

## Medical Policy



An Independent Licensee of the  
Blue Cross and Blue Shield Association

### **Title: Measurement of Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk**

#### **Professional**

Original Effective Date: March 13, 2009

Revision Date(s):

Current Effective Date: March 13, 2009

#### **Institutional**

Original Effective Date: March 13, 2009

Revision Date(s):

Current Effective Date: March 13, 2009

#### **DESCRIPTION**

Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase, is an enzyme that hydrolyses phospholipids and is primarily associated with low density lipoproteins. Accumulating evidence has suggested that Lp-PLA2 is a biomarker of coronary artery disease and may have a proinflammatory role in the progression of atherosclerosis. The recognition that atherosclerosis represents, in part, an inflammatory process has created considerable interest in measurement of proinflammatory factors as part of cardiovascular disease risk assessment. Recently, the U.S. Food and Drug Administration (FDA) cleared for marketing an enzyme-linked immunoabsorbent assay (ELISA) test, the PLAC test (diaDexus, San Francisco, CA), to measure levels of Lp-PLA2.

Note: Measurement of lipoprotein A enzyme is a distinct laboratory test. Lipoprotein A enzyme is addressed in a separate policy.

#### **POLICY**

Measurement of lipoprotein-associated phospholipase A2 (Lp-PLA2) is considered **investigational**.

#### **RATIONALE**

Results of 2 large-scale observational studies have suggested that Lp-PLA2 is an independent risk factor for coronary heart disease in men. For example, the West of Scotland Coronary Prevention Study (WOSCOPS) was a 5-year, case control trial evaluating 6,595 men with elevated cholesterol levels and no history of a heart attack. (1) Researchers looked at a smaller population of this study to determine if inflammatory markers such as Lp-PLA2 and high sensitivity C-reactive protein were correlated with coronary heart disease events. The 580 men who went on to have a myocardial infarction or revascularization were compared to 1,160 age- and smoking-matched men

who did not have an event. The results showed that those with the highest levels of Lp-PLA2 had twice the risk of an event compared to those with the lowest levels, even after adjustment for traditional risk factors and other inflammatory mediators.

The Atherosclerosis Risk in Communities (ARIC) study evaluated the various risk markers and their association with increased risk in a large, diverse population of over 12,000 individuals. At enrollment in the study, patients were free of coronary heart disease and were followed up for the development of the disease for the next 9 years. The case-cohort component of the study examined 2 inflammatory markers, Lp-PLA2 and high sensitivity C-reactive protein, in a subset of 608 cases and 740 controls. (2) The results showed that elevated levels of Lp-PLA2 are higher in incident coronary heart disease cases. In individuals with non-elevated LDL levels (<130 mg/dL), Lp-PLA2 levels were independently associated with coronary heart disease, even after adjustment for traditional risk factors and C-reactive protein. As noted in the FDA press release accompanying the FDA approval for the PLAC test, "an elevated PLAC test result with an LDL-cholesterol level of less than 130 mg/dL gives doctors increased confidence that patients have two to three times the risk of having coronary heart disease when compared with patients having lower PLAC test results." (3) Koenig and colleagues reported similar results in a study of 934 apparently healthy men aged 45 to 64 who were followed up between 1984 until 1998. During this period of time 97 men experienced a coronary event. Elevated levels of Lp-PLA2 appeared to be predictive of future coronary events in middle-aged men with moderately elevated total cholesterol, independent of C reactive protein. (4)

However, the key outcome of cardiac risk assessment is an improvement in health outcomes. Improved risk prediction does not by itself result in improved health outcomes. To improve outcomes, clinicians must have the tools to translate this information into clinical practice. To do this requires guidelines that incorporate emerging risk factors into existing risk prediction models and that have been demonstrated to classify patients into risk categories with greater accuracy. Predictive models also need to be accompanied by treatment guidelines that target intervention toward patients who will get the most benefit. At present, measurements of Lp-PLA2 are not a component of the guidelines developed by the National Cholesterol Education Program Adult Treatment Panel III. While studies have suggested that statin drugs and fibrates may reduce levels of Lp-PLA2, it is not known whether such drug therapy in patients not already considered candidates based on other well-established risk factors will ultimately decrease the incidence of coronary heart disease.

### **April 2006 Update**

A search of the literature for the period of 2005 through January 2006 did not identify any additional published literature that would prompt reconsideration of the policy statement, which remains unchanged. Ballantyne and colleagues studied Lp-PLA2 in the 12,762 apparently healthy individuals participating in the Atherosclerosis Risk in

Communities (ARIC) study. (5) Mean levels of both Lp-PLA2 and C-reactive protein were higher in the 194 stroke cases; the authors concluded that Lp-PLA2 levels may provide complementary information beyond traditional risk factors in identifying those at risk for ischemic stroke. However, as noted above, improved risk prediction does not necessarily result in improved outcomes. In addition, an accompanying editorial focuses on the challenges of incorporating the results from epidemiologic studies, such as the ARIC trial, into clinical management, and distinguishing between statistical significance and clinical utility. (6)

### **December 2006 update**

Many observational studies of Lp-PLA2 were published since the last update. These studies generally report the utility of Lp-PLA2 as an independent biomarker for coronary artery disease (CAD) (7), recurrent cardiac events. (8) However, Lp-PLA2 was not found to be an independent marker for subclinical atherosclerosis (9), and a study of the ARIC cohort found that routine measurement of Lp-PLA2 did not improve existing risk stratification models that use traditional risk factors. (10)

Three recently published interventional studies involving Lp-PLA2 suggest that the level of Lp-PLA2 is modifiable by antihyperlipidemics (statins, fibrates, and niacin). An ad hoc study of the PROVE IT-TIMI 22 (Pravastatin Or atorvastatin Evaluation and Infection Therapy—Thrombolysis In Myocardial Infarction) trial where Lp-PLA2 levels were measured at baseline (n=3,648) and at 30 days (n=3,265) and patients were followed up for a mean of 24 months for death, myocardial infarction, unstable angina, revascularization, or stroke suggested that patients randomized to atorvastatin 80mg/day, but not pravastatin 40 mg/day, experienced a 20% reduction of Lp-PLA2 levels at 30 days, independent of other cardiac risk factors. The 30 day, Lp-PLA2 level was independently associated with an increased risk of cardiovascular events. (11) Another ad hoc study from the DIACOR (Diabetes and Combined Lipid Therapy Regimen) trial demonstrated improved Lp-PLA2 levels (overall 16.8% reduction) compared to baseline, with no difference found between treatment groups among the 300 patients with diabetes and mixed dyslipidemias randomized to either fenofibrate 160 mg/day, simvastatin 20 mg/day, or both, for 12 weeks. (12) Last, a placebo-controlled study of 54 patients with stable coronary artery disease involved adding niacin to the existing antihyperlipidemic regimens for 3 months. A 20% ( $p<0.05$ ) reduction of Lp-PLA2 was reported for the niacin group compared to no significant change from baseline in the placebo group. (13)

Despite the intriguing results of studies of the Lp-PLA2 test, its biological role is not yet understood, its ability to improve on existing risk stratification methods is uncertain, and its clinical utility remains in question, particularly when compared to currently available methods for cardiovascular risk reduction. In particular, the extent to which antihyperlipidemic agents modify the level of Lp-PLA2 beyond their established therapeutic use, and therefore alter cardiac outcomes, is unknown. There is insufficient

evidence to recommend changing the policy statements regarding the use of the Lp-PLA2 immunoassay.

### **2007 Update**

A search of the literature was performed for the period November 2006 through mid-November 2007. Relevant evidence identified by this search included observational studies that evaluated Lp-PLA2 as a predictor of cardiac disease (14-18), and 1 treatment study (19) that evaluated changes in Lp-PLA2 associated with pharmacologic treatment.

Observational studies of the predictive ability of Lp-PLA2 were reported in a variety of patient populations. As part of the PEACE study (14), Lp-PLA2 levels were measured in 3,766 patients with stable CAD followed for a median of 4.8 years. After adjustment for other baseline risk factors, patients in the highest quartile of Lp-PLA2 were 1.4 times more likely (95% CI: 1.17-1.70,  $p < 0.001$ ) to experience an adverse cardiovascular outcome compared to patients in the lowest quartile. Winkler and colleagues (15) studied 3,232 consecutive patients referred for coronary angiography and reported that Lp-PLA2 levels were an independent predictor of cardiac mortality (hazard ratio: 2.0; 95% CI 1.4-3.1,  $p < 0.001$ ) after adjusting for established risk factors, including C-reactive protein and N-terminal b-natriuretic peptide. Persson and colleagues (16) evaluated the relationship between Lp-PLA2 and the metabolic syndrome in 4,480 nondiabetic patients without a history of CAD. Both Lp-PLA2 (relative risk: 1.54; 95% CI: 1.07-2.24) and the metabolic syndrome (relative risk: 1.42; 95% CI: 1.06-1.90) were significant predictors of a first cardiac event. The combination of both elevated Lp-PLA2 and metabolic syndrome conferred a further increase in risk (relative risk: 1.97; 95% CI: 1.34-2.90).

Not all observational studies reported a positive association of Lp-PLA2 with cardiovascular outcomes. Allison and colleagues (17) studied 508 patients with peripheral vascular disease followed for an average of 6.7 years. While there was a modest univariate association of Lp-PLA2 with cardiovascular events, this association disappeared after adjustment for established risk factors. In the Rotterdam Coronary Calcification Study (18), similar results were reported. This population-based study followed 520 patients for 7 years and evaluated the association between Lp-PLA2 and coronary calcification by EBCT scan. The unadjusted odds ratio for each standard deviation increase in Lp-PLA2 was 1.6 (95% CI: 1.1-2.4), however this association became nonsignificant after controlling for lipid levels.

One trial was identified that evaluated the response of Lp-PLA2 to pharmacologic treatment. (19) In this study, Lp-PLA2 levels were followed up in 89 obese patients with the metabolic syndrome. Patients were prescribed a low-fat diet and randomized to orlistat, fenofibrate, or combination therapy with both agents. Lp-PLA2 levels decreased in all treatment groups, with a larger decrease reported for the combined group ( $p < 0.05$ ).

These studies provide additional evidence on the predictive ability of Lp-PLA2 for cardiovascular outcomes, with the majority reporting that Lp-PLA2 is an independent predictor of outcomes. However, there is still some uncertainty as to whether the predictive ability of Lp-PLA2 is truly independent of lipid levels, particularly LDL. The treatment study (19) provides some evidence that various pharmacologic agents can have an impact on Lp-PLA2 levels, but does not address whether changes in Lp-PLA2 can improve outcomes when used as a target of treatment in this manner.

### **CODING**

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

### **CPT/HCPCS**

83698 Lipoprotein-associated phospholipase A2 (Lp-PLA2)  
83516 Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, qualitative or semiquantitative; multiple step method

Effective January 1, 2007, there is a specific CPT code for this test:

83698: Lipoprotein-associated phospholipase A2 (Lp-PLA2).

Prior to 2007, there was no specific CPT code for this test. CPT code 83516

(immunoassay, analyte, quantitative, not otherwise specified) might have been used.

### **REFERENCES**

1. Packard CJ, O'Reilly DS, Caslake MJ et al. Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 2000; 343(16):1148-55.
2. Ballantyne CM, Hoogeveen RC, Bang H et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2004; 109(7):837-42.
3. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Available at <http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf>
4. Koenig W, Khuseyinova N, Lowel H et al. Lipoprotein-associated phospholipase A2 adds to risk prediction of incidence coronary events by C-reactive protein in apparently healthy middle-aged men from the general population: results from the 14-year follow-up of a large cohort from southern Germany. *Circulation* 2004; 110(14):1903-8.
5. Ballantyne CM, Hoogeveen RC, Bang H et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Arch Intern Med* 2005; 165(21):2479-84.

6. Greenland P, O'Malley PG. When is a new prediction marker useful? A consideration of lipoprotein-associated phospholipase A2 and C-reactive protein for stroke risk. *Arch Intern Med* 2005; 165(21):2454-6.
7. Johnston N, Jernberg T, Lagerqvist B et al. Improved identification of patients with coronary artery disease by the use of new lipid and lipoprotein biomarkers. *Am J Cardiol* 2006; 97(5):640-5.
8. Koenig W, Twardella D, Brenner H et al. Lipoprotein-associated phospholipase A2 predicts future cardiovascular events in patients with coronary heart disease independently of traditional risk factors, markers of inflammation, renal function and hemodynamic stress. *Arterioscler Thromb Vasc Biol* 2006; 25(7):1586-93.
9. Kardys I, Oei HH, van der Meer IM et al. Lipoprotein-associated phospholipase A2 and measures of extracoronary atherosclerosis: the Rotterdam Study. *Arterioscler Thromb Vasc Biol* 2006; 26(3):631-6.
10. Folsom AR, Chambless LE, Ballantyne CM et al. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the atherosclerosis risk in communities study. *Arch Intern Med* 2006; 166(3):1368-73.
11. O'Donoghue M, Morrow DA, Sabatine MS et al. Lipoprotein-associated phospholipase A2 and its association with cardiovascular outcomes in patients with acute coronary syndromes in the PROVE IT-TIMI 22 (PRavastatin Or atorVastatin Evaluation and Infection Therapy – Thrombolysis In Myocardial Infarction) trial. *Circulation* 2006; 113(14):1745-52.
12. Muhlestein JB, May HT, Jensen JR et al. The reduction of inflammatory biomarkers by statin, fibrate and combination therapy among diabetic patients with mixed dyslipidemia: the DIACOR (Diabetes and Combined Lipid Therapy Regimen) study. *J Am Coll Cardiol* 2006; 48(2):396-401.
13. Kuvin JT, Dave DM, Sliney KA et al. Effects of extended-release niacin on lipoprotein particle size, distribution and inflammatory markers in patients with coronary artery disease. *Am J Cardiol* 2006; 98(6):743-5.
14. Sabatine MS, Morrow DA, O'Donoghue M et al. Prognostic utility of lipoprotein-associated phospholipase A2 for cardiovascular outcomes in patients with stable coronary artery disease. *Arterioscler Thromb Vasc Biol* 2007; 27(11):2463-9.
15. Winkler K, Hoffmann MM, Winkelmann BR et al. Lipoprotein-associated phospholipase A2 predicts 5-year cardiac mortality independently of established risk factors and adds prognostic information in patients with low and medium high-sensitivity C-reactive protein (the Ludwigshafen risk and cardiovascular health study). *Clin Chem* 2007; 53(8):1440-7.
16. Persson M, Hedblad B, Nelson JJ et al. Elevated Lp-PLA2 levels add prognostic information to metabolic syndrome on incidence of cardiovascular events among middle-aged nondiabetic subjects. *Arterioscler Thromb Vasc Biol* 2007; 27(6):1411-6.
17. Allison MA, Denenberg JO, Nelson JJ et al. The association between lipoprotein-associated phospholipase A2 and cardiovascular disease and total mortality in vascular medicine patients. *J Vasc Surg* 2007; 46(3):500-6.
18. Kardys I, Oei HH, Hofman A et al. Lipoprotein-associated phospholipase A2 and coronary calcification. The Rotterdam Coronary Calcification Study. *Atherosclerosis* 2007; 191(2):377-83.
19. Filippatos TD, Gazi IF, Liberopoulos EN et al. The effect of orlistat and fenofibrate, alone or in combination, on small dense LDL and lipoprotein-associated phospholipase A2 in obese patients with metabolic syndrome. *Atherosclerosis* 2007; 193(2):428-37.