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.

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. 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). 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. The second element is a hydrophilic glycoprotein called apo(a) that shares homology with plasminogen, giving the particle atherogenic properties. Plasminogen has five kringle (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) isoform size are different. 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. The second element is a hydrophilic glycoprotein called apo(a) that shares homology with plasminogen, giving the particle atherogenic properties. Plasminogen has five kringle (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) isoform size are different.
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\(^{26}\).

**Lp(a) Catabolism**

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**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 tetraneectin, 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

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**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.
Lipoprotein(a) and Atherosclerotic Cardiovascular Disease

The side effects of particular drugs targeting molecule “X,” as demonstrated in multiple lipid-modifying drugs. 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. 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. 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. 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.
development. Furthermore, elevated Lp(a) levels enhance the calcific aortic valvulopathy progression and, thus, the need for aortic valve replacement (Fig. 4)..

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 and Lp(a) 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, 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. 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. 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) 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. Recently, AKCEA-APO(a)-LRx (ISIS 681257), a second-generation, N-acetyl-galactosamine-conjugated ASO targeted to apolipoprotein(a), was reported to
lower the mean plasma Lp(a) levels by 92%.\textsuperscript{50}

**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.

**Acknowledgments and Notice of Grant Support**

None.

**Conflicts of Interest**

None.

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