Recent Updates of Lipoprotein(a) and Cardiovascular Disease

Taili Liu, Won-Sik Yoon, and Sang-Rok Lee*

Division of Cardiology, Department of Internal Medicine, Chonbuk National University Hospital, Jeonju, Korea

In recent years, epidemiological studies, genome-wide association studies, and Mendelian randomization studies have shown a strong association between increased levels of lipoproteins and increased risks of coronary heart disease and cardiovascular disease (CVD). Although lipoprotein(a) [Lp(a)] was an independent risk factor for ASCVD, the latest international clinical guidelines do not recommend direct reduction of plasma Lp(a) concentrations. The main reason was that there is no effective clinical medicine that directly lowers plasma Lp(a) concentrations. However, recent clinical trials have shown that proprotein convertase subtilisin/kexin-type 9 inhibitors (PCSK9) and second-generation antisense oligonucleotides can effectively reduce plasma Lp(a) levels. This review will present the structure, pathogenicity, prognostic evidences, and recent advances in therapeutic drugs for Lp(a).

Key Words: Atherosclerosis; Lipids; Cardiovascular Diseases

INTRODUCTION

One of standard therapies to reduce cardiovascular disease is statin therapy, but there are still residual risks after potent statin treatments. Several primary and secondary prevention clinical trials showed that statins significantly reduced the incidence of recurrent coronary heart disease events1-4 and the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction-22 (PROVE-IT/TIMI-22) study has shown that lower LDL levels can provide greater clinical benefits.5 However, in the recent Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) after a six-year follow-up period, the incidence of major adverse cardiac events (MACEs) in the simvastatin/ezetimibe group was lower.6 This result showed that aggressive cholesterol lowering was good for decreasing cardiac events. In addition, the LIPID and Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) studies have shown that lipoprotein(a) [Lp(a)] is an important determinant of residual risk for cardiovascular events.7

Lp(a) was discovered about 60 years ago and is an independent risk factor for cardiovascular diseases such as coronary artery disease, peripheral vascular disease and calcified aortic valve disease.8,11 Previous studies have shown that there are still residual risks after using statins to reduce low-density lipoprotein (LDL) cholesterol, and the plasma Lp(a) concentration is an important risk factor for the residual risk of coronary heart disease.7,12 However, most clinicians do not check Lp(a) in daily practice due to the lack of an effective drug treatment. This review will present forgotten biomarker Lp(a) which can be another target to decrease residual risks. We will present the structure, pathogenicity, prognostic evidence, and recent advances in therapeutic drugs for treating Lp(a).

STRUCTURE AND PATHOGENICITY OF Lp(a)

1. Structure

Lp(a) is composed of two parts: a low-density lipoprotein (LDL)-like particle with apolipoprotein B100 (apo-B100), which is shared with apolipoprotein(a) [apo(a)] through disulfide binding (Fig. 1).13-16 The existence of apo(a) determines the unique function of Lp(a). Apo(a) is composed of repeating kringle IV (KIV) and a protease-like domain.17 According to the amino acid sequence, the KIV domain in apo(a) can be divided into 10 types (KIV1 to KIV10). Only KIV2 is repeated in the apo(a) sequence and the number of KIV2 repetitions is determined by the Lp(a) gene.18,19 Genetic polymorphism of apo(a) by variable KIV2 repetition determines the level of plasma Lp(a).20,21 Both Kringle
V and the protease-like domains in apo(a) are highly similar to the plasminogen.24,25

2. Pathogenicity

The plasma concentration of Lp(a) and individual differences are obvious. It is affected genetically, but hardly affected by environmental and dietary factors.26,27 The pathogenicity of Lp(a) can be roughly divided into three categories: atherosclerosis, inflammation and thrombosis (Fig. 2).

The most common method of measuring Lp(a) is to use a monoclonal anti-apo(a) antibody to determine the concentration of apo(a). Enzyme immunoassay (ELISA) is commonly used in clinical situations.28-30 However, due to the wide variation of the molecular weight of apo(a), the ratio of mass to molar concentration between individuals varies. Therefore, it is difficult to use a standardized method to determine the concentration of Lp(a). In addition, the abnormal level of Lp(a) in distinct risk and ethnic populations has not been completely determined clinically. Generally, the population average and the median level of Lp(a) vary with race/ethnicity, and are affected by certain diseases.

The concentration of Lp(a) can range from undetectable levels to >1,000 mg/dL, but numerous clinical studies have shown that an elevated plasma Lp(a) concentration (50 mg/dL) is an independent risk factor for cardiovascular diseases.

1) Atherosclerosis: The apo(a) in Lp(a) mediates the various atherosclerotic processes by accumulating Lp(a) during endothelial injury combined with several components of vascular endothelial cells and smooth muscle cells to interfere with normal endothelial function, and stimulating chemotactic activation of monocytes and macrophages. The strong lysine binding site in Apo(a) promotes Lp(a) accumulation in vascular tissues and enhances endothelial contraction and permeability through rhoa/rho kinase/mypt1-dependent pathways.31 Apo(a) can also mediate the concentration-dependent rejection of smooth muscle cells during migration assays through the action of integrin αvβ3 and rhoa/rho kinase.32 Lp(a) binds to macrophages through endocytosis by high-affinity VLDL-receptors to promote foam cell formation and cholesterol deposition.33,34

2) Thrombosis: Lp(a) mainly promotes thrombosis through a variety of mechanisms, the most important of which is to inhibit and interfere with fibrinolysis. Due to the homology of apo(a) and plasminogen, the formation of active plasmin can be inhibited, while Lp(a) competes with plasminogen to bind to fibrin, preventing plasmin-mediated thrombolysis.35-37 The apo(a) in Lp(a) can inhibit platelet aggregation by replacing fibrinogen to bind with integrin αIIbβ3, and through the effects of urokinase-type plasminogen activa-
tor inhibit plasminogen activation. 39,40

3) Inflammation: Lp(a) is susceptible to oxidative modification and produce the oxidation specific epitope (OSE), which is an important mediator of inflammation and atherosclerotic formation. The OSE is mainly composed of oxidized LDL, apoptotic cells, and oxidized phospholipids and oxidized sterols. 41,42

The lysine binding sites in certain KIV domains in apo(a) are associated with specific functions related to the pathogenicity of Lp(a). 43 In particular, KIV10 also contains sites for covalent attachment of pro-inflammatory oxidized phospholipids (oxPLs). 44,45 Lp(a) has a high proportion of oxPLs and is also one of the main carriers of oxPLs. 45 The oxPLs have pro-inflammatory effects and also participate in the formation of atherosclerosis. Lp(a) can promote inflammation by inducing the inflammatory cytokines. Apo(a) can induce macrophages to release interleukin-8, tumor necrosis factor-α and monocyte chemotactic protein. 44,46 Lp(a) can directly induce monocyte chemotaxis and attract monocytes by direct and indirect mechanism by vascular endothelial cells. 47,48

EPIDEMIOLOGY AND CLINICAL CORRELATION

The plasma Lp(a) concentration is mainly determined by the LPA gene. In addition, more than 90% of the variability of plasma Lp(a) levels can be explained by the polymorphism of the apo(a) gene. However, race/ethnic factors also have an extremely important influence on the plasma Lp(a) concentration. The greater genetic difference in allele frequency produced the different average and median level of Lp(a).

In the Copenhagen General Population and Copenhagen City Heart Study, it was proved that the increased risk of myocardial infarction in the general population was associated with increased plasma Lp(a) levels. 29,30 Secondly, in the Copenhagen General Population study, the increased Lp(a) levels were related to decreased KIV-2 repeats. The number of KIV-2 repeats explained 27% of the change in plasma Lp(a) concentration.

In the Genetic Variants Associated study, gene chip detection technology is used to investigate the relationship between genetic variation and the risk of coronary heart disease (CHD). 31 They found two variants in the LPA gene (rs10455872 and rs3798220), which explained 36% of the total variation in plasma Lp(a) levels, and two variations were associated with increased risk of CHD. In addition, it has been found that the LPA gene in the 6q26-27 region and its surrounding genetic variants are closely related to plasma Lp(a) levels and the risk of CHD.

In the Emerging Risk Factors collaboration study, 126,634 participants from 36 prospective studies were collected. After adjusting for age and gender, Lp(a) has been continuously associated with the risk of coronary heart disease, which is represented by the RR for CHD was 1.16 (95% CI, 1.11-1.22) for every 3.5-fold increase in Lp(a) levels. There is a continuous, independent, and moderate correlation between Lp(a) concentration and the risk of CHD, and this correlation seems to be only related to vascular outcomes. 9

Some prospective studies also support that Lp(a) is indeed an independent risk factor for cardiovascular disease. 29,52 Mehta et al. 53 reviewed the results of a long-term cohort study of a total of 15,000 patients based on two asymptomatic populations in the community. The study found that the increase in Lp(a) can independently predict long-term atherosclerotic cardiovascular disease (ASCVD) and CHD risks in asymptomatic populations of the community. Increased Lp(a) combined with family history were effective at predicting the risk of ASCVD and CHD.

In the existing prospective analysis and meta-analysis, it is generally believed that the Lp(a) level in people of African descent is two to three times higher than that of Caucasians followed by Hispanics and East Asians. 29,52,54 In addition, some studies have shown that Chinese Lp(a) levels are lower than those of Caucasians. 55 A total of 4,593 participants were included in the MESA study, including Caucasian, Black, Hispanic, and Chinese Americans. 56 After adjusting for race/ethnicity and other CHD risk factors, the plasma Lp(a) levels in the Black and White populations are significantly correlated with the incidence of CHD. However, there is no significant correlation among Chinese Americans and Hispanics. In addition, a higher Lp(a) level (≥50 mg/dL) was associated with higher risks of coronary heart disease in all races except Chinese Americans.

A total of 6,086 first myocardial infarction and 6,857 control patients were included in the INTERHEART study, including Africans, Chinese, Arabs, Europeans, Latin Americans, south Asians and southeast Asians. 57 After adjusting for age, gender, apoB and apoA1, Lp(a)>50 mg/dL was associated with an increased risk of myocardial infarction (odds ratio 1.48; 95% CI 1.32-1.67). In the Korean population, Lp(a) has been identified as an independent risk factor for 6,252 patients with CHD, and associated with poorer prognosis. 58 However, Lee et al. 59 showed a close relationship between Lp(a) (carries of OxPLs) and MACE despite significant ethnic differences. LPA SNPs, apo(a) isoforms, Lp(a), and OxPLs levels were measured in 1792 Black, 1030 White, and 597 Hispanic subjects in Dallas Heart Study. The prevalence and association of LPA SNPs with size of apo(a) isoforms, Lp(a), and OxPLs levels are highly variable and ethnicity-specific. The relationship to MACE is best explained by elevated plasma Lp(a) or OxPLs levels, despite significant ethnic differences in LPA genetic markers.

The prospective study enrolled 77,680 patients from the Copenhagen City Heart Study and the Copenhagen General Population Study showed the relationship between increased levels of Lp(a) and severe aortic valve stenosis in the Caucasian population. 60 In addition, the relationship between rs10455872 genotype and aortic stenosis risk was observed. Another genome-wide association study was performed by standard CT scanning on 6,942 patients to ana-
lyze the relationship between aortic valve calcification and Lp(a). The study showed that the rs10455872 genotype was closely related to the aortic valve calcification in European Caucasian participants. Moreover, the increased level of Lp(a) was associated with the progression of aortic stenosis.

Madsen et al. have reported the results of a population-based study of 3,600 patients. The study found that the higher Lp(a) level was associated with recurrent cardiovascular disease. However, the reduction of Lp(a) < 50 mg/dL within 5 years will reduce the 20% risk of cardiovascular disease recurrence. Xu et al. reviewed the results of a long-term cohort study of 6,175 patients. The study found that the incidence of serious adverse events was significantly higher in patients with both high Lp(a) levels and three-vessel coronary diseases. On the other hand, it showed that higher Lp(a) levels can be potential biomarkers for risk stratification and prognostic factors. Secondly, Liu et al. published a long-term prospective study of 4,078 patients. The study found that in patients with stable coronary heart disease after coronary intervention, plasma Lp(a) levels have a good predictive value for cardiovascular events, and that high Lp(a) levels (≥30 mg/dL) indicate a poor prognosis.

**Lp(a) GUIDELINES AND CARDIOVASCULAR DISEASE**

Numerous clinical studies in the past twenty years have confirmed the association between plasma Lp(a) and the risk of cardiovascular disease. Although Lp(a) was an independent risk factor for ASCVD, the latest international clinical guidelines do not recommend direct reduction of plasma Lp(a) concentrations. The main reasons have been that there were no good clinical medicine that directly lowered plasma Lp(a) concentrations, and that the data had not fully shown the prognostic benefit.

The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines for the management of dyslipidemia recommend that every adult have at least one Lp(a) assessment in his lifetime in order to determine the populations with extremely high levels of Lp(a) genetics (Lp(a) > 180 mg/dL). This is because patients with hereditary high Lp(a) levels are likely to be at risk of ASCVD in their lifetime (Table 1, class IIa, C). The 2018 American Heart Association/American College of Cardiology (AHA/ACC) Guidelines on the Management of Blood Cholesterol recommend Lp(a) as a primary risk prevention for adults aged 40-75. However, there is limited guidance on when Lp(a) should be measured.

**TREATMENT OF INCREASED Lp(a)**

1. **Nicotinic acid**

   Current lipid-lowering therapies are unable to specifically reduce the concentration of Lp(a). However, niacin has been widely used to treat dyslipidemia, and especially in the case of using high doses, the Lp(a) concentration has been significantly reduced. High-dose niacin (2-4 g/day) can reduce Lp(a) by 25-40%. However, niacin did not show any ability to reduce the concentration of Lp(a) at low doses. The mechanism by which niacin reduces Lp(a) may be by reducing the synthesis of triglycerides required for lipoprotein lipidation and reducing the global liver cAMP levels which is required to stimulate apo(a) transcription. However, due to the potential adverse reactions, such as migraines, tachycardia, blushing, and liver toxicity, the recent European guideline do not recommend the use of niacin as a way to reduce Lp(a). In the AIM-HIGH study, a total of 3,414 patients were randomly assigned to receive niacin. They showed that adding niacin to statin therapy did not increase the clinical benefit during the 36-month follow-up period. In addition, poor tolerability and potential adverse events (skin, gastrointestinal system, bleeding, myopathy, infection and diabetes) were observed in the HPS2-THRIVE study.

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**Table 1. Guideline recommendations for screening of Lp(a)**

| Screen Recommendations | Target |
|------------------------|--------|
| 2018 AHA/ACC | 50 mg/dL |
| - Relative indications for its measurement are family history of premature ASCVD or personal history of ASCVD not explained by major risk factors. |
| - Useful in adults 40-75 years of age without diabetes mellitus and intermediate risk for ASCVD. |
| - This is especially in those with higher Lp(a) values and, if used in women, only in the presence of hypercholesterolemia. |
| 2019 ESC/EAS | 50 mg/dL |
| - Lp(a) measurement should be considered at least once in each adult person’s lifetime to identify those with very high Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to heterozygous familial hypercholesterolaemia. (class II, C) |
| - Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk. (class II, C) |

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2018 AHA/ACC: The 2018 American Heart Association/American College of Cardiology (AHA/ACC) Guideline on the Management of Blood Cholesterol, 2019 ESC/EAS: The 2019 European Society of Cardiology/European Atherosclerosis Society Guidelines for the management of dyslipidemia.
2. Antibody-based therapeutics

1) Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors: PCSK9 inhibitors such as evolocumab or alirocumab can decrease the degradation of LDL receptors. They can increase the number of hepatocyte LDL receptors and enhance the ability of LDL clearance from plasma. In the FOURIER study, evolocumab reduced the plasma Lp(a) and enhanced the ability of LDL clearance from plasma. In contrast, the use of alirocumab increased the number of hepatocyte LDL receptors and increased the ability and fewer adverse reactions in phase I of the trial.

In addition, after the use of alirocumab, for every 5 mg/L reduction of Lp(a), the total number of cardiovascular events was relatively reduced by 2.5%. Although PCSK9 inhibitors can reduce plasma Lp(a) levels, the mechanism of action and clinical correlation remains to be explored.

3. Nucleic acid-based therapeutics

1) Mipomersen: Mipomersen is a 2′-O-methoxy ethyl (2′-MOE)-modified second-generation antisense oligonucleotide (ASO), which binds to the homologous apolipoprotein B messenger ribonucleic acid (mRNA). Due to the inhibition of the synthesis of apolipoprotein B-100 (apoB-100), the plasma concentration of LDL, apoB and Lp(a) can be significantly reduced. In the existing phase III randomized trial, in patients with hypercholesterolemia of different causes, mipomersen continuously reduced the median plasma Lp(a) level by 26.4%. Mipomersen is approved by the FDA for lowering low-density lipoprotein cholesterol, apoB and other lipoprotein in homozygous familial hypercholesterolemia. A meta-analysis found that the level of Lp(a) was reduced 26% from baseline.

2) ISIS-APO(a)Rx and AKCEA-APO(a)-LRx: ISIS-APO(a)Rx and AKCEA-APO(a)-LRx are 2′-O-methoxy ethyl (2′-MOE) modified antisense DNA oligonucleotides, targeting apolipoprotein (a) and Lp(a), by binding to the complementary apol(a) mRNA sequence to form a DNA double strand, thereby reducing the translation of apol(a). Both ISIS-APO(a)Rx and AKCEA-APO(a)-LRx showed better tolerability and fewer adverse reactions in phase I of the trial. In both phase II trials, healthy participants with elevated Lp(a) significantly reduced plasma Lp(a) concentration in a dose-dependent manner. In the Phase II trial of AKCEA-APO(a)-LRx, the Lp(a) concentration was reduced by an average of 80% at dose of 20 mg per week, and 98% of patients reached the lipoprotein(a) level of 50 mg/dL or lower.

CONCLUSIONS AND FUTURE PERSPECTIVES

In the past two decades, epidemiological studies have shown that Lp(a) is an independent causal risk factor for CVD and its clinical importance. However, the more direct mechanism between Lp(a) and atherosclerosis still needs clarification. On the other hand, specific therapies such as nucleic acid based medication for reducing Lp(a) will be important in clinical practice to decrease the residual risk of CHD.

CONFLICT OF INTEREST STATEMENT

None declared.

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Recent Updates of Lipoprotein(a)

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