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Lipoprotein (a) A complex risk factor for coronary heart disease

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This issue of *Endocrinology Rounds* reviews the evidence for using lipoprotein (a) [Lp(a)] to assess cardiovascular risk and guide therapeutic decisions in primary and secondary prevention. Central to this discussion is the question: Does Lp(a) act alone or interact with other known risk factors? In order to understand Lp(a), it is necessary to explain the analytic issues. The role of Lp(a) in heart disease has always been controversial. Initial debate was fueled by the observation that Lp(a) accounts for only ~ one-tenth of the plasma cholesterol compared to LDL. How can such a relatively small amount of cholesterol cause coronary heart disease (CHD)?

Lipoprotein (a): a historical perspective

Lp(a) (the "a" stands for antigen) was recognized as a modified low-density lipoprotein (LDL) by Kare Berg. The presence of the apo (a) protein doubles the protein content of an LDL-like particle, simultaneously increasing the hydrated diameter *and* the density. This results in a lipoprotein with a *larger* diameter than LDL, but with a density that overlaps small, dense LDL and large, high-density lipoproteins (HDL). Lp(a) can be distinguished from LDL and HDL because of its prebeta-electrophoretic mobility in agarose gel electrophoresis, making it possible to score for the "presence" of sinking prebeta lipoprotein.¹

An early cross-sectional, case-controlled study comparing patients with CHD to age- and sex-matched controls, first reported the possibility of an interaction between Lp(a) concentration and LDL cholesterol.² The odds ratio for observing Lp(a) >30 mg/dL (~90th percentile) for the whole cohort was 2.7. This decreased to 1.47 when subjects with LDL cholesterol levels less than the 50th percentile were considered, and increased to 4.5 when subjects with LDL cholesterol levels greater than the 50th percentile were considered.

Cloning of apo(a): a paradigm shift

The apolipoprotein(a) protein proved very difficult to study because it is a very large glycoprotein (molecular weight >250,000 Da) with poor solubility. The sequencing of apo(a) revealed a remarkable, unexpected property; it contained multiple repeated domains that were highly homologous to plasminogen kringle domain IV and one copy of a domain homologous to plasminogen kringle domain V and the protease domain (Figure 1).³ Suddenly, the hypothetical physiological and pathophysiological function of Lp(a) shifted from a role in cholesterol metabolism to a combined role in cholesterol metabolism *and* coagulation. Indeed, it was subsequently shown that Lp(a) could inhibit the activation of plasminogen, albeit through a mechanism that is complex in its kinetic and molecular details.⁴

Genetic heterogeneity

Analysis of the molecular weight of apolipoprotein(a) by denaturing electrophoresis reveals heterogeneity, or isoforms. State-of-the-art phenotyping separates over 30 different isoforms of apo(a) that vary in the number of repeats of kringle IV.³

Studies of DNA separated the genetic determinants of Lp(a) into the "cis-acting" elements and the protein polymorphism. In Caucasians, 90% of the concentration is genetically determined, with ~50% contributed by the cis-acting elements and ~40% contributed by



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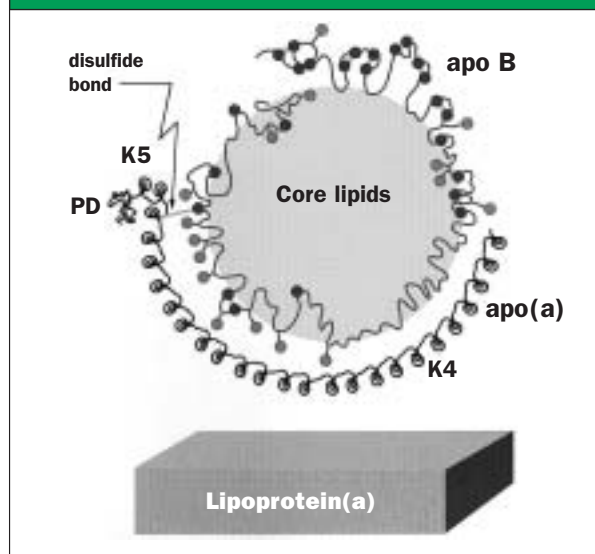
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Figure 1: Schematic of an Lp(a) particle. The Lp(a) particle consists of an LDL particle (represented by the apoB and the “core lipids”) plus apo(a).³



apoB = apolipoprotein B-100; apo(a) = apolipoprotein (a); K4 = plasminogen kringle 4-like; K5 = plasminogen kringle 5-like; PD = plasminogen protease-like domain.

the number of kringle IV repeats.⁵ It is clear that, if the protein polymorphism codes for a very high molecular weight isoform, then Lp(a) concentration is always very low, whereas if the protein polymorphism codes for a middle or low molecular weight isoform, then the apo(a) concentration can be high or low, depending upon the cis-acting elements.

Endocrine factors and Lp(a)

Two endocrine states have been identified that alter Lp(a) concentrations. Both hyper- and hypothyroidism raise Lp(a).⁶⁻¹¹ Treatment to achieve an euthyroid state results in a lowering of Lp(a). Lp(a) concentrations are also affected by androgens and estrogens. Lp(a) is increased in concentration in postmenopausal women compared with premenopausal women, and is reduced by hormone replacement therapy.^{12,13} The response of Lp(a) to hormonal treatment in men is dependent upon the route of administration and endocrine status.¹⁴

Studies of the importance of insulin and diabetes as a determinant of Lp(a) have been inconclusive. There are some reports of increased Lp(a) in patients with “uncontrolled” Type 2 diabetes, but there are also reports that Lp(a) concentration is unaffected by diabetes and unresponsive to treatment.

Why should Lp(a) cause atherosclerosis?

Lp(a) could contribute to atherosclerosis by its presence in serum and/or by its selective retention by the normal extracellular matrix of the arterial wall.¹⁵ Lp(a) may impair fibrinolysis by inhibiting the activation of

plasminogen to plasmin.^{4,16} This could contribute to plaque growth and late-stage occlusion of coronary arteries. Lp(a) and the proteolytic fragments of apo(a) have also been shown to increase the proliferation and migration of smooth muscle cells, possibly contributing to the atherosclerotic remodeling of arteries.

Consistent with these hypotheses, it has been reported that survivors of a myocardial infarction (MI) with Lp(a) >30 mg/dL have more myocardial necrosis and impaired left ventricular function compared to those with Lp(a) ≤30 mg/dL.¹⁷

Lp(a), the analytic challenge “Buyer beware”

Lp(a) can be measured by its cholesterol content,¹⁸ or by immunoassay with the results expressed as mg of total Lp(a) mass/dL or nmol of apo(a)/L.¹⁹ The structural heterogeneity of Lp(a) has created difficulties for the development of immunoassays. Assays must be shown to react with unique epitopes so that the concentration of Lp(a) is not confounded by the immunologic properties of the apo(a) isoforms.

Lp(a) results vary between manufacturers due to assay calibration and sensitivity to apo(a) isoforms.¹⁹ Some commercial assays overestimate the low molecular weight isoforms, while others overestimate the high molecular weight isoforms. It is the exception rather than the rule when commercial assays are fully documented for the effects of isoforms by the manufacturer before commercial release.

When is Lp(a) elevated? Does the number matter?

No consensus has emerged on the definition of “elevated” Lp(a). Many studies have divided the study population into tertiles, while others have used a population reference to define a 90th or 95th percentile. There is no consensus on whether the relationship of Lp(a) with disease follows a dose-response or occurs at a threshold concentration. Most studies have found that defining the presence of Lp(a) as exceeding the 50th or 90th percentile, is sufficient to identify risk for coronary artery disease. State-of-the-art Lp(a) values are determined by a method that is unaffected by apo(a) isoform, and interpreted relative to a reference population of known ethnicity. A simple number for Lp(a) concentration cannot be interpreted without this background knowledge. As discussed below, there is no convincing evidence that knowing the precise value of Lp(a) adds additional information.

Lp(a) and CHD: prospective studies Population-based cohorts

Danesh et al published a meta-analysis of prospective studies of Lp(a) and atherosclerotic heart disease.²⁰ They concluded that the overall relative risk for coronary heart disease (CHD) due to an elevated Lp(a) was 1.8.

Lp(a) was measured in fresh serum in a subset of 820 men from the Prospective Cardiovascular Munster study (PROCAM).²¹ At 10-years of follow-up, 44 men had a major coronary event and 8 had a stroke. While the incidence of a coronary end-point by Lp(a) quintile was not consistent, the upper quintile (defined as Lp(a) >0.17 g/L) in combination with either HDL-C <0.9 mmol/L or LDL-C >4.1 mmol/L or systolic hypertension or triglycerides >2.3 mmol/L, resulted in increased relative risk. The relative risk for the combination of upper quintile Lp(a) and HDL C <0.9 mmol/L was 8.3 (95% CI, 2-35.5). Paradoxically, the increased relative risk was negated by diabetes, smoking, or triglycerides >2.3 mmol/L, all conditions associated with HDL-C <0.9 mmol/L. These inconsistencies and the wide confidence intervals on the relative risk estimate likely reflect the exploratory nature of the subgroup analysis that was performed and highlights the importance of replication of these results in an independent sample.

The PRIME study²² reported a relative risk of 1.5 at the 5-year follow-up of 9,133 French and Northern Irish men aged 50-59 at entry. However, Lp(a) \geq 33 mg/dL was not a risk factor in men with LDL-C in the lowest quartile, whereas the combination of Lp(a) \geq 33 mg/dL and LDL-C >4.2 was significant, with a relative risk of 1.58. While statistically significant, the small magnitude of the relative risk is surprising.

A study of 5,632 Italian patients \geq 65 years of age, reported that the relative risk for CAD of the combination of Lp(a) \geq 20 mg/dL, diabetes, and LDL cholesterol \geq 3.63 mmol/L, was 6.65 (95% CI, 1.25-35.4), while Lp(a) alone was not a significant risk factor.²³ This contrasts with the PROCAM study, where Lp(a) did not add to the risk associated with diabetes.

The Quebec Cardiovascular Study of 2,125 men found that Lp(a) alone was not a risk factor for CHD, whereas fibrinogen >4.05 g/L was a risk factor (RR 2.5, 95% CI, 1.4-4.2, adjusted for age, smoking, diabetes, blood pressure, cholesterol, LDL cholesterol).²⁴ Further subgroup analysis showed that fibrinogen >4.05 g/L was only a risk factor when Lp(a) was >30 mg/dL (RR 2.5, 95% CI, 1.2-5.1).

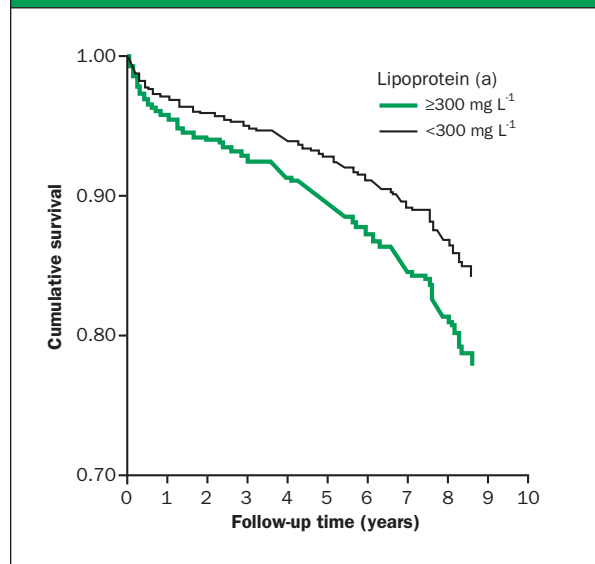
Lp(a) was an independent predictor of CHD in a 10-year follow-up of the ARIC study cohort.²⁵ Overall, it did not substantially increase predictive value in the context of other risk factors. It was reported that Lp(a) was predictive in white women and men, but not in black women and men.

The Physicians' Health Study is notable as a negative study, even after reanalysis of the data to take into account randomization to aspirin.²⁶

CHD patient-based cohorts

Given the hypothesized mechanisms for the role of Lp(a) in heart disease, it is surprising to find few published prospective studies of Lp(a) in patients with

Figure 2: Effects of lipoprotein (a) concentration on risk of survival²⁷



existing disease. A study of a Swedish cohort concluded that an Lp(a) concentration equivalent to the 75th percentile conferred a significant risk for recurrent heart attack and mortality (Figure 2).²⁷ The study by Stubbs et al²⁸ followed 266 patients presenting with MI and 197 patients presenting with unstable angina for 3 years. An Lp(a) value \geq 30 mg/dL (~90th percentile) was associated with a 62% increase in cardiac death in the MI group. An Lp(a) value \geq 7.9 mg/dL (~50th percentile) was a significant predictor of cardiac death in the unstable angina group. This is the first study to suggest that the risk factor value of Lp(a) has a different threshold depending upon the nature of the clinical presentation.

Lp(a) and secondary prevention studies

Lp(a) was a significant predictor of mortality in the 4S study for patients receiving simvastatin, but not in the patients receiving placebo.²⁹ The FATS trial specifically noted that lowering LDL improved outcome in patients in whom Lp(a) was correlated with disease at baseline.³⁰

The HERS trial reported that women in the bottom quartile for Lp(a) at baseline did not benefit from hormone replacement therapy, whereas women in the top quartile for Lp(a) showed reduction in recurrent heart attacks.³¹

Lp(a) and coronary heart disease: familial studies

It has been reported that Lp(a) >90th percentile significantly increases the risk of familial coronary artery disease *only* in the presence of a total cholesterol/HDL-cholesterol ratio \geq 4.5 or non-lipid risk factors, including hypertension, smoking, and total homocysteine >90th percentile.³² Although somewhat controversial, risk for

CHD in familial hypercholesterolemia is increased by Lp(a)³³ and Lp(a) is increased by familial hypercholesterolemia.³⁴

Lp(a) : observational data in stroke

Willeit et al^{35,36} observed that the relationship of Lp(a) with carotid thickness was modified by fibrinogen. Nowak-Gottl et al have reported that Lp(a) is a predictor of recurrent stroke in children.³⁷ Ridker et al found no association between Lp(a) and stroke in a nested case-controlled study of the Physicians' Health Study cohort.³⁸ This contrasted with the significant association of elevated Lp(a) with stroke in a cross-sectional study by Jurgens et al³⁹ and the observation of Nagayama et al that Lp(a) was increased in stroke patients <50 years compared with older stroke patients.⁴⁰

The variable results for a relationship of Lp(a) with stroke suggest that study design and/or interaction with other factors are significant issues that need to be addressed.

Lp(a) and South Asians: cross-sectional studies

Geethanjali et al⁴¹ reported in a cross-sectional study of a South Indian cohort that Lp(a) concentration was higher in CHD patients versus controls. Using a value for Lp(a) of 30 mg/dL (~75th percentile), gave a relative risk of 2.8. They noted significant overlap between patients and controls in Lp(a) concentration.

Anand et al⁴² reported that Lp(a) is higher in Canadian residents of South Asian origin compared to those of European or Chinese origin.

Diabetes, Lp(a), and retinopathy

The studies of Lp(a) and diabetes are numerous, but are variable in design and quality. Suehiro et al⁴³ reported that in a Japanese cohort of patients with type 2 diabetes, Lp(a) was elevated in patients with retinopathy. Within the group with retinopathy, Lp(a) was highest in patients with proliferative retinopathy. The cross-sectional observation of elevated Lp(a) in patients with diabetic retinopathy was independently reported by Tarkun et al in a study of Turkish subjects.⁴⁴ However, in another cross-sectional study, Deepa et al⁴⁵ found a modest, statistically significant association between elevated Lp(a) and the presence of vascular complications, but no relationship with retinopathy. The cross-sectional study of retinopathy in the ARIC study⁴⁶ reported a very modest relationship (an odds ratio/10 mg/dL Lp(a) of 1.02) of Lp(a) concentration with the hard exudate phenotype.

Pharmacologic treatments that lower Lp(a)

Nearly 20 years ago, niacin was reported to lower Lp(a).⁴⁷ Niaspan, a new formulation of long-acting niacin, alone or in combination with a statin, has been shown to be highly effective in reducing Lp(a).⁴⁷⁻⁵¹ Statins alone are known to be ineffective at lowering Lp(a) and, in the 4S high-risk cohort, insufficient to neutralize the risk due to Lp(a).²⁹

Recently, it has been reported that aspirin reduces Lp(a) concentration in patients with heart disease.⁵² This is consistent with a report that aspirin can reduce the expression of apo(a) by human hepatocytes.⁵³

Fenofibrate has been reported to lower Lp(a)⁵⁴ and it is well-established that fenofibrate increases HDL cholesterol and decreases fibrinogen, making it an interesting choice for the treatment of patients with elevated Lp(a).

Hormone replacement therapy is well-known to reduce Lp(a) concentrations and, as reviewed above, in the HERS trial,^{31,55} was associated with improved outcome. However, given the controversy surrounding the use of hormone replacement therapy to prevent coronary events, it is unlikely that new studies will be designed to test this observation.

Conclusion

Does the reductionist approach fail in studies of Lp(a)?

In virtually all studies of risk markers, risk factors, and predictors of CHD and stroke, authors have designed studies, either *a priori*, or *a posteriori*, to identify new factors that are *independent* from established risk factors. However, the data that emerge for Lp(a) strongly suggest that, while Lp(a) is *genetically and metabolically* independent from other risk factors, its contribution to disease progression is interdependent on the presence of at least one other factor, such as high LDL cholesterol, high fibrinogen, or low HDL cholesterol.

The clinical implications of Lp(a) combined with other risk factors

Traditionally, new risk factors are added to the list of differential diagnoses for causes of CHD and included in investigations when established risk factors are not found. However, the evidence, as reviewed here, indicates that Lp(a) does *not* work alone, even in familial syndromes.^{32,33} Rather, the evidence to date suggests that Lp(a) primarily contributes to premature CHD in the *presence* of multiple risk factors. Thus, there is a benefit in knowing the Lp(a) status for primary prevention in patients

with multiple risk factors. The benefit of knowing Lp(a) status for primary prevention in subjects with few risk factors would be to provide additional motivation to adhere to a healthy life-style, to avoid acquiring those risk factors that interact with Lp(a) to cause CHD, and to help in the decision to prescribe lipid-lowering drugs. Based on the limited number of prospective secondary prevention studies to date, it would be reasonable to determine Lp(a) in all patients with CHD.

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Abstract of Interest

Is lipoprotein(a) a predictor for survival in patients with established coronary artery disease? Results from a prospective patient cohort study in northern Sweden.

C. A. GLADER, L. S. BIRGANDER, H. STENLUND, AND G. H. DAHLEN.

OBJECTIVES: Lipoprotein(a) [Lp(a)] is a known risk factor for the development of atherosclerosis. The aim of the present study was to test the importance of Lp(a) as a predictor for the further prognosis in patients with established coronary artery disease.

DESIGN: A prospective patient cohort study was carried out.

SETTING AND SUBJECTS: The cohort consists of 1216 patients who were examined with coronary angiography at the University Hospital in Umea, Sweden, because of stable effort angina.

MAIN OUTCOME MEASURES: Lipids, Lp(a), fibrinogen, antithrombin III (AT III), sedimentation rate and clinical data were registered at angiography. After a mean follow-up time of 6.7 years information on survival was collected from the municipal census lists and death certificates were examined. Total mortality and mortality because of cardiovascular disease were both used as outcome variables in the survival analyses.

RESULTS: The total mortality in the patient cohort was 16.4%. An Lp(a) level of 300 mg L⁻¹ or more was found in 30% of the study population

and was found to be an independent predictor for death. A high fibrinogen, a low AT III level, a depressed left ventricular function and a high coronary obstruction score were other significant independent predictors of death. Total cholesterol, HDL- and LDL-cholesterol were not related to survival in this study, but a substantial proportion of the population probably received lipid-lowering agents during the study period.

CONCLUSIONS: An Lp(a) level exceeding 300 mg L⁻¹ indicates a poor further prognosis and may help to identify patients who probably need powerful secondary prevention programmes to improve their prognosis.

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