Lipoprotein(a) as an Old and New Causal Risk Factor of Atherosclerotic Cardiovascular Disease

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Lipoprotein(a) [Lp(a)], discovered in 1963, has been associated with atherosclerotic cardiovascular disease (ASCVD) independent of other traditional risk factors, including LDL cholesterol. Lp(a) is an apolipoprotein B (apoB)-containing lipoprotein, which contains an LDL-like particle. Unlike LDL, which is a primary therapeutic target to decrease ASCVD, current guidelines recommend measuring Lp(a) for risk assessments because there is no clear evidence demonstrating the clinical benefit of decreasing Lp(a) using classical drugs such as niacin. However, recent Mendelian randomization studies indicate that Lp(a) causally correlates with ASCVD. In addition, novel drugs, including PCSK9 inhibitors, as well as antisense oligonucleotide for apo(a), have exhibited efficacy in decreasing Lp(a) substantially, invigorating a discussion whether Lp(a) could be a novel therapeutic target for further ASCVD risk reduction. This review aims to provide current understanding, and future perspectives, of Lp(a), which is currently considered a mere biomarker but may emerge as a novel therapeutic target in future clinical settings.

Key words: Lipoprotein(a), Aortic valve stenosis, Atherosclerotic cardiovascular disease, LDL

Introduction

Atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease and stroke, is the leading cause of mortality worldwide. Despite advancements in ASCVD prevention through LDL-lowering therapies, using statins and various other agents, so-called "residual risk" remains a significant challenge[1-3]. Of several biomarkers shown as residual risks, lipoprotein(a) [Lp(a)], an apolipoprotein B (apoB)-containing lipoprotein containing a LDL-like particle, has been reported as a causal risk factor for ASCVD by Mendelian randomization studies, as well as genome-wide association studies (GWAS)[4-6]. Conversely, the incidence of aortic valve stenosis, based on calcific aortic valvulopathy, where no effective option exists for its progression, is growing among industrialized countries because of aging societies[7, 8]. Moreover, Lp(a) is considered a causal factor in calcific aortic valvulopathy development[9, 10], making Lp(a) a potential therapeutic target to decrease calcific aortic valvulopathy progression.

This review aims to provide a current understanding, and future perspectives, of Lp(a), which is currently considered a mere biomarker but may emerge as a novel therapeutic target in future clinical settings.

What is Lp(a)?

Lp(a) is a particle containing two different elements (**Fig. 1**). The first element is an LDL-like particle containing an apoB-100 particle, which is insoluble in water. Reportedly, the LDL-like particle in Lp(a) is larger in size and higher in lipid content, with a density marginally lower than the LDL particle isolated from the same individual[11]. The second element is a hydrophilic glycoprotein called apo(a) that shares homology with plasminogen, giving the particle atherogenic properties. Plasminogen has five kringles (KI–KV); apo(a) does not contain KI–KIII but has 10 subtypes of KIV (with KIV1, and KIV3–KIV10 have one copy, and KIV2 has one to >40 copies), and one copy of KV. The apo(a) isoform size and the Lp(a)
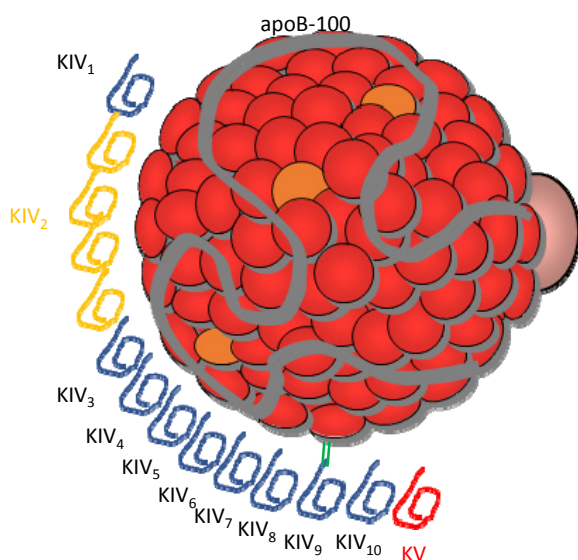
Fig. 1. The structure of lipoprotein [Lp(a)]

Lp(a) is composed of an LDL-like particle, including apolipoprotein B-100 (apoB-100) and apolipoprotein(a) [apo(a)], which has kringle IV (KIV) and KV. Apo(a) contains 10 subtypes of KIV repeats, containing one copy each of KIV1, multiple copies of KIV2 (yellow colored), and one copy of KIV3-10, KV.

concentration correlate inversely since smaller isoforms can be made in larger quantities compared to larger isoforms. Both components, LDL-like particle and apo(a), are linked by a single disulfide bond that was localized in one of apo(a) (kringle IV9)'s repeat structures[12].

Evolution of the *Apo(a)* Gene

In primates, the *apo(a)* gene arose from a plasminogen gene ~40 million years ago during evolution[12]. Remarkably, apo(a) is present in humans, nonhuman primates, and Old World monkeys, but not in prosimians, or lower mammals.

Lp(a) Concentration and its Related Factors

The distribution of Lp(a) concentration in most populations is highly positively skewed[13]. Moreover, there are high differences in Lp(a) concentrations across populations; Africans have higher Lp(a) than Caucasian or Asian populations (**Fig. 2**)[13,14]. Although the Lp(a) concentration is primarily evaluated by common, single-nucleotide polymorphisms in the *LPA* gene[15] and is only minimally affected by environmental factors, several other conditions, including renal

dysfunction[16] and familial hypercholesterolemia (FH), have been reported to affect its level[14, 17].

Lp(a) Catabolism

The serum Lp(a) concentration is primarily measured by the rate of apo(a) synthesis, rather than the apo(a) degradation[18, 19]. In addition, the liver has been reported as a major site of apo(a) synthesis, evidenced by studies of patients undergoing therapeutic liver transplantation[20]. The Lp(a) assembly is a two-step process that begins with docking apo(a) to an LDL particle, followed by creating a disulfide bond between the kringle structure and apoB-100; this has been reported to occur at the hepatocyte cell surface, rather than at the endoplasmic reticulum or Golgi[21]. Conversely, an Lp(a) catabolism pathway remains unclear. The liver is now considered the main organ that clears Lp(a) from the circulation[21], and some studies using mice models have also suggested the kidneys are contributors[22, 23]. Moreover, kinetic studies in humans have revealed that Lp(a) catabolism was slower than that of LDL, independent of the Lp(a) concentration[24, 25]. Those results suggested that synthesis, rather than catabolism, determines the Lp(a) concentration. Likewise, a plasmapheresis study reported similar results[26].

Measurements of Lp(a)

Some assays of Lp(a) measurements are reportedly affected by the number of KIV2 repeats[27]. Nevertheless, several studies using methods sensitive to the apo(a) size reported significant correlations between Lp(a) and the ASCVD risk, consistent with those using methods independent of apo(a) size variations. Accordingly, we intend to highlight that the critical question of whose Lp(a) should be measured is more pertinent than how to measure Lp(a).

Pathological and Physiological Roles of Lp(a)

Lp(a) and/or apo(a) have been correlated with prothrombotic properties through interfering with reactions in fibrinolysis regulation, including plasminogen binding to fibrinogen, fibrin, and tetranectin, plasminogen activation by tissue plasminogen activator (t-PA), and augmentation of plasminogen activator inhibitor-1 (PAI-1) activity[28-30]. Besides those interactions with the fibrinolytic system, other functional properties have been explained as its pathophysiology, including the release of monocyte chemotactic activity from endothelial cells[31], inhibition of the
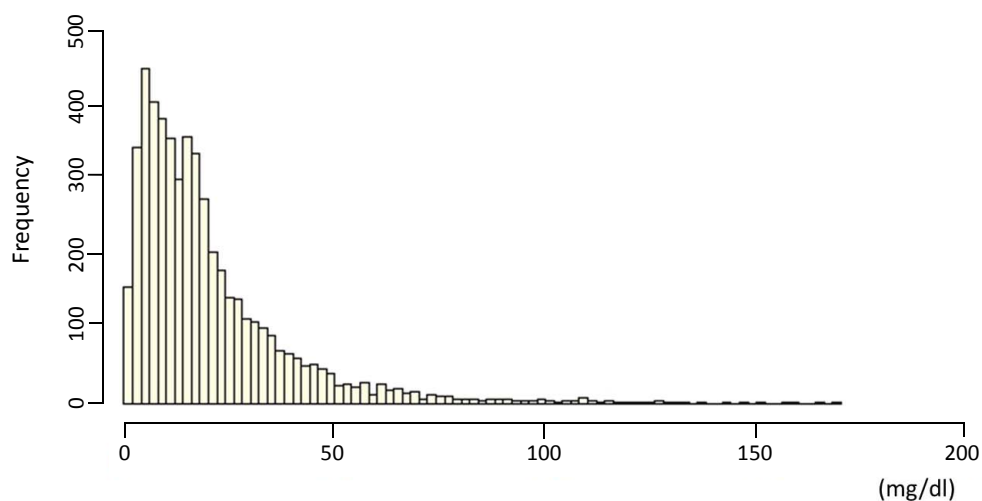
Fig. 2. The distribution of the lipoprotein [Lp(a)] frequency
The *X*-axis represents the serum Lp(a) level, while the *Y*-axis represents the frequency.

plasma catalyzed activation of transforming growth factor-β (TGF-β)[32], enhanced proliferation and migration of smooth muscle cells[33], proliferation of endothelial cells[34], as well as mesangial cells[35], and stimulation of the expression of adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin[36, 37].

Lp(a) as a Causal Factor for the ASCVD Development: A Standpoint from Genetic Studies

Since the initial results from a GWAS focusing on seven major diseases using 2000 cases and 2000 controls[38], several GWAS have been conducted to determine novel loci related to various diseases. Of these, correlations between common variants in LPA loci and cardiovascular disease, including coronary artery disease and aortic valve stenosis, have been reported often[39, 40]. Notably, common variants in an LDL receptor markedly correlated with ASCVD, whereas these were not related to calcific aortic valvulopathy outcome[40]. Conversely, common variants in the *LPA* gene markedly correlate with ASCVD, as well as calcific aortic valvulopathy outcomes as well. Such correlations between genetic variants, resulting in an increase/decrease of a particular biomarker and an outcome, could be considered a proxy of a randomized controlled trial using a particular inhibitor; these are known as "Mendelian randomization studies"[41]. Of note, Mendelian randomization studies could be useful for validating, as well as estimating, the effects/

side effects of particular drugs targeting molecule "X," as demonstrated in multiple lipid-modifying drugs[42-44]. Accordingly, Lp(a) could be a causal factor for ASCVD and related diseases, including coronary heart disease, stroke, chronic kidney disease, calcific aortic valvulopathy, heart failure, and peripheral vascular disease[45]. Overall, meta-analyses of epidemiological and genetic studies have demonstrated that elevated Lp(a) levels correlated with an increased risk for ASCVD (**Fig. 3**).

Lp(a) and Calcific Aortic Valvulopathy

Calcific aortic valvulopathy, characterized by calcium deposition and thickening of the aortic valve, correlates with aortic valve stenosis. In addition, epidemiological studies have reported several risk factors, including classical coronary risk factors, such as age, male, body mass index, hypertension, diabetes, smoking, renal dysfunction, and LDL cholesterol related to calcific aortic valvulopathy, indicating that treating or preventing those risk factors might decrease the risk of developing aortic valve stenosis[7]. Under these hypotheses, a randomized controlled trial (RCT) was conducted to determine whether further reduction of LDL cholesterol, using ezetimibe on the top of statins, could effectively slow the progression of aortic valve stenosis[46]. Nevertheless, no medical treatment, thus far, has been reported to affect disease progression in patients with calcific aortic valvulopathy. Accordingly, Lp(a) has emerged as a "causal" risk factor based on genetic associations, which could be potential therapeutic targets to prevent calcific aortic valvulopathy
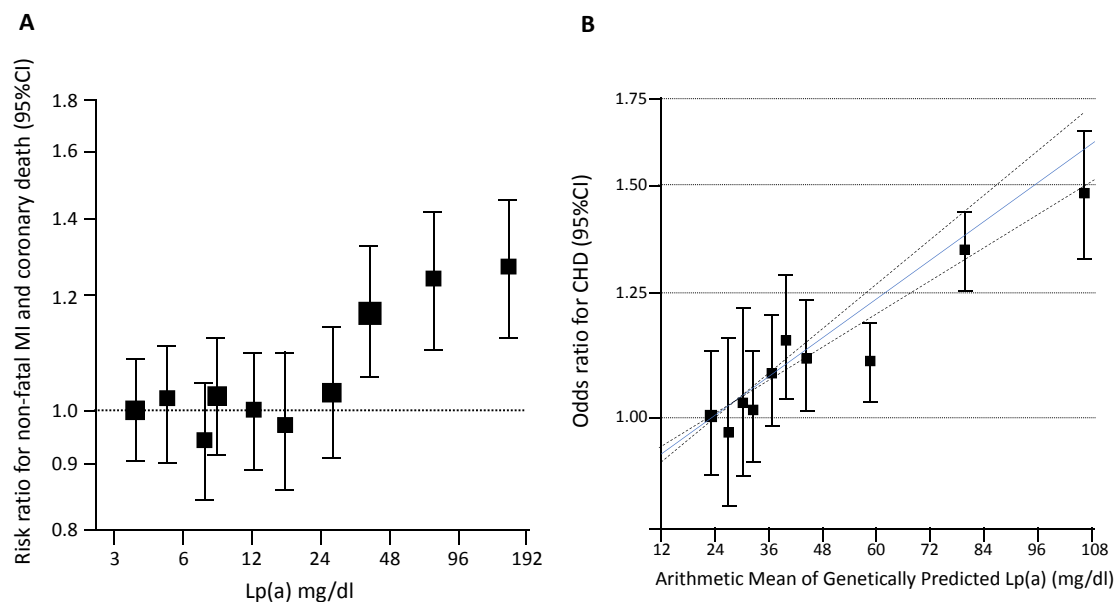
Fig. 3. The evidence for lipoprotein [Lp(a)] as an independent and causal risk factor for atherosclerotic cardio-vascular disease (ASCVD)

A, A meta-analysis of epidemiological studies, adjusted for usual levels of systolic blood pressure, smoking status, history of diabetes, body mass index, and total cholesterol. The *X*-axis represents the serum Lp(a) level, while the *Y*-axis represents the risk ratio for non-fatal MI and coronary death. B, the correlation between genetically predicted Lp(a) and CHD risk. The *X*-axis represents the serum Lp(a) level, while the *Y*-axis represents the odds ratio for the CHD risk. The blue solid line represents the best-fitting fractional polynomial to model the dose-dependent relationship; the dotted lines show the 95% confidence intervals for the relationship.

development. Furthermore, elevated Lp(a) levels enhance the calcific aortic valvulopathy progression and, thus, the need for aortic valve replacement (**Fig. 4**)[47].

Lp(a) as One of the Residual Factors of Statin Therapies

Several biomarkers are considered so-called "residual risk of statin therapies;" of those, the evidence level obtained from sub-analyses, using RCTs, could be considered higher than those obtained from single-center observational studies. Thus, only a few biomarkers, including triglycerides[48, 49] and Lp(a)[50, 51], have been explicitly "established" as the residual risk of statin therapies through RCT investigations. Remarkably, both biomarkers have been projected to be causal factors for ASCVD development through Mendelian randomization studies. These facts motivate us to lower those biomarkers, especially among patients with ASCVD under statin therapies.

Lp(a)-Lowering Therapies

For a long time, no satisfactory therapeutic approach existed to lower Lp(a) levels. We, among

other groups, have reported Lp(a) levels among FH patients were caused by LDL receptor mutations[14, 17], resulting in the estimation that LDL-lowering therapies, such as statins, resins, and ezetimibe, could be useful for this purpose. However, studies using those drugs have recurrently reported almost no effect on decreasing Lp(a) levels[52, 53]. Conversely, recently approved proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which elevate LDL receptor levels by inhibiting its degradation, have been reported to lower Lp(a) levels as much as 30%, with the extent of Lp(a) lowering correlating with the LDL reduction[54-56]. The mechanism underlying this effect was recently the subject of a comprehensive investigation. Another option could be mipomersen, an apoB inhibitor, which could correlate with the reduction of Lp(a) ~30%[57]; however, it almost always causes fatty liver since it blocks the secretion of apoB-containing lipoproteins from the liver. Another emerging option could be antisense oligonucleotide (ASO) targeted to apolipoprotein(a). The first-generation drug called IONIS-APO(a)Rx has been reported as a tolerable, potent therapy for decreasing Lp(a) concentrations[54]. Recently, AKCEA-APO(a)-LRx (ISIS 681257), a second-generation, N-acetyl-galactosamine-conjugated, ASO targeted to apolipoprotein(a), was reported to
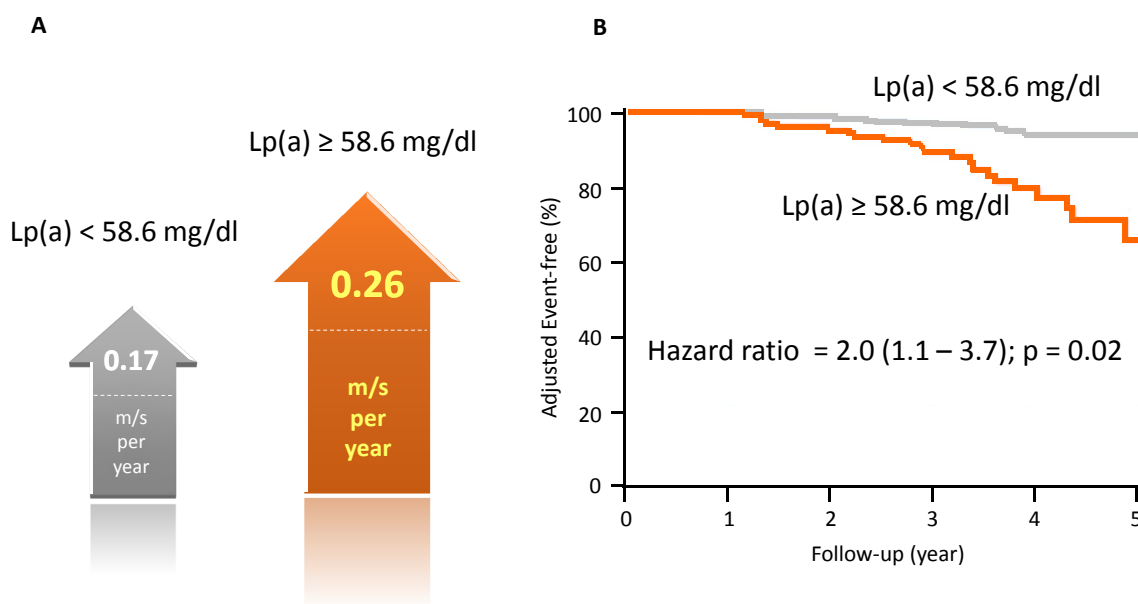
A

Lp(a) ≥ 58.6 mg/dl

Lp(a) < 58.6 mg/dl

0.17

m/s per year

0.26

m/s per year

B

Lp(a) < 58.6 mg/dl

Lp(a) ≥ 58.6 mg/dl

Hazard ratio = 2.0 (1.1 − 3.7); p = 0.02

Adjusted Event-free (%)

Follow-up (year)

Fig. 4. Lipoprotein [Lp(a)] and progression of aortic valve stenosis, as well as the incidence of aortic valve replacement

A, both arrows indicate the predicted progression of preexisting mild-to-moderate calcific aortic valve stenosis (CAVS) on echocardiography in meters/second/year in the ASTRONOMER trial. The gray arrow shows the progression of aortic valve stenosis among patients whose Lp(a) <58.6 mg/dL; the orange arrow shows the progression of aortic valve stenosis among patients whose Lp(a) ≥ 58.6 mg/dL. B, the event-free survival curve divided into two groups based on the Lp(a) level. The gray line represents patients whose Lp(a) <58.6 mg/dL; the orange arrow represents patients whose Lp(a) ≥ 58.6 mg/dL.

lower the mean plasma Lp(a) levels by 92%[58].

Conclusions and Perspectives

Lp(a), an old molecule, has long been considered a vital causal factor of ASCVD, including calcific aortic valvulopathy. Now, specific therapies reducing Lp(a) quite effectively are projected to become available soon in clinical practice. We would witness whether such emerging novel approaches could tamp down the residual risk, as well as the progression, of calcific aortic valvulopathy.

Conflicts of Interest

None.

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