Medical Policy Manual Laboratory, Policy No. 63

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) is an enzyme that is primarily associated with low-density lipoproteins (LDLs). Lp-PLA2 has been proposed as a biomarker in cardiovascular disease risk assessment.

MEDICAL POLICY CRITERIA

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

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Apolipoprotein E for Risk Assessment and Management of Cardiovascular Disease, Genetic Testing, Policy No. 05

BACKGROUND

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.

LDLs 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 LDL-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.

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) cleared for marketing an enzyme-linked immunoabsorbent assay (ELISA) test, the PLAC test (diaDexus), to measure levels of Lp-PLA2.

EVIDENCE SUMMARY

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.

Validation of the clinical use of any diagnostic test focuses on three main principles:

1. Analytic validity of the test;
2. Clinical validity of the test (i.e., sensitivity, specificity, and positive and negative predictive values in relevant populations of patients and compared to the gold

standard); and
3. Clinical utility of the test (i.e., how the results of the diagnostic test will be used to improve the management of the patient).

ANALYTIC VALIDITY

According to the FDA's Summary of Safety and Effectiveness for the diaDexus' lipoprotein-associated phospholipase A2 (Lp-PLA2) assay, the intra-assay precision (n=80) for the assay was < 7% coefficient of variability (CV), and the inter-assay precision (n=20) was < 9% CV, with a detection limit of 1.2 ng/mL.[2] Reference intervals for the Lp-PLA2 assay were calculated from samples for 251 apparently healthy males and 174 apparently healthy females aged 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

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 cardiovascular disease. A number of systematic reviews and meta-analysis have been published that summarize these observational studies regarding the association of Lp-PLA2 and cardiovascular disease:

Li (2015) published a systematic review on the association between Lp-PLA2 and coronary heart disease, which included 15 studies with 30,857 participants.[3] They found no association between Lp-PLA2 activity or mass and mortality, but did see an independent association between both Lp-PLA2 activity and mass and cardiovascular events (hazard ratio [HR] 1.55, 95% confidence interval [CI] 1.08 to 2.23 and HR 1.62, 95% CI 1.09 to 2.41, respectively).

Holst-Albrechtsen (2013) reported on a systematic review of seven nonrandomized studies that focused on Lp-PLA2 as a biomarker in patients with acute coronary syndrome.[4] 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."

The systematic review by Vittos (2012) 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. Recent studies show associations between Lp-PLA2 and cardiovascular events in a nonwhite multiethnic population, severity of angiographically defined CAD in a Chinese sample and subclinical atherosclerosis in young adults.[6-8]

In 2012, the Emerging Risk Factors Collaboration performed a patient-level meta-analysis of the association of novel lipid risk factors with cardiovascular risk.[9] 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 HR of 1.12 (95% CI 1.09 to 1.21) for each one 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 (95% CI -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.[10] 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 three outcome measures. For every one 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 non-vascular 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-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.

Garza (2007) published results from a review of 14 observational studies enrolling 20,549 patients.[11] 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 to 1.89) for the development of future cardiac events.

Nonrandomized Studies

Most, but not all, observational studies reported a positive association of Lp-PLA2 with cardiovascular or stroke outcomes.[12-18] For example:

Acosta (2017) published results from a prospective cohort study evaluating the relationship of Lp-PLA2 and abdominal aortic aneurysms (AAA)[19]. The authors concluded that the cumulative incidence of AAA was 1.5% (men 2.9%, women 0.5%) during a median follow-up period of 20.7 years. Overall, 84 individuals had an incident AAA, of whom 22 (26.2%) were operated on and 16 (19.0%) had ruptured. Mean age of individuals with incident AAA was 59.7 years at study entry and AAA was diagnosed on average 14 years later. When adjusting for age, gender, smoking, body mass index, hypertension, and diabetes mellitus, Lp-PLA2 activity (HR 1.40; 95% CI 1.15-1.72) and Lp-PLA2 mass (HR 1.23; 95% CI 1.00-1.51) were independently associated with incident AAA.

Lin (2015) published results from an association study that examined the relationship between Lp-PLA2 activity (Lp-PLA2-A) and early recurrence of vascular events after a transient ischemic attack (TIA) and minor stroke.[15] A subset of patients enrolled in the clopidogrel in high-risk patients with acute non-disabling cerebrovascular events (CHANCE) who had a TIA or minor stroke were enrolled within 24 hours of symptoms and were treated with either single or dual antiplatelet therapy. The authors found that in addition to some demographic factors, such as age and gender, Lp-PLA2-A levels were significantly associated were significantly associated with an ischemic stroke, myocardial infarction, or death [adjusted HR 1.07, 95% CI

1.01 to 1.13 for every 30 nmol/min/mL increase). Although the authors found an association between Lp-PLA2-A, clinical utility was not demonstrated.

Allison (2007) published results from a study that included 508 patients with peripheral vascular disease followed for an average of 6.7 years.[12] While there was a modest univariate association of Lp-PLA2 with cardiovascular events, this association disappeared after adjustment for established risk factors.

Kardys (2007) published results from the Rotterdam Coronary Calcification Study, similar results were reported. This population-based study followed 520 patients for seven years and evaluated the association between Lp-PLA2 and coronary calcification by electron-beam computed tomography (CT) scan.[20] The unadjusted OR 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.

Several studies have specifically evaluated Lp-PLA2 as a risk factor in the diabetic population. Saremi (2010) 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.[21] Lp-PLA2 mass was one of two significant independent predictors that remained (p=0.01) after adjustment for standard risk factors. Hatoum (2010) 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.[22]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 to 1.90, p=0.03).

Other studies have correlated Lp-PLA2 levels with different parameters of cardiovascular disease. For example, Constantinides (2011) studied the carotid intima media thickness (IMT), which they used as a measure of asymptomatic atherosclerosis, and Lp-PLA2 mass in diabetic (n=74) and nondiabetic (n=64) subjects.[23] 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.

Studies have also reported and association between Lp-PLA2 and other characteristics, such as, “vulnerable atherosclerotic plaques”, both in the coronary[24] and the carotid[25] arteries, low fractional flow reserve on cardiac catheterization,[26] incidence of coronary heart disease,[27] arterial stiffness,[28] smoking,[29] and with plaque rupture[30].

Another study evaluated the discriminatory ability of Lp-PLA2 for incident CAD in 421 cases and 800 controls from the Nurses’ Health Study.[31] Lp-PLA2 was a significant predictor of CAD 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 CAD (p=0.004).

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 cardiovascular events. This association has been demonstrated in a variety of clinical populations, in individuals both with and without cardiovascular disease.

Lp-PLA2 as a Treatment Target

Interventional studies involving Lp-PLA2 suggest that the level of Lp-PLA2 is modifiable by antihyperlipidemics (statins, fibrates, and niacin).[32-39] In addition, several 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.[40-43] 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.

Section Summary

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.

CLINICAL UTILITY

While there have been no published studies that demonstrate that health outcomes are improved as a result of measuring Lp-PLA2, an important study by Gregson (2017) evaluated the causal role of Lp-PLA2 in cardiovascular disease using genetic variants that are known to reduce Lp-PLA2 function.[44] Genotyping for five such variants was performed on 72,657 participants with coronary heart disease (CHD) and 110,218 controls from 23 epidemiologic studies, and data from an additional 45,823 CHD patients and 88,680 controls were added from public databases. The authors also performed a systematic review of randomized trials to assess the effect of darapladib, an Lp-PLA2 inhibitor, on Lp-PLA2 activity and cardiovascular risk and compare them with the effects of the Lp-PLA2 variants. The variants decreased Lp-PLA2 activity by 45% to 64%, while darapladib (160 mg once daily) reduced Lp-PLA2 activity by 65%. There was no significant association of either the Lp-PLA2 variants or darapladib treatment with coronary heart disease risk. These results suggest that Lp-PLA2 is unlikely to play a causal role in the development of CHD.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION/AMERICAN HEART ASSOCIATION[45, 46]

The 2019 joint American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines for cardiovascular risk assessment no longer address Lp PLA2 testing. In their prior guideline (2010), Lp PLA2 was given a IIb recommendation, defined as having less well established usefulness or efficacy with greater conflicting evidence from single randomized trial or nonrandomized studies with limited populations.

AMERICAN HEART ASSOCIATION/AMERICAN STROKE ASSOCIATION[47]

The 2011 guidelines from the American Heart Association/American Stroke Association (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) AND AMERICAN COLLEGE OF ENDOCRINOLOGY (ACE)[48]

The 2017 AACE/ACE guidelines for the management of dyslipidemia and prevention of cardiovascular disease made Grade A recommendation in favor of assessing 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

There is not enough research to show that measurement of lipoprotein-associated phospholipase A2 (Lp-PLA2) can improve health outcomes for patients at risk for cardiovascular disease. In addition, there is no evidence that lowering Lp-PLA2 levels improves cardiovascular risk. Therefore, measurement of Lp-PLA2 is considered investigational for all indications.

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CODES

Codes	Number	Description
CPT	83698	Lipoprotein-associated phospholipase A_2 (Lp-PLA_2)
HCPCS	None	

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