.”28 Thus, the ATP III guidelines recognize the potential clinical utility of inflammatory markers in selected cases, although they do not promote them for screening low-risk individuals. ATP III also acknowledges the imperative to improve on traditional risk factor assessment of cardiovascular risk: “Nonetheless, when major risk factors are present, they account for only about half of the variability in CHD risk in the US population; other factors, yet to be identified, seemingly influence how much the major risk factors affect absolute CHD risk.”29

Building on the ATP III guidelines, an expert panel of the American Heart Association (AHA) and the Centers for Disease Control (CDC) in 2003 reviewed several inflammatory markers and made recommendations on how an inflammatory marker might be used in conjunction with traditional risk factors to refine the assessment of a person’s Framingham cardiovascular risk category.30 This guideline also did not recommend the use of inflammatory markers for universal screening, but it did state that “hs-CRP measurement appears to be best employed to detect enhanced absolute risk in persons in whom multiple risk factor scoring projects a 10-year CHD risk in the range of 10% to 20%” (ie, in intermediate-risk persons). Again, CRP measurement was not mandated in these individuals but was recommended as optional.30

At that time, the writing group recommended limiting the use of inflammatory markers to CRP because “the laboratory tests to assess inflammation are limited to those that are employable in clinical settings, have commercially available assays that can be standardized, and have adequate precision.” Lp-PLA2 measurement was not standardized nor commercially available at that time, but it subsequently has been standardized and become widely available through national commercial and reference laboratories. In addition, an immunoassay for Lp-PLA2 mass concentration has received US Food and Drug Administration (FDA) clearance for use as an aid in the prediction of coronary events and stroke. It also is worth noting that the AHA/CDC writing group recommended against testing inflammatory markers in high-risk patients, arguing that they already should receive maximum therapy.30

The recommendation to consider inflammatory marker assessment in intermediate-risk patients could have a major epidemiologic impact. Greenland et al31 made important proposals in a seminal article “Improving Coronary Heart
Disease Risk Assessment in Asymptomatic People: Role of Traditional Risk Factors and Noninvasive Cardiovascular Tests” in 2001.31 They did not recommend the use of novel noninvasive risk marker tests in the low-risk population, which “constitutes approximately 35% of the US adult population 20 years of age and over. In the short-term, they can be offered general public health recommendations, and they can usually avoid further risk assessments for approximately 5 years.” In contrast, they stated that refining risk assessment with noninvasive testing after traditional risk assessment could make a large impact. Citing the National Health and Nutrition Examination Survey III (NHANES III), they stated, “This is a sizable group, judging from NHANES III data, roughly 40% of the US adult population.” Global risk assessment using Framingham risk scoring continues to be recommended, but patients found at intermediate risk might be further stratified (eg, into a higher cardiovascular risk category), based on the now substantial literature identifying Lp-PLA2 as an independent risk marker for cardiovascular events.

Metabolic Syndrome: A Clinical Marker of Intermediate Cardiovascular Risk

The Neptune survey of 5,000 patients determined that metabolic syndrome was highly correlated with risk in the intermediate category.32 Because Framingham risk scoring is often regarded as cumbersome for use in routine clinical practice, it has been suggested that the recognition of metabolic syndrome might more easily be used to identify an important subset of persons who are at intermediate cardiovascular risk, and therefore, who would be appropriate for further risk assessment with the use of inflammatory biomarkers, such as CRP and/or Lp-PLA2.

As patients with the metabolic syndrome progress toward diabetes, their cardiovascular risk increases substantially. The Nurse’s Health Study observed >100,000 female nurses for up to 20 years.33 Subjects who did not have diabetes during the entire follow-up period had the lowest rate of developing CVD. Those with prevalent diabetes at the time of the baseline questionnaire had a 5-fold increased risk of CVD. Nurses with prediabetes who developed diabetes by the end of the study had a 2.8-fold increased risk of CVD relative to subjects who never developed diabetes, reflecting the rapidly increasing cardiovascular risk in insulin-resistant persons who do not yet have diabetes.33 This link among metabolic syndrome, prediabetes, and CVD is becoming increasingly important as the epidemic of obesity continues to grow. In parallel, the prevalence of metabolic syndrome is now approaching 50% for individuals aged >50 years.

Because Lp-PLA2 has been shown to be independent of insulin resistance, it should be additive to the metabolic syndrome as a risk predictor. In a careful analysis of 78 healthy women evaluated for insulin resistance using the insulin suppression test, there was no association between Lp-PLA2 mass concentration levels and increasing insulin resistance.34 Indeed, Lp-PLA2 has been shown to be independent of body mass index in a dozen epidemiologic studies.1,3–5,8–10,17–20,24 In 2 recent studies, findings showed that an elevated Lp-PLA2 level increases cardiovascular risk beyond the risk of having metabolic syndrome.24,35 In the Malmö Diet and Cancer study, 4,480 subjects without diabetes without manifest CVD were studied for 10 years. An incident first CVD event included stroke or myocardial infarction (MI).26 As Figure 2 shows, when Lp-PLA2 enzyme activity is low and metabolic syndrome is not present, subjects are at significantly lower risk than persons with either metabolic syndrome or elevated Lp-PLA2 activity. When metabolic syndrome is not present but Lp-PLA2 is high, the CVD risk is similar to those subjects with low Lp-PLA2 and metabolic syndrome (ie, intermediate). However, subjects with a combination of both metabolic syndrome and high Lp-PLA2 activity exhibited the highest risk for cardiovascular events.

The Malmö Study findings are consistent with a recent report from the Intermountain Heart Collaborative Study, where 1,493 angiographically studied patients were observed for 7.5 years.35 The average age was 63 ± 12 years, 70% were men, 67% had CAD, and 42% had the metabolic syndrome. Lp-PLA2 mass concentration above the median was more predictive of angiographic CAD in metabolic syndrome subjects than in non–metabolic syndrome subjects, and these results remained significant after adjustment for traditional risk factors. Lp-PLA2 predicted CAD death significantly whether or not patients had the metabolic syndrome.

In summary, Lp-PLA2 is independent of insulin resistance, a relatively unique characteristic for an inflammatory marker, and elevated Lp-PLA2 adds to cardiovascular risk prediction in patients with the cardiovascular metabolic syndrome.

Secondary Prevention: A Heterogeneous “High-Risk” Category

A log-linear relation exists between LDL cholesterol levels and relative risk for CAD, with event rates increasing more steeply with increasing LDL cholesterol concentrations.36 Randomized clinical trials of primary and secondary prevention have studied a variety of lipid-lowering agents at various degrees of intensity with LDL levels in placebo and treated groups ranging from 200 mg/dL to <50 mg/dL. For every 30-mg/dL change in LDL cholesterol, the relative risk for CAD is changed by about 30%. In the 2004 ATP III guidelines, a new risk subcategory beyond high risk called “very high risk” was introduced, whereby lowering the LDL cholesterol target to <70 mg/dL would be a “reasonable clinical strategy.”36 The option to further intensify LDL lowering to <100 mg/dL created a need to understand
which high-risk patients with an LDL cholesterol at the “optimal” <100 mg/dL level might benefit from even more intensive lipid modification. Very-high-risk patients were defined as those having established CVD plus 1 of several criteria: (1) multiple major risk factors, especially diabetes; (2) severe and poorly controlled risk factors, especially continued cigarette smoking; (3) multiple risk factors of the metabolic syndrome, especially high levels of triglycerides ≥200 mg/dL plus elevated non–HDL cholesterol ≥130 mg/dL with HDL cholesterol levels ≤40 mg/dL; and (4) acute coronary syndromes (ACS).

In 2006, the AHA/American College of Cardiology (ACC) updated the guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular diseases, confirming the ATP III panel recommendation in 2004 that it would be reasonable to treat LDL cholesterol to the target of ≤70 mg/dL plus elevated non–HDL cholesterol ≥130 mg/dL in patients with coronary artery disease and (4) acute coronary syndromes (ACS).

Figure 2. High levels of lipoprotein-associated phospholipase A2 (Lp-PLA2) and metabolic syndrome (MS): independent and additive risk factors. In the Malmö study comprising 4,480 patients without diabetes mellitus with 261 hard cardiovascular (CV) events over 10 years, Lp-PLA2 activity was determined to be independent of and additive to insulin resistance–associated cardiovascular risk, a relatively unique characteristic compared with other inflammatory markers. (Adapted from Arterioscler Thromb Vasc Biol.38)
hs-CRP was also predictive of angiographic CAD. How-
ter death, MI, or cerebrovascular accident, in this specific pa-
tient population referred for angiography. In this study, hs-CRP was also predictive of angiographic CAD. How-
ter, it did not attenuate the association of Lp-PLA2 with angiographic CAD. Instead, Lp-PLA2 showed an additive
effect with CRP on CAD risk prediction. Compared with high CRP/low Lp-PLA2 levels, high CRP/high Lp-PLA2
levels predicted a significant risk increment for CAD death (p = 0.048).12

An important issue faced by physicians treating high-risk, and even very-high-risk patients is determining when atherosclerosis disease activity has subsided (ie, when has rupture-prone, inflamed, thin fibrous cap plaque stabilized?)
In the PROVE-IT–TIMI 22 trial, an average LDL choles-
terol level of 62 mg/dL was achieved in the atorvastatin
80-mg/day arm, and yet despite this very aggressive lipid-
lowering therapy, 22.4% of post-ACS patients had a recur-
tent cardiovascular event in just 2 years (Figure 3).38

A better predictor of low risk was the combined presence of low levels of LDL (regardless of treatment group) and a low inflammatory index as measured by hs-CRP.39 Thus, although lipids are a well-established treatment target, they should not be perceived as a reliable predictor of low sub-
sequent risk (ie, of whether atherosclerotic plaques have fully stabilized).

Because Lp-PLA2 is involved in a causal pathway of plaque inflammation, is found in thin fibrous cap atheroma, and is lowered by all lipid-modifying medications, it is tempting to hypothesize that lower Lp-PLA2 may be a predictor of stabilized plaque. Indeed, several studies sug-
gest that low Lp-PLA2 may have a particularly useful role as a negative predictor (ie, that it more reliably indicates plaque stabilization with a low risk of subsequent ACS). In the Langzeiterfolge der Kardiologischen Anschlussheil-
Behandlung (KAROLA) study (Figure 4), plasma concen-
trations and activity of Lp-PLA2 were determined at base-
line in a cohort of 1,051 patients aged 30–70 years with CAD.11 A total of 95 secondary CVD events occurred, despite fairly intensive treatment and despite baseline LDL cholesterol levels of 100 mg/dL. In multivariable analyses, Lp-PLA2 mass and activity were strongly associated with CVD events after controlling for traditional risk factors, lipids, severity of CAD, statin treatment, cystatin C, and N-terminal pro–brain natriuretic peptides (NT-proBNP), with a hazard ratio (HR) for the top versus bottom tertile of Lp-PLA2 of 2.09 (95% confidence interval [CI], 1.10–3.96). Also, after 4–6 years of follow-up, 95% of high-risk pa-
tients remained free of cardiovascular events if their Lp-
PLA2 levels were <223 ng/mL. Thus, not only does a high level of Lp-PLA2 predict residual risk in high-risk ACS patients, but a low level of Lp-PLA2 was associated with a remarkably low 5% risk of recurrent cardiovascular events, suggesting that plaque stabilization was achieved in patients in the bottom tertile for Lp-PLA2.

Similar results were noted in the Mayo Heart Study of 504 patients with CAD. After 4 years of follow-up, 72 major adverse events occurred in 61 of 466 patients.7 Pa-
tients with Lp-PLA2 mass concentrations in the bottom tertile (<200 ng/mL) had only a 5% cardiovascular event rate compared with an event rate >10% for patients in the top tertile for Lp-PLA2.7 In the Ludwigshafen Risk and Cardiovascular Health Study (LURIC), 2,513 patients with angiographic evidence of ≥10% stenosis were observed for 6.5 years.12 Similar to results in the KAROLA and Mayo Heart Studies, the Kaplan-Meier survival curve demon-
strated residual rates of only about 5% of cardiac death for persons in the bottom tertile for Lp-PLA2 enzyme activity, whereas risk approximately doubled for other patients (HR, 1.9; 95% CI, 1.4–2.5; p <0.001). Taken together, these consistent results suggest that low Lp-PLA2 has a high negative predictive value in patients at secondary risk, and this may be hypothesized to indicate successful therapeutic plaque stabilization.

A marker of rupture-prone plaque should intuitively pre-
dict near-term cardiovascular event risk. The results of 3 recent secondary prevention studies—the Thrombogenic Factors and Recurrent Coronary Events (THROMBO) study, a Mayo study of the residents of Olmsted County, and the North Wuerttemberg and Berlin Infarction Study–II (NOBIS-II)17,18,22—suggest that Lp-PLA2 may represent such a marker. The THROMBO study evaluated the role of Lp-PLA2 activity in the risk of recurrent coronary events after a 2-year follow-up in 766 MI survivors.17 After full multivariable adjustment for a very wide range of 17 differ-
ent lipid, lipoprotein subfractions, and hemostatic and in-
flammatory markers, apolipoprotein B was the only signif-
icient predictor (HR, 1.66; 95% CI, 1.14–2.40) for the top quartile versus the bottom 3 quartiles together. However, when Lp-PLA2 activity was entered into the model, athero-
genic particle concentration (apolipoprotein B) lost signific-
ance, and Lp-PLA2 emerged as the single best predictor of recur-
rent MI, with an HR of 1.90 (95% CI, 1.31–2.75).17

A Mayo Clinic study observed 271 residents of Olmsted County after MI to evaluate the role of Lp-PLA2 as a pre-
dictor of death 1 year after acute MI.18 During the first year of follow-up, 42 deaths occurred. The survival estimates (95% CIs) at 1 year were 92% (86%–98%), 85% (78%–93%), and 74% (65%–84%) in the lowest, middle, and upper Lp-PLA2 tertiles, respectively (p = 0.007). After adjustment for age and sex, HRs for death in the middle and upper Lp-PLA2 tertiles were 2.20 (95% CI, 0.88–5.54) and
4.93 (95% CI, 2.10–11.60) compared with the lowest tertile, respectively (p trend <0.001). Further adjustment for other risk indicators resulted in even stronger associations. It is important to note that blood was drawn at 43 ± 39 hours, and that Lp-PLA2 is generally suppressed (as is LDL cholesterol) early post MI (see below). Patients with an Lp-PLA2 mass <218 ng/mL had a 95% 1-year survival rate, and those with <166 ng/mL had approximately a 98% 1-year survival rate, again highlighting the negative predictive value of this biomarker for cardiovascular events when it is low.

In the NOBIS-II study, 429 consecutive patients were admitted to the emergency room with suspected ACS. Classification and regression tree analysis was conducted to examine 4 biomarkers as predictors of near-term, 42-day cardiovascular outcomes. Assessment of NT-proBNP and then troponin levels identified most persons at high cardiovascular risk, but an important subgroup of 35.9% of the patients with borderline NT-proBNP and negative troponin levels were identified; in this group Lp-PLA2 mass concentration provided a significant further risk stratification at a cutoff of 210 ng/mL (event rate with elevated Lp-PLA2, 17.9% vs 6.9%; relative risk, 2.6; 95% CI, 1.1–6.6). None of the clinical or electrocardiographic variables of the thrombolysis in myocardial infarction (TIMI) risk score provided comparable incremental information for risk stratification. The investigators commented that “these 3 biomarkers represent different pathways in the pathophysiology of the ACS, and this represents the rationale behind the application of a panel of biomarkers in the assessment of ACS patients.” CRP did not emerge as a significant independent marker of cardiovascular risk.

Timing of the blood draw for Lp-PLA2 post ACS may be important because Lp-PLA2 is suppressed as is LDL cholesterol. In the Air Pollution and Inflammatory Response in Myocardial Infarction Survivors: Gene-Environment Interaction in a High-Risk Group (AIRGENE) study, Lp-PLA2 mass concentrations were measured in 204 post-MI survivors monthly for 6 months. Levels did not return to baseline until 60–90 days post MI. This is a possible explanation for why in PROVE-IT, Lp-PLA2 in blood drawn 7 days post ACS was not a significant predictor of recurrent cardiovascular events, whereas Lp-PLA2 activity in blood drawn 30 days post ACS in PROVE-IT significantly predicted residual risk (adjusted HR, 1.33; 95% CI, 1.01–1.74; p = 0.002) after full multivariable adjustment, including CRP. In the NOBIS-II study of ACS patients, Lp-PLA2 in blood drawn within 6–7 hours of symptom onset was predictive of future events and suggests that a brief window exists in the first several hours after ACS onset when Lp-PLA2 has not yet been suppressed and may be useful for risk prognostication. Lp-PLA2 in blood drawn an average of >1 day post
ACS in the Mayo study of Olmsted County residents\textsuperscript{18} and in the Global Use of Strategies to Open Occluded Coronary Arteries/Fragmin During Instability in Coronary Artery Disease (GUSTO/FRISC) study\textsuperscript{21} gave mixed results (ie, it was a significant predictor of recurrent cardiovascular events in the first but not in the second case, although the trend was positive). Thus, the impact of timing of Lp-PLA\textsubscript{2} measurements post MI on clinical risk prediction is unresolved and is an important area for future investigation.

Conclusion

Putting these observations and considerations together, the question arises of how Lp-PLA\textsubscript{2} should be best used in clinical practice? The evidence seems to support its use in intermediate-risk persons for further primary risk stratification and, more recently, for stratification of risk for secondary prevention (by definition, a high-risk category) in patients in whom a more aggressive strategy would be implemented if Lp-PLA\textsubscript{2} is still elevated. These implications also apply to hs-CRP. Lp-PLA\textsubscript{2}, which measures an independent aspect of vascular inflammation, is a more vascular-specific marker and is also incremental to hs-CRP in risk assessment.\textsuperscript{4,5,12} In contrast to intermediate- and high-risk persons, low-risk individuals are not recommended for testing with Lp-PLA\textsubscript{2}. Lp-PLA\textsubscript{2}, as with CRP and other biomarkers, is not recommended for general population screening. However, once a patient is determined to be at intermediate or high cardiovascular risk, elevated Lp-PLA\textsubscript{2} might be used to move the patient to the next higher-risk category, and low Lp-PLA\textsubscript{2} might increase confidence that the patient is optimally treated or at lower risk.

Among the simplest means of identifying a large and relevant subset of intermediate-risk persons is to evaluate them for the presence of the metabolic syndrome. These patients appear to be promising candidates for inflammatory marker testing, including Lp-PLA\textsubscript{2} testing, to further stratify those who are at higher risk. AHA/CDC and ATP III guidelines now also recognize a fourth risk subcategory of patients deemed to be at very high risk, and Lp-PLA\textsubscript{2} appears to be a relatively inexpensive and noninvasive way to identify which high-risk or coronary-risk-equivalent patients are at very high residual risk. Whereas intermediate-risk patients have an LDL cholesterol target of <130 mg/dL, high-risk patients have an LDL cholesterol target of <100 mg/dL, and very-high-risk patients may be targeted to an LDL cholesterol level of <70 mg/dL. Other important

Figure 4. The Langzeiterfolge der Kardiologischen Anschlussheil-Behandlung (KAROLA) study: cardiovascular event-free survival with optimal low-density lipoprotein levels of 100 mg/dL (1 mg/dL = 0.02586 mmol/L) by lipoprotein-associated phospholipase A\textsubscript{2} (Lp-PLA\textsubscript{2}) tertiles. Kaplan-Meier estimate of secondary fatal and nonfatal cardiovascular disease events during follow-up (time = days) according to tertiles of Lp-PLA\textsubscript{2} mass at baseline. (Reprinted with permission from Arterioscler Thromb Vasc Biol.\textsuperscript{11})
considerations in patients with high Lp-PLA₂ levels include intensification of therapeutic lifestyle changes and combination lipid-lowering therapy. A basic principle of preventive therapies is to match the intensity of treatment to individual patient risk.

Given its role in plaque pathology and consistent results from clinical trials to date as summarized above, Lp-PLA₂ may be hypothesized to be unique as a biomarker of patients with rupture-prone plaque, and conversely, of patients whose plaques have been successfully stabilized therapeutically. This interesting hypothesis is an important area for future research into Lp-PLA₂ diagnostics as well as therapeutics, including interventions that are targeted to inhibit Lp-PLA₂ activity.

Author Disclosures

The author who contributed to this article has disclosed the following industry relationships.

Jeffrey L. Anderson, MD, has received speaker honoraria from diaDexus, Inc. who has also supported research projects with his institution.


