BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.32 Measurement of Lipoprotein-Associated Phospholipase A2 in the Assessment of Cardiovascular Risk

Annual Effective Policy Date: April 1, 2024

Original Policy Date: December 2023

Related Policies:

2.04.65 - Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease

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

Description

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Lipoprotein-associated phospholipase A_2 (Lp-PLA_2), also known as platelet-activating factor acetylhydrolase, is an enzyme that hydrolyzes phospholipids and is primarily associated with low-density lipoproteins. Accumulating evidence has suggested that Lp-PLA_2 is a biomarker of coronary artery disease and may have a proinflammatory role in the progression of atherosclerosis.

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 acetylhydrolase, 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.

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 the risk of cardiovascular disease.

POLICY STATEMENT

Measurement of lipoprotein-associated phospholipase A_2 is considered **not medically necessary**.

POLICY GUIDELINES

Measurement of lipoprotein (a) enzyme is a distinct laboratory test. Measurement of lipoprotein (a) enzyme is addressed in evidence review 2.04.65, and genetic testing for lipoprotein (a) variants is addressed in evidence review 2.04.70.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA 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.

RATIONALE

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

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.[11,12,] 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.	A	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.[11,] 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.

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.

Medicare National Coverage

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

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New policy-FEP	Policy updated with literature review through September 19, 2022; no references added. Policy statement unchanged. FEP Benefit Changes, new FEP policy