Role of Lipoprotein(a) in Cardiovascular Disease
Current and Future Perspectives*

Lars Berglund, MD, PhD, FAHA,†‡
Erdembileg Anuurad, MD, PhD†
Davis and Sacramento, California

The clinical interest in lipoprotein(a) [Lp(a)] is largely derived from its role as a cardiovascular risk factor. Although not considered an established risk factor, Lp(a) levels have been associated with cardiovascular disease in numerous studies (1–3). Further, there is emerging evidence of interaction between Lp(a) and other established and potential cardiovascular risk factors, such as low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and homocysteine (4–6).

Lipoprotein(a) has many features in common with LDL. However, in contrast to LDL, the distribution of plasma Lp(a) levels is very skewed, ranging from <0.1 to >300 mg/dl (7). Notably, especially among Caucasians, only a minority of individuals have Lp(a) levels >30 mg/dl, which are commonly associated with risk (1,8). This skewed distribution and the fact that very few subjects have high levels of Lp(a) represent challenges in firmly associating Lp(a) with disease. Another challenge has been the standardization of Lp(a) measurements. Although LDL is expressed as cholesterol levels, the Lp(a) level reflects particle concentrations, including both lipid and protein components. The use of mass units in many Lp(a) assays requires an assumption of a particular apolipoprotein(a) [apo(a)] mass, that is, ignoring apo(a) size variation. The use of molar units (e.g., nmol/l) is therefore preferable. Because many immunological assays are based on epitopes in the repeating units of apo(a), the high degree of heterogeneity of apo(a) and the high degree of sequence similarity between apo(a) and plasminogen represent additional challenges for measurement of Lp(a). However, assays are available based on unique, nonrepeating apo(a) epitopes. Further, beyond methodological issues, in the majority of cases the plasma Lp(a) level constitutes a sum of Lp(a) carried in particles representing 2 different sizes of apo(a) molecules, that is, allele-specific apo(a) levels. For a given apo(a) size, there is considerable variability in allele-specific apo(a) levels. To date, available commercial assays do not take the relative distribution across apo(a) alleles into account.

In this issue of the Journal, Danik et al. (9) report results from a cohort study addressing the effect of hormone replacement therapy (HT) on Lp(a) and cardiovascular risk. Confirming previous findings suggesting a lowering effect of estrogen on Lp(a), the investigators showed that Lp(a) values were lower among women taking HT. They have further explored the effect of HT on the relationship of Lp(a) with cardiovascular disease (CVD). In women not taking HT, after appropriate adjustment for confounders, the hazard ratio of future CVD for the highest Lp(a) quintile compared with the lowest quintile was 1.77 (p < 0.0001 for trend). In contrast, among women taking HT there were no such significant associations with CVD. Notably, the effect of HT was observed only in women with high LDL cholesterol levels, in agreement with previous studies suggesting an interaction between Lp(a) and LDL cholesterol (Fig. 1). Further, the association was not linear and was limited to the highest Lp(a) quintile. This interesting observation suggests that there may be a threshold effect in the role of Lp(a) as a risk factor. Further, the interaction observed with LDL cholesterol levels indicates that Lp(a) might have more pronounced risk factor properties in a high-risk environment. The article has a number of strengths, including the use of an assay insensitive to apo(a) size variation, the inclusion of a relatively large number of subjects, and the ability to address whether HT has an impact on cardiovascular risk associated with Lp(a).

Although an apo(a) size-insensitive assay was used, allele-specific levels were not analyzed. Previous studies have shown an association between plasma Lp(a) levels and cardiovascular disease or pre-clinical vascular changes in subjects who carry at least 1 small apo(a) isoform (10–13). These results indicate that cardiovascular risk associated with Lp(a) may be pronounced among subjects carrying small apo(a) sizes. Availability of isoform-specific or allele-specific levels may therefore provide further information in assessing risk attributable to Lp(a) (13,14). In the study by Tuck et al. (15), estrogen treatment among healthy postmenopausal women resulted in a decrease of Lp(a) levels, and notably a reduction was observed for both small and large apo(a) sizes. Further studies may provide insight on whether the modification of risk in the present study may be attributable to a reduction of risk conveyed by small apo(a).

*Editorsials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the †Department of Medicine, University of California, Davis, California; and the ‡Veterans Affairs Northern California Health Care System, Sacramento, California. Dr. Berglund has received consulting fees from Merck, Novartis, and Merck/Schering-Plough; has received lecture fees from Merck, AstraZeneca, and Merck/Schering-Plough; and has equity interest in Pfizer. This work was supported in part by the University of California, Davis Clinical and Translational Science Center (RR 024146), and Dr. Anuurad is a recipient of an American Heart Association Postdoctoral Fellowship (0725125Y).
In assessing appropriate cardiovascular preventive measures, the issue of whether an intervention to lower Lp(a) is clinically warranted arises. At present, there are no guidelines recommending intervention based on high Lp(a) levels (16,17). The current study, as well as recent findings from other studies (4–6,18,19), suggest that Lp(a)-lowering therapy might be beneficial, at least in some subgroups of patients with high Lp(a) levels. However, at present, details are lacking on how to define such subgroups with regard to Lp(a) levels, apo(a) size, and the presence of other risk factors. Shlipak et al. (20) reported that a combination of estrogen and progestin seems to have a more favorable effect in women with high initial Lp(a) levels, and this effect occurs among women with known coronary artery disease. However, except for this subgroup of women in the HERS (Heart and Estrogen/Progestin Replacement Study) (20), no conclusive effect of Lp(a) lowering on coronary artery disease has previously been reported. The present findings are encouraging because they provide evidence that high Lp(a) levels in a high-risk setting might be appropriate to consider an intensified intervention. However, further studies are needed to firmly assess any possible therapeutic benefits of a reduction of Lp(a) levels.

Reprint requests and correspondence: Dr. Lars Berglund, Department of Medicine, University of California, Davis Medical Center, Clinical and Translational Science Center, 2921 Stockton Boulevard, Suite 1400, Sacramento, California 95817. E-mail: lars.berglund@ucdmc.ucdavis.edu.

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**Key Words:** Lp(a) • allele-specific apo(a) levels • risk factors • hormone replacement therapy • cardiovascular disease.