Lipid Biomarkers and Coronary Heart Disease: Part I
Lipoprotein A [Lp(a)] and Lipoprotein A Associated Phospholipase A (Lp(a)-PLA)

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There are many risk factors for coronary heart disease (coronary artery disease, CAD). These include genetic factors, diet, high blood pressure as well as a number of biomarkers (serum markers). Cholesterol may have been the first of these and has been followed by several dozen more. One of the intriguing questions for both clinicians and laboratorians is which of these should be measured and when should they be measured (i.e., starting at an early age for everyone, only on those patients with a history of CAD, those suspected of ACS in the ED or after an event such as a stroke or AMI).

For a number of years, there has been interest in some of the lipoproteins including HDL and LDL and their various forms. Lipoprotein A, another of these, has more recently sparked the interest of clinicians and hence, the laboratory. There are now rapid, automated assays for Lipoprotein A [Lp(a)], often called “L P little A” and Lipoprotein A associated phospholipase A (Lp(a)-PLA). This short review touches on some of the material that has made these two markers your clinical staff may have asked about or have ordered and that you are sending out.

For example, a large study found that in a prospective study of 5,888 community-dwelling older adults (65 years of age or older), some 4,000 women and men who were free of vascular disease provided base-line serum samples for analysis for levels of Lp(a) lipoprotein. These subjects were followed for a median of 7.4 years to evaluate the development of stroke and to track deaths from vascular causes and all causes. The men and women were divided into quintile groups (e.g., the lower 20%, etc.) according to the Lp(a) lipoprotein level at base line. The risk of an event was determined for each of the quintiles; the lowest quintile served as the reference group. Compared with this lowest quintile, men in the highest quintile had three times the unadjusted risk of stroke, almost three times the risk of death associated with vascular events, and nearly twice the risk of death from all causes. Adjustment for age, sex, total cholesterol, low-density lipoprotein cholesterol (LDL), and triglycerides, carotid-wall thickness, smoking status, the presence or absence of diabetes and systolic and diastolic hypertension, body-mass index, and other traditional risk factors had little effect on the final assessments. Similar analyses for women, which also included adjustment for estrogen use or non-use, revealed no such relation.

In another study, 490 patients (average age 60.5) who underwent coronary angiography to evaluate chest pain were classified into two groups, a CAD group (n = 256), who had significant stenosis, and a control group (n = 234) who had normal or minimally occluded coronary arteries. The Lp(a) level and mean LDL particle size were significantly correlated (Figure 1.) with the level of stenosis.

A report from India that discussed three groups of patients: non-insulin dependent diabetics (NIDDM) with CAD (Group 1), and without CAD (Group 2), as well as a group of control patients (neither NIDDM or CAD, Group 3) found that Lp(a) concentrations were significantly higher in Group 1 patients when compared with Groups 2 and 3. There was only a weak correlation of the only total cholesterol and low-density cholesterol concentrations with the Lp(a) levels in Group 1, suggesting that these are independent risk factors (Figure 1.). (When two risk factors are independent, there is a better argument to measure both of them than if they are dependent.)

While most of the studies suggest that measurement of Lp(a) is a useful marker of future risk, not all do. For example, in a study of 490 patients (mean: 60.5 ± 11.5 years old) who underwent coronary angiography to evaluate chest pain were classified into two groups, a CAD group (n = 256), who had significant stenosis observed by coronary angiogram, and a control group (n = 234), who had normal, or minimal, coronary arteries. The results indicate that an increased Lp(a) was correlated with the severity of CAD. In a similar study, the

Figure 1.
Turning to Lp-PLA2 (one commercial assay is termed PLAC) is a recently described and potentially useful serum marker also associated with cardiovascular disease. This enzyme was originally named platelet-activating factor acetylhydrolase (PAF-AH). The current consensus is that Lp-PLA2 is positively associated with coronary disease. The initial evidence for this came largely from the West of Scotland Coronary Prevention Study Group (WOSCOPS) in which Lp-PLA2 was compared in 580 cases and 1,160 age-matched controls. In addition, the quantitative contribution of Lp-PLA2 to risk assessment was assessed in a substudy of the Atherosclerosis Risk in Communities (ARIC) study. Although positively correlated with disease, the addition of Lp-PLA2 “did not appreciably enhance risk prediction beyond the traditional risk factors.” This study concluded that “population screening for subclinical disease using Lp-PLA2 does not appear to be warranted.” Presently, the most useful application of Lp-PLA2 testing is to adjust individual risk assessment for those patients found to be at borderline risk using traditional models. In this regard, the marker appears to be particularly useful for gauging risk among patients with metabolic syndrome or diabetes.

This conclusion is not universally accepted as evidenced in a recent article in which the authors measured plasma concentrations of Lp-PLA2 in 1,051 patients aged 30 to 70 years with coronary heart disease (CHD) who were followed for four years. Lp-PLA2 mass and activity were strongly correlated with cardiovascular events even after controlling for traditional risk factors: severity of CHD, statin treatment, cystatin C, and N-terminal proBNP. The likelihood of an event during the four year period was more than two and one-half times in the upper quartile of the study group compared to the lower quartile. The Lp-PLA2 levels were independent of a variety of potential risk factors including markers of inflammation, renal function, and hemodynamic stress.

In a large study from Houston, TX, 12,762 apparently healthy middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) were observed for about six years. Both Lp-PLA2 and hs-CRP levels were associated with ischemic stroke after adjustment for age, sex, and race. Likelihood ratios were more than twice as high for the upper vs. the lowest third of Lp-PLA2 and nearly three times higher for CRP level higher than 3 vs. lower than 1 mg/L. Individuals with high levels of both CRP and Lp-PLA2 were at the highest risk after adjusting for traditional risk factors compared with individuals with low levels of both.

From Boston came a study of 3,766 patients with stable CAD. These patients were monitored for a median of 4.8 years for adverse cardiovascular events including death, myocardial infarction (MI), coronary revascularization, hospitalization for unstable angina (UA), and stroke. Patients in the higher quartiles of Lp-PLA2 levels were at greater risk for the composite of cardiovascular death, MI, coronary revascularization, UA, or stroke. This was true regardless of the patient’s sex, cholesterol levels, or use of lipid-lowering therapy. When analyzed together, both hs-CRP and Lp-PLA2 were highly significant predictors of acute coronary syndromes.

The measurement of Lp-PLA2 is currently substantially manual — using a microtitre plate with total incubations of more than three hours. More than likely, if the early data hold through larger, longitudinal studies, we can expect the assay to be automated on the larger analyzers.

There are a number of assays, some old, such as uric acid, and some newer, the two mentioned here that have been touted as markers of risk for cardiac death, as well as a number of others. Some researchers suggest combining several of these into a “risk panel.” Care must be taken in those panels using independent tests, as increasing the number of assays in the panel increases the number of false positive results. These positive results increase the amount of follow-up work and adds to the financial burden on society and stress to the patient.

It is without question an exciting time in laboratory medicine. The excitement needs be tempered with careful thinking.

**References**


Questions for STEP Participants

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In the following, choose the one best answer for each question.

1 Which is not a risk factor for CAD?
   A. Blood pressure
   B. Rh factor
   C. Diabetes
   D. Diet

2 LDL levels have been found to be correlated with stenosis.
   A. True
   B. False

3 hs-CRP has been found associated with stroke.
   A. True
   B. False

4 The more tests run on a patient, the more likely an abnormal value will appear.
   A. True
   B. False

5 If two markers are independent, there is not a good reason to measure them both.
   A. True
   B. False

6 At this time, both Lp(a) and Lp(a)-PLA are recommended by the Task Force on Preventive Medicine.
   A. True
   B. False

7 The Task Force recommends beginning testing for CAD at age
   A. 21-30
   B. 31-40
   C. >40
   D. It makes no recommendations

8 Cholesterol is found bound to protein in serum.
   A. True
   B. False

9 Lp-PLA2 is an enzyme.
   A. True
   B. False

10 Running more tests per patient will yield more positive results on ‘normal’ people.
   A. True
   B. False