An Overview on Lipoprotein (a)

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Abstract:

High lipoprotein(a) concentrations present in 10%–20% of the population have long been linked to increased risk of ischemic cardiovascular disease. It is unclear whether high concentrations represent an unmet medical need. Lipoprotein(a) is currently not a target for treatment to prevent cardiovascular disease.

Keywords: Lipoprotein (a), cardiovascular disease, coronary artery disease.

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Introduction:

1. Introduction to Lipoprotein (a):

1.1. Definition and Structure of Lipoprotein (a).

Lipoprotein(a) is a low-density lipoprotein–like molecule with an apolipoprotein (b) moiety that is covalently attached to apolipoprotein (a) (Apo(a)), a plasminogen-like protein that confers several pathologic features to Lp(a). Produced mainly in the liver, Lp(a) has a wide spectrum of characteristics, including atherogenicity, thrombogenicity, and proinflammatory properties **(1)**.

Human Lp(a) was first described in 1963 by the Norwegian physician Kåre Berg. Ever since its discovery, this enigmatic particle has intrigued basic researchers and clinicians due to its unknown physiological function and its association with atherosclerotic diseases, in particular CHD. Lp(a) is composed of one molecule of an LDL-particle containing apoB-100 and one molecule of a large highly polymorphic glycoprotein named apo(a) **(2)**.

ApoB and apo(a) are present in Lp(a) in a molar ratio of 1:1, and apo(a) can be separated from the LDL-like moiety only by reductive cleavage. Heterozygotes for two differently sized apo(a) isoforms have two distinct particles in plasma. The LDL moiety of Lp(a) is spherical and similar in lipid composition to LDL. The assembly of the Lp(a) particle occurs in two steps. The first is noncovalent docking of the KIV-5 to KIV-8 domains to the N terminus of apoB-100. In the second step, the covalent binding of apo(a) to apoB occurs through the formation of a disulfide bond between the only unpaired cysteine in apo(a) in KIV-9 with Cys4326 in apoB Figure 1 **(3)**.

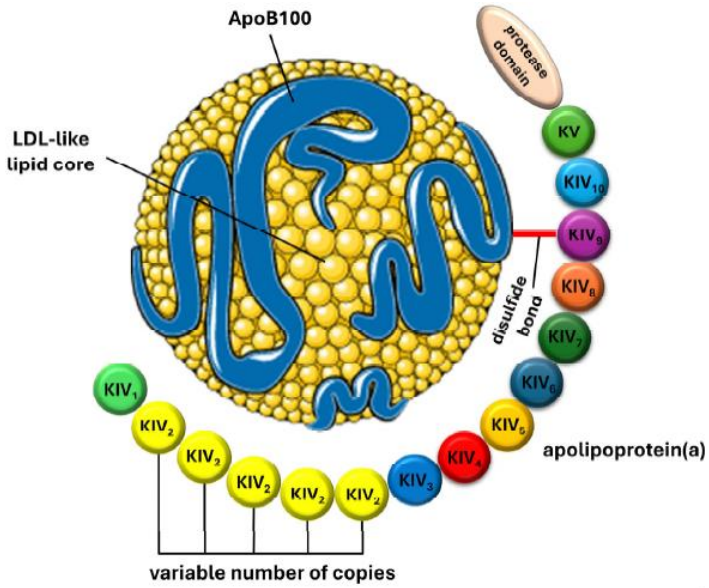

Figure 1: Structure of lipoprotein (4).

Images from atomic force microscopy suggest that apo(a) is attached to LDL at two sites with its N- and C-terminal domains. This proposed structure is, however, difficult to reconcile with the well-established assembly process. Small angle X-ray scattering suggests that apo(a) is placed above the surface and wrapped around the LDL moiety. It underwent a conformational change from a compact to an extended form upon binding to a lysine analog. A study using hydrodynamic techniques and electron microscopy concluded, however, that the bulk of apo(a) is extended away from the lipoprotein surface. This model is attractive because it allows for ready interactions of the floating N-terminal "tail" of apo(a) with potential ligands **(5)**.

2. Pathophysiology of Lipoprotein (a):

2.1. Mechanisms of Action in Atherosclerosis

Atherosclerosis is a multifactorial disease, high serum cholesterol concentrations carried by low density lipoproteins (LDL), high blood pressure and cigarette smoking have been established as major risk factors for coronary heart disease. A number of epidemiological and clinical studies have now established that high plasma concentrations of the lipoprotein Lp(a), an LDL-like particle, is also a major and independent risk factor for myocardial infarction. Lp(a) is a complex particle in which the lipid core and apo B-100 of Lp(a) are shared with LDL; in contrast, the apo(a) glycoprotein confers its characteristic properties on Lp(a) **(6)**.

Apo(a) shows a high degree of homology with plasminogen, the precursor of the fibrinolytic enzyme plasmin. The mechanism by which Lp(a) may favor atherosclerosis is still a matter of debate but the fact that Lp(a) has both LDL and plasminogen-like moieties suggests that Lp(a) may constitute a link between the processes of atherosclerosis and thrombosis. Indeed, Lp(a) and fibrin have been identified in atherosclerotic plaques; moreover, in transgenic mice expressing human apo(a), apo(a) co-localizes with lipid deposition on the arterial wall **(7)**.

In order to understand the basis of this connection, the plasminogen activation system should be explained and consider recent evidence indicating that Lp(a) is a major risk factor for coronary

heart disease. Modification of protein synthesis. Lp(a) may stimulate the expression of PAI-1 and inhibit the synthesis of t-PA by endothelial cells in culture. Thus, inhibition of t- PA by PAI-1 and low t-PA antigen levels may enhance Lp(a)-dependent hypo fibrinolysis by decreasing the amount of t-PA available for the activation of plasminogen **(8).**

Binding of Lp(a) to extracellular matrix components. Recent reports suggest that Lp(a) and recombinant apo(a) display high affinity for fibronectin and that Lp(a) may form complexes with proteoglycans or glycosaminoglycans of the extracellular matrix. These interactions are not related to the lysine-binding function of kringle 4 and may contribute to the accumulation of Lp(a) in the vascular wall. Oxidation of Lp(a). The Lp(a) and LDL particles are sensitive to oxidative processes. Phagocytosis of oxidized Lp(a) and LDL particles results in the formation of foam cells. Antioxidants such as probucol and vitamins C, E and ß-carotenes may prevent such reactions. Figure represents an overall view of these different mechanisms **(9).**

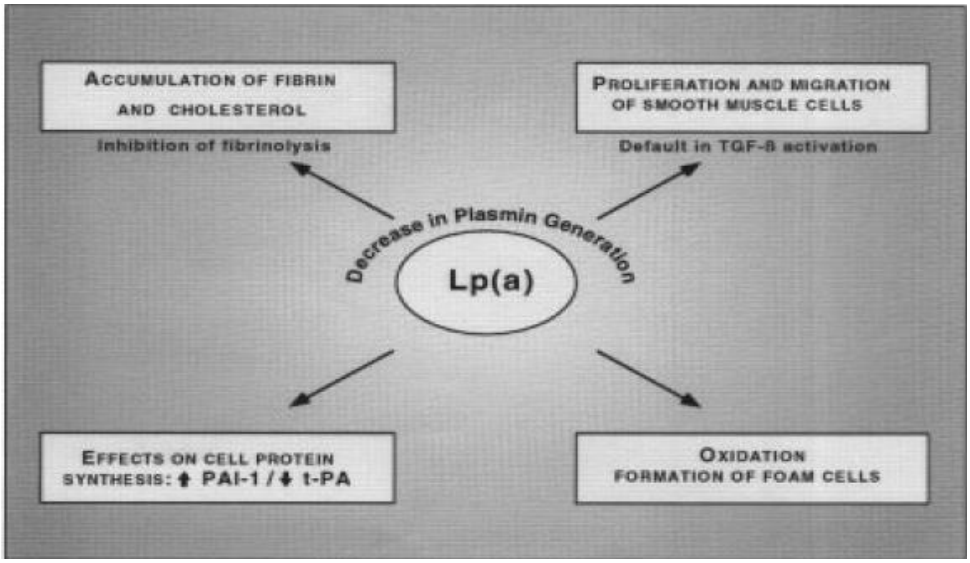

Figure 2: General scheme representing different modes of action of Lp(a) in the vascular wall (9).

Oxidized Phospholipids in LP(a) Atherogenicity:

Oxidized phospholipids (OxPLs) play a significant role in the pathogenesis of cardiovascular disease, particularly in the development and progression of atherosclerosis. OxPLs are bioactive molecules that accumulate in atherosclerotic lesions and exert various effects on vascular cells, including endothelial cells, macrophages, smooth muscle cells, and dendritic cells. These molecules promote inflammation, oxidative stress, and thrombogenesis, all of which contribute to the destabilization of atherosclerotic plaques. In endothelial cells, OxPLs regulate the expression of genes involved in atherogenesis, coagulation, and cholesterol synthesis. Some OxPLs, such as PEIPC (1-palmitoyl-2-(5,6-epoxyisoprostane E2)-sn-glycero-3-phosphoryl choline), have been shown to be potent inducers of pro-inflammatory pathways, further contributing to plaque development **(10).**

Additionally, OxPLs are known to enhance the formation of foam cells by interacting with receptors like CD36 on macrophages. Foam cell formation is a hallmark of early atherosclerotic lesions and plays a crucial role in plaque progression. OxPLs also contribute to the recruitment of

monocytes and macrophages to the vessel wall, leading to a chronic inflammatory state. This inflammatory environment facilitates the accumulation of lipids and the proliferation of smooth muscle cells, further aggravating the atherosclerotic process. Moreover, OxPLs are associated with increased platelet activation and aggregation, which enhances the risk of thrombus formation and acute cardiovascular events such as myocardial infarction **(11).**

In clinical settings, elevated levels of OxPLs, particularly when bound to lipoproteins like Lp(a), have been identified as independent risk factors for coronary artery disease, stroke, and peripheral artery disease. OxPLs on apolipoprotein B-100 particles (OxPL/apoB) have been shown to predict cardiovascular events and are considered a biomarker of atherosclerotic plaque vulnerability. Overall, the role of OxPLs in promoting atherosclerosis and their contribution to cardiovascular events highlights their importance as both therapeutic targets and prognostic biomarkers in cardiovascular disease **(11).**

3. Epidemiology of Lipoprotein (a) Levels:

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) **(12).**

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. 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 **(13).**

In the Genetic Variants Associated study, gene chip detection technology is used to investigate the relationship between genetic variation and the risk of CAD. 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 CAD. 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 CAD **(14).**

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 artery disease, which is represented by the RR for CAD 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 CAD, and this correlation seems to be only related to vascular outcomes **(15).**

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. 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. After adjusting for race/ethnicity and other CAD risk factors, the plasma Lp(a) levels in the Black and White

populations are significantly correlated with the incidence of CAD. However, there is no significant correlation among Chinese Americans and Hispanics **(16)**.

In addition, a higher Lp(a) level (≥50 mg/dL) was associated with higher risks of coronary artery 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. After adjusting for age, gender, apo(B) 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 CAD, and associated with poorer prognosis. However, it was 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 **(17)**.

4. Lipoprotein (a) as a Cardiovascular Risk Factor:

4.1. Association with Atherosclerotic Cardiovascular Disease (ASCVD)

Genetic, experimental, and observational data consistently identify Lp(a) as an independent risk factor for ASCVD, aortic valve stenosis (AVS), and cardiovascular mortality in both men and women, spanning various ethnic groups. This correlation is particularly pronounced for myocardial infarction, stroke, atherosclerotic stenosis, and AVS. In a study conducted on individuals with MI/CAD and controls, researchers observed a significant association between elevated levels of Lp(a) and the risk of CAD. Specifically, individuals in the top tertile (highest third) of Lp(a) levels had a substantially increased risk of CAD compared to those in the lower tertiles **(18)**.

Elevated levels of Lp(a) have also been associated with recurrent cardiovascular events, particularly when LDL-C levels are high. However, the nature of this correlation may change in subjects with extremely low LDL-C concentrations. Furthermore, serum Lp(a) seems to remain elevated six months after an acute MI, and high levels are associated with a more severe clinical expression of CAD. Regarding cerebrovascular disease, a large-scale Danish study showed that elevated Lp(a) concentrations are associated with a higher incidence of ischemic stroke. Interestingly, a large systematic review showed an approximately two-fold increase in the relative risk for ischemic stroke related to high Lp(a) concentrations **(19)**.

Moreover, meta-analysis data suggest that high Lp(a) levels are associated with increased odds of cognitive impairment and disability related to stroke. However, the impact of Lp(a) levels on PAD is less clear, with conflicting findings in the literature. While some studies report a direct association between Lp(a) concentrations and PAD, others have found conflicting results. Recent research suggests that high Lp(a) levels may be a significant predisposing factor for PAD, particularly in female subjects. Lp(a) has been identified as an independent predictor of carotid artery stenosis and occlusion. Notably, carotid intima-media thickness (CIMT) serves as an

ultrasound index for assessing CVD risk in both primary and secondary prevention, particularly among individuals with subclinical and asymptomatic CVD **(20)**.

Elevated CIMT values have been identified as predictors of future CVD events and cardiovascular mortality, as well as markers of response to hypolipidemic therapy. The American Society of Echocardiography (ASE) suggests that a CIMT value exceeding the 75th percentile should be considered pathological. However, the 2021 ESC Guidelines on CVD prevention in clinical practice have discouraged the use of CIMT for assessing CVD burden due to concerns regarding methodological standardization. Moreover, the relationship between Lp(a) levels and CIMT and carotid plaque formation remains contentious in the literature, albeit recent studies have attempted to address this issue **(21)**.

A large population cross-sectional study involving 411,634 healthy Chinese individuals reported that Lp(a) concentrations ≥50 mg/dL were associated with a higher prevalence of carotid atherosclerosis, as determined using CIMT measurements and an assessment of carotid plaques. Mendelian randomization studies have further supported the association between genetic variants related to increased Lp(a) levels and the prevalence and incidence of cardiovascular events. Conversely, variants associated with decreased Lp(a) concentrations have shown a protective effect against ASCVD. While much of the research initially focused on white populations, data from studies such as the UK Biobank, ARIC, INTERHEART, and MESA have confirmed that the association between Lp(a) levels and ASCVD risk extends across different ethnicities. Furthermore, epidemiological studies have demonstrated a continuous and linear correlation between serum Lp(a) levels and ASCVD risk, unaffected by a threshold effect **(22)**.

Individuals with very high serum Lp(a) levels (>180mg/dL or >430 nmol/L) are considered to have an equivalent lifetime ASCVD risk to those with untreated heterozygous familial hypercholesterolemia (HeFH). Notably, Lp(a) is recognized as an independent cardiovascular risk factor irrespective of LDL-C levels. This was highlighted in studies, where residual ASCVD risk attributed to Lp(a) remained significant even in patients with low LDL-C levels, indicating that Lp(a)-related risk is distinct from that associated with LDL-C. Recent studies have highlighted a significant additional association between high-sensitivity C-reactive protein (hs-CRP) and Lp(a) levels as joint predictors of major adverse cardiovascular events (MACEs) **(23)**.

4.2. Impact On Other Cardiovascular Conditions:

4.2.1. The Role of Lp(a) in Calcific Aortic Vascular Disease (CAVD)

Calcific aortic valvular disease (CAVD), which encompasses both aortic valvular sclerosis and stenosis, represents the most prevalent heart valve disorder in developed countries. Despite its high prevalence, there is currently no available medical treatment for CAVD. However, recent research has shed light on the role of serum Lp(a) as an independent causal risk factor in the development of CAVD, highlighting its significance in the pathogenesis and progression of this common heart valve disorder **(24)**.

Studies have ident

ified Lp(a) as a key contributor to the pathogenesis of CAVD through a ‘’three hit” mechanism involving lipid deposition, inflammation, and the transport of autotoxin, an important enzyme

used for generating the lipid-signaling molecule lysophosphatidic acid. These processes ultimately lead to the transition of valve interstitial cells into osteoblast-like cells and subsequent parenchymal calcification, a hallmark of CAVD progression **(25)**.

4.2.2. The Role of Lp(a) in Thrombosis

In vitro studies have demonstrated that Lp(a) can interfere with various stages of hemostasis, resulting in the inhibition of fibrinolysis. However, as of now, this apparent prothrombotic effect of Lp(a) has not been conclusively demonstrated in vivo. Lp(a) may exert its effect on fibrinolysis due to the structural homology between the KIV domain of apo(a) and the fibrin-binding domain of plasminogen (PLG). This structural similarity suggests that there may be competition between apo(a) and PLG for fibrin affinity sites. Moreover, research has shown that Lp(a) can attenuate the tissue plasminogen activator (tPA)-induced conversion of plasminogen to plasmin in the presence of fibrin **(26)**.

This inhibition occurs through the upregulation of plasminogen activator inhibitor-1 (PAI-1), a key inhibitor of fibrinolysis. Several studies have provided evidence that Lp(a) plays a role in platelet activation and aggregation, particularly in response to certain agonists. While Lp(a) appears to play a role in arterial thrombosis and atherosclerosis-related events, its association with non-atherosclerotic thrombotic disorders such as venous thromboembolism (VTE) is less pronounced, suggesting distinct pathophysiological mechanisms underlying these conditions. Thus, despite its role in atherosclerosis and arterial thrombosis, Lp(a) does not appear to be a risk factor for some non-atherosclerotic thrombotic disorders such as VTE, deep vein thrombosis, and pulmonary embolism **(27)**.

4.2.3. The Role of Lp(a) beyond Atherosclerosis

The exact physiological role of Lp(a) in humans remains a topic of ongoing research and debate. Its potential involvement in wound healing is intriguing, given its ability to transport essential molecules and its accumulation at sites of endothelial barrier disruption. Through its interactions with various components of the vessel wall and subendothelial matrix, Lp(a) can stimulate the activation of immune cells like monocytes/ macrophages, trigger the hemostatic mechanism, and modulate angiogenesis. These effects are largely mediated by apo(a), the unique component of Lp(a) **(28)**.

On the other hand, emerging evidence suggests that Lp(a) may possess anti-angiogenic properties. It seems to interfere with the activation of proteases essential for angiogenesis, such as MMPs. This anti-angiogenic potential, combined with its structural similarity to plasminogen, raises the possibility of Lp(a) acting as an anti-neoplastic factor. Given that inflammation and endothelial dysfunction are key drivers of the atherosclerotic process, the properties of Lp(a) related to wound healing and angiogenesis may provide insights into its role in atherosclerosis. However, further research is warranted to fully elucidate the mechanisms underlying these potential functions of Lp(a) and their implications for human health and disease. The role of lipoprotein(a) in human disease is illustrated in Figure 3 **(29)**.

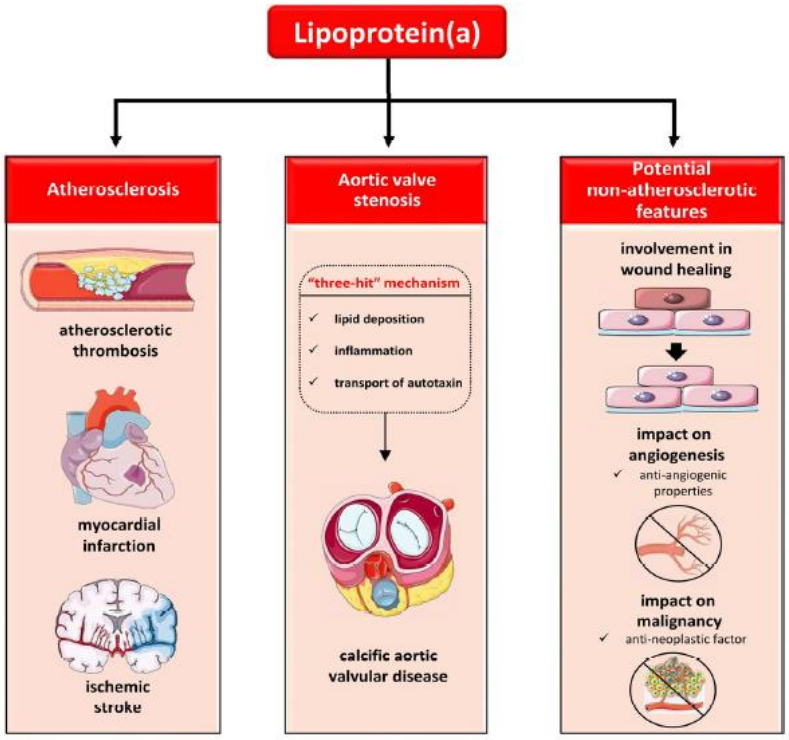

Figure 3: The role of lipoprotein(a) in human disease (30).

1. Assessment and Measurement of Lipoprotein (a):

The measurement of Lp(a) concentration remains a challenge given the high heterogeneity of Lp(a) structure among the human population. Firstly, the molecular mass of Lp(a) varies according to the size of apo(a). Secondly, because the lipid content is also variable in Lp(a) particles, Lp(a) is the only lipoprotein not routinely measured by its cholesterol content. Indeed, Lp(a) concentration cannot be predicted adequately by lipid profiling, i.e., LDL-cholesterol (LDL-C) measurements **(31)**.

Despite this heterogeneity, specific tests targeting the apo(a) moiety of the Lp(a) particle are used, based on immunological methods such as ELISA or immunoturbidimetry. These assays use an antibody against apo(a) that does not recognize a unique epitope in each particle and cross-react with multiple KIV-2 domains. Even if calibrators (apo(a) isoforms of different sizes) are used to overcome this pitfall and calculate protein mass concentration in mg/dL, Lp(a) levels may be overestimated or underestimated in clinical samples containing large or small isoforms, respectively **(32)**.

Moreover, the absence of standardization between assays may lead to important variation between results obtained with each test used. To avoid this isoform size bias, Marcovina et al. developed an antibody targeting KIV-9 (a nonrepeating kringle domain) which was used to evaluate the particle number and report results in nanomoles per liter (nmol/l). To allow clinical interpretation of changes in Lp(a) between studies and the establishment of diagnostic cut-offs, it is advisable to measure and report particle concentration rather than protein mass concentrations **(33)**.

This is gaining acceptance as more standardized and calibrated tests are used. Conversion of actual protein mass to particle concentration depends on apo(a) isoform size, threshold concentration, and method used, meaning that a single conversion factor between mg/dL and nmol/L for all assays is not appropriate. Plasma concentrations of Lp(a) vary widely over a greater than 10-fold range. For instance, in the Framingham Heart Study cohort and the AIM-HIGH trial patients, median values were 20 nmol/L and 33.8 nmol/L, respectively, with some individuals having undetectable Lp(a) levels and others having >300 nmol/L. While those two cohorts are almost all comprised of Caucasian subjects, median Lp(a) levels differ according to ethnic background. A recent investigation of 7 ethnic groups in the INTERHEART study revealed that plasma Lp(a) level varies widely and that the inverse association between concentration and isoform size remains consistent in all of them **(34)**.

There is a general agreement that the variation in Lp(a) level is almost entirely (90%) driven by the genetic architecture of the LPA gene. In fact, 69% of the variation in Lp(a) concentration was attributed to the polymorphism in the KIV- 2 domain associated with isoform size and 22% from cis-acting factors in the gene, such as single-nucleotide polymorphisms (SNPs) in the LPA promoter **(35)**.

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 **(36)**.

Table 1: Guideline recommendations for screening of Lp(a) (18).

Screen Recommendations	Target
2018 AHA/ACC - 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.	50 mg/dL

2019 ESC/EAS - 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 hypercholesterolemia. (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)	50 mg/dL

2. Management Strategies for Elevated Lipoprotein (a):

Elevated Lp(a) levels are challenging to manage, as traditional lipid-lowering therapies **Table 2**, such as statins, niacin, and CETP inhibitors, have shown limited effectiveness in reducing Lp(a). Statins, while effective for lowering cholesterol, can paradoxically increase Lp(a) levels by 10-20%, as demonstrated in trials. Despite their cholesterol-lowering benefits, drugs like ezetimibe, either alone or in combination with statins, do not significantly affect Lp(a) levels. Niacin, previously noted for reducing Lp(a) by 38-40%, has been largely abandoned due to side effects such as hot flashes and hepatotoxicity, alongside the failure to demonstrate a reduction in primary cardiovascular events in large trials **(37).**

Newer therapies have shown more promise. PCSK9 inhibitors, such as alirocumab and evolocumab, significantly reduce Lp(a) levels by approximately 25-30%, in addition to their LDL-lowering effects. Clinical studies like the Odissey and Fourier trials revealed substantial reductions in Lp(a) after treatment with PCSK9 inhibitors, although these drugs are not specifically approved for Lp(a) reduction. Inclisiran, a small interfering RNA (siRNA)-based drug, has also been shown to lower Lp(a) levels by around 18-25% in clinical trials like ORION. Another emerging treatment, mipomersen, an antisense oligonucleotide, reduces Lp(a) by 25-40%, though its use is restricted due to significant side effects such as hepatic steatosis and injection site reactions. Despite these advances, targeted therapies specifically approved for lowering Lp(a) are still under investigation, and further studies are needed to optimize their clinical application **(38).**

Table 2: different treatment options for elevated Lp(a) levels (8).

Treatment	Mechanism of Action	Effect on Lp(a) Levels	Notable Findings and Remarks
Statins	Lowers cholesterol levels	No significant reduction; may increase slightly	Statins do not significantly affect Lp(a) levels and may even lead to a slight increase in some cases. Further research is needed to understand the underlying mechanisms of this increase.
Niacin	Athero-protective agent, lowers lipids	Reduction in Lp(a) levels by 38–40%	Niacin has been effective in reducing Lp(a) levels, but its use is limited due to side effects

CETP inhibitors	Reduces CETP activity, increases HDL	Reduction in Lp(a) levels; varying effects	CETP inhibitors have shown varying effects on Lp(a) levels, with some drugs reducing levels by up to 40%. The effects of fibrates on Lp(a) levels remain uncertain.
PCSK9 inhibitors	Blocks PCSK9 enzyme, increases LDL receptor expression	Reduction in Lp(a) levels by 25–30%	PCSK9 inhibitors have been found to be effective in reducing Lp(a) levels by 25–30%, along with lowering LDL-C. Alirocumab has shown promising results in reducing Lp(a) levels independently of factors such as race, sex, FH, and baseline Lp(a).
Inclisiran	Inhibits the hepatic synthesis of PCSK9	Reduction in Lp(a) levels	Inclisiran has shown reductions in Lp(a) levels in clinical trials. The ORION studies demonstrated significant reductions in Lp(a) levels over the course of treatment.
Mipomersen	Inhibits apo-B synthesis without affecting apo(a)	Reduction in Lp(a) levels by 25–40%	Mipomersen can reduce Lp(a) levels but has limited therapeutic use due to serious side effects.
Apheresis	Extracorporeal removal of lipoproteins	Lowering of LDLc and Lp(a) concentrations by 60–70%	Apheresis has been found to be the most efficient and well-tolerated therapy for individuals with Lp(a) hyperlipoproteinemia. It achieves substantial reductions in LDL-C and Lp(a) levels, leading to significant improvements in cardiovascular outcomes.

3. Future Directions in Lipoprotein (a) Research

Various clinical trials are ongoing. For example, Pelacarsen uses the ASO technology and results in an approximately 80% reduction in Lp(a) plasma levels with 60–80 mg subcutaneous dosing once every 4 weeks. The phase III cardiovascular outcomes study will be finished probably by the end of 2025 (HORIZON, NCT 04023552). The siRNA technology is used by Olpasiran which reported a reduction of Lp(a) levels of up to more than 95%. The recruitment for the cardiovascular outcomes study started and the study is expected to be finished by the end of 2026 (Ocean(a), NCT05581303). Zerlasiran (SNL360) is a further siRNA therapy, which resulted in the phase 1 study in a 98% reduction of Lp(a) concentrations following a single subcutaneous administration of 600 mg **(39)**

The phase II study is currently ongoing and is expected to be completed in the middle of 2024 (NCT05537571). Finally, Lepodisiran is also using an siRNA approach and reported in a phase I study median dose-dependent decreases in Lp(a) concentrations > 90% for the 3 highest doses studied. The treatment effect lasted the longest in the highest dose of 608 mg and was still – 94% after 337 days of observation. These mRNA-targeting therapies are highly effect therapies in terms of Lp(a)-lowering with only small side effects reported up to now. It has to be seen in

the cardiovascular outcome trials, whether this pronounced Lp(a)-lowering translates in a lowering of the cardiovascular outcomes of interest **(40)**.

A different approach is followed by Muvalaplin (LY3473329) which is an orally administered small molecule that inhibits Lp(a) formation. It binds to apo(a) KIV type 7 and KIV type 8 and thereby prevents the initial noncovalent interaction between apo(a) and apolipoprotein B100 of the LDL-particle. As a consequence, the disulfide bond between the two molecules is not built and the formation of Lp(a) is prevented. A phase I multiple ascending dose treatment evaluated the effect of taking daily doses of Muvalaplin (30 to 800 mg) or placebo for 14 days in patients with Lp(a) levels of 30 mg/dL or higher. The drug was tolerated well and resulted in a maximum placebo-adjusted Lp(a) reduction of 63 to 65%. Interestingly, similar effects were observed with daily doses of 100, 300, 500, and 800 mg **(41)**.

A phase II, randomized, double-blind, placebo-controlled Study (KRAKEN) is currently running to investigate the efficacy and safety of oral once-daily administration of this drug in adults with elevated Lp(a) concentrations at high risk for cardiovascular events and is expected to be completed at the beginning of 2024 (NCT 05563246). Somatic gene-editing therapies shoot for long-lasting and highly likely permanent effects by editing the somatic DNA by introducing DNA changes. CRISPR/Cas9 system is one of the preferred technologies with high efficiency as discussed by Stankov and Cuchel. PCSK9, ANGPTL3, LDLR, and APOC3 are current targets mostly in preclinical phase but LPA is already in the focus of some companies **(42)**.

Since this technology results in a permanent change of the somatic genome of an individual, long-term safety and ethical considerations are of high importance. In case these issues can be solved, a further interesting option might become available for persons with extremely high Lp(a) concentrations which will also circumvent compliance issues of oral lipid-lowering medications **(43)**.

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