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

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Section: Medicine
Place(s) of Service: Outpatient

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.

There is a large body of literature evaluating Lp-PLA2 as a predictor of cardiovascular risk. These studies demonstrate that Lp-PLA2 is an independent predictor of cardiovascular (CVD). To improve outcomes, clinicians must have the tools to incorporate emerging risk factors into existing risk prediction models, and these models should demonstrate improved classification into risk categories that will lead to more appropriate treatment. Direct evidence for improved health outcomes with the use of Lp-PLA2 in clinical practice is lacking. Although Lp-PLA2 levels have been shown to be associated with CVD risk, the changes in patient management that would occur as a result of obtaining Lp-PLA2 levels in practice are not well-defined. The available evidence is insufficient to determine that the use of Lp-PLA2 for risk stratification for CVD improves the net health outcome.

Preliminary clinical trials of Lp-PLA2 inhibitors showed some improvements in physiologic outcomes, such as reduction in high-sensitivity C-reactive protein. However, 2 phase 3 clinical trials of Lp-PLA2 inhibitors failed to demonstrate significant improvements in patient outcomes and use a pharmacologic agent that is not yet approved for use in the United States. The available evidence, including 2 randomized controlled trials, indicates that Lp-PLA2 inhibitors do not improve health outcomes. The available evidence is insufficient to determine that the use of Lp-PLA2 as a treatment target improves the net health outcome.

II. Criteria/Guidelines
Measurement of lipoprotein-associated phospholipase A2 (Lp-PLA2) is not covered because scientific evidence has not shown it to be effective in improving 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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**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.

**Regulatory Status**

In December 2014, FDA cleared for marketing through the 510(k) process a quantitative enzyme assay for Lp-PLA2 activity PLAC® Test for (diaDexus, San Francisco, CA). It was considered substantially equivalent to a previous version of the PLAC test (diaDexus) which was cleared for marketing in July 2003. FDA product code: NOE

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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 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 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.

Is Lp-PLA2 and Independent Risk Factor for Cardiovascular Disease

Lp-PLA2 as a predictor of cardiovascular disease.
Results of numerous, large-scale observational studies have examined whether lipoprotein-associated phospholipase A2 (Lp-PLA2) is an independent risk factor for coronary heart disease. A representative sample of some of the larger studies is given below.

Systematic Reviews
Several systematic reviews and meta-analyses have summarized the association between Lp-PLA2 and CVD in general populations.
The Emerging Risk Factors Collaboration performed a patient-level meta-analysis of the association of novel lipid risk factors with cardiovascular risk. Records from 37 prospective cohort studies enrolling 165,544 participants were combined to predict cardiovascular risk over a median follow-up of 10.4 years. The authors examined the independent association of markers with cardiovascular risk and the ability to reclassify risk into clinically relevant categories. For Lp-PLA2, there were 11 studies enrolling 32,075 participants that measured this factor. Overall, Lp-PLA2 was an independent risk factor for cardiovascular events with a hazard ratio of 1.12 (95% confidence interval [CI]: 1.09-1.21) for each 1 standard deviation (SD) increase in Lp-PLA2 activity. There was no significant improvement in risk reclassification following the addition of Lp-PLA2 to the reclassification model, with a net reclassification improvement of 0.21 (-0.45 to 0.86). The net reclassification improvement crossing 0.0 indicates that the addition of Lp-PLA2 to the model may result in either improvement or worsening of reclassification.
Measurement of Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk

A number of systematic reviews have been published that summarize the observational studies on the association of Lp-PLA2 and CV disease. For example, Garza et al. reviewed 14 observational studies enrolling 20,549 patients. This study reported the predictive ability of Lp-PLA2 levels for CVD after adjustment for traditional cardiac risk factors. The combined odds ratio (OR) for an elevated Lp-PLA2 was reported as 1.60 (95% CI, 1.36 to 1.89) for the development of future cardiac events. A patient-level meta-analysis evaluated the association between Lp-PLA2 levels, coronary artery disease (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 risk ratio (RR) adjusted for conventional risk factors was 1.10 (95% CI, 1.04 to 1.17) for CAD, 1.08 (95% CI, 0.97 to 1.20) for stroke, and 1.16 (95% CI, 1.09 to 1.24) for vascular death. There was also a significant association found between Lp-PLA2 levels and nonvascular deaths (RR=1.10; 95% CI, 1.04 to 1.17). The authors estimated that this strength of association was similar to that seen for non-high-density lipoprotein (HDL) cholesterol and systolic blood pressure.

Nonrandomized Comparative Studies of Lp-PLA2 in General Populations

Some of the representative cohort and case-control studies evaluating the association between Lp-PLA2 and cardiovascular outcomes are described next.

The West of Scotland Coronary Prevention Study

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. 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 evaluated the various risk markers and their association with increased risk in a large, diverse population of more than 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 low-density lipoprotein (LDL) levels (less than 130 mg/dL), Lp-PLA2 levels were independently associated with CHD, even after adjustment for traditional risk factors and C-reactive protein. Koenig and colleagues 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 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, 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 (9) 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 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 [RR]: 1.54; 95% CI: 1.07–2.24) and the metabolic syndrome (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 (RR: 1.97; 95% CI: 1.34–2.90).

The Rancho Bernardo Study 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.

Another study evaluated the discriminatory ability of Lp-PLA2 for incident CHD in 421 cases and 800 controls from the Nurses’ Health Study.16 Lp-PLA2 was a significant predictor of CHD after adjustment for traditional risk factors with a RR of 1.75 (95% CI, 1.09 to 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).

Other studies have correlated Lp-PLA2 levels with different parameters of CVD. Multiple publications have reported that Lp-PLA2 levels are associated with characteristics of “vulnerable atherosclerotic plaques,” both in the coronary 17 and in the carotid arteries. Subsequent publications also found an association between Lp-PLA2 levels and plaque rupture and fibrous cap thickness in patients with acute coronary syndrome.20 Muller et al reported that Lp-PLA2 levels are associated with low fractional flow reserve on cardiac catheterization in 197 patients with stable CAD.21 Tehrani et al evaluated the association between Lp-PLA2 levels and the protective effect of high-density lipoprotein-cholesterol (HDL-C) on incident CHD among 3888 adults with known cardiovascular disease.22 Among patients with the highest tertile of Lp-PLA2, the relationship between HDL-C and incident CHD was attenuated, although there was no consistent association of higher levels of Lp-PLA2 with CHD risk across HDL-C categories.

Most, but not all, observational studies reported a positive association of Lp-PLA2 with cardiovascular outcomes. Allison and colleagues 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, 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 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.

**Nonrandomized Comparative Studies of Lp-PLA2 in Subpopulations**

Some studies have specifically evaluated Lp-PLA2 as a risk factor in the diabetic population. For example, Saremi et al. 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. 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).

**Section Summary**

There is a large amount of evidence establishing that Lp-PLA2 levels are an independent predictor of cardiovascular risk factors, physiologic measures of cardiac disease, and CV events. This association has been demonstrated in a variety of clinical populations, in people both with and without CV disease. The evidence on the ability of Lp-PLA2 to reclassify patients into clinically relevant categories is less convincing, with the largest patient-level meta-analysis reporting no significant improvement.

**Lp-PLA2 as Treatment Target**

Interventional studies involving Lp-PLA2 suggest that the level of Lp-PLA2 is modifiable by antihyperlipidemic drugs (e.g., 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, (25) 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 (26) 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. Fenofibrate treatment was associated with a 13% reduction in Lp-PLA2 mass compared to placebo. Saougos et al. studied the effect of 3 lipid-lowering agents, rosuvastatin, ezetimibe, and fenofibrate, on Lp-PLA2 levels. All 3 agents significantly lowered Lp-PLA2 levels; fenofibrate also selectively increased HDL-associated Lp-PLA2 levels.

At least 2 clinical trials have examined the change in Lp-PLA2 levels in patients treated with statins versus placebo and evaluated whether the utility of Lp-PLA2 for risk stratification is
modified by statin treatment. Ridker et al. analyzed the changes in Lp-PLA2 levels among patients in the JUPITER trial, a randomized controlled trial (RCT) of 17,802 individuals randomized to rosuvastatin or placebo. Among patients assigned to rosuvastatin, Lp-PLA2 mass decreased by 33.8%. In the placebo group, Lp-PLA2 levels were predictive of subsequent cardiac events, but this was not true in the rosuvastatin group. In a similar analysis of the MIRACL RCT, Ryu et al. analyzed 2,587 patients treated with high-dose atorvastatin or placebo. Atorvastatin reduced Lp-PLA2 levels in 2,587 patients treated with high-dose atorvastatin or placebo. Atorvastatin reduced Lp-PLA2 mass by 32.1% and Lp-PLA2 activity by 29.5%. In the placebo group, Lp-PLA2 levels were predictive of adverse cardiac outcomes, but no relationship was found in the atorvastatin group. The authors estimated that treatment with statins reduced the attributable risk of death due to Lp-PLA2 by approximately 50%.

Section Summary

Levels of Lp-PLA2 decrease substantially following treatment with antilipid medications, including statins. However, there are not currently well accepted thresholds for using Lp-PLA2 as a treatment target. Some studies have reported that treatment with statins eliminates the predictive ability of Lp-PLA2 as a treatment target; this may potentially reduce the potential of Lp-PLA2 for this purpose.

Will Identification of Lp-PLA2 Levels Lead to Changes in Patient Management, and Will These Changes in Management Lead to Improved Patient Outcomes?

Multiple studies have identified Lp-PLA2 as an independent risk factor for CV events and CVD and have suggested that medication treatment for hyperlipidemia is associated with changes in Lp-PLA2 levels. However, no studies were identified that addressed whether testing strategies that use Lp-PLA2 levels lead to changes in patient management. Clinical trials of Lp-PLA2 inhibitors have been published, although none of the Lp-PLA2 inhibitors have been approved by FDA for any indication. Darapladib was the first drug of this class that was tested. In 2014, results of the STABILITY trial of darapladib were published. This study was a double-blind, placebo-controlled randomized trial in which 15,828 patients with stable coronary disease were randomized to receive once-daily darapladib or placebo. Analysis was intention-to-treat. Over a median 3.7-year follow-up, the study’s primary end point of CV death, MI, or stroke, occurred in 769 of 7924 (9.7%) of the darapladib group and in 819 of 7904 (10.4%) of those in the placebo group (HR for darapladib, 0.94; 95% CI, 0.85 to 1.03; p=0.20). Darapladib was associated with improvements in the rates of major coronary events (9.3% vs 10.3%; HR=0.90; 95% CI, 0.82 to 1.00; p=0.045) and all coronary events (14.6% vs 16.1%; HR=0.91; 95% CI, 0.84 to 0.98; p=0.02).

The Stabilization of plaques using Darapladib–Thrombolysis in Myocardial Infarction 52 (SOLID-TIMI 52) was a double-blinded, multicenter trial which randomized 13,026 subjects within 30 days of acute MI to darapladib or placebo and followed patients for 3 years to evaluate for the composite end point of CHD related death, MI, or urgent coronary revascularization for myocardial ischemia. Results were published by O’Donoghue et al in 2014. Over a median 2.5-year follow-up, rates of the primary composite end point did not differ significantly between groups (16.3% in the darapladib group at 3 years vs 15.6% in the placebo group; HR=1.00; 95% CI, 0.91 to 1.09; p=0.93). Other primary and secondary end
points, including rates of individual components of the composite end point or all-cause mortality, did not differ significantly between groups.

Earlier studies compared darapladib with placebo in smaller study populations and with shorter follow-up periods than the SOLID-TIMI 52 and STABILITY trials and reported primarily surrogate end points. Mohler et al randomized 959 patients with hyperlipidemia receiving atorvastatin to placebo or 1 of 3 doses of darapladib. 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. This study found no difference in plaque deformability but a reduction in plaque necrotic core was reported for the darapladib group. LpPLA2 levels were decreased by 59%, but there were no significant differences in hscRP levels between groups.

A second phospholipase A2 inhibitor, varespladib, has also been tested in clinical trials. The VISTA-16 trial was a randomized, phase 3 trial comparing varespladib in addition to atorvastatin with atorvastatin alone in patients with acute coronary syndrome, which was terminated after enrollment of 5189 subjects for futility and possible harm. The study’s primary efficacy outcome was a composite of cardiovascular mortality, nonfatal MI, nonfatal stroke, or unstable angina with evidence of ischemia requiring hospitalization at 16 weeks. The primary end point occurred in 6.1% of the varespladib-treated subjects compared with 5.1% of placebo-treated subjects (HR=1.25; 95% CI, 0.97 to 1.61; p=0.08). Rates of MI were higher among varespladib-treated patients (3.4% vs 2.2%; HR=1.66; 95% CI, 1.16 to 2.39; p=0.005). The composite secondary end point of cardiovascular mortality, MI, and stroke was more common in varespladib-treated subjects (4.6% vs 3.8%; HR=1.36; 95% CI, 1.02 to 1.82; p=0.04).

**Summary of Evidence**

There is a large body of literature evaluating lipoprotein-associated phospholipase A2 (Lp-PLA2) as a predictor of cardiovascular risk. These studies demonstrate 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. Improved risk prediction does not by itself result in improved health outcomes. To improve outcomes, clinicians must have the tools to incorporate emerging risk factors into existing risk prediction models, and these models should demonstrate improved classification into risk categories that will lead to more appropriate treatment. These tools are not currently available to the practicing clinician for Lp-PLA2. As a result, use of Lp-PLA2 for risk stratification for cardiovascular disease is considered investigational.

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 high-sensitivity C-reactive protein (hscRP), and use a pharmacologic agent that is not yet approved for use in the U.S. At least 3 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. Therefore, Lp-PLA2 has not demonstrated improved outcomes as a treatment target and is considered investigational for this purpose.
Practice Guidelines and Position Statements

The American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) published joint guidelines on the assessment of cardiovascular risk in asymptomatic patients in 2010. The guidelines contained the following statement concerning testing for Lp-PLA2:

- Lipoprotein-associated phospholipase A2 might be reasonable for cardiovascular risk assessment in intermediate-risk asymptomatic adults. (Class IIb recommendation; Level of Evidence B)

In 2013, the ACCF/AHA published updated guidelines on the assessment of cardiovascular risk, which do not mention Lp-PLA2 testing.

American Association of Clinical Endocrinologists

The American Association of Clinical Endocrinologists published guidelines for the management of dyslipidemia and prevention of atherosclerosis in 2012. These guidelines made the following recommendations for Lp-PLA2 testing:

- Assess markers of inflammation in patients where further stratification of risk is necessary. Highly sensitive CRP and Lp-PLA2 provide useful information in these instances and appear to be synergistic in predicting risk of CVD and stroke. (Grade B recommendation; best level of evidence 1)
- Measure Lp-PLA2, which in some studies has demonstrated more specificity than highly sensitive CRP (hsCRP), when it is necessary to further stratify a patient’s CVD risk, especially in the presence of systemic highly sensitive CRP elevations (Grade B recommendation; best level of evidence 2).

European Society of Cardiology and Other Societies

In 2012, the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice issued guidelines on cardiovascular disease prevention. These guidelines include the following statements about Lp-PLA2 testing:

- LpPLA2 may be measured as part of a refined risk assessment in patients at high risk of a recurrent acute atherothrombotic event (Class IIb recommendation; Level of Evidence B; weak evidence).

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for the measurement of Lp-PLA2 have been identified.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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.
9. 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


