Measurement of Lipoprotein-Associated Phospholipase A2 in the Assessment of Cardiovascular Risk

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 (LDLs) have been identified as major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project 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-C. Although treatment for elevated coronary disease risk with statins targets cholesterol levels, selection for treatment involves estimation of future CAD risk using well-validated prediction models that use additional variables.

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. 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.

Interest in Lp-PLA2 as a possibly causal risk factor for CAD has generated development and testing of Lp-PLA2 inhibitors as a new class of drugs to reduce risk of CAD. However, clinical trials of Lp-PLA2 inhibitors have not shown significant reductions in CAD end points. Furthermore, assessment of Lp-PLA2 levels has not been used in the selection or management of subjects in the clinical trials.
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.

Related Policies

2.04.65  Novel Lipid Risk Factors in Risk Assessment and Management of Cardiovascular Disease
2.04.70  Genetic Testing for Lipoprotein(a) Variants as a Decision Aid for Aspirin Treatment

Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

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

Policy Guidelines

Measurement of lipoprotein A enzyme is a distinct laboratory test. Measurement of Lipoprotein A enzyme is addressed in policy No. 2.04.65, and genetic testing for lipoprotein(s) variants is addressed in policy 2.04.70.

Rationale

A large body of literature has accumulated on the utility of risk factors in the prediction of future cardiac events. The evidence assessed for this review consists of large, prospective cohort studies that have evaluated the association between lipoprotein-associated phospholipase A2 (Lp-PLA2) and cardiovascular outcomes.

The National Cholesterol Education Program (NCEP) ATP-III guidelines have indicated that to determine the clinical significance of Lp-PLA2, the emerging risk factors should be evaluated against the following criteria:

- 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.

ANALYTIC VALIDITY

According to the U.S. Food and Drug Administration's (FDA) Summary of Safety and Effectiveness for the PLAC Lp-PLA2 assay, the intraassay precision for the test using the coefficient of variation (CV) was 7%, and the interassay precision using the CV was 9%, with a detection limit of 1.2 ng/mL. Reference intervals for the Lp-PLA2 assay were calculated from samples for 251 apparently healthy males and 174 apparently healthy females ages 40 to 70 years; the reference interval calculated from the samples (central 90%) was determined to be 120 to 342 ng/mL for females and 131 to 376 ng/mL for males. FDA concluded that the assay demonstrated acceptable analytical performance.

CLINICAL VALIDITY

Lp-PLA2 as a Predictor of Coronary Artery Disease

Results of numerous, large-scale observational studies have examined whether lipoprotein-associated phospholipase A2 (Lp-PLA2) is an independent risk factor for cardiovascular disease. Some of these observational studies have been evaluated in systematic reviews and meta-analyses. A representative sample of some of the larger studies is given below.

Systematic Reviews of the Association Between Lp-PLA2 and CAD

Several systematic reviews and meta-analyses have summarized the association between Lp-PLA2 and CAD in general populations.

The Emerging Risk Factors Collaboration performed a patient-level meta-analysis of the association between novel lipid risk factors and 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. Reviewers examined the independent association of markers with cardiovascular risk and the ability to reclassify risk into clinically relevant categories. For Lp-PLA2, 11 studies (total N=32,075 participants) measured this factor. Overall, Lp-PLA2 was an independent risk factor for cardiovascular events with a hazard ratio (HR) of 1.12 (95% confidence interval [CI], 1.09 to 1.21) for each 1 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 (95% CI, -0.45 to 0.86). The fact that the net reclassification improvement crossed 0.0 indicates that the addition of Lp-PLA2 to the model did not result in an important magnitude of change.

Garza et al reviewed 14 observational studies enrolling 20,549 patients. This systematic review reported the predictive ability of Lp-PLA2 levels for cardiovascular disease (CVD) after adjustment for
A patient-level meta-analysis by Thompson et al evaluated the association among Lp-PLA2 levels, CAD, stroke, and mortality. A total of 79,036 participants from 32 prospective studies were included in this review. Significant associations were found between Lp-PLA2 and all 3 outcome measures. For every 1 SD increase in Lp-PLA2 levels, the relative risk (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 between Lp-PLA2 levels and nonvascular deaths (RR=1.10; 95% CI, 1.04 to 1.17). Reviewers estimated that this strength of association was similar to that seen for non–high-density lipoprotein cholesterol (HDL-C) and systolic blood pressure.

### Association Between Lp-PLA2 and CAD in General Population Samples

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 (WOSCOPS) was a 5-year, case-control trial evaluating 6595 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) correlated with coronary heart disease (CHD) events. The 580 men who went on to have a myocardial infarction or revascularization were compared with 1160 age- and smoking-matched men who did not have an event. Results showed that those with the highest levels of Lp-PLA2 had twice the risk of an event compared with 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 people. At enrollment, patients were free of CHD and were followed 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 hs-CRP, in a subset of 608 cases and 740 controls. Results showed that elevated levels of Lp-PLA2 were higher in incident CHD cases. In people with nonelevated low-density lipoprotein (LDL) levels (<130 mg/dL), Lp-PLA2 levels were independently associated with CHD, even after adjustment for traditional risk factors and CRP. Koenig et al reported similar results in a study of 934 apparently healthy men ages 45 to 64 who were followed 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 CRP levels.

Ballantyne et al studied Lp-PLA2 in the 12,762 apparently healthy subjects participating in the ARIC study. Mean levels of both Lp-PLA2 and CRP 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 3766 patients with stable CAD followed for a median of 4.8 years. After adjusting for other baseline risk factors, patients in the highest quartile of Lp-PLA2 were 1.4 times more likely (95% CI, 1.17 to 1.70; p<0.001) to experience an adverse cardiovascular outcome compared with patients in

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the lowest quartile. Winkler et al studied 3232 consecutive patients referred for coronary angiography and reported that Lp-PLA2 levels were an independent predictor of cardiac mortality (HR=2.0; 95% CI, 1.4 to 3.1; p<0.001) after adjusting for established risk factors, including CRP and N-terminal b-natriuretic peptide. Persson et al evaluated the relation between Lp-PLA2 and the metabolic syndrome in 4480 nondiabetic patients without a history of CAD. Both Lp-PLA2 (RR=1.54; 95% CI, 1.07 to 2.24) and the metabolic syndrome (RR=1.42; 95% CI, 1.06 to 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 to 2.90).

The Rancho Bernardo Study enrolled 1077 community-dwelling elderly people without known heart disease and followed patients a mean of 16 years for 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. Lp-PLA2 was a significant predictor of CHD after adjustment for traditional risk factors (RR=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 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. Muller et al reported that Lp-PLA2 levels were associated with low fractional flow reserve on cardiac catheterization in 197 patients with stable CAD. Tehrani et al evaluated the association between Lp-PLA2 levels and the protective effect of HDL-C on incident CHD among 3888 adults with known CVD. Among patients with the highest tertile of Lp-PLA2, the relation between HDL-C and incident CHD was attenuated, although there was no consistent association between higher levels of Lp-PLA2 and CHD risk across HDL-C categories. Recent studies have shown associations between Lp-PLA2 and cardiovascular events in a nonwhite multiethnic population, in the severity of angiographically defined CAD in a Chinese sample, and in subclinical atherosclerosis in young adults.

Some studies have shown that the association between Lp-PLA2 and CAD diminishes or disappears after adjustment for other risk factors. For example, Allison et al studied 508 patients with peripheral vascular disease followed an average of 6.7 years. While there was a modest univariate association between Lp-PLA2 and cardiovascular events, this association disappeared after adjusting for established risk factors. In the Rotterdam Coronary Calcification Study, a similar diminution of risk was observed. This population-based study followed 520 patients for 7 years and evaluated the association between Lp-PLA2 and coronary calcification using electron beam computed tomography scan. The unadjusted odds ratio for each SD increase in Lp-PLA2 was 1.6 (95% CI, 1.1 to 2.4); however, this association became nonsignificant after controlling for lipid levels.
Association of Lp-PLA2 and CAD in Specific Populations

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 examining risk factors that predicted the progression of coronary artery calcification over an average of 4.6 years of follow-up.\(^{30}\) 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 CHD in 1517 diabetic patients enrolled in the Health Profession Follow-Up Study.\(^{31}\) After adjusting for standard risk factors, the relative risk for incident CHD for the upper quartile of Lp-PLA2 activity compared with the lower quartile was 1.39 (95% CI, 1.01 to 1.90; p=0.03).

Association Between Lp-PLA2 and CAD in Patients Receiving CAD Preventive Drugs

If levels of Lp-PLA2 change in response to effective CAD preventive drugs such as statins, and there is an association between CAD risk on treatment and Lp-PLA2 levels, then measurement of Lp-PLA2 levels may be useful in monitoring treatment response.

Interventional studies of antihyperlipidemic drugs (eg, statins, fibrates, niacin) have shown that Lp-PLA2 levels decrease during treatment. A secondary analysis of the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction) trial, in which Lp-PLA2 levels were measured at baseline (n=3648) and at 30 days (n=3265), showed that patients randomized to atorvastatin 80 mg/d, but not pravastatin 40 mg/d, experienced a 20% reduction of Lp-PLA2 levels at 30 days.\(^{32}\) The 30-day, Lp-PLA2 level was independently associated with an increased risk of cardiovascular events. A secondary analysis from the DIACOR (Diabetes and Combined Lipid Therapy Regimen) trial demonstrated lower Lp-PLA2 levels (16.8% overall reduction) after treatment compared with baseline.\(^{33}\)

Rosenson randomized 55 hyperlipidemic subjects with metabolic syndrome to fenofibrate or placebo.\(^{34}\) Fenofibrate treatment was associated with a 13% reduction in Lp-PLA2 levels compared with placebo. Saougos et al studied the effect of 3 lipid-lowering agents (rosuvastatin, ezetimibe, fenofibrate) on Lp-PLA2 levels.\(^{35}\) All 3 agents significantly lowered Lp-PLA2 levels; fenofibrate also selectively increased HDL-associated Lp-PLA2 levels.

Although Lp-PLA2 levels respond to CAD preventive drugs, some studies have shown that Lp-PLA2 levels do not correlate with subsequent CAD risk in treated patients. 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 levels for risk stratification is modified by statin treatment.\(^{36,37}\) Ridker et al analyzed the changes in Lp-PLA2 levels among patients in the JUPITER trial, an RCT of 17,802 subjects allocated to rosuvastatin or placebo.\(^{36}\) Among patients who received 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 2587 patients treated with high-dose atorvastatin or placebo.\(^{37}\) Atorvastatin reduced Lp-PLA2 levels in 2587 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 relation was found in the atorvastatin group. In a 2014 clinical trial by White et al, patients were randomized to placebo or darapladib, an Lp-PLA2 inhibitor.\(^{1}\) A secondary analysis of this trial by Wallentin et al demonstrated that, although baseline Lp-PLA2 levels
were associated with cardiovascular risk, there was no association between changes in Lp-PLA2 levels and outcomes.\textsuperscript{38}

**Section Summary: Clinical Validity**

A large consistent body of evidence has established that Lp-PLA2 level is an independent predictor of CAD. Relatively few studies have examined the degree to which Lp-PLA2 improves on existing CAD prediction models in terms of clinically important magnitudes of reclassification.

Levels of Lp-PLA2 decrease substantially after treatment with antilipid medications, including statins. However, in treated patients, Lp-PLA2 levels may no longer be associated with risk of CAD, and thus may not be useful as a measure of treatment response.

**Clinical Utility**

Although the preceding studies have shown that Lp-PLA2 is an independent risk factor for CAD, clinical utility depends on whether the use of Lp-PLA2 levels improves on existing models of CAD prediction, which then to translate into differences in treatment that improve patient outcomes. Establishing improved outcomes compared to existing prediction models could be demonstrated with clinical trials, but the expected difference in outcomes would probably be so small that the sample size of the trial would be impractically large. Decision modeling is another approach to estimating differences in patient outcomes due to improved reclassification of risk. A robust validated model using Lp-PLA2 levels to predict CAD outcomes is necessary to use the test to manage patients. No studies identified evaluated whether a testing strategy that uses Lp-PLA2 levels improves health outcomes.

**Section Summary: Clinical Utility**

Changes in patient management that could potentially occur with a strategy using Lp-PLA2 levels are not well-established. Studies that directly evaluate patient management changes and/or health outcome improvements are needed to conclude that the use of Lp-PLA2 measurement has efficacy in CVD. Alternatively, robust decision modeling studies may demonstrate clinically important changes in health outcomes by incorporating Lp-PLA2 levels into CAD prediction models. Groups such as the American Heart Association have often incorporated results from decision models to inform their guidelines, when the data underlying the models is robust.

**Practice Guidelines and Position Statements**

**American College of Cardiology and American Heart Association**

The American College of Cardiology and American Heart Association published joint guidelines on the assessment of cardiovascular risk in asymptomatic patients in 2013.\textsuperscript{39} Lipoprotein-associated phospholipase A\textsubscript{2} (Lp-PLA2) testing was not mentioned in these guidelines, which was a change from 2010 guidelines.\textsuperscript{40} In this prior guideline, Lp-PLA2 was given a IIb recommendation for assessing cardiovascular risk in intermediate-risk asymptomatic adults.

**American Association of Clinical Endocrinologists**

The American Association of Clinical Endocrinologists published guidelines on the management of dyslipidemia and prevention of atherosclerosis in 2012.\textsuperscript{41} These guidelines made the following recommendations for Lp-PLA2 testing (see Table 1).
Table 1. AACE Guidelines on Dyslipidemia and Atherosclerosis

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<tr>
<th>Recommendation</th>
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<td>Assess markers of inflammation in patients where further stratification of risk is necessary. Highly sensitive CRP (hsCRP) and Lp-PLA2 provide useful information in these instances and appear to be synergistic in predicting risk of CVD and stroke</td>
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<td>Measure Lp-PLA2, which in some studies has demonstrated more specificity than hsCRP, when it is necessary to further stratify a patient’s CVD risk, especially in the presence of systemic highly sensitive CRP elevations</td>
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AACE: American Association of Clinical Endocrinologists; CRP: C-reactive protein; CVD: cardiovascular disease; LOE: level of evidence; Lp-PLA2: lipoprotein-associated phospholipase A2.

European Society of Cardiology et al

In 2012, the European Society of Cardiology and other cardiovascular disease societies issued clinical practice guidelines on CVD prevention. These guidelines included 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

There is no mention of Lp-PLA2 in U.S. Preventive Services Task Force recommendations on assessment of cardiovascular risk.

Summary of Evidence

For individuals who have a risk of cardiovascular disease (CVD) who receive lipoprotein-associated phospholipase A2 (Lp-PLA2) testing, the evidence includes studies of analytic validity and studies of the association between Lp-PLA2 and various coronary artery disease outcomes. Relevant outcomes are overall survival, disease-specific survival, and test validity. The studies have demonstrated that Lp-PLA2 levels are an independent predictor of CVD. Evidence of clinical utility is lacking. To improve outcomes, clinicians must have the tools to incorporate Lp-PLA2 test results into existing risk prediction models, and these models should demonstrate improved classification into risk categories that will improve treatment and health outcomes. Direct evidence for improved health outcomes with the use of Lp-PLA2 in clinical practice is lacking. Although Lp-PLA2 levels are associated with CVD risk, changes in patient management that would occur as a result of obtaining Lp-PLA2 levels in practice are not well-defined. The evidence is insufficient to determine the effects of the technology on health outcomes.

Medicare National Coverage

No national coverage determination.

References


34. Rosenson RS. Fenofibrate reduces lipoprotein associated phospholipase A2 mass and oxidative lipids in hypertriglyceridemic subjects with the metabolic syndrome. Am Heart J. Mar 2008;155(3):499 e499-416. PMID 18294485


Policy History

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<td>June 2012</td>
<td>Update Policy</td>
<td>Policy statement changed to not medically necessary. Updated literature search. Reference 19 added. Policy updated with literature search; references added. No change to policy statement.</td>
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### Keywords

Cardiac Risk Factor, Lp-PLA2  
Lipoprotein-Associated Phospholipase A2, Cardiac Risk Factor  
Lp-PLA2, Cardiac Risk Factor  
PLAC, Laboratory Test

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This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 17, 2017 and is effective April 15, 2017.

**Signature on file**

Deborah M. Smith, MD, MPH