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REVIEW ARTICLE

# Lipoprotein(a) and Atherosclerotic Cardiovascular Disease: Current Understanding and Future Perspectives

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## Abstract

**Purpose** To review current knowledge of elevated lipoprotein(a) [Lp(a)] levels in relation to atherosclerotic cardiovascular disease (ASCVD) and discuss their potential use as biomarkers and therapeutic approaches in clinical practice.

**Methods** We summarized the current understanding and recent advances in the structure, metabolism, atherogenic mechanisms, standardized laboratory measurement, recommended screening populations, and prognostic value of Lp(a), with a special focus on the current potential treatment approaches for hyperlipoprotein(a)emia in patients with ASCVD.

**Results** Lp(a) is composed of LDL-like particle and characteristic apolipoprotein(a) [apo(a)] connected by a disulfide bond. Substantial evidence shows that elevated plasma Lp(a) level is a heritable, independent, and possibly causal risk factor for ASCVD through its proatherogenic, proinflammatory, and potentially prothrombotic properties. Current guidelines recommend Lp(a) measurement for patients with an intermediate-high risk of ASCVD, familial hypercholesterolemia, a family history of early ASCVD or elevated Lp(a), and progressive ASCVD despite receiving optimal therapy. Traditional Lp(a)-lowering approaches such as niacin, PCSK9 inhibitors, mipomersen, lomitapide, and lipoprotein apheresis were associated with a non-specific and limited reduction of Lp(a), intolerable side effects, invasive procedure, and high expense. The phase 2 randomized controlled trial of antisense oligonucleotide against the apo(a) encoding gene LPA mRNA showed that IONIS-APO(a)-$L_{RX}$ could specifically reduce the level of Lp(a) by 90% with good tolerance, which may become a promising candidate for the prevention and treatment of ASCVD in the future.

**Conclusions** It is reasonable to measure Lp(a) levels to reclassify ASCVD risk and manage individuals with elevated Lp(a) to further reduce the residual risk of ASCVD, especially with IONIS-APO(a)-$L_{RX}$.

**Keywords** Lipoprotein(a) · Atherosclerotic cardiovascular disease · PCSK9 inhibitors · Lipoprotein apheresis · Apolipoprotein(a) antisense oligonucleotides

## Introduction

Although death caused by atherosclerotic cardiovascular disease (ASCVD) in the USA reached an inflection point in the 1970s, mainly owing to strict control of low-density lipoprotein cholesterol (LDL-C), the latest American Heart Disease and Stroke Statistics show that ASCVD still accounts for one-third of all deaths [1]. Therefore, it is of great importance to actively seek new avenues to control the residual risk of ASCVD.

Lipoprotein(a) [Lp(a)] is composed of LDL-like particle and characteristic glycoprotein apolipoprotein(a) [apo(a)] connected by a disulfide bond [2]. Recently, evidence from both epidemiological and genetic studies reveals that Lp(a) may be an independent and genetic risk factor for ASCVD [3, 4] and may partially explain the residual risk of ASCVD in the background of intensive LDL-C-lowering therapy [5, 6]. However, there still exist a lot of unsolved mysteries regarding the metabolism, proatherogenic mechanisms, standardized measurement, and prognostic value of Lp(a). More importantly, the appropriate population, potential therapeutic strategies, and required effect size of Lp(a) lowering are still not fully elucidated. Here, we review the current understanding of Lp(a) and attempt to summarize the challenges of Lp(a) in clinical ASCVD management.

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## Structure of Lp(a)

Lp(a) was first discovered by Berg et al. in the Nordic population in 1963 [7]. This type of lipoprotein is structurally similar to LDL and contains a characteristic glycoprotein apolipoprotein(a) [apo(a)], which covalently associates apolipoprotein B-100 (apoB-100) through a disulfide bond [2]. The LDL-like component consists of a single molecule of apoB-100, an outer shell of phospholipids and free cholesterol, and a neutral lipid core containing cholesterol esters and triglycerides. Apo(a) is highly homologous with plasminogen (PLG) in structure. PLG is composed of an amino-terminal tail domain, followed by five kringle domains and a trypsin-like protease domain, whereas apo(a) only includes multiple, repeated copies of sequences homologous to plasminogen kringle 4 domain [named KIV in apo(a)], followed by a kringle 5-like (KV) and a protease-like domain [8]. Apo(a) has ten types of KIV domains differing in their amino acid sequences; of these, KIV type 2 ($KIV_2$) has a variety of copy numbers ranging from 2 to 40, leading to apo(a) isoform size polymorphism and Lp(a) heterogeneity among races, regions, and individuals [9].

## Heritability of Lp(a)

Studies have demonstrated that the apo(a) encoding gene LPA only exists in humans, Old World nonhuman primates, and the European hedgehog [10]. The LPA gene encoding human apo(a) is located on the long arm of chromosome 6 at 6q2.6–2.7 and determines more than 90% of the variation of circulating Lp(a) concentrations, especially by a size polymorphism of apo(a) caused by a variable number of KIV repeats [11]. In general, the apo(a) isoform size (i.e., LPA gene KIV2 repeat copy number) links negatively with plasma levels of Lp(a) [11–13]. Within individuals, > 80% carry 2 different-sized apo(a) isoforms, each inherited from 1 parent, with the major contribution generally driven by the small isoform [2]. In addition, single-nucleotide polymorphisms of LPA alleles such as rs10455872, rs3798220, and rs3777392 can also determine the plasma levels of Lp(a) [14–16]. Different from LDL-C, plasma Lp(a) levels in the population presents a positive skewness distribution, with a difference of 1000 times between individuals [17]. It is traditionally believed that Lp(a) levels in the blood are constant throughout a person's life, but recent studies by Marcovina et al. have found that about 40% of people will experience a fluctuation of Lp(a) concentration by more than 25% during the follow-up period, and the higher the baseline Lp(a) level is, the greater the absolute value changes during the follow-up period [18].

## Metabolism of Lp(a)

It has been demonstrated that the plasma Lp(a) concentration is predominantly determined by the rate of production of Lp(a) particles, independent of apo(a) isoform size and background cholesterol-lowering therapy, and Lp(a) particle catabolism only plays a modest role in determining Lp(a) concentration in subjects with larger apo(a) isoform size [19]. Apo(a), the characteristic component of Lp(a), is first synthesized in the liver and then covalently assembled into Lp(a) by combining with apoB-100 containing lipoprotein. The exact assembly site of Lp(a) is still unclear, and it may be within the hepatocyte, the space of Disse, or the plasma compartment [20, 21]. Lp(a) catabolism also occurs mainly in the liver, and there are multiple receptors on the hepatocytes involved in the endocytosis of Lp(a), including LDL-C receptor and other LDL-C receptor family members [22], scavenger receptor B1 [23], and fibrinogen receptor [24], among which the relative contributions of various receptors are still unclear. In addition, studies have shown that Lp(a) can be cleared by the kidney as apo(a) fragments can be detected in the urine when the intact human Lp(a) was injected into rats [25]. An in-vivo turnover study showed that the fractional catabolic rates of apoB-100 and apo(a) in hemodialysis patients were significantly lower than those in healthy controls, while there was no significant difference in the synthesis rate [26]. In the future, it is necessary to further elucidate the synthetic and catabolic processes of Lp(a), so as to develop targeted drugs to reduce Lp(a).

## Proatherogenic Mechanisms of Lp(a)

The presence of Lp(a) and its specific component apo(a) in human coronary atheroma confers its proatherogenic property [27, 28]. It is commonly suggested that Lp(a) participates in the pathophysiological process of ASCVD by promoting atherosclerosis, inducing inflammation and possibly facilitating thrombosis. Lp(a) destroys the vascular endothelial barrier by stimulating endothelial cells to express adhesion molecules. After being oxidized within the atherosclerotic lesion, Lp(a) is phagocyted by macrophages, which transform into foam cells and release proinflammatory cytokines. Additionally, Lp(a) stimulates the migration and proliferation of vascular smooth muscle cells [29]. Recent studies revealed that the proinflammatory effects of Lp(a) were mainly mediated by its component oxidized phospholipids (Ox-PLs), which were largely carried by Lp(a) in the plasma by covalently binding with the strong lysine-binding sites in apo(a) $KIV_{10}$ domain [30–32]. In vitro studies have shown that Ox-PLs-containing Lp(a) can induce the secretion of inflammatory cytokines by monocytes from normal subjects, and the

pro-inflammatory effect of Lp(a) is weakened when OxPLs are inhibited by using specific antibodies [33]. Since apo(a) is highly homologous to PLG in structure and can interfere with the normal function of PLG, thereby inhibiting plasmin activation and fibrinolysis, it is believed that Lp(a) can promote thrombosis, but this view remains controversial [34].

## Standardized Measurement and Appropriate Levels of Lp(a)

Due to the influence of apo(a) size polymorphism, different measurement calibration, and the lack of a universal expression unit, Lp(a) measurement lacks a globally unified method and the results between different laboratories are not comparable. The currently recommended standardized test should meet the following requirements: expressed in nmol/L, independent on the apo(a) isoform size, linking the results to the World Health Organization/International Federation of Clinical Chemistry reference material, and using a five-point calibration system [35]. Previous literature has generally used mass concentration (mg/dL) to express the plasma concentration of Lp(a): however, due to different apo(a) KIV2 repeat copy number between individuals, the results of Lp(a) mass concentration may be overvalued or undervalued and may lead to inaccurate assessment of a patient's risk for cardiovascular disease. In addition, some laboratories multiply the mass concentration (mg/dL) of Lp(a) by 2.5 to obtain the molar concentration (nmol/L) of Lp(a), which ignores the influence of apo(a) size heterogeneity, and the results may be inaccurate [36].

The appropriate level of Lp(a) in the population is still not clearly determined. Epidemiological studies suggest that Lp(a) > 20–25 mg/dL or > 50–75 nmol/L increases the risk of ASCVD for people with no previous history of ASCVD, while Lp(a) > 40–50 mg/dL increases the risk of ASCVD recurrence for people with established ASCVD. The European Atherosclerosis Society recommends Lp(a) < 50 mg/dL as a desirable level, while China, the USA, and Canada take Lp(a) < 30 mg/dL as the appropriate cutoff point [37]. The recently published scientific statements from the National Lipid Association recommend Lp(a) ≥ 50 mg/dL or ≥ 100 nmol/L as levels suggesting increased ASCVD risk in Caucasian patients [38]. It is estimated that Lp(a) > 20–25 mg/dL and > 50 mg/dL account for about 30% and 20% of the global population, respectively [39].

## Association of Lp(a) with ASCVD and Death

Large epidemiological studies, Mendelian randomized studies, and genome-wide association studies confirmed that elevated Lp(a) levels are an independent genetic risk factor for ASCVD incidence [3, 4]. In contrast, individuals with LPA null allele had very low or undetectable plasma Lp(a) levels and decreased risk for ASCVD [40]. Current studies suggest that Lp(a) elevation is a residual risk factor for ASCVD patients, even in those with LDL-C below 70 mg/dL. However, the association between increased Lp(a) levels and increased ASCVD risk in healthy individuals may be related to baseline LDL-C levels, gender, race, age, and family history. Moreover, increased Lp(a) levels are associated with an increased risk of cardiovascular and all-cause death.

Lp(a) elevation is a residual risk factor for patients with ASCVD who have received statin therapy, even in those with LDL-C below 70 mg/dL [5, 6]. A recent meta-analysis involving seven RCTs about statins and cardiovascular outcomes (including AFCAPS, CARDS, 4 d, JUPITER, LIPID, MIRACL, and 4S, a total of 29,069 patients; 14,536 patients treated with statins) found that elevated baseline and on-statin treatment lipoprotein (a) levels are independently correlated with composite cardiovascular risk (including fatal or nonfatal coronary heart disease, stroke, or any revascularization) during 3 years of follow-up. Patients with Lp(a) levels of 50 mg/dL or higher at baseline and on-statin treatment increased the risk of cardiovascular disease by 31% and 43%, respectively, relative to those with Lp(a) levels less than 15 mg/dL, after adjustment for age, sex, previous cardiovascular disease, diabetes, smoking, systolic blood pressure, LDL-C corrected for Lp(a) cholesterol, and HDL cholesterol. The association of on-statin Lp(a) with cardiovascular disease risk was stronger than for on-placebo and was more pronounced at younger ages [41]. Ruotolo et al. analyzed 12,092 ASCVD patients in the ACCELERATE trial who received statin treatment and found that increased Lp(a) levels predicted the risk of future major adverse cardiovascular events (MACE) only in the subgroup with LDL-C less than 78 mg/dL [42]. Zhao et al. analyzed 1602 patients with stable coronary artery disease (CAD) receiving optimal drug treatment in 5 hospitals in China and found that the baseline plasma Lp(a) level was positively correlated with the severity of coronary artery disease ($P < 0.001$). After a median follow-up of 39.6 months, 166 patients (10.4%) developed MACE (defined as all-cause death, nonfatal myocardial infarction, nonfatal stroke, and unplanned coronary artery revascularization). There was a significant difference in the adjusted event-free survival rate among subgroups by quartiles of Lp(a) levels, and the MACE risk ratio was 1.291 (95% confidence interval (CI) 1.091–1.527, $P = 0.003$) for each standard deviation increase in the log-transformed Lp(a) level adjusted for traditional cardiovascular risk factors [43]. Thus, plasma Lp(a) may be a strong residual cardiovascular risk when the cardiovascular risk associated with LDL-C elevation is corrected [44]. However, Schwartz et al. conducted a nested case-cohort analysis of the dal-Outcomes study and found that Lp(a) levels

were not associated with recurrent ischemic events (coronary death, nonfatal coronary events, and fatal or nonfatal stroke) in patients with acute coronary syndrome (ACS) treated with statins [45].

The positive association between Lp(a) and ASCVD risk in healthy populations may be related to baseline LDL-C levels and gender. By analyzing data in 3 cohorts of women from the Women's Health Study ($N = 24,558$), Women's Health Initiative Observational Study ($n = 1815$ cases, subcohort $n = 1989$), and the JUPITER (Justification for Use of Statins in Prevention) trial ($n = 2569$), and in men from JUPITER ($n = 5161$). Cook et al. found that Lp(a) > 50 mg/dL was associated with an increased risk of CVD only among women with total cholesterol level > 220 mg/dL in a primary prevention setting. Among men, in the JUPITER trial, however, increased Lp(a) levels were associated with increased CVD risk even if the total cholesterol level is low [46]. Similarly, Verbeek et al. performed parallel statistical analyses of two large prospective population studies (the EPIC-Norfolk prospective population study ($n = 16,654$) and the Copenhagen City Heart Study ($n = 9448$)) and observed that a corrected baseline LDL-C level (corrected LDL-C had cholesterol content of Lp(a) subtracted) < 2.5 mmol/L and elevated Lp(a) (> 80th percentile) were not associated with an increased ASCVD risk [47].

Whether there is a racial difference in the correlation between Lp(a) and increased ASCVD risk remains controversial. Loh et al. demonstrated that after adjustment for age, smoking, and familial hypercholesterolemia (FH), Lp(a) was only associated with coronary calcification score in an asymptomatic Caucasian population, but not in Asia or other ethnicities [48]. Steffen et al. also found that the association between Lp(a) and risk of carotid atherosclerosis may vary by race. Elevated Lp(a) level may have a greater impact on plaque load in white people than in black people; white people with Lp(a) > 50 mg/dL had a greater risk of plaque progression and a higher plaque score compared with black people during 9.4 years of follow-up [49]. Conversely, some studies analyzed black, white, and Hispanic populations and revealed that the positive correlation between Lp(a) and MACE risk was not related to race, LPA single-nucleotide polymorphism, and apo(a) isoform [50, 51]. Recently, Pare et al. analyzed the correlation between Lp(a) and myocardial infarction (MI) in seven different ethnic groups and reached the same conclusion. The study included 6086 patients with first myocardial infarction and 6857 controls that were stratified by race and adjusted for age and sex. A total of 775 Africans, 4443 Chinese, 1352 Arabs, 1856 Europeans, 1469 Latin Americans, 1829 South Asians, and 1221 Southeast Asians were included. Overall, Lp(a) > 50 mg/dL was associated with an increased risk of MI (OR = 1.48, 95% CI 1.32–1.67, $P < 0.001$), and the correlation was independent of known MI risk factors including diabetes, smoking, hypertension, ApoB, and ApoA1 ratio. The study also found that the correlation between increased Lp(a) concentration and increased MI risk was particularly significant in South Asian and Latin American populations [52].

Additionally, the correlation between Lp(a) and increased ASCVD risk may be related to age and family history. A case-control study showed that elevated Lp(a) levels (> 50 mg/dL) increased ACS risk nearly three times and 2 times in younger (< 45 years) and middle-aged adults (45 to 60 years), respectively, but not in older individuals (> 60 years) [53]. Anurag et al. analyzed 2756 subjects in the Dallas Heart Study who were free of CVD at baseline. After a median follow-up of 10 years, 251 individuals developed MACE (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary artery/carotid artery/peripheral artery revascularization), among which 47% have a family history of myocardial infarction. After adjustment for the pooled cohort equation risk factors and statin use, elevated Lp(a) levels were associated with MACE only in subjects with a family history of myocardial infarction, but not in those without a family history of myocardial infarction [54].

Lp(a) is associated with an increased risk of death. To date, most studies have demonstrated that increased Lp(a) is associated with an increased risk of cardiovascular death or all-cause death [55]. Langsted et al. analyzed individual data from two large prospective studies of the Denmark general population and showed that participants with Lp(a) > 93 mg/dL were associated with a hazard ratio of 1.50 (95% CI 1.28–1.76) for cardiovascular death and 1.20 (1.10–1.30) for all-cause death, respectively, when compared with those with Lp(a) < 10 mg/dL. The median survival of subjects with Lp(a) > 93 mg/dL and < 93 mg/ dL was 83.9 years and 85.1 years, respectively (logarithmic rank $P = 0.005$). A 50-mg/dL (105 nmol/L) increase in Lp(a) levels was associated with an increased risk of cardiovascular death and all-cause death by 16% and 5%, respectively. For a similar increase in cholesterol content, Lp(a) is more strongly associated with cardiovascular and all-cause mortality than LDL-C, suggesting that the mortality effect of high Lp(a) is more than can be explained by its cholesterol content [56]. However, there exists an inconsistent argument on whether Lp(a) elevation is associated with cardiovascular and all-cause mortality in patients who have established cardiovascular disease. Zhou et al. showed that, for patients receiving coronary angiography or interventional therapy, Lp(a) ≥ 16 mg/dL was associated with a significantly higher mortality compared with Lp(a) < 16 mg/dL (5.8% vs 2.5%, $P < 0.05$) during a median follow-up of 1.95 years. After adjustment for relevant confounding factors, Lp(a) ≥ 16 mg/dL can independently predict the long-term risk of death (HR = 1.96, 95% CI 1.07–3.59, $P = 0.029$) [57]. However, studies carried out by Zewinger et al. showed that Lp(a) and LPA rs10455872 and rs3798220 were not associated with cardiovascular and all-cause mortality in patients who

already had coronary heart disease [58]. In addition, studies have also shown that increased Lp(a) is associated with an increased risk of death only in patients with diabetes mellitus [59, 60].

## Predictive Value of Lp(a)

A 15-year prospective follow-up of 826 participants in the general community showed that for individuals with intermediate CVD risk based on the Framingham risk score and Reynolds risk score, if Lp(a) level is included as an additional risk factor, nearly 40% of individuals need to be reclassified [61]. Similarly, Kamstrup et al. followed 8720 participants in the Danish general population and found that Lp(a) ≥ 80th percentile (47 mg/dL) could improve the risk prediction ability of MI and coronary heart disease by 23% and 12%, respectively, on the basis of traditional risk factors [62]. Verbeek et al. analyzed 16,777 EPIC Norfolk study subjects and found that addition of Lp(a) to the ACC/AHA and SCORE risk algorithms could improve CVD risk prediction, but this effect was only found in patients with intermediate risk [63]. Recent studies by Cook et al. have confirmed that Lp(a) cannot further improve CVD risk prediction beyond conventional risk factors in lower-risk women in primary prevention [46].

## Lp(a) Lowering Therapies

Although a large number of studies have documented a causal association between Lp(a) and increased ASCVD risk, there still lacks large RCT data demonstrating the cardiovascular benefits of lowering Lp(a). Emdin et al. used genetic methods to estimate the potential clinical benefits of Lp(a) reduction. For every standard deviation reduction (approximately 28 mg/dL) in Lp(a), the risk of coronary heart disease, peripheral vascular disease, stroke, heart failure, and aortic stenosis was reduced by 29%, 31%, 13%, 17%, and 37%, respectively [64]. Afshar et al. used data from a large prospective European cohort to estimate the population impact of Lp(a) lowering and found that treating individuals with an Lp(a) ≥ 50 mg/dL to < 50 mg/dL could prevent 13 cases of MI and 7 cases of aortic stenosis per 1000 individuals, respectively [65]. Thus, lowering Lp(a) may have a significant contribution to reducing the burden of cardiovascular disease. A Mendelian randomized analysis showed that lowering Lp(a) by 100 mg/dL is required to reduce the risk of CVD similar to that achieved by lowering LDL-C level by 38.67 mg/dL (i.e., 1 mmol/L), and the clinical benefits of Lp(a) reduction seem to be independent of the change of LDL-C [66]. However, another Mendelian randomized analysis by Lamina C et al. estimated that the required reduction in Lp(a) effect would be 65.7 mg/dL to reach the same potential effect on clinical outcomes as a 38.67 mg/dL lowering of LDL-C [67].

Since plasma Lp(a) levels are largely determined by genetic factors and are not significantly reduced by existing lifestyle interventions such as diet and exercise, lowering Lp(a) levels can only be achieved by drug therapy. The first-line LDL-C-lowering drug statins have been shown to slightly elevate Lp(a) [68]. The other drugs approved to lower LDL-C such as PCSK9 inhibitors and apoB-100 antisense oligonucleotides (ASO) have been proved to decrease Lp(a) levels as well, but the reduction is only 20–30%, which may translate into limited clinical benefits. At present, lipoprotein apheresis is the only method that has been demonstrated by observational studies and RCT to effectively reduce Lp(a) levels and cardiovascular events and has been recommended by German and British guidelines, but this therapy is invasive and expensive, which may limit its application in clinics. Fortunately, the apo(a) ASO IONIS-Apo(a)-$L_{RX}$ has been recently proved to significantly reduce the level of Lp(a) in phase 2 clinical trials with good tolerance, which may become a promising drug for the management of elevated Lp(a) in the future.

### PCSK9 Inhibitors

It is traditionally believed that PCSK9 inhibitors mainly reduce Lp(a) levels by enhanced LDL receptor-mediated Lp(a) clearance. Recent studies have revealed that PCSK9 inhibitors may reduce Lp(a) by a dual mechanism. When PCSK9 inhibitors are used alone, Lp(a) lowering mainly associates with inhibition of Lp(a) synthesis. However, when PCSK9 inhibitors are added to statins, Lp(a) lowering is mainly driven by accelerated Lp(a) catabolism mediated by enhanced LDL receptor activity [69]. Clinical trials have shown that PCSK9 inhibitors can reduce LDL-C by 50~60% and Lp(a) by 25~30% [70–72], a ratio of about 2 to 1. However, LDL-C and Lp(a) do not always concordantly respond to PCSK9 inhibitors, especially in patients with higher baseline Lp(a) whose Lp(a) decrease by as much as 60% [73, 74]. A post hoc analysis of the FOURIER trial showed that increased Lp(a) levels of ASCVD patients were associated with cardiovascular death, MI, and emergency revascularization independently of LDL-C levels, and evolocumab was able to reduce Lp(a) levels by 26.9%, with patients with higher baseline Lp(a) levels more likely to benefit from the PCSK9 inhibitor [75]. The ODYSSEY OUTCOMES trial also documented that the PCSK9 inhibitor alirocumab reduced both Lp(a) levels and cardiovascular events. After adjusting for LDL-C levels, patients with higher baseline Lp(a) had a significantly larger reduction of Lp(a) levels and MACE events [76]. In spite of this, it is not clear whether the decrease in cardiovascular events with PCSK9 inhibitors is due to the decrease in Lp(a) or to the further decrease in LDL-C on the basis of statin therapy [77]. Conversely, a multicenter RCT study enrolled

129 patients with median Lp(a) 200.0 (interquartile range 155.5–301.5) nmol/L, mean LDL-C 3.7 (standard deviation 1.0) mmol/L, and National Cholesterol Education Program high risk, and randomized them to monthly subcutaneous evolocumab 420 mg or placebo. Compared with placebo, evolocumab reduced LDL-C by 60.7% and Lp(a) by 13.9%, respectively. However, the artery wall inflammation assessed by 18F-fluorodeoxyglucose positron-emission tomography/computed tomography was not significantly altered with evolocumab vs. placebo [78]. In summary, future studies are needed to further elucidate the mechanisms of PCSK9 inhibitors in lowering Lp(a), the extent of Lp(a) reduction, and whether it can be translated into clinical benefits.

## Lipoprotein Apheresis

Currently, lipid-lowering drugs commonly used in clinical practice have no significant lowering effect on Lp(a). LA is recommended clinically for patients with elevated Lp(a) and progressive ASCVD despite receiving optimal therapy. A longitudinal multicenter cohort study allocated 120 patients with Lp(a) ≥ 60 mg/dL and progressive coronary heart disease who had received the maximum tolerable dose of statins to receive lipoprotein apheresis and statins in combination. The results showed that LA reduced the median Lp(a) level from 112 to 30 mg/dL ($P < 0.0001$) by 73% and the corresponding annual MACE incidence from 1.056 to 0.144 per patient [79]. In another prospective observational multicenter study investigating the effects of LA in 170 cases of patients with high Lp (a) concentration and progressive CAD, the incidence of MACE events for 2 years during LA was less than a quarter of that for 2 years prior to LA, with a number needed to treat of 3 to prevent one MACE per person per year [80]. Long-term follow-up of 5 years confirmed that LA has a lasting effect on the prevention of cardiovascular events in patients with elevated Lp(a) and progressive coronary heart disease [81]. In 2017, the first prospective, randomized, sham-controlled, single-blind, and cross-design study evaluated the effect of LA on patients with CAD complicated with hyperlipoprotein(a)emia. Twenty patients with refractory angina complicated with Lp(a) > 50 mg/dL and LDL-C < 4 mmol/L were included in the study and randomly assigned to receive weekly LA or sham operation intervention for 3 months. The results showed that plasma Lp(a), LDL-C, HDL cholesterol, triglyceride, and apoB-100 levels in the LA group were significantly lower than those in the sham group, and the myocardial perfusion reserve, carotid atheroma burden, 6-min walking test, angina symptoms, and quality of life were significantly improved [82]. However, given that LA simultaneously improved other components of the lipid profile, especially LDL-C, the clinical benefits of cardiovascular events reduction could not be attributed specifically to the decrease of Lp(a). It is worth mentioning that a Russian small clinical study has investigated the specific effects of Lp(a) apheresis on coronary atherosclerosis regression in stable CAD with elevated Lp(a) levels and showed that specific Lp(a) apheresis for 18 months can lower Lp(a) by 73% and improve coronary stenosis percentage and minimal lumen diameter [83]. In view of this, German and British guidelines recommend Lp(a) ≥ 60 mg/dL as the cutoff point for LA to prevent CVD recurrence [2]. However, the invasive, costly, and time-consuming nature of LA has limited its clinical application.

## IONIS-APO(a)$_{RX}$ and IONIS-APO(a)-L$_{RX}$

None of the above drugs or methods to reduce Lp(a) is specific to Lp(a), and the reduction is limited [84, 85]. Considering the apo(a) is the characteristic component of the Lp(a) particle, drugs that directly target apo(a) can better indicate whether Lp(a) lowering can bring cardiovascular benefits (i.e., lipoprotein(a) hypothesis). The apo(a) ASO is the first drug to lower Lp(a) specifically. Mechanistically, apo(a) ASO is absorbed into the bloodstream after subcutaneous injection and taken up by hepatocytes, directly binding to apo(a) mRNA in the nucleus, which then leads to destruction of the antisense:mRNA complex by RNase H1 and the specific inhibition of apo(a) synthesis, ultimately reducing plasma Lp(a) levels [86]. IONIS-APO(a)$_{RX}$ (formerly known as ISIS-APO(a)$_{RX}$) is a second-generation ASO drug. Phase 1 clinical trial evaluated IONIS-APO(a)$_{RX}$ in 47 healthy adults aged 18 to 65 years with plasma Lp(a) concentration ≥ 25 nmol/L (10 mg/dL) and body mass index < 32 kg/m(2). Among them, 37 patients were randomized to receive a single dose of IONIS-APO(a)$_{RX}$ (50 mg, 100 mg, 200 mg, or 400 mg) or six doses of IONIS-APO(a)$_{RX}$ (100 mg, 200 mg, or 300 mg, for a total dose exposure of 600 mg, 1200 mg, or 1800 mg), and 10 patients received placebo. The results showed that although single doses of ISIS-APO(a)$_{RX}$ (50~400 mg) did not decrease Lp(a) concentrations at day 30, six doses of ISIS-APO(a)$_{RX}$ (100~300 mg) decreased Lp(a) concentration by 39.6%, 59.0%, and 77.8% in the 100-mg, 200-mg, and 300-mg group, respectively. Additionally, the plasma concentrations of OxPL-apoB-100 and OxPL-apo(a) were also decreased significantly, with good dose tolerance in each group [87]. As a ligand-conjugated variant of IONIS-APO(a)$_{RX}$, the N-acetylgalactosamine complex (GalNAc 3) modified molecule IONIS-APO(a)-L$_{RX}$ (AKCER-APO(a)-L$_{RX}$) was developed for fast and specific uptake by hepatocytes, which increased the potency more than 30 times. A phase 1 clinical trial assessing the efficacy and safety of IONIS-APO(a)-L$_{RX}$ for healthy volunteers with Lp(a) ≥ 75 nmol/L showed that multiple doses of 10 mg, 20 mg, or 40 mg IONIS-APO(a)-L$_{RX}$, subcutaneously injected six times during a 3-week period, can decrease the plasma concentration of Lp(a) by 66%, 80%, and 92%, respectively ($P < 0.05$), along with good tolerability [88]. Recently, a phase 2b RCT trial presented at the AHA Scientific Sessions evaluated the efficacy and safety of

IONIS-APO(a)-$L_{RX}$ in 286 patients with established CVD and raised Lp(a) levels (≥ 60 mg/dL). Patients were randomly assigned to receive IONIS-APO(a)-$L_{RX}$ 20 mg every 4 weeks, 40 mg every 4 weeks, 20 mg every 2 weeks, 60 mg every 4 weeks, or 20 mg every week for 6–12 months. The primary efficacy endpoint was the percentage change from baseline at 6 months; the secondary endpoints included the average percentage change of LDL-C, apoB-100, OxPL-apoB-100, and OxPL-apo(a) from baseline at 6 months; and the percentage of patients with Lp(a) achieving a predetermined goal (< 50 mg/dL). The results showed that IONIS-APO(a)-$L_{RX}$ 20 mg every 4 weeks, 40 mg every 4 weeks, 20 mg every 2 weeks, 60 mg every 4 weeks, and 20 mg every week decreased Lp(a) from baseline by 35%, 56%, 58%, 72%, and 80%, respectively. The proportion of patients with Lp(a) reaching the target was 25%, 62.5%, 64.6%, 80.9%, and 97.7%, respectively. There were no serious adverse events in all groups. Future studies assessing whether IONIS-APO(a)-$L_{RX}$ can reduce cardiovascular disease risk in individuals with elevated Lp(a) are warranted [89].

## Closing Remarks and Future Perspectives

Due to the lack of ideal animal models, the current understanding of Lp(a) still has many unanswered questions [90]. In early 2018, the National Heart, Lung, and Blood Institute (NHLBI) organized a working group to fully elucidate the role of Lp(a) in cardiovascular disease, including Lp(a) metabolism, pathophysiology, standardized measurement, current and emerging Lp(a) lowering therapy, identification of Lp(a)-associated ASCVD risk, and enhancement of public awareness of the atherogenic role of Lp(a) [37]. In addition, the US Centers for Disease Control and Prevention recently approved two ICD-10 diagnostic codes for Lp(a)—namely, "elevated lipoprotein(a)" (E78.41) and "family history of elevated lipoprotein(a)" (Z83.430)—for use in diagnosis, documentation, and electronic medical records [29]. Although the current "Lp(a) hypothesis" that lowering Lp(a) can reduce cardiovascular events has not been confirmed by clinical trials, clinicians should still improve their awareness of the pathological role of high Lp(a) in ASCVD development and actively screen plasma Lp(a) levels in appropriate populations [91].

Currently, most of the guidelines recommend screening for Lp(a) only in high-risk individuals. The 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias recommend Lp(a) measurement in patients with early onset of cardiovascular disease, FH, a family history of premature atherothrombotic disease or elevated Lp(a), recurrent CVD despite optimal lipid-lowering treatment, and ≥ 5% 10-year risk of fatal CVD according to SCORE, and Lp(a) ≥ 50 mg/dL as a significant CVD risk factor, which should be considered in risk evaluation in patients at intermediate to high cardiovascular risk [92]. The Canadian guidelines make similar recommendations, but define Lp(a) > 30 mg/dL as hyperlipoprotein(a)emia [93]. The 2018 AHA/ACC cholesterol management guidelines recommend Lp(a) measurement in patients with a family history of premature ASCVD or personal history of ASCVD not explained by major risk factors, and Lp(a) ≥ 50 mg/dL as a risk-enhancing factor which may favor statin therapy in patients at borderline risk. The guidelines also emphasize that, in women, Lp(a) is associated with CVD only among those with hypercholesterolemia, and improvement in prediction was minimal [94]. Recent studies by Ellis et al. have shown that measuring Lp(a) during cascade screening for FH may help to better identify relatives with a heightened risk of ASCVD [95]. Chan et al. demonstrated that Lp(a) measurement improved the diagnostic accuracy of FH in patients with Lp(a) > 100 mg/dL and LDL-C < 6.5 mmol/L, and suggested Lp(a) should be measured in all patients suspected of having FH [96]. In addition to the above recommendations, the scientific statements from 2019 National Lipid Association also recommend adults at very high risk of ASCVD to measure Lp(a) to better define those who are more likely to benefit from PCSK9 inhibitor therapy [38].

For high Lp(a) levels, existing lifestyle interventions did not significantly alter Lp(a) levels, but did reduce the Lp(a) associated ASCVD risk [97]. In light of present evidence, the primary target of ASCVD management should still be LDL-C goal achievement. For very high-risk patients on statins with Lp(a) ≥ 50 mg/dL or ≥ 100 nmol/L, more aggressive LDL-C-lowering therapy by adding ezetimibe or PCSK9 inhibitor is considered reasonable to achieve greater ASCVD risk reduction [38]. It is worth noting that the clinically measured LDL-C value is about 30–45% derived from the LDL-C contained in the Lp(a) particle [98]. Considering that the existing LDL-C-lowering drugs such as statins, ezetimibe, and PCSK9 inhibitors have limited effects in reducing Lp(a), the LDL-C in Lp(a) may account for a larger proportion of the total detected LDL-C levels for those who use the above drugs treatment and achieved an LDL-C goal < 70 mg/dL, thus contributing significantly to the residual risk of ASCVD. In addition, genetic evidence showed that reductions in Lp(a) of approximately 65.7 mg/dL or 100 mg/dL may be required to produce a clinically meaningful reduction in the risk of ASCVD similar in magnitude to what can be achieved by lowering LDL-C level by 1mmol/L. IONIS-APO etc IONIS-APO(a)-$L_{RX}$ has been proved in preliminary clinical trials to specifically and extensively reduce Lp(a) and is well tolerated. Therefore, IONIS-APO(a)-$L_{RX}$ is expected to be a promising drug for ASCVD residual risk management in the current "intensive LDL-C-lowering therapy" era [99].

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

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