

Medical Policy Manual

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

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

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.

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 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.

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.

MEDICAL POLICY CRITERIA

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

SCIENTIFIC EVIDENCE

Predicting risk or prognosis does not, by itself, directly improve health outcomes. In order to understand whether measurement of lipoprotein-associated phospholipase A2 (Lp-PLA2) has a positive impact on health outcomes, there must be evidence from prospective, comparative studies that patient management decisions based on Lp-PLA2 measurements increase the duration or quality of life or decrease adverse events.

The National Cholesterol Education Program (NCEP) ATP-III guidelines on high cholesterol in adults noted that emerging risk factors should be evaluated against the following criteria in order to determine their clinical significance:^[1]

- 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 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment summarized the three steps necessary to determine utility of a novel cardiac risk factor as follows:^[2]

- 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 with standard methods of assessing risk, and whether any subsequent changes in patient management result in an improvement in patient outcomes.

LpA-PLA2 as a Predictor of Cardiovascular Disease

Systematic Reviews

Results of numerous, large-scale observational studies have examined whether Lp-PLA2 is an independent risk factor for coronary artery disease (CAD). A number of systematic reviews have been published that summarized the observational studies on the association of Lp-PLA2 and cardiovascular disease:

- In a 2013 systematic review, Holst-Albrechtsen et al. reported on 7 nonrandomized studies that focused on Lp-PLA2 as a biomarker in patients with acute coronary syndrome.^[3] The authors reported inconsistency in the findings regarding the potential use of Lp-PLA2, and recommended “more focused studies concerning genetic variations, time-window impact, patients with and without cardiovascular risk factors (e.g., diabetes), and treatment effects.”
- Garza and colleagues reviewed 14 observational studies enrolling 20,549 patients.^[4] This study reported the predictive ability of Lp-PLA2 levels for cardiovascular disease after adjustment for traditional cardiac risk factors. The combined odds ratio (OR) for an elevated Lp-PLA2 was reported as 1.60 (95% CI: 1.36–1.89) for the development of future cardiac events.
- Similarly, the systematic review by Vittos et al. found a significant association between Lp-PLA2 levels and cardiovascular events after multivariate adjustment.^[5] The association was consistent across a wide variety of subjects of both sexes and different ethnic backgrounds.
- The Emerging Risk Factors Collaboration performed a patient-level meta-analysis of the association of novel lipid risk factors with cardiovascular risk.^[6] 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% 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.
- In 2010, the Lp-PLA2 Studies Collaboration updated their 2007 meta-analysis evaluating the association between Lp-PLA2 levels, CAD, stroke, and mortality.^[7] Individual patient records were included in this analysis of 79,036 participants from 32 prospective studies. There were significant associations found between Lp-PLA2 and all 3 outcome measures. For every 1 standard deviation (SD) increase in Lp-PLA2 levels, the risk ratio (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.

Reported limitations of this analysis included sparse and apparently divergent serial Lp-LPA2 measurements, and follow-up periods “too brief to enable informative study of the incremental value of Lp-PLA2 measurement in standard 10-year prediction of vascular disease risk. Therefore, the authors noted the need for large, long-term studies, particularly of first-ever CAD with serial measurements.

Nonrandomized Clinical Trials

Most, but not all, observational studies reported a positive association of Lp-PLA2 with cardiovascular outcomes.^[8-11] For example:

- Allison and colleagues studied 508 patients with peripheral vascular disease followed for an average of 6.7 years.^[8] 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 (CT) scan.^[9] 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.

A number of studies specifically evaluated Lp-PLA2 as a risk factor in the diabetic population:

- 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.^[12] 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.^[13] After adjustment for standard risk factors, the RR for incident CAD for the upper quartile of Lp-PLA2 activity compared to the lower quartile was 1.39 (95% CI 1.01-1.90, $p=0.03$).

Other studies have correlated Lp-PLA2 levels with different parameters of cardiovascular disease:

- Constantinides et al studied the carotid intima media thickness (IMT), which they used as a measure of asymptomatic atherosclerosis, and Lp-PLA1 mass in diabetic ($n=74$) and nondiabetic ($n=64$) subjects.^[14] While IMT and Lp-PLA2 showed an independent association in nondiabetic patients, no correlation was found between these two measures in diabetic patients. The relationship of Lp-PLA2 and cholesterol/high-density lipoprotein (HDL) cholesterol ratio also differed between diabetic and nondiabetic subjects. The authors concluded that these findings raise questions about how useful Lp-PLA2 mass measurement is as a marker of asymptomatic atherosclerosis in patients with type II diabetes.
- Associations have also been reported with characteristics of “vulnerable atherosclerotic plaques”, both in the coronary^[15] and the carotid^[16] arteries, and with plaque rupture^[17].

Another study evaluated the discriminatory ability of Lp-PLA2 for incident CAD in 421 cases and 800 controls from the Nurses’ Health Study.^[18] Lp-PLA2 was a significant predictor of CAD 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 CAD ($p=0.004$).

Conclusions

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 cardiovascular events. This association has been demonstrated in a variety of clinical populations, in individuals both with and without cardiovascular disease. However, no studies have been published that demonstrate that health outcomes are improved as a result of measuring Lp-PLA2.

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).^[19-25] In addition, 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.^[26,27] These studies could not be used to assess of the clinical validity and

clinical utility of Lp-LPA2 as a biomarker for cardiovascular risk because they did not study the impact of the reported reductions in Lp-PLA2 levels on health outcomes.

Conclusions

- Levels of Lp-PLA2 decreased substantially following treatment with anti-lipid medications including statins. However, there are currently no 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.
- Inhibitors of Lp-PLA2 have been developed and tested in clinical trials, but no trials have demonstrated an improvement in health outcomes with these inhibitors.

Clinical Practice Guidelines

American College of Cardiology Foundation/American Heart Association (ACCF/AHA)^[28]

The 2010 joint ACCF/AHA guidelines for cardiovascular risk assessment state that Lp-PLA2 “might be reasonable for cardiovascular risk assessment in intermediate-risk asymptomatic adults.” This was a Class IIb recommendation, defined as having less well-established usefulness/efficacy, with greater conflicting evidence from single randomized trial or nonrandomized studies with limited populations. The guidelines do not provide specific recommendations on how Lp-PLA2 risk assessment may be used in patient management to improve health outcomes.

American Heart Association/American Stroke Association (AHA/ASA)^[29]

The 2011 guidelines from the AHA/ASA provided a Class IIb recommendation stating that measurement of inflammatory markers such as Lp-PLA2 in patients without cardiovascular disease “may be considered to identify patients who may be at increased risk of stroke, although their effectiveness (i.e., usefulness in routine clinical practice) is not well established (Level of Evidence B).”

American Association of Clinical Endocrinologists (AACE)^[30]

The 2012 AACE guidelines for the management of dyslipidemia and prevention of atherosclerosis made Grade B (intermediate strength) recommendations in favor of assessing markers of inflammation (i.e., CRP and Lp-PLA2) in patients where further stratification of cardiovascular or stroke risk is necessary. The guidelines do not address how this information may be used in clinical practice to improve patient health outcomes.

Summary

In order to understand whether measurement of lipoprotein-associated phospholipase A2 (Lp-PLA2) has a positive impact on health outcomes there must be evidence that patient management decisions based on Lp-PLA2 measurements improve health outcomes. Risk prediction studies have corroborated previous research demonstrating that lipoprotein-associated phospholipase A2 (Lp-PLA2) is an independent predictor of cardiovascular disease but did not demonstrate that health outcomes improved as a result of measuring Lp-PLA2. In addition, studies of Lp-PLA2 as a treatment target are preliminary and do not report the impact of reduction in Lp-PLA2 levels on health outcomes. Therefore, measurement of Lp-PLA2 is considered investigational for all indications.

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CROSS REFERENCES

[Apolipoprotein E for Risk Assessment and Management of Cardiovascular Disease](#), Genetic Testing, Policy No. 05

[Gene Expression Testing to Predict Coronary Artery Disease](#), Genetic Testing, Policy No. 46

CODES	NUMBER	DESCRIPTION
CPT	83698	Lipoprotein-associated phospholipase A ₂ (Lp-PLA ₂)
HCPCS	None	