

## Medical Policy



### Title: Lipoprotein(a) Enzyme Immunoassay in the Management of Cardiovascular Disease

#### Professional

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#### DESCRIPTION

Lipoprotein(a) (lp[a]) is a lipid-rich particle similar to low-density lipoprotein (LDL). Apolipoprotein B is the major apolipoprotein associated with LDL; in lp(a), however, there is an additional apolipoprotein A covalently linked to the apolipoprotein B. The apolipoprotein (a) molecule is structurally similar to plasminogen, suggesting that lp(a) may contribute to the thrombotic and atherogenic basis of cardiovascular disease. Levels of lp(a) are relatively stable in individuals over time, but vary up to 1000-fold between individuals, presumably on a genetic basis. The similarity between apolipoprotein (a) and fibrinogen has stimulated intense interest in lp(a) as a link between atherosclerosis and thrombosis. In addition, approximately 20% of patients with coronary artery disease (CAD) have elevated levels of lp(a). Therefore, it has been proposed that levels of lp(a) may be an independent risk factor for coronary artery disease.

Traditional lipid risk factors such as 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 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.

#### POLICY

Measurement of lipoprotein(a) in the evaluation and management of cardiovascular disease is considered **investigational**.

Determination of lipoprotein(a) (lp[a]) may be included as a component of a comprehensive cardiovascular risk assessment offered by reference laboratories. Comprehensive risk assessment may include evaluation of small low-density lipoproteins, subclassification of high-density lipoproteins, evaluation of apolipoprotein E genotype or phenotype, total plasma homocysteine, apolipoprotein B, and high-sensitivity C-reactive protein.

## **RATIONALE**

Numerous studies have evaluated lp(a) as a cardiovascular risk factor. A large number of retrospective studies consistently suggested that elevated levels of lp(a) were associated with cardiovascular disease. (1) However, they could not determine whether the elevation of lp(a) preceded the development of cardiovascular disease or was a result of cardiovascular disease.

Prospective studies designed to answer this question have produced mixed results. The following are representative prospective trials drawn from the extensive literature on this topic.

The Lipid Research Clinics (LRC) Coronary Prevention Primary Trial, one of the first large-scale, randomized, controlled trials of cholesterol-lowering therapy, measured initial lp(a) levels and reported that lp(a) was an independent risk factor for coronary artery disease (CAD) when controlled for other lipid and non-lipid risk factors. (2) As part of the Framingham offspring study, (3) lp(a) levels were measured in 2,191 asymptomatic men between the ages of 20 and 54 years. After a mean follow-up of 15 years, there were 129 coronary heart disease events, including myocardial infarction, coronary insufficiency, angina, or sudden cardiac death. Comparing the lp(a) levels of these patients with the other participants, the authors concluded that elevated lp(a) was an independent risk factor for the development of premature coronary heart disease (i.e., before age 55 years). The Atherosclerosis Risk in Communities (ARIC) study evaluated the predictive ability of lp(a) in 12,000 middle-aged individuals free of CAD at baseline who were followed up for 10 years. (4) Lp(a) levels were significantly higher among those patients who developed CAD compared with those who did not, and lp(a) levels were an independent predictor of CAD above traditional lipid measures.

Other studies, however, have failed to demonstrate such a relationship. In the Physicians' Health Study, initial lp(a) levels in the 296 participants who subsequently experienced a myocardial infarction were compared with lp(a) levels in matched controls who remained free from CAD. (5) The authors found that the distribution of lp(a) levels between the 2 groups was identical. The European Concerted Action on Thrombosis (ECAT) study, a trial of secondary prevention, evaluated lp(a) as a risk factor for coronary events in 2,800 patients with known angina pectoris. (6) In this study, lp(a) levels were not significantly different among patients who did and did not have subsequent events, suggesting that lp(a) levels were not useful risk markers in this population.

Evaluation of lp(a) as a risk factor is complicated by the lack of a standardized assay, different study methodologies, the variation of lp(a) levels in different races and ethnic groups, and the complicated interplay of various lipid cardiovascular risk factors. For example, further studies have suggested that elevated lp(a) levels markedly affect the cardiovascular risk associated with other lipid parameters. For example, The Quebec Cardiovascular Study (7) evaluated the ability of lp(a) levels and other lipid parameters to predict subsequent CAD events in a prospective cohort study of 2,155 men followed up

for 5 years. While elevated lp(a) was not found to be an independent risk factor for ischemic heart disease, the risk associated with a moderately increased LDL was further increased by the simultaneous presence of increased lp(a) levels. In addition, the protective effect of increased levels of HDL was diminished in the presence of increased lp(a). Lipoprotein(a) has been identified as an "emerging risk factor" in the Adult Treatment Panel (ATP) III report of the National Cholesterol Education Program. (8) However, improved risk prediction does not by itself result in better health outcomes. (9) To improve outcomes, clinicians must have the tools to translate this information into clinical practice, which requires guidelines that incorporate emerging risk factors into existing risk prediction models and that have been demonstrated to classify patients into risk categories with greater accuracy. Predictive models also need to be accompanied by treatment guidelines that target interventions toward patients who will get the most benefit.

Such tools for linking lp(a) to clinical decision making, both in risk assessment and treatment response, are currently not available. The Adult Treatment Panel III (ATP III) practice guidelines continue to tie clinical decision making to conventional lipid measures, such as total cholesterol, LDL-C, and HDL-C. As a result, there is a lack of recommendations from this body regarding how the additional information from lp(a) levels might be used in clinical practice. As a result, there is considerable uncertainty regarding its clinical role, specifically how knowledge of lp(a) levels can be used in clinical care of patients who are being evaluated for lipid disorders.

### **2005 Update**

A search of the literature from 2003 through June 2005 did not identify any published literature that would prompt reconsideration of the policy statement, which remains unchanged. Several randomized studies of lipid-lowering therapy have included measurements of lipoprotein(a) as an intermediate outcome measurement, but data are still inadequate to demonstrate how this laboratory test can be used to improve patient management. (10, 11)

### **2006–2007 update**

A literature search was formed for the period of July 2005 through December 2006. Several studies were identified that further evaluated the predictive ability of lp(a) for cardiovascular events. (12-14) A number of these studies focused on the predictive ability of lp(a) for ischemic stroke, with mixed results. In the Atherosclerotic Risk in Communities (ARIC) prospective cohort study of 14,221 participants (13), elevated lp(a) was an significant independent predictor of stroke in African-American women (relative risk [RR] 1.84, 95% CI: 1.05-3.07) and white women (RR 2.42, 95% CI: 1.30-4.53) but not in African-American men (RR 1.72, 95% CI 0.86-3.48) or white men (RR 1.18, 95% CI: 0.47-2.90). In another prospective cohort study of 100 consecutive patients with ischemic stroke, Rigal and co-workers (14) reported that an elevated lp(a) level was an independent predictor of ischemic stroke in men (odds ratio [OR] 3.55, 95% CI: 1.33-9.48) but not in women (OR 0.42, 95% CI: 0.12-1.26).

No published studies were found that would prompt reconsideration of the policy statement.

### **2008 update**

A literature search was formed for the period of January 2007 through March 2008. Publications identified during this period primarily evaluated lp(a) levels as a potential predictor of risk for cardiovascular events.

Publications from 3 large, prospective cohort studies evaluated the predictive ability of lp(a) in relation to established and/or other emerging cardiac risk factors. Kamstrup and colleagues (15) analyzed data from the Copenhagen City Heart Study, which followed 9,330 individuals from the Copenhagen general population over a period of 10 years. This study reported a graded increase in risk of cardiac events with increasing lp(a) levels. At extreme levels of lp(a) above the 95th percentile, the adjusted hazard ratio for myocardial infarction was 3.6 (95% CI: 1.7-7.7) for women and 3.7 (95% CI: 1.7-8.0) in men. Tzoulaki and colleagues (16) reported data from the Edinburgh Artery Study, which was a population cohort study that followed 1,592 individuals for a mean of 17 years. These authors reported that lp(a) was an independent predictor of myocardial infarction, with an odds ratio of 1.49 (95% CI: 1.0-2.2) for the highest one-third versus the lowest one-third. Zakai and co-workers (17) evaluated 13 potential biomarkers for independent predictive ability compared to established risk factors, using data from 4,510 individuals followed up for 9 years in the Cardiovascular Health Study. Lp(a) was 1 of 7 biomarkers that had incremental predictive ability above established risk factors. The adjusted hazard ratio for each standard deviation increase in lp(a) was 1.07 (95% CI: 1.0-1.12).

A meta-analysis summarized evidence from observational studies of the relationship between lp(a) and stroke. (18) There were 5 prospective cohort studies and 23 case-control studies included in this analysis. From prospective cohort studies, lp(a) added a modest amount of incremental predictive information (combined RR for the highest one-third of lp(a) 1.22, 95% CI: 1.04-1.43). From case-control studies, an elevated lp(a) level was also associated with an increased risk of stroke (combined OR 2.39, 95% CI: 1.57-3.63).

The new evidence identified for this update largely confirms evidence from previous studies on the predictive ability of lp(a). Data from these studies does not prompt reconsideration of the policy statement.

## **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**

83695        Lipoprotein (a)  
82172        Apolipoprotein, each

## **REFERENCES**

1. Harjai KJ. Potential new cardiovascular risk factors: left ventricular hypertrophy, homocysteine, lipoprotein (a), triglycerides, oxidative stress, and fibrinogen. *Ann Intern Med* 1999; 131(5):376-86.
2. Schaefer EJ, Lamon-Fava S, Jenner JL et al. Lipoprotein (a) levels and risk of coronary heart disease in men. The Lipid Research Clinics Coronary Primary Prevention Trial. *JAMA* 1994; 271(13):999-1003.
3. Bostom AG, Cupples LA, Jenner JL et al. Elevated plasma lipoprotein(a) and coronary artery disease in men aged 55 years and younger. A prospective study. *JAMA* 1996; 276(7):544-8.
4. Sharrett AR, Ballantyne CM, Coady SA et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL subfractions: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2001; 104(10):1108-13.
5. Ridker PM, Hennekens CH, Stampfer MJ. A prospective study of lipoprotein(a) and the risk of myocardial infarction. *JAMA* 1993; 270(18):2195-9.
6. Bolibar I, von Eckardstein A, Assmann G et al. Short term prognostic value of lipid measurements in patients with angina pectoris. The ECAT Angina Pectoris Study Group: European Concerted Action on Thrombosis and Disabilities. *Thromb Haemost* 2000; 84(6):955-60.
7. Cantin B, Gagnon F, Moorjani S et al. Is lipoprotein(a) an independent risk factor for ischemic heart disease in men? The Quebec Cardiovascular Study. *J Am Coll Cardiol* 1998; 31(3):519-25.
8. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the 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). *JAMA* 2001; 285(19):2486-97.
9. 2002 TEC Assessments; Tab 23 (Special Report).
10. Bays HE, Dujovne CA, McGovern ME et al. Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the ADVICOR Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol* 2003; 91(6):667-72.
11. van Wissen S, Smilde TJ, Trip MD et al. Long term statin treatment reduces lipoprotein(a) concentrations in heterozygous familial hypercholesterolaemia. *Heart* 2003; 89(8):893-6.
12. Suk Danik J, Rifai N, Buring JE et al. Lipoprotein(a), measured with an assay independent of apolipoprotein(a) isoform size, and risk of future cardiovascular events among initially healthy women. *JAMA*, 2006; 296(11):1363-70.

13. Ohira T, Schreiner PJ, Morrisett JD et al. Lipoprotein(a) and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke* 2006; 37(6):1407-12.
14. Rigal M, Ruidavets JB, Viguier A et al. Lipoprotein (a) and risk of ischemic stroke in young adults. *J Neurol Sci* 2007; 252(1):39-44.
15. Kamstrup PR, Benn M, Tybaerg-Hansen A et al. Extreme lipoprotein (a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. *Circulation* 2008; 117(2):176-84.
16. Tzoulaki I, Murray GD, Lee AJ et al. Relative value of inflammatory, hemostatic, and rheological factors for incident myocardial infarction and stroke: the Edinburgh Artery Study. *Circulation* 2007; 115(16):2119-27.
17. Zakai NA, Katz R, Jenny NS et al. Inflammation and hemostasis biomarkers and cardiovascular risk in the elderly: the Cardiovascular Health Study. *J Thromb Haemost* 2007; 5(6):1128-35.
18. Smolders B, Lemmens R, Thijs V. Lipoprotein (a) and stroke: a meta-analysis of observational studies. *Stroke* 2007; 38(6):1959-66.