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

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I. Description
Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase, is an enzyme that hydrolyzes phospholipids and is primarily associated with low-density lipoproteins (LDLs). Accumulating evidence has suggested that Lp-PLA2 is a biomarker of coronary artery disease (CAD) and may have a proinflammatory role in the progression of atherosclerosis.

Background
Low-density lipoproteins (LDL) have been identified as the major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project (NCEP) as the primary target of cholesterol-lowering therapy. LDL particles consist of a surface coat composed of phospholipids, free cholesterol, and apolipoproteins, surrounding an inner lipid core composed of cholesterol ester and triglycerides. Traditional lipid risk factors such as low-density lipoprotein-cholesterol (LDL-C), while predictive on a population basis, are weaker markers of risk on an individual basis. Only a minority of subjects with elevated LDL and cholesterol levels will develop clinical disease, and up to 50% of cases of coronary artery disease (CAD) occur in subjects with ‘normal’ levels of total and LDL cholesterol. Thus, there is considerable potential to improve the accuracy of current cardiovascular risk prediction models.

Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase, is an enzyme that hydrolyzes phospholipids and is primarily associated with LDLs. Accumulating evidence has suggested that Lp-PLA2 is a biomarker of CAD 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.
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**Regulatory Status**
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.

**II. Criteria/Guidelines**
Measurement of lipoprotein-associated phospholipase A2 (Lp-PLA2) does not meet payment determination criteria as randomized controlled studies have not been conducted and other scientific evidence has not shown improved long-term health outcomes.

**III. Administrative Guidelines**
The provider cannot bill or collect charges for these services unless a written acknowledgement of financial responsibility, specific to the service, is obtained from the Member prior to the time services are rendered. Modifier code GA should be appended to the CPT when billing for these services.

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**IV. Rationale**
A large body of literature has accumulated on the utility of risk factors in the prediction of future cardiac events. The evidence reviewed for this policy statement consists of large, prospective cohort studies that have evaluated the association of lipoprotein-associated phospholipase A2 (Lp-PLA2) with cardiovascular outcomes. A smaller amount of literature is available on the utility of Lp-PLA2 as a treatment target.

The National Cholesterol Education Program (NCEP) ATP-III guidelines (1) document notes that to determine their clinical significance, the emerging risk factors should be evaluated against the following criteria in order to determine their clinical significance:

- Significant predictive power that is independent of other major risk factors
- A relatively high prevalence in the population (justifying routine measurement in risk assessment)
- Laboratory or clinical measurement must be widely available, well standardized, inexpensive, have accepted population reference values, and be relatively stable biologically.
- Preferable, but not necessarily, modification of the risk factor in clinical trials will have shown reduction in risk
A 2002 TEC Assessment (2) summarized the steps necessary to determine utility of a novel cardiac risk factor. Three steps were required:

- Standardization of the measurement of the risk factor
- Determination of its contribution to risk assessment. As a risk factor, it is important to determine whether the novel risk factor [...] independently contributes to risk assessment compared to established risk factors.
- Determination of how the novel risk assessment will be used in the management of the patient, compared to standard methods of assessing risk, and whether any subsequent changes in patient management result in an improvement in patient outcome.

**LpA-PLA2 as a predictor of cardiovascular disease.** Results of numerous, large-scale observational studies have examined whether Lp-PLA2 is an independent risk factor for coronary heart disease. A representative sample of some of the larger studies is given below. 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. (3) Researchers looked at a smaller population of this study to determine if inflammatory markers such as Lp-PLA2 and high sensitivity C-reactive protein (hsCRP) were correlated with coronary heart disease (CHD) events. The 580 men who went on to have a myocardial infarction (MI) 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 (4) 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 CHD 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 hsCRP, in a subset of 608 cases and 740 controls. The results showed that elevated levels of Lp-PLA2 are higher in incident coronary heart disease cases. In individuals with nonelevated LDL levels (less than 130 mg/dL), Lp-PLA2 levels were independently associated with coronary heart disease, even after adjustment for traditional risk factors and C-reactive protein. Koenig and colleagues (5) reported similar results in a study of 934 apparently healthy men aged 45 to 64 who were followed up between 1984 and 1998. During this period, 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.

Ballantyne and colleagues (6) studied Lp-PLA2 in the 12,762 apparently healthy individuals participating in the ARIC study. 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. As part of the PEACE study, (7) Lp-PLA2 levels were measured in 3,766 patients with stable CAD followed up 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% confidence interval [CI]: 1.17–1.70, p<0.001) to experience an adverse cardiovascular outcome compared to patients in the lowest quartile. Winkler and colleagues (8) 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 (9) evaluated the relationship between Lp-PLA2 and the metabolic syndrome in 4,480 nondiabetic patients without a history of coronary artery disease (CAD). Both Lp-PLA2 (relative risk: 1.54; 95% CI: 1.07–2.24) and the metabolic syndrome (relative risk [RR]: 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).

The Rancho Bernardo Study (10) enrolled 1,077 community-dwelling elderly individuals without known heart disease and followed up patients a mean of 16 years for the development of heart disease. Lp-PLA2 was an independent predictor of cardiac events, with a relative risk for patients in the second, third, and fourth quartiles of 1.66, 1.80, and 1.89, respectively, compared with the first quartile. Sabatine et al. reported on 3,766 patients with stable CAD followed up for a mean of 4.8 years from the PEACE trial. (11) This study reported a significantly elevated RR for adverse cardiac events for patients with Lp-PLA2 levels in the fourth quartile compared to the first (RR 1.41, 95% CI: 1.17–1.70).

Most, but not all, observational studies reported a positive association of Lp-PLA2 with cardiovascular outcomes. Allison and colleagues (12) 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, (13) 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 electron-beam computed tomography (CT) scan. The unadjusted odds ratio (OR) for each standard deviation (SD) increase in Lp-PLA2 was 1.6 (95% CI: 1.1–2.4); however, this association became nonsignificant after controlling for lipid levels.

At least two systematic reviews have been published that summarize the observational studies on the association of Lp-PLA2 and cardiovascular disease. Garza and colleagues (14) reviewed 14 observational studies enrolling 20,549 patients. This study reported the predictive ability of Lp-PLA2 levels for cardiovascular disease after adjustment for traditional cardiac risk factors. The combined OR for an elevated Lp-PLA2 was reported as 1.60 (95% CI: 1.36–1.89) for the development of future cardiac events. A patient-level meta-analysis (15) evaluated the association between Lp-PLA2 levels, CAD, stroke, and mortality. A total of 79,036 participants from 32 prospective studies were included in this report. There were significant associations found between Lp-PLA2 and all 3 outcome measures. For every 1 SD increase in Lp-PLA2 levels, the RR adjusted for conventional risk factors was 1.10 (95% CI: 1.04–1.17) for CAD, 1.08 (95% CI 0.97–1.20) for stroke, and 1.16 (95% CI: 1.09-1.24) for vascular death. There was also a significant association found between Lp-PLA2 levels and
non-vascular deaths (RR 1.10, 95% CI 1.04–1.17). The authors estimated that this strength of association was similar to that seen for non-HDL cholesterol and systolic blood pressure.

For the 2011 update, numerous additional studies were identified that evaluated Lp-PLA2 as a risk factor for cardiovascular outcomes. The majority of these evaluated Lp-PLA2 as an independent risk factor for coronary disease in various patient populations. A number of studies specifically evaluated Lp-PLA2 as a risk factor in the diabetic population. For example, Saremi et al. (16) performed a substudy of the Veterans Affairs Diabetes trial (VADT) examining risk factors that predicted the progression of coronary artery calcification over an average of 4.6 years of follow-up. Lp-PLA2 mass was 1 of 2 significant independent predictors that remained (p=0.01) after adjustment for standard risk factors. Hatoum et al. (17) evaluated Lp-PLA2 as a risk factor for incident coronary heart disease in 1,517 diabetic patients enrolled in the Health Profession Follow-Up Study. After adjustment for standard risk factors, the RR for incident CHD for the upper quartile of Lp-PLA2 activity compared to the lower quartile was 1.39 (95% CI 1.01-1.90, p=0.03).

Another study evaluated the discriminatory ability of Lp-PLA2 for incident CHD in 421 cases and 800 controls from the Nurses’ Health Study. (18) Lp-PLA2 was a significant predictor of CHD after adjustment for traditional risk factors with a RR of 1.75 (95% CI 1.09-2.84). It also added significantly to the discriminatory ability, as judged by an increase in the area under the curve from 0.720 without Lp-PLA2 to 0.733 with Lp-PLA2, and improved the net reclassification improvement index for discriminating between patients with and without CHD (p=0.004).

**Lp-PLA2 as treatment target.** 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, (19) in which 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, MI, unstable angina, revascularization, or stroke suggested that patients randomized to atorvastatin 80 mg/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. Another ad hoc study from the DIACOR (Diabetes and Combined Lipid Therapy Regimen) trial (20) 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.

Rosenson randomized 55 hyperlipidemic subjects with metabolic syndrome to fenofibrate or placebo. (21) Fenofibrate treatment was associated with a 13% reduction in Lp-PLA2 mass compared to placebo. Saougos et al. studied the effect of three lipid-lowering agents, rosuvastatin, ezetimibe, and fenofibrate, on Lp-PLA2 levels. (22) All three agents significantly lowered Lp-PLA2 levels; fenofibrate also selectively increased high-density lipoprotein (HDL)-associated Lp-PLA2 levels.
Preliminary clinical trials of Lp-PLA2 inhibitors have been published, although none of the Lp-PLA2 inhibitors have been approved by the FDA for any indication. Darapladib was the first drug of this class that was tested. Mohler et al. randomized 959 patients with hyperlipidemia receiving atorvastatin to placebo or 1 of 3 doses of darapladib. (23) Dose-dependent inhibition of Lp-PLA2 was noted, ranging from 43% to 66% compared with placebo. The inflammatory markers interleukin-6 and hsCRP were also reduced by 12.3% and 13%, respectively. Serruys et al. randomized 330 patients with documented CAD to darapladib or placebo, and reported the impact of 12 months of treatment with darapladib on Lp-PLA2 levels, hsCRP levels, and coronary plaque composition as measured by intravascular ultrasound. (24) This study found no difference in plaque deformability but a reduction in plaque necrotic core was reported for the darapladib group. Lp-PLA2 levels were decreased by 59%, but there were no significant differences in hsCRP levels between groups.

A second phospholipase A2 inhibitor, varespladib, is also being tested in early clinical trials. There are at least 2 Phase III studies underway on these agents. (25) The STABILITY trial is a randomized, double-blind placebo-controlled trial of darapladib for patients with chronic CAD. The trial is projected to enroll over 15,000 patients from 800 clinical centers worldwide and report on the primary outcome of major adverse cardiovascular events. The FRANCIS-ACS trial is a randomized, double-blind, placebo-controlled trial of varespladib for patients with acute coronary syndrome. This trial is projected to enroll 700 patients, with follow-up for at least 24 weeks and report on the primary endpoint of major cardiovascular events.

For the 2011 update, there were no articles reporting on results of clinical trials using phospholipase inhibitors. A third ongoing Phase III trial was identified using darapladib as treatment for CAD. (26) The Stabilization of plaques using Darapladib – Thrombolysis in Myocardial Infarction 52 (SOLID-TIMI 52) trial will enroll approximately 11,500 participants within 30 days of acute MI. Participants will be randomized to darapladib or placebo and followed for 3 years for the outcomes of cardiovascular death, nonfatal MI, or stroke. This trial is currently in the recruitment phase.

Summary

None of the identified studies provide evidence that would lead to a change in the current policy statement. The risk prediction studies corroborate previous research demonstrating that Lp-PLA2 is an independent predictor of cardiovascular disease but do not demonstrate that health outcomes are improved as a result of measuring Lp-PLA2. Thus, this is considered investigational.

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. Clinical trials of Lp-PLA2 inhibitors are a new line of research with therapeutic potential. However, the available trials are preliminary, reporting only on physiologic outcomes such as reduction in hsCRP and using a pharmacologic agent that is not yet approved for use in the U.S. At least three Phase III clinical trials that utilize clinical outcomes as the primary endpoint(s) are currently in progress, and results from these may be available starting in 2012.

V. Important Reminder
The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VI. References
2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). C-Reactive Protein as a Cardiac Risk Marker (Special Report). TEC Assessments 2002; Volume 17, Tab 23.


