Medical Policy

BlueCross BlueShield Kansas
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Title: Measurement of Lipoprotein-Associated Phospholipase A_2 in the Assessment of Cardiovascular Risk

See Also: *Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease*

Professional
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Populations	Interventions	Comparators	Outcomes
Individuals: • With a risk of cardiovascular disease	Interventions of interest are: • Lipoprotein-associated phospholipase A_2 testing	Comparators of interest are: • Standard cardiovascular risk assessment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity

DESCRIPTION

Lipoprotein-associated phospholipase A_2 (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.

Objective

The objective of this evidence review is to determine whether lipoprotein-associated phospholipase A_2 testing leads to improved net health outcomes for patients being evaluated for risk of cardiovascular disease.

Background

Low-Density Lipoproteins

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, 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 low-density lipoprotein cholesterol.

Treatment

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 A_2 (Lp-PLA_2), also known as platelet-activating factor acetyl hydrolase, is an enzyme that hydrolyzes phospholipids and is primarily associated with LDLs. Accumulating evidence has suggested that Lp-PLA_2 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 the measurement of pro-inflammatory factors as part of cardiovascular disease risk assessment.

Interest in Lp-PLA_2 as a possible causal risk factor for CAD has generated the development and testing of Lp-PLA_2 inhibitors as a new class of drugs to reduce the risk of CAD. However, clinical trials of Lp-PLA_2 inhibitors have not shown significant reductions in CAD endpoints.[1,2,3,] Furthermore, assessment of Lp-PLA_2 levels has not been used in the selection or management of subjects in the clinical trials.

REGULATORY STATUS

In December 2014, the PLAC® Test (diaDexus), a quantitative enzyme assay, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for Lp-PLA_2 activity. It was considered substantially equivalent to a previous version of the PLAC® Test (diaDexus), which was cleared for marketing by the FDA in July 2003. FDA product code: NOE.

POLICY

Measurement of lipoprotein-associated phospholipase A_2 (Lp-PLA2) is considered **experimental / investigational**.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through October 26, 2020.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Lipoprotein-Associated Phospholipase A_2 and Cardiovascular Risk

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 several systematic reviews ,of prospective cohort studies that have evaluated the association between lipoprotein-associated phospholipase A_2 (Lp-PLA_2) and cardiovascular outcomes.

The National Cholesterol Education Program ATP-III guidelines have indicated that to determine the clinical significance of Lp-PLA_2, the emerging risk factors should be evaluated against the following criteria[4,]:

- 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 measurements must be widely available, well-standardized, inexpensive, have accepted population reference values, and be relatively stable biologically.
- Preferably, but not necessarily, modification of the risk factor in clinical trials will have shown a reduction in risk.

A TEC Assessment (2002) summarized the steps necessary to determine the utility of a novel cardiac risk factor.[5,] The following 3 steps were required:

- Standardize the measurement of the risk factor.
- Determine 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 with established risk factors.
- Determine 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 outcome.

Clinical Context and Test Purpose

The purpose of Lp-PLA_2 testing in patients who have a risk of cardiovascular disease (CVD) is to inform, improve patient stratification using risk prediction models that alter management decisions and improve health outcomes.

The question addressed in this evidence review is: Does testing for Lp-PLA_2 improve the net health outcome for individuals at risk for CVD?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals at risk for coronary artery disease (CAD).

Interventions

The relevant intervention of interest is testing for Lp-PLA_2 as a biomarker of CAD.

Asymptomatic patients are typically evaluated by primary care physicians. Symptomatic patients are referred to cardiology.

Comparators

The following practice is currently being used to manage CAD risk: standard assessment of cardiovascular risk.

Outcomes

The primary outcomes of interest are the development of CVD such as CAD, stroke, and mortality. The development of CVD typically occurs over many years or decades.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

CLINICALLY VALID

Lipoprotein-Associated Phospholipase A_2 as a Predictor of Coronary Artery Disease

Results of numerous, large-scale observational studies have examined whether Lp-PLA_2 is an independent risk factor for CAD. These observational studies have been analyzed in several systematic reviews.[6,7,8,] The largest, conducted by The Emerging Risk Factors Collaboration (2012), included 37 cohort studies and performed a patient-level meta-analysis of the association between novel lipid risk factors and cardiovascular risk over a median follow-up of 10.4 years in patients without CVD.[6,] The review found Lp-PLA_2 was an independent risk factor for cardiovascular events with a hazard ratio of 1.12 (95% confidence interval [CI], 1.09 to 1.21) for each 1 standard deviation increase in Lp-PLA_2 activity based on 11 studies (N=32075). However, there was no significant improvement in risk reclassification following the addition of Lp-PLA_2 to the reclassification model, with a net reclassification change of 0.21 (95% CI, -0.45 to 0.86).

Two other systematic reviews reported similar results. One review of 32 studies (N=79036) found for every 1 standard deviation increase in Lp-PLA_2 levels, the relative risk 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, following adjustment for traditional risk factors. There was also a significant association between Lp-PLA_2 levels and nonvascular deaths (RR 1.10; 95% CI, 1.04 to 1.17).[7,] The second, smaller review (14 studies, N = 20,549) reported a pooled odds ratio of 1.60 (95% CI, 1.36 to 1.89), adjusted for traditional cardiac risk factors, for the development of future cardiac events with elevated Lp-PLA_2 levels.[8,]

Section Summary: Clinically Valid
Several large meta-analyses found consistent evidence that Lp-PLA_2 level is an independent predictor of CAD. Based on these reviews, it is less clear the degree to which Lp-PLA_2 improves on existing CAD prediction models regarding clinically important magnitudes of reclassification.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No studies were identified that assessed the clinical utility of Lp-PLA_2 test to define CAD risk.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Although studies have shown that Lp-PLA_2 level is an independent risk factor for CAD, clinical utility depends on whether the use of Lp-PLA_2 levels improves on existing models of CAD prediction, which then translates into differences in treatment that improve patient outcomes. Establishing improved outcomes compared with 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 the improved reclassification of risk. A robust, validated model using Lp-PLA_2 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-PLA_2 levels improves health outcomes.

Section Summary: Clinically Useful
Changes in patient management that could potentially occur with a strategy using Lp-PLA_2 levels are not well-established. Studies that directly evaluate patient management changes and/or health outcome improvements are needed to determine whether the use of Lp-PLA_2 measurement has efficacy in CVD. Alternatively, robust decision modeling studies may demonstrate clinically important changes in health outcomes by incorporating Lp-PLA_2 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 are robust. Incorporation of Lp-PLA_2 into decision models is necessary to demonstrate the potential clinical utility of the biomarker.

Summary of Evidence

For individuals who have a risk of CVD who receive Lp-PLA_2 testing, the evidence includes studies of the association between Lp-PLA_2 and various CAD outcomes. Relevant outcomes are overall survival, disease-specific survival, and test validity. The studies have demonstrated that Lp-PLA_2 levels are an independent predictor of CVD. Although Lp-PLA_2 levels are associated with CVD risk, changes in patient management that would occur as a result of obtaining Lp-PLA_2 levels in practice are not well-defined. To demonstrate clinical utility, clinicians must have the tools to incorporate Lp-PLA_2 test results into existing risk prediction models that improve classification into risk categories, alter treatment decisions, and lead to improved health outcomes. Direct evidence for such improved health outcomes with Lp-PLA_2 testing in clinical practice is lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American College of Cardiology and American Heart Association

In 2019, the American College of Cardiology and the American Heart Association published joint guidelines on the assessment of cardiovascular risk in asymptomatic patients.[9,] Lp-PLA_2 testing was not mentioned in these guidelines, which was a change from 2010 guidelines.[10,] In their prior guideline, Lp-PLA_2 was given a IIb recommendation for assessing cardiovascular risk in intermediate-risk asymptomatic adults.

American Association of Clinical Endocrinologists and American College of Endocrinology

In 2012, the American Association of Clinical Endocrinologists and the American College of Endocrinology published guidelines on the management of dyslipidemia and the prevention of atherosclerosis.[11,] These guidelines made the following recommendations for Lp-PLA_2 testing (see Table 1).

Table 1. Guidelines on Dyslipidemia and Atherosclerosis

Recommendation	GOE	LOE
Assess markers of inflammation in patients where further stratification of risk is necessary. Highly sensitive CRP (hsCRP) and Lp-PLA_2 provide useful information in these instances and appear to be synergistic in predicting the risk of CVD and stroke.	B	1
Measure Lp-PLA_2, 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	B	2

CRP: C-reactive protein; CVD: cardiovascular disease; GOE: grade of evidence; hsCRP: high-sensitivity C-reactive protein; LOE: level of evidence; Lp-PLA_2: lipoprotein-associated phospholipase A_2.

In 2017, an update to guidelines published jointly by the American Association of Clinical Endocrinologists and the American College of Endocrinology recommended the measurement of

Lp-PLA_2 as an additional indication of cardiovascular risk.[12,] Citing several studies in which Lp-PLA_2 was comparable with high-sensitivity CRP as a risk predictor, the guidelines accordingly recommended the use of Lp-PLA_2 data in situations requiring a more specific evaluation of the risk of atherosclerotic cardiovascular disease that is provided by high-sensitivity CRP.

European Society of Cardiology et al
In 2016, the European Society of Cardiology and other cardiovascular disease societies issued clinical practice guidelines on cardiovascular disease prevention. [13,] These guidelines included the following statement :

- Routine assessment of circulating or urinary biomarkers is not recommended for refinement of CVD risk stratification (Class IIIB recommendation)

The guideline also noted that "there is evidence of publication bias in the field of novel biomarkers of CV risk, leading to inflated estimates of strength of association and potential added value".

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations on the use of Lp-PLA_2 in the assessment of cardiovascular risk have been identified.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in October 2020 did not identify any ongoing or unpublished trials that would likely influence this review.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)
0052U	Lipoprotein, blood, high resolution fractionation and quantitation of lipoproteins, including all five major lipoprotein classes and subclasses of HDL, LDL, and VLDL by vertical auto profile ultracentrifugation

ICD-10 DIAGNOSIS
Experimental / investigational for all diagnoses related to this policy.

REVISIONS

02-10-2011	Updated Description section
	In Coding section: Removed CPT code 83516
	Updated Rationale section
	Updated References section

07-19-2011	Updated Description section
	Updated Rationale section
	Updated References section
08-13-2012	Updated Description section
	Updated Rationale section
	Updated References section
10-31-2013	Description section reviewed
	Rationale section updated
	In Coding section: ▪ Removed Coding information bullet of "Effective January 1, 2007, there is a specific CPT code for this test: 83698."
	References updated
10-06-2015	Description section updated
	Rationale section updated
	References updated
03-24-2016	▪ In Title removed "(Lp-PLA2)" to read "Measurement of Lipoprotein-Associated Phospholipase A_2 in the Assessment of Cardiovascular Risk" ▪ Added reference to another policy: " See Also: Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease"
	Description section updated
	Rationale section updated
	In Coding section: ▪ Coding notations added
	References updated
02-15-2018	Description section updated
	Rationale section updated
	References updated
03-13-2019	Description section updated
	Rationale section updated
	In Coding section: ▪ Added PLA Code: 0052U
	References updated
03-11-2021	Update Description section
	Updated Rationale section
	Updated Reference section

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