



MASSACHUSETTS

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Medical Policy

Measurement of Lipoprotein-Associated Phospholipase A2 - Lp-PLA2 - in the Assessment of Cardiovascular Risk

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Policy Number: 558

BCBSA Reference Number: 2.04.32

NCD/LCD: NA

Related Policies

- Novel Lipid Risk Factors in Risk Assessment and Management of Cardiovascular Disease, #[283](#)
- Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disease #[016](#)

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

Measurement of lipoprotein-associated phospholipase A2 (Lp-PLA2) is considered [INVESTIGATIONAL](#).

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is not a covered service.
Commercial PPO and Indemnity	This is not a covered service.
Medicare HMO Blue SM	This is not a covered service.
Medicare PPO Blue SM	This is not a covered service.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code 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 as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes

CPT codes:	Code Description
83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)

Description

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 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 the measurement of proinflammatory factors as part of cardiovascular disease risk assessment.

Interest in Lp-PLA₂ as a possible causal risk factor for CAD has generated development and testing of Lp-PLA₂ inhibitors as a new class of drugs to reduce the risk of CAD. However, clinical trials of Lp-PLA₂ inhibitors have not shown significant reductions in CAD endpoints.^{1,2,3} Furthermore, assessment of Lp-PLA₂ levels has not been used in the selection or management of subjects in the clinical trials.

Summary

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. Accumulating evidence has suggested that Lp-PLA₂ is a biomarker of coronary artery disease and may have a proinflammatory role in the progression of atherosclerosis.

For individuals who have a risk of cardiovascular disease who receive Lp-PLA₂ testing, the evidence includes studies of the association between Lp-PLA₂ and various coronary artery disease outcomes. The relevant outcomes are overall survival, disease-specific survival, and test validity. The studies have demonstrated that Lp-PLA₂ levels are an independent predictor of cardiovascular disease. Although Lp-PLA₂ levels are associated with cardiovascular disease risk, changes in patient management that would occur as a result of obtaining Lp-PLA₂ levels in practice are not well-defined. To demonstrate clinical utility, clinicians must have the tools to incorporate Lp-PLA₂ 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-PLA2 testing in clinical practice is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy History

Date	Action
2/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
3/2018	New references added from BCBSA National medical policy.
1/2017	New references added from BCBSA National medical policy.
8/2015	New references added from BCBSA National medical policy.
9/2014	New references added from BCBSA National medical policy.
8/2013	New references from BCBSA National medical policy.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
4/2011	Reviewed - Medical Policy Group – Cardiology and Pulmonology. No changes to policy statements.
10/20/2010	New policy, effective 10/20/2010 describing ongoing non-coverage.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

References

1. Stability Investigators, White HD, Held C, et al. Darapladib for preventing ischemic events in stable coronary heart disease. *N Engl J Med.* May 1 2014;370(18):1702-1711. PMID 24678955
2. O'Donoghue ML, Braunwald E, White HD, et al. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. *JAMA.* Sep 10 2014;312(10):1006-1015. PMID 25173516
3. Nicholls SJ, Kastelein JJ, Schwartz GG, et al. Varespladib and cardiovascular events in patients with an acute coronary syndrome: the VISTA-16 randomized clinical trial. *JAMA.* Jan 15 2014;311(3):252-262. PMID 24247616
4. National Institutes of Health, National Heart Lung and Blood Institute. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NIH Publication No. 01-3670). 2001; <http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf> Accessed November 21, 2018.
5. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Special Report: C-Reactive Protein as a Cardiac Risk Marker. TEC Assessment. 2002;17:Tab 23.
6. Emerging Risk Factors Collaboration, Di Angelantonio E, Gao P, et al. Lipid-related markers and cardiovascular disease prediction. *JAMA.* Jun 20 2012;307(23):2499-2506. PMID 22797450
7. Thompson A, Gao P, Orfei L, et al. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. *Lancet.* May 1 2010;375(9725):1536-1544. PMID 20435228
8. Garza CA, Montori VM, McConnell JP, et al. Association between lipoprotein-associated phospholipase A2 and cardiovascular disease: a systematic review. *Mayo Clin Proc.* Feb 2007;82(2):159-165. PMID 17290721
9. Packard CJ, O'Reilly DS, Caslake MJ, et al. Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group. *N Engl J Med.* Oct 19 2000;343(16):1148-1155. PMID 11036120

10. Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. Feb 24 2004;109(7):837-842. PMID 14757686
11. Koenig W, Khuseynova N, Lowel H, et al. Lipoprotein-associated phospholipase A2 adds to risk prediction of incident coronary events by C-reactive protein in apparently healthy middle-aged men from the general population: results from the 14-year follow-up of a large cohort from southern Germany. *Circulation*. Oct 5 2004;110(14):1903-1908. PMID 15451783
12. Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Arch Intern Med*. Nov 28 2005;165(21):2479-2484. PMID 16314544
13. Sabatine MS, Morrow DA, O'Donoghue M, et al. Prognostic utility of lipoprotein-associated phospholipase A2 for cardiovascular outcomes in patients with stable coronary artery disease. *Arterioscler Thromb Vasc Biol*. Nov 2007;27(11):2463-2469. PMID 17766330
14. Winkler K, Hoffmann MM, Winkelmann BR, et al. Lipoprotein-associated phospholipase A2 predicts 5-year cardiac mortality independently of established risk factors and adds prognostic information in patients with low and medium high-sensitivity C-reactive protein (the Ludwigshafen risk and cardiovascular health study). *Clin Chem*. Aug 2007;53(8):1440-1447. PMID 17573419
15. Persson M, Hedblad B, Nelson JJ, et al. Elevated Lp-PLA2 levels add prognostic information to the metabolic syndrome on incidence of cardiovascular events among middle-aged nondiabetic subjects. *Arterioscler Thromb Vasc Biol*. Jun 2007;27(6):1411-1416. PMID 17431184
16. Daniels LB, Laughlin GA, Sarno MJ, et al. Lipoprotein-associated phospholipase A2 is an independent predictor of incident coronary heart disease in an apparently healthy older population: the Rancho Bernardo Study. *J Am Coll Cardiol*. Mar 4 2008;51(9):913-919. PMID 18308160
17. Hatoum IJ, Cook NR, Nelson JJ, et al. Lipoprotein-associated phospholipase A2 activity improves risk discrimination of incident coronary heart disease among women. *Am Heart J*. Mar 2011;161(3):516-522. PMID 21392606
18. Liu YS, Hu XB, Li HZ, et al. Association of lipoprotein-associated phospholipase A(2) with characteristics of vulnerable coronary atherosclerotic plaques. *Yonsei Med J*. Nov 2011;52(6):914-922. PMID 22028154
19. Sarlon-Bartoli G, Boudes A, Buffat C, et al. Circulating lipoprotein-associated phospholipase A2 in high-grade carotid stenosis: a new biomarker for predicting unstable plaque. *Eur J Vasc Endovasc Surg*. Feb 2012;43(2):154-159. PMID 22075154
20. Liu CF, Qin L, Ren JY, et al. Elevated plasma lipoprotein-associated phospholipase A(2) activity is associated with plaque rupture in patients with coronary artery disease. *Chin Med J (Engl)*. Aug 2011;124(16):2469-2473. PMID 21933589
21. Gu X, Hou J, Yang S, et al. Is lipoprotein-associated phospholipase A2 activity correlated with fibrous-cap thickness and plaque volume in patients with acute coronary syndrome? *Coron Artery Dis*. Jan 2014;25(1):10-15. PMID 24089018
22. Muller O, Ntalianis A, Wijns W, et al. Association of biomarkers of lipid modification with functional and morphological indices of coronary stenosis severity in stable coronary artery disease. *J Cardiovasc Transl Res*. Aug 2013;6(4):536-544. PMID 23670230
23. Tehrani DM, Gardin JM, Yanez D, et al. Impact of inflammatory biomarkers on relation of high density lipoprotein-cholesterol with incident coronary heart disease: cardiovascular Health Study. *Atherosclerosis*. Dec 2013;231(2):246-251. PMID 24267235
24. Garg PK, McClelland RL, Jenny NS, et al. Lipoprotein-associated phospholipase A2 and risk of incident cardiovascular disease in a multi-ethnic cohort: The multi ethnic study of atherosclerosis. *Atherosclerosis*. Jul 2015;241(1):176-182. PMID 26004387
25. Cai A, Li G, Chen J, et al. Increased serum level of Lp-PLA2 is independently associated with the severity of coronary artery diseases: a cross-sectional study of Chinese population. *BMC Cardiovasc Disord*. Feb 26 2015;15:14. PMID 25879827
26. Celik O, Ozturk D, Akin F, et al. Evaluation of lipoprotein-associated phospholipase A2 and plaque burden/composition in young adults. *Coron Artery Dis*. May 2015;26(3):266-271. PMID 25647459

27. Allison MA, Denenberg JO, Nelson JJ, et al. The association between lipoprotein-associated phospholipase A2 and cardiovascular disease and total mortality in vascular medicine patients. *J Vasc Surg.* Sep 2007;46(3):500-506. PMID 17681710
28. Kardys I, Oei HH, Hofman A, et al. Lipoprotein-associated phospholipase A2 and coronary calcification. The Rotterdam Coronary Calcification Study. *Atherosclerosis.* Apr 2007;191(2):377-383. PMID 16678183
29. Saremi A, Moritz TE, Anderson RJ, et al. Rates and determinants of coronary and abdominal aortic artery calcium progression in the Veterans Affairs Diabetes Trial (VADT). *Diabetes Care.* Dec 2010;33(12):2642-2647. PMID 20807873
30. Hatoum IJ, Hu FB, Nelson JJ, et al. Lipoprotein-associated phospholipase A2 activity and incident coronary heart disease among men and women with type 2 diabetes. *Diabetes.* May 2010;59(5):1239-1243. PMID 20185811
31. O'Donoghue M, Morrow DA, Sabatine MS, et al. Lipoprotein-associated phospholipase A2 and its association with cardiovascular outcomes in patients with acute coronary syndromes in the PROVE IT-TIMI 22 (PRavastatin Or atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) trial. *Circulation.* Apr 11 2006;113(14):1745-1752. PMID 16537575
32. Muhlestein JB, May HT, Jensen JR, et al. The reduction of inflammatory biomarkers by statin, fibrate, and combination therapy among diabetic patients with mixed dyslipidemia: the DIACOR (Diabetes and Combined Lipid Therapy Regimen) study. *J Am Coll Cardiol.* Jul 18 2006;48(2):396-401. PMID 16843192
33. 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
34. Saougos VG, Tambaki AP, Kalogirou M, et al. Differential effect of hypolipidemic drugs on lipoprotein-associated phospholipase A2. *Arterioscler Thromb Vasc Biol.* Oct 2007;27(10):2236-2243. PMID 17656665
35. Ridker PM, Macfadyen JG, Wolfert RL, et al. Relationship of lipoprotein-associated phospholipase A2 mass and activity with incident vascular events among primary prevention patients allocated to placebo or to statin therapy: an analysis from the JUPITER Trial. *Clin Chem.* May 2012;58(5):877-886. PMID 22419750
36. Ryu SK, Mallat Z, Benessiano J, et al. Phospholipase A2 enzymes, high-dose atorvastatin, and prediction of ischemic events after acute coronary syndromes. *Circulation.* Feb 14 2012;125(6):757-766. PMID 22230483
37. Wallentin L, Held C, Armstrong PW, et al. Lipoprotein-associated phospholipase A2 activity is a marker of risk but not a useful target for treatment in patients with stable coronary heart disease. *J Am Heart Assoc.* Jun 21 2016;5(6). PMID 27329448
38. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* Jun 24 2014;129(25 Suppl 2):S49-73. PMID 24222018
39. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* Dec 14 2010;56(25):e50-103. PMID 21144964
40. Jellinger PS, Smith DA, Mehta AE, et al. American Association of Clinical Endocrinologists' guidelines for management of dyslipidemia and prevention of atherosclerosis. *Endocr Pract.* Mar-Apr 2012;18 Suppl 1:1-78. PMID 22522068
41. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. *Endocr Pract.* Apr 2017;23(Suppl 2):1-87. PMID 28437620
42. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J.* Jul 2012;33(13):1635-1701. PMID 22555213