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## What Do We Know About the Role of Lipoprotein(a) in Atherogenesis 57 Years After its Discovery?

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**ABSTRACT:**

Elevated circulating concentrations of lipoprotein(a) [Lp(a)] is strongly associated with increased risk of atherosclerotic cardiovascular disease (CVD) and degenerative aortic stenosis. This relationship was first observed in prospective observational studies, and the causal relationship was confirmed in genetic studies. Everybody should have their Lp(a) concentration measured once in their lifetime. CVD risk is elevated when Lp(a) concentrations are high i.e. >50 mg/dL ( $\geq 100$  mmol/L). Extremely high Lp(a) levels >180 mg/dL ( $\geq 430$  mmol/L) are associated with CVD risk similar to that conferred by familial hypercholesterolemia. Elevated Lp(a) level was previously treated with niacin, which exerts a potent Lp(a)-lowering effect. However, niacin is currently not recommended because, despite the improvement in lipid profile, no improvements on clinical outcomes have been observed. Furthermore, niacin use has been associated with severe adverse effects. Post hoc analyses of clinical trials with proprotein convertase subtilisin/kexin type-9 (PCSK9) inhibitors have shown that these drugs exert clinical benefits by lowering Lp(a), independent of their potent reduction of low-density lipoprotein cholesterol (LDL-C). It is not yet known whether PCSK9 inhibitors will be of clinical use in patients with elevated Lp(a). Apheresis is a very effective approach to Lp(a) reduction, which reduces CVD risk but is invasive and time-consuming and is thus reserved for patients with very high Lp(a) levels and progressive CVD. Studies are ongoing on the practical application of genetic approaches to therapy, including antisense oligonucleotides against apolipoprotein(a) and small interfering RNA (siRNA) technology, to reduce the synthesis of Lp(a).

**Keywords:** lipoprotein(a), risk factor, observational studies, genetic studies, atherogenesis, management

## LIST OF ABBREVIATIONS:

ACC	-	American College of Cardiology
ACS	-	acute coronary syndrome
AHA	-	American Heart Association
apo(a)	-	apolipoprotein(a)
AS	-	aortic valve stenosis
ASCVD	-	atherosclerotic cardiovascular disease
AVC	-	aortic valve calcifications
CAC	-	coronary artery calcifications
CAD	-	coronary artery disease
CAVD	-	calcific aortic valve disease
CI	-	confidence interval
CKD	-	chronic kidney disease
CVD	-	cardiovascular disease
EAS	-	European Atherosclerosis Society
EFLM	-	European Federation of Clinical Chemistry and Laboratory Medicine
ESC	-	European Society of Cardiology
FCR	-	fractional catabolism rate
GFR	-	glomerular filtration rate
GWAS	-	genome-wide association studies
HR	-	hazard ratio
heFH	-	heterozygous familial hypercholesterolemia
ILEP	-	International Lipid Expert Panel
Lp(a)	-	lipoprotein(a)
LDL-C	-	low-density lipoproteins cholesterol
LPO	-	lipoxxygenase
MACE	-	major adverse coronary events
MESA	-	Multi-Ethnic Study of Atherosclerosis
MI	-	myocardial infarction
NADPH	-	nicotinamide adenine dinucleotide phosphate
NLA	-	National Lipid Association
NNT	-	number needed to treat
non-HDL-C	-	non-high-density lipoprotein cholesterol
OR	-	odds ratio

OxPL	-	oxidized phospholipids
PAI-1	-	plasminogen activator inhibitor-1
PCSK9	-	proprotein convertase subtilisin/kexin type- 9
PoLA	-	Polish Lipid Association
PSLD	-	Polish Society of Laboratory Diagnostics
ROS	-	reactive oxygen species
RR	-	relative risk
SD	-	standard deviation
siRNA	-	small interfering RNA
SNP	-	single nucleotide polymorphisms
TFPI	-	tissue factor pathway inhibitor
WMD	-	weighted mean difference

Lipoprotein(a) [Lp(a)] was first described by a Norwegian physician Kare Berg in 1963 [1]. The association between Lp(a) and the risk of cardiovascular disease (CVD) was observed long ago in prospective observational studies. However, the interest of lipid experts has been predominantly focused on low-density lipoproteins (LDL) due to their major role in atherogenesis and the therapeutic success of CVD event reduction with plasma LDL cholesterol (LDL-C) level lowering, and less attention has been paid to Lp(a). The renewed interest in Lp(a) has been stimulated by novel research findings and the potential for therapeutic Lp(a) reduction. Genetic studies have demonstrated that elevated Lp(a) is causally associated with CVD risk [2]. Therapeutically, the use of proprotein convertase subtilisin/kexin type-9 (PCSK9) inhibitors in large clinical trials (FOURIER and ODYSSEY OUTCOMES) led to a reduction in Lp(a) concentrations which was associated with a reduction in the rate of CVD events in rate in secondary prevention [3,4]. The positive results of these studies and development of new therapies targeted at inhibiting Lp(a) synthesis, such as antisense oligonucleotides against the LPA gene which encodes apolipoprotein(a) [apo(a)] and antibodies against oxidized phospholipids (OxPL), prompted the National Lipid Association (NLA) to publish an expert statement with the insightful title: “Use of lipoprotein(a) in clinical practice: a biomarker whose time has come”[5].

### **Structure of Lp(a)**

Circulating concentrations of Lp(a) are almost entirely (approximately 90%) determined genetically by the LPA gene, with minimal contribution of dietary or environmental factors. Concentrations of Lp(a) are thought to be stable level throughout life; thus a single measurement is sufficient unless Lp(a) level is found to be elevated and needs to be monitored during treatment [5].

The Lp(a) particle has a unique and complicated structure [2,6,7,8]. It consists of two subunits, a cholesterol-rich LDL-like particle, the apolipoprotein B element of which is connected by a disulfide bond to one molecule of apolipoprotein(a) [apo(a)]. Apo(a) is a glycoprotein synthesized mainly in the liver, with a structure similar to plasminogen, which includes five tri-loop structure called kringles (KI-KV) and a protease domain. In contrast to plasminogen, apo(a) lacks KI to KIII but contains KV and ten subtypes of KIV (KIV<sub>1</sub>-KIV<sub>10</sub>), with the predominant KIV<sub>2</sub> subtype which occurs in multiple copies (from 3 to more than 40), depending on the number of KIV<sub>2</sub> copies in the LPA gene. Thus, more than 40 isoforms of apo(a) exist, leading to heterogeneity of Lp(a) particle size. The protease domain is not present in apo(a) [6-8].

Most people inherit two different apo(a) isoforms, one from each parent. The resultant serum Lp(a) concentration depends on the length of the LPA gene and consequently, Lp(a) size. A negative correlation has been noted between Lp(a) concentration and Lp(a) particle size. High concentrations of smaller Lp(a) particles (with fewer KIV<sub>2</sub> copies on apo(a)) are associated with elevated cardiovascular risk [6-8].

### **Lipoprotein(a) Metabolism**

Apo(a) is exclusively synthesized in the liver [9]. It is not certain where apo(a) is combined with the apoB of LDL; however, this process is likely to occur on the surface of hepatocytes, or in the extrahepatic space, away from the bloodstream [10,11]. Apo(a) first adheres to LDL, and then a disulfide bond is formed between the KIV<sub>9</sub> of apo(a) and the apoB molecule in LDL [10].

Lp(a) is catabolized in the liver and kidneys [12]; however, these mechanisms have not been completely elucidated. The role of the LDL-receptor is unclear, and other receptors may also be involved. In their review, Reys-Soffer, Ginsberg and Ramakrishnan wrote: “The uniformly observed lower fractional catabolism rate (FCR) for Lp(a) versus LDL do not rule out for the LDL receptor, but if the latter is involved, then either Lp(a) has a lower affinity for the LDL receptor than LDL or the LDL receptor is only one of several receptors involved in Lp(a) clearance. The affinity of Lp(a) for other receptors, along with proportion of Lp(a) cleared via each of those receptors, will determine the background FCR of Lp(a) in an individual, as well the change in FCR when the number of LDL receptors increases” [10].

The kidneys are involved in the catabolism of Lp(a), and Lp(a) concentration is elevated in patients with chronic kidney disease (CKD) [2,13]. Lp(a) level increases very early in the course of CKD, even before the glomerular filtration rate (GFR) begins to decrease [14]. Apo(a) fragments are normally excreted by the kidneys at a rate of 1-1.5 mg/d, but this excretion is compromised in patients with renal failure [15], leading to an elevated plasma concentration of Lp(a). In patients with extensive proteinuria (nephrotic syndrome), Lp(a) level is markedly increased secondary to increased hepatic synthesis [16]. Thus, elevated Lp(a) level may be an acquired phenomenon in CKD, related to GFR reduction, the degree of proteinuria, and increased synthesis. The presence of LDL receptor-related protein (LRP) in various renal cell-types confirms the role of the kidneys in Lp(a) clearance [15].

The mechanisms regulating plasma Lp(a) concentrations are not entirely understood. Some studies indicate that both catabolism (FCR) and the production rate correlate significantly with each other, and with plasma Lp(a) concentrations [17]. However, other

studies showed a correlation only between the production rate and Lp(a) concentration [18]. Thus, 57 years after its discovery, the metabolism of Lp(a) has not been completely elucidated despite multiple studies.

### **The Physiological Roles of Lp(a)**

The physiological roles of Lp(a) have not been definitively established. No abnormalities have been reported in humans with low concentrations of Lp(a) [7]. Historically, the beneficial role of Lp(a) was thought to be related to wound healing, tissue repair, and vascular remodelling. A hemostatic effect is important in this process. Lp(a) is a thrombogenic lipoprotein with significant structural similarity to plasminogen. Lp(a) reduces plasmin generation by competing with plasminogen [19,20], resulting in stabilization of the fibrin clot. Lp(a) is, therefore thought to have evolved to prevent haemorrhage [20]. Lp(a) accumulates at loci of endothelial damage and binds to the vessel wall components and the subendothelial matrix via complex mechanisms. Orso and Schmitz have described how Lp(a) affects endothelial function, stimulates smooth muscle cell recruitment and migration from the media to the intima, and activates monocytes/macrophages. These cellular effects mean that Lp(a) plays important roles in vascular remodelling [7]. This possibly beneficial mechanism of action may become harmful (atherogenic) in the presence of high concentrations of Lp(a).

### **Plasma Concentrations of Lp(a)**

Substantial inter-individual variations in Lp(a) levels are observed (from 0.1 mg/dL to more than 200 mg/dL), and the mean and median concentrations vary as much as 4-fold between ethnic groups [2]. The distribution of Lp(a) concentrations is asymmetric in most populations. The majority of individuals have Lp(a) levels below 10 mg/dL or even undetectable or barely detectable levels. The threshold level has been defined at 50 mg/dL, as observational studies indicate that concentrations equal to or higher than 50 mg/dL are associated with a clearly increased CVD event risk [21,22,23]. Nevertheless, even below 50 mg/dL, risk increased gradually with Lp(a) concentration from at least 30 mg/dL [21,24, 25]. The threshold level of 50 mg/dL to indicate individuals at increased risk was first adopted in the 2018 American Heart Association/American College of Cardiology (AHA/ACC) guidelines [26] and the 2016 European Society of Cardiology (ESC) guidelines [27] based upon evidence from the JUPITER trial, in which a trend towards an increased risk of CVDevents was seen starting at this level in patients treated with rosuvastatin [28]. Lp(a)



levels  $\geq 30$  mg/dL are noted in about 30% of individuals in the USA, and levels  $\geq 50$  mg/dL occur in about 20% [29].

As noted above, the distribution of Lp(a) concentrations varies between populations. Caucasians have generally lower levels, and Afro-Americans have higher levels [5]. The Multi-Ethnic Study of Atherosclerosis (MESA) indicates that while Lp(a)  $\geq 50$  mg/dL is a useful predictor of coronary artery disease in white Americans, this threshold should be  $\geq 30$  mg/dL in blacks [30]. However, the National Lipid Association has recommended adopting a single threshold Lp(a) level for all Americans, i.e., 50 mg/dL (100 mmol/L) [5]. In their opinion, it is unlikely that observations suggesting two different threshold values “reflect differences in the underlying pathobiology of Lp(a)” but rather result from “a selection bias, different statistical power in individual studies, and other confounding effects”.

A different approach to Lp(a) has been adopted in the recent 2019 ESC/European Atherosclerosis Society (EAS) guidelines on the management of dyslipidemia [31]. The authors did not adopt the 50 mg/dL threshold level but recommended that Lp(a) level should be measured at least once in all adults to identify those with a very high level, i.e.  $>180$  mg/dL (430 nmol/L), in whom the risk of atherosclerotic CVD is equal to that in subjects with heterozygous familial hypercholesterolemia (heFH). The combination of above summarized approaches has been recently adopted by the 2020 Guidelines of the Polish Society of Laboratory Diagnostics (PSLD) and the Polish Lipid Association (PoLA) on laboratory diagnostics of lipid metabolism disorders [32]. The authors suggested that the recommended Lp(a) values should be  $<30$  mg/dL ( $<70$  nmol/L), and the individuals with the values 30-50 mg/dL (70-125 nmol/L) are already at the moderate CVD risk, those  $>50$  mg/dL ( $>125$  nmol/L) at high CVD risk, and very high risk of myocardial infarction (MI) and aortic valve stenosis (AS) exist for patients with very high Lp(a) levels ( $>180$  mg/dL/450 nmol/L) [32] (**Figure 1**).

## **Lp(a) as a Risk Factor for CVD and Calcific AS**

### ***Epidemiology***

Large observational studies and meta-analyses indicate an association between Lp(a) concentration and the risk of coronary artery disease (CAD) and ischemic stroke [33]. A good example of a single population observational study is the Copenhagen City Heart Study, which included a range of subjects, including those with extremely high Lp(a) levels ( $\geq 120$  mg/dL) [34]. Lp(a) level measurements were performed shortly after serum sampling, a

correction for regression dilution bias was performed, the relative hazard (HR) was calculated, and the absolute risk was estimated [34]. In this study, 9330 subjects were followed up for ten years to investigate whether there was an association between baseline Lp(a) level and incidence of MI. In men with baseline Lp(a) level of 5-29 mg/dL, 30-84 mg/dL, 85-119 mg/dL and  $\geq 120$  mg/dL, HR was 1.5 (95% confidence interval [CI] 0.9-2.3), 1.6 (1.0-2.6), 2.6 (1.2-5.5), and 3.7 (1.7-8.0), respectively, whereas in women, the equivalent values were 1.1 (0.6-1.9), 1.7 (1.0-3.1), 2.6 (1.2-5.9) and 3.6 (1.7-7.7), when compared to Lp(a) levels  $< 5$  mg/dL. The authors concluded that a gradual increase in the risk of MI with increasing Lp(a) levels was observed without a threshold value. Compared to levels  $< 5$  mg/dL, extremely high Lp(a) levels were associated with a 3- to 4-fold risk increase in risk in the general population [34].

A weaker, albeit “continuous and independent” association between Lp(a) level and the risk of major CVD events was found in the Emerging Risk Factors Collaboration meta-analysis that included 36 prospective studies with 126 634 participants [21]. The overall duration of follow-up was 1.3 million person-years. A continuous, independent, moderate association was found between Lp(a) level and the risk of CAD and stroke. The relation between Lp(a) concentration and CAD events (non-fatal MI + CAD death) and ischemic stroke was curvilinear, indicating a growing risk with high Lp(a) levels [21]. The mean Lp(a) levels differed between studies. The median level was 12.6 mg/dL (interquartile range 4.9-32.1 mg/dL). The relative risk (RR) of CAD adjusted for age and gender was 1.16 (95% CI 1.11-1.22) for a 3.5-fold higher (1 SD) Lp(a) level and 1.13 (1.09-1.18) with further adjustment for lipid levels [total cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), HDL-C, and triglycerides) and other risk factors (systolic blood pressure, history of diabetes, body mass index). Stroke incidence was also the highest in subjects with the highest concentrations of Lp(a) (RR 1.10, 95% CI 1.02-1.18) [21].

Recently, a meta-analysis of 11 case-control and nine prospective studies investigating the association between Lp(a) level and ischemic stroke risk was published, comparing the highest and lowest concentrations of Lp(a) [35]. In individual studies, Lp(a) comparisons were made “from dichotomous, tertile, quartile or quintile categorization, or when treated as the continuous variable (eg. per unit or per SD increase)”. Based on this, the authors of the meta-analysis compared the stroke risk in subjects with high and low Lp(a) levels. Of note, this meta-analysis data from 126,694 participants. In case-control studies, the estimated odds ratio (OR) for high compared to low Lp(a) levels was 1.41 (95% CI 1.26-1.57), while the RR in prospective studies was 1.29 (1.06-1.58). In younger populations (mean age  $< 55$  years),

this risk was higher than for older populations, in both case-control and prospective studies [35].

Regarding the relationship between elevated Lp(a) as a CVD risk factor and plasma concentration of LDL-C, some observational studies have demonstrated that Lp(a) increases CVD risk only if LDL-C level exceeds a certain threshold. However, other observational and interventional studies, in fact most of them, indicate that Lp(a) is a residual risk factor independent of LDL-C, even in patients who achieved target LDL-C values on lipid-lowering therapy. The results of studies addressing this question [3,4,28,36-43] are summarised in **Table 1**.

Elevated Lp(a) in the general population is also associated with the risk of AS and aortic valvular lesions preceding clinically significant stenosis, as highlighted by Vuorio et al. in a recent review [44]. However, this fact is less commonly known than the association between elevated Lp(a) levels and CVD risk. In this context, it is useful to consider two notable studies: one conducted in a single population [44], and the other involving many populations [46].

In a prospective 20-year follow-up of 77,680 individuals in Denmark (combined results of the Copenhagen City Heart Study and the Copenhagen General Population Study), elevated Lp(a) levels were associated with a risk of AS in the general population [45]. HRs for Lp(a) levels of 5-19 mg/dL (22<sup>nd</sup>-66<sup>th</sup> percentile), 20-64 mg/dL (67<sup>th</sup>-89<sup>th</sup> percentile), 65-90 mg/dL (90<sup>th</sup>-95<sup>th</sup> percentile) and >90 mg/dL (>95<sup>th</sup> percentile) compared to <5 mg/dL were 1.2 (95% CI 0.8-1.7), 1.6 (1.1-2.4), 2.0 (1.2-3.4) and 2.9 (1.8-4.9), respectively. The authors concluded that a threefold risk increase may be expected with Lp(a) levels >90 mg/dL [45].

The MESA investigators evaluated whether threshold Lp(a) levels used for the assessment of CVD risk were associated with the incidence and severity of subclinical calcific aortic valve disease (CAVD) which was diagnosed by computed tomography. The study included 4678 participants and additionally investigated whether significant relationships could be observed for individuals of a range of races/nationalities [46]. The conventional threshold Lp(a) level of  $\geq 30$  mg/dL was associated with a significantly higher rate of aortic valve calcifications (AVC) in Caucasians (RR 1.56, 95% CI 1.24-1.96,  $P < 0.01$ ) compared to levels <30 mg/dL. In blacks, the association between Lp(a) level and AVC was borderline significant (RR 1.55, 95% CI 0.98-2.44,  $P = 0.059$ ). Lp(a) levels  $\geq 50$  mg/dL were significantly associated with AVC in Caucasians (RR 1.72, 95% CI 1.36-2.17) compared to levels <50 mg/dL but no significant association was seen in blacks (RR 1.24, 95% CI 0.85-1.89,  $P = 0.26$ ) [46]. A greater likelihood of severe AVC was seen in both white and black MESA study

participants if Lp(a) level was above 30 or 50 mg/dL. No association between Lp(a) level and the risk and severity of AVC was seen in Hispanic and Chinese participants (living in the USA). The authors concluded that the threshold Lp(a) levels used for the assessment of CVD risk seem to be applicable also for calcific AS, but further studies are required to investigate whether race/ethnicity affects the association between Lp(a) concentration and the risk and progression of AS [46].

In patients with heFH, AVC is more common, and Lp(a) levels are higher than in subjects without heFH. A recent study evaluated aortic valve lesions in heFH [47]. AVC was identified by computed tomography in 59 (41%) of 145 asymptomatic patients with heFH (aged 52±8 years) treated with statins compared to 27 (21%) of 131 control subjects (aged 56±9 years) ( $P<0.0001$ ). Thus, AVC was nearly 2-fold more common in patients with FH compared to controls. The severity of AVC was also higher, as indicated by the median AVC score of 51 (interquartile range 9-117) vs 21 (3-49). Age, untreated maximum LDL-C level, coronary artery calcifications (CAC), LDL receptor-negative mutation, and diastolic blood pressure were positively associated with AVC. In this study, the plasma concentration of Lp(a) was not measured. The authors concluded that FH was associated with a high prevalence of extensive, subclinical AVC, particularly in patients with receptor-negative mutations, highlighting a key role of LDL metabolism in the aetiology of AVC [47].

On the other hand, patients with heFH are known to have significantly higher Lp(a) levels compared to subjects without heFH in the general population, which may also contribute to higher rates of CVD and AVC [48-50]. Recently, two studies addressing this issue have been published, including a comparative case-control study (SAFEHEART) [48] and a prospective population study (Copenhagen General Population Study) [49]. In the SAFEHEART study with 2917 participants (1960 subjects with FH and 957 relatives without FH), patients with FH had higher Lp(a) levels compared to the relatives without FH, particularly those with CVD [48]. Median Lp(a) level in patients with FH and CVD was 43.8 mg/dL (interquartile range 18.2-84.3) compared to 21.5 mg/dL (8.4-37) in those with FH but no CVD ( $P<0.005$ ). The proportion of patients with Lp(a) level  $>50$  mg/dL also differed significantly between these two groups (46.2% vs 14.6%,  $P<0.0001$ ). CVD event-free survival was significantly shorter in patients with FH and Lp(a) levels  $>50$  mg/dL compared to those with FH and Lp(a) levels  $<50$  mg/dL (log-rank P value  $<0.0001$ ). In addition, patients with Lp(a) levels  $>50$  mg/dL who were carriers of LDL receptor-negative mutations, had a higher CVD risk compared to those with less severe mutations. Of note, Lp(a) level was an independent prognostic factor for CVD risk in both men and women with FH. As concluded by the

authors, the risk was higher in patients with Lp(a) level >50 mg/dL and carriers of LDL receptor-negative mutations compared to other less severe mutations. Aortic valve lesions were not evaluated [48]. In the prospective Copenhagen General Population Study [49] with 46,200 participants, mean Lp(a) level in those with definite or likely FH was 35 mg/dL, compared to 32 mg/dL in participants with possible FH and 23 mg/dL in those free from FH, but no differences in the mean Lp(a) level were found between these three groups after adjustment for contribution of Lp(a) cholesterol to LDL-C (21 mg/dL vs. 22 mg/dL vs. 24 mg/dL) [49]. However, differences were noted in HR for MI. Compared to FH(-) subjects with Lp(a) level ≤50 mg/dL, HR was 1.4 (95% CI 1.1-1.7) in FH(-) subjects with Lp(a) level >50 mg/dL, 5.3 (3.6-7.6) in FH(+) subjects (including definite, likely, and possible FH) with Lp(a) level >50 mg/dL, and 3.2 (2.5-4.1) in FH(+) subjects with Lp(a) level ≤50 mg/dL. As with the previous study, aortic valve lesions were not evaluated [49].

An increased Lp(a) level in some patients with FH may not only increase already high CVD risk but also affect the development of AVC. This is evidenced by the results of the study by Vongpromek et al. who evaluated the association between AVC and Lp(a) levels in 129 asymptomatic patients with heFH (median age of 51 years) who were treated with statins [50]. It was shown that plasma Lp(a) level correlated significantly with the presence and severity of AVC. No correlation was found between Lp(a) level and CAC. AVC were significantly associated with Lp(a) level, age, body mass index, systolic and diastolic blood pressure, duration of statin treatment, cholesterol-year score, and CAC. Each 10 mg/dL increase in Lp(a) level was associated with an 11% increase in the risk of developing AVC (95% CI 1.01-1.20, P<0.03). Thus, concomitant high LDL cholesterol and Lp(a) levels are associated not only with increased CVD risk, but also more rapid development of AVC [50].

### ***Genetics***

Key evidence supporting Lp(a) as an independent risk factor for atherosclerotic CVD (in particular CAD, MI, and ischemic stroke) and calcific AVS has been provided by the results of genetic studies that are free from potential confounding, i.e., genome-wide association studies (GWAS) and large Mendelian randomization studies [51,52]. The goal of GWAS was to identify genes that modify Lp(a) concentrations, while Mendelian randomization studies evaluated the association between the presence of single nucleotide polymorphisms (SNP) or the number of KIV<sub>2</sub> repeats in the LPA gene and Lp(a) level, CVD risk, and the risk of AVC and AS [51].

Of 48,742 SNPs in 2100 candidate genes that were investigated in 2009 in patients with CAD and control subjects, two SNPs in the LPA gene, rs 10 455 872 and rs 3 798 220, were most strongly associated with Lp(a) levels. Both SNPs were associated with a high risk of CAD [24]. Of note, both these SNPs are associated with fewer KIV<sub>2</sub> repeats, small apo(a) isoforms and high Lp(a) concentrations. However, more than 50% of all subjects with small apo(a) isoforms are not carriers of either of these SNPs [52]. Therefore, a genetic diagnosis cannot be established in half the subjects with high CVD risk because of Lp(a), and therefore measuring the Lp(a) concentration remains of paramount importance.

To investigate the genetic link between plasma Lp(a) level and the risk of MI and AS, Nordestgaard and Langsted [51] updated their previous epidemiological studies [34,53,54] and large Mendelian Randomization studies [53-55], combining the data from the Copenhagen City Heart Study and the Copenhagen General Population Study to achieve maximal statistical power. This new analysis confirmed an elevated MI risk with Lp(a) levels >30 mg/dL. The risk of MI was increased 2.4-fold in subjects with Lp(a) levels >100 mg/dL compared to <5 mg/dL. Each doubling of Lp(a) level was associated with a 15% higher risk of MI (95% CI 11-20%) based on the number of LPA KIV<sub>2</sub> repeats (lowest versus highest) and a 10% higher risk (95% CI 6-13) based on the presence of rs 10 455 872 SNP in the LPA gene, and the risk of AS was increased by 13% (95% CI 1.04-1.22%) and 21% (1.14-1.29), respectively. In observational studies, each doubling of Lp(a) level was associated with a 9% higher MI risk (95% CI 7-12%). The authors of the meta-analysis highlighted a large (1000-fold) individual variation of Lp(a) levels indicating that Lp(a) may confer considerable risk in individuals with the highest values of Lp(a) [54,55].

A genetic association was also found between atherosclerotic coronary, carotid, and femoral artery stenoses and Lp(a) concentration. The association was demonstrated by comparing the number of KIV<sub>2</sub> repeats (lowest vs. highest tertile). The lowest number of KIV<sub>2</sub> repeats was associated with a high risk of stenosis, suggesting a causal relationship [56]. Nordestgaard and Langsted [51] noted that associations between CVD risk-related LPA genotypes and a high risk of arterial stenoses were also found in other studies. These genetic associations confirm a causal relationship between Lp(a) level and the risk of atherosclerotic CVD which was suggested by the results of prospective observational studies. It has been demonstrated that an established strong genetic risk factor for MI, i.e., rs 10 455 872 SNP in the LPA gene, is also a genetic causal factor for AVC and AS [57]. Furthermore, the combination of rs 10 455 872 and rs 3 798 220 SNP in the LPA gene and a low number of KIV<sub>2</sub> repeats is causally associated with AS [45], thus confirming the results of prospective

observational studies that suggested an association between Lp(a) level and the risk of developing AS.

Observational and genetic evidence supports a relationship between plasma Lp(a) level and the risk of heart failure, which is mostly (63%) attributable to MI and AS [51]. However, other mechanisms cannot be excluded.

### **Mechanisms of Atherogenesis**

Lp(a) is a proatherogenic and prothrombotic lipoprotein. However, the precise mechanism of its atherogenic action is not known. The available data have been summarized in several recent reviews [13,20,58-60] and a detailed discussion of this issue is beyond the scope of the present article. Lp(a) is known to bind with proteoglycans and fibronectin on the endothelial surface and penetrate into the subendothelial space [20]. It is believed that the risk of atherosclerotic CVD is largely determined by the presence of OxPL in Lp(a) particles [13,58,59,61].

Lp(a) trapping (by binding to proteoglycans and fibronectin) results in a prolonged oxidation time, leading to oxidation of polyunsaturated fatty acid moieties in phospholipids. Phospholipids undergo oxidation, either enzymatically by cellular lipoxygenases (LPO), or when acted upon by reactive oxygen species (ROS) generated by such cellular enzymes as myeloperoxidase and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [13]. Most OxPL in the bloodstream (85%) is associated with Lp(a), and only small amounts are associated with LDL and HDL. This observation suggests that Lp(a) may be the preferred carrier of OxPL. A strong correlation has been noted between Lp(a) and OxPL levels. The ability of Lp(a) to bind OxPL to its apo(a) moiety, particularly to small isoforms, may partially explain the increased atherogenicity of small Lp(a) isoforms and their association with higher CVD risk compared to larger isoforms [59]. OxPL-Lp(a) promotes inflammation, initiating the expression and synthesis of a range of proinflammatory chemokines and cytokines by the cells of the vessel wall [58]. One major consequence is that monocytes adhere to the endothelium and penetrate into the intima, where they first transform into macrophages and then accumulate cholesterol and become foam cells. Lp(a) may bind to macrophages via scavenger receptors via phosphocholine in OxPL. Following Lp(a) endocytosis into macrophages, its catabolism occurs in lysosomes, resulting in accumulation of cholesterol. OxPL-Lp(a) also induces smooth muscle cells to migrate from the media to the intima where they proliferate [58].

There are similarities between the atherogenic effect of Lp(a) and its role in the pathogenesis of calcific AVS [51]. The latter process is also mediated by OxPL, which exert a proinflammatory effect and promotes calcification. The role of OxPL in the progression of AVS is suggested by the results of the prospective ASTROMER study [62]. During a 3.5-year follow-up of 269 patients aged 18-82 years with mild to moderate AVS, as evaluated using Doppler echocardiography, the highest levels (upper tertile) of Lp(a) and proinflammatory OxPL associated with apolipoprotein B-containing lipoproteins (OxPL-apo B), were found to be independent predictors of AVS progression [62].

When discussing the pathogenic role of Lp(a), its thrombogenic properties should not be overlooked. Apo(a), with a structure homologous to plasminogen, inhibits its conversion to plasmin, which is a fibrinolytic and proteolytic enzyme. Lp(a) thereby promotes fibrin clot stabilization by inhibition of fibrin degradation. This mechanism explains the increased thrombotic risk observed in subjects with elevated Lp(a). In addition, Lp(a) affects platelet activation and aggregation, increases plasminogen activator inhibitor-1 (PAI-1) synthesis, and inhibits synthesis of the tissue factor pathway inhibitor (TFPI). These thrombogenic effects of Lp(a) have been described in detail in recent reviews [13,20,63] (**Figure 1**).

## **Management**

Recognizing the important role of elevated Lp(a) in the development of atherosclerosis and its clinical sequelae, American experts from the NLA have recently developed a separate statement on the management of this lipid disorder [5]. First, it is necessary to define the indications for measuring the Lp(a) level. The recommendations have been categorized into class IIa and class IIb indications. The following clinical situations have been considered class IIa recommendations for measuring Lp(a) level in adults  $\geq 20$  years of age:

1. A family history of premature atherosclerotic CVD (ASCVD) events in first-degree relatives (<55 years of age in men, <65 years of age in women);
2. A personal history of premature ASCVD, particularly without conventional risk factors;
3. Severe primary hypercholesterolemia (LDL-C  $\geq 190$  mg/dl) or suspected FH;
4. A very high risk of ASCVD to better define patients who are more likely to benefit from PCSK9 inhibitor therapy.

The most important class IIb recommendations include:

1. A family history or elevated Lp(a) level;



2. Calcific AS;

3. Recurrent and progressive atherosclerotic CVD despite optimal lipid-lowering therapy.

In the 2018 AHA/ACC guidelines on the management of blood cholesterol, screening Lp(a) measurement was considered to be relatively indicated in subjects with a family history of atherosclerotic CVD (<55 years of age in men, <65 years of age in women) and in subjects with a personal history of ASCVD without other major CVD risk factors [26]. Measuring Lp(a) has also been considered beneficial in adults aged 40-75 years with an intermediate risk of ASCVD (CVD event risk 7.5-19.9% over 10 years, as estimated using the US primary prevention risk calculator) [26].

Targeting Lp(a) measurements (at least initially) to individuals with acute coronary syndrome (ACS) and FH should be expected to yield a substantial population of individuals with elevated Lp(a), for whom risk can be re-assessed and treatment options such as PCSK9 inhibitors can be considered. Even 20-40% of individuals with ACS and FH are expected to have elevated Lp(a) [64]. 3.6 million new cases of CAD were reported in 2017 for the 54 countries covered by ESC statistics, contributing to a prevalence of 34.9 million [65,66]. FH is estimated to occur in 1/225-1/250 individuals in many populations, thus yielding large numbers of individuals with (probably undiagnosed) elevated Lp(a) [67].

In the 2019 ESC/EAS guidelines on the management of dyslipidemia, it was recommended to consider Lp(a) measurement at least once in a lifetime (as the level is strongly determined genetically), where testing is available [31]. As noted above, the goal is to identify subjects with a very high Lp(a) level ( $\geq 180$  mg/dL or  $\geq 430$  mmol/L) and thus a very high risk of ASCVD which is approximately equivalent to the risk associated with heFH. It has also been recommended to consider measuring Lp(a) in selected patients with a family history of premature of ASCVD and in order to re-classify subjects with borderline (moderate to high) risk. While the American experts defined the abnormal Lp(a) level as  $\geq 50$  mg/dL ( $\geq 100$  mmol/L) [5,26], no specific threshold value was given in the European guidelines [31].

Lp(a) level lowering may lead to a reduction in the risk of ASCVD. However, as indicated by estimation from genetic Mendelian randomization studies, Lp(a) level lowering could result in a smaller reduction in the risk of CAD compared to the same magnitude of LDL-C level lowering [68,69]. It has been estimated that to achieve the level of CAD event risk reduction (by 22%) that is associated with lowering LDL-C level by 38.7 mg/dL (approximately 1.0 mmol/L), Lp(a) level would need to be lowered by 65.7 mg/dL (95% CI

46.3-88.3) [56]. Thus, it is believed that a large reduction in Lp(a) level would be necessary to achieve a clinically meaningful reduction in the coronary event risk, and large benefits may be expected in patients with particularly high Lp(a) levels.

Despite an established association between high Lp(a) levels and CVD event risk, no specific recommendations on drug therapy targeted at Lp(a) level lowering have been included in the expert statements and guidelines on the management of dyslipidemia [5,26,31].

The effect of statins on Lp(a) level is controversial. Statins do not lower Lp(a) level, and some studies have even demonstrated an increase in Lp(a) levels related to statin treatment. In a meta-analysis of head-to-head randomized controlled trials, an increase in Lp(a) level has been noted in the statin arm [weighted mean difference (WMD) 4.14 mg/dL, 95% CI 0.15-8.12, P=0.042] [70]. A similar effect of statins on Lp(a) levels has been shown in another meta-analysis [71,72]. After exclusion of rosuvastatin trials, this effect was attenuated and not significant. Verhoeven *et al.* noted an increase in Lp(a) level from 66.4 (23.5-148.3) to 97.4 (24.9-160) mg/dL after 2 months since statin treatment initiation in patients with FH and high Lp(a) levels who had a small molecular mass apo(a) ( $\leq 22$  KIV<sub>2</sub> repeats), while no such effect was observed in patients with a large molecular mass apo(a) [73]. Based on this, the experts supported by the International Lipid Expert Panel (ILEP) suggested that in those with the baseline Lp(a) levels over 30 mg/dL and especially over 50 mg/dL the combination therapy of statins and ezetimibe and/or nutraceuticals with confirmed Lp(a)-reduction properties should be considered [72,74]. Statins are recommended in patients with elevated Lp(a) level not to reduce it but to decrease CVD risk [5].

Recently, the experts who developed the consensus-based recommendations from EAS and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) entitled “Quantified atherogenic lipoproteins for lipid-lowering strategies” have recommended that Lp(a) be measured to obtain a correct measurement of LDL-C when patients experience a poor response to LDL-C lowering therapy [75]. In such patients, the Lp(a) cholesterol moiety can contribute substantially to the measured or calculated LDL-C, and may be the reason for lower than expected reduction of LDL-C with statins. The correction of LDL-C with Lp(a) values reported in mg/dL or mmol/L can be performed as follows:

$$\text{Lp(a) corrected LDL-C (mg/dL)} = \text{LDL-C (mg/dL)} - [\text{Lp(a) mg/dL} \times 0.30]$$

$$\text{Lp(a) corrected LDL-C (mmol/L)} = \text{LDL-C (mmol/L)} - [\text{Lp(a) mmol/L} \times 0.0078]$$

As indicated by a meta-analysis of randomized clinical trials, ezetimibe monotherapy leads to small decrease in plasma Lp(a) level but in the light of the above presented data, this may be not a clinically meaningful effect [76].

Until now, niacin has been the most potent Lp(a) level-lowering drug (by up to 30%). Niacin also lowers triglycerides and increases circulating concentrations of HDL-C [5]. However, combination therapy with niacin and statins does not lower the risk of CVD events, but causes serious adverse effects [77-79]. For these reasons, niacin has not been licensed for use in Europe.

Recently, after the publication of subanalyses of two secondary prevention trials with PCSK9 inhibitors, including the FOURIER study of evolocumab [3] and the ODYSSEY OUTCOMES study with alirocumab [4], hope has emerged that these drugs may become useful in patients with high Lp(a) levels. Both drugs potently reduce LDL-C by inhibiting PCSK9 and thereby upregulating hepatic LDL-receptors. However, the PCSK9 inhibitors also reduce circulating concentrations of Lp(a). In a recently published meta-analysis of 27 randomized clinical trials, including 11,864 patients, a substantial, 21% reduction in Lp(a) level (95% CI 19.5-24.3) was noted in patients treated with evolocumab or alirocumab [80]. In the the most current analysis the authors evaluated the effects of evolocumab on non-HDL, ApoB as well as Lp(a) in various patient populations over time [81]. Finally, data from 7690 patients from 15 phase 2 and phase 3 studies with a duration ranging from 12 weeks to 5 years were pooled. Compared with placebo, evolocumab at both approved dosing regimens substantially reduced median Lp (a) (Q2W dose: -22% to -38%, monthly dose: -20% to -33%) at 12 weeks. The effect persisted over 5 years and was consistent among the patient populations examined (hypercholesterolemia/mixed dyslipidemia, statin intolerance, heterozygous FH, and type 2 diabetes mellitus) [81].

Post hoc analyses of the FOURIER and ODYSSEY OUTCOMES study data showed that Lp(a) level lowering induced by treatment with evolocumab or alirocumab was independently associated with a reduction in the CVD event rate [3,4]. In the FOURIER study, the median Lp(a) level in patients with stable CAD treated with statins was 37 mg/dl [3]. The relative risk of CAD death, non-fatal MI or the need for immediate coronary revascularization over 2.2 years of follow-up was the highest in the upper quartile of Lp(a) level (1.22, 95% CI 1.01-1.48 compared to the lowest quartile) and did not depend on LDL-C level. After 48 weeks of evolocumab therapy, the Lp(a) level was significantly reduced by 26.9% (6.2-46.7%) and compared to placebo. The risk of the composite endpoint was reduced by 23% (HR 0.77, 95% CI 0.67-0.88) in patients with Lp(a) level above the median and only by 7% (HR 0.93, 95%

CI 0.80-1.08) in patients with Lp(a) level below the median. The numbers needed to treat (NNT; 3 years of treatment) were 40 and 105, respectively [3]. In the ODYSSEY OUTCOMES study in statin-treated patients after an ACS, the results were similar to the FOURIER study. Baseline Lp(a) concentration in the placebo group was a predictor of CAD death, non-fatal MI, ischemic stroke or hospitalization due to unstable angina (major adverse CAD events, MACE) over 2.8 years of follow-up [4]. Baseline Lp(a) quartiles (<6.7 mg/dL, 6.7 to <21.2 mg/dL, 21.2 to <59.6 mg/dL,  $\geq$ 59.6 mg/dL) also predicted Lp(a) lowering with alirocumab after 4 months of treatment, as well as the relative (HR 0.95, 95% CI 0.97-1.15; 0.85, 0.71-1.03; 0.79, 0.66-0.94; and 0.83, 0.70-0.98, respectively), and absolute risk reduction, at 0.4% (-1.2 to 2.1), 1.4% (-0.3 to 3.1), 2.3% (0.6 to 4.1), and 2.1% (0.2 to 3.9), respectively. Each 1.0 mg/dL decrease in Lp(a) with alirocumab was associated with a significant reduction in MACE (HR 0.994, 95% CI 0.990-0.999), and a 1.0 mg/dL decrease in Lp(a) corrected LDL-C was also associated with a reduced risk of MACE (HR 0.996, 95% CI 0.994-0.998). The authors concluded: “Baseline lipoprotein(a) and corrected LDL-C levels and their reductions by alirocumab predicted the risk of MACE after ACS. Lp(a) lowering by alirocumab is an independent contributor to MACE reduction, which suggests lipoprotein (a) should be an independent treatment target after ACS” [4].

However, the recent post hoc analysis of 10 phase-III ODDYSSEY studies (not including the ODYSSEY OUTCOMES study) showed that reducing baseline Lp(a) level by 23.5 mg/dL (8.0-67.0) with alirocumab (by 26.6% vs 2.5% with placebo and by 21.4% vs 0.0% with ezetimibe) did not result in a significant reduction in major adverse coronary events (MACE) independently of LDL-C level lowering [82]. The authors concluded that reducing the risk of MACE by targeting Lp(a) may require greater reductions in Lp(a), with more potent therapies and/or higher initial Lp(a) levels. Thus, the results of the ODYSSEY OUTCOMES study are not consistent with the results of the meta-analysis of the phase-III ODDYSSEY studies [82].

Currently, NLA experts believe that adding ezetimibe or a PCSK9 inhibitors is reasonable only in very high-risk patients with LDL-C $\geq$ 70 mg/dL (non-HDL-C $\geq$ 100 mg/dL and Lp(a)  $\geq$ 50 mg/dL or  $\geq$ 100 mmol/L) [5]. Thus, PCSK9 inhibitors are mainly used for LDL-C reduction and are not commonly employed in the management of elevated Lp(a). A clinical trial is needed to investigate the effectiveness PCSK9 inhibition on CVD risk in subjects with elevated Lp(a).

The most desirable reduction in Lp(a) level, leading to a large reduction in the ASCVD event risk can be achieved by Lp(a)-specific apheresis. This therapy reduces Lp(a) level by 60-70% per each therapeutic session [83], but needs to be repeated every 1-2 weeks. In one

study, patients with progressive CAD and Lp(a) level elevated to  $>2.14$  mmol/L (median 4.0 mmol/L), Lp(a) apheresis (on a background of statin therapy) reduced the mean annual major CAD event rate to 0.144 at 5 years ( $5.0\pm 3.6$  years) compared to 1.056 in the pre-apheresis period ( $5.6\pm 5.8$  years) [84]. The median Lp(a) level after apheresis sessions was reduced to 1.07 mmol/L. In another study, the annual CVD event rate at 5 years of apheresis in statin-treated patients was reduced to  $0.11\pm 0.15$  compared to  $0.58\pm 0.53$  in the two years before the therapy [85]. Baseline Lp(a) level was  $108.1\pm 46.1$  mg/dL, and the mean reduction after apheresis was 68.1%. Another study evaluated the effect of apheresis on coronary atherosclerosis in atorvastatin-treated patients with coronary artery disease and Lp(a)  $>50$  mg/dL [86]. Compared to the control group (receiving only atorvastatin treatment), a regression in atherosclerotic plaque volume was noted in patients treated with apheresis for 18 months. However, apheresis was not included as a therapy of high Lp(a) levels in the National Lipid Association statement [5]. It is a time-consuming method and thus it is reserved for patients with high Lp(a), and progressive, severe CVD.

Studies on genetic approaches to therapy are currently underway. These methods involve inhibiting apo(a) synthesis; either with antisense oligonucleotides against apo(a), or by employing small interfering RNA (siRNA) technology. It has been demonstrated that in patients with atherosclerotic CVD and Lp(a)  $\geq 60$  mg/dL, an antisense oligonucleotide against apo(a) [AKCEA-Apo(a)-LRX] reduced Lp(a) level by up to 80% when administered subcutaneously at the dose of 20 mg/week [87-89]. Recently, it has been reported that subcutaneous administration of AKCEA-Apo(a)-LRX at a range of doses (20, 40 or 60 mg) and at different time intervals (every week, every two weeks or every four weeks) in patients with established CVD and Lp(a) levels of at least 60 mg/dl, resulted in dose-dependent reduction of Lp(a) (by 35% to 80%) [90]. The cardiovascular outcomes trial with antisense oligonucleotide (TQJ230) (Lp(a)HORIZON trial) is still ongoing [91] (**Figure 1**).

### **Summary & Clinical Perspective**

High plasma concentration of Lp(a) (already over 30 mg/dL, and especially  $\geq 50$  mg/dL or  $\geq 100$  mmol/L) is a risk factor for ASCVD and AVC, albeit not as strong as LDL-C. The independent association of Lp(a) with the risk of these diseases has been proven by genetic studies. The atherogenicity of Lp(a) is mostly related to its OxPL content.

In order to identify individuals with elevated Lp(a), it is reasonable to measure Lp(a) once in a lifetime in every individual. A single measurement is sufficient as Lp(a) concentration is determined predominately by genetics. Lp(a) measurements are most

warranted in subjects with premature ASCVD (<55 years of age in men, <60 years of age in women) without conventional CVD risk factors. Lp(a) measurement should also be considered if premature ASCVD developed in a first-degree relative. This recommendation also applies to individuals with severe primary or suspected FH, as FH may be associated with an elevated Lp(a) level. The above class IIa recommendations also include a high risk of ASCVD to define better patients who will benefit more from additional PCSK9 inhibitor therapy. Weaker (class IIb) recommendations include patients with recurrent ASCVD events or progression of atherosclerosis despite optimal lipid-lowering therapy, those with calcific AS, and subjects with a family history of high Lp(a) levels. In fact, based on some available data, the measurement of Lp(a) should be considered in all patients at very high and extremely high CVD risk, especially in those after ACS in order to reduce Lp(a) related residual risk; however, we still need some more data in order to confirm this indication in such a wide group of patients, also taking into account the cost-effectiveness.

A specific therapy to lower Lp(a) levels is not yet available. The most important therapeutic goal is to reach the target LDL-C or non-HDL-C level depending on the risk category, mostly using statins, and possibly with an addition of ezetimibe. Adding a PCSK9 inhibitor is recommended in patients at very high risk in whom the target LDL-C level has not been reached. Studies are underway on genetic therapy to inhibit apo(a) synthesis, and thereby reduce. The initial results regarding the efficacy of such approaches to Lp(a)- lowering are very promising.

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**Table 1.** Relationship between Lp(a) level as a risk factor for CVD and LDL-C level – summary of main data.

Authors	Study	N	Elevated Lp(a) vs. low or lower level	Elevated Lp(a) as a risk factor for CVD events in relation to LDL-C level
Kronenberg MF, et al. 1999 (36)	Observational: Bruneck study	500	>32 mg/dL	associated with risk when LDL-C >3.3 mmol/L
Luc G, et al. 2002 (37)	Observational: PRIME	9133	≥33 mg/dL	associated with risk when LDL-C >3.7 mmol/L
Suk Danik J, et al. 2006 (38)	Observational: Women's Health Study	27,791	≥44 mg/dL	associated with risk when LDL-C >3.1 mmol/L
Khera AV, et al. 2014 (28)	Interventional: JUPITER (rosuvastatin therapy)	7730 (baseline) 7739 (on statin white cohort)	baseline Lp(a) 23 nmol/L (median)	<ul style="list-style-type: none"> <li>● baseline Lp(a) associated with risk (adjusted per 1-SD increment in Ln [Lp(a)]) independently of LDL-C and other factors</li> <li>● on-statin Lp(a) associated with risk (adjusted per 1-SD increment in Lp(a) independently of LDL-C and other factors</li> </ul>
Konishi H, et al. 2015 (39)	Interventional (percutaneous coronary intervention)	599	>30 mg/dL	associated with all cause deaths and ACS, even when LDL-C < 2.5 mg/dL
Zhao Y, et al. 2016 (40)	Observational: Cardiovascular Health Study (high risk: DM, 10-year Framingham risk >20%)	3,251	≥65 mg/dL	associated with CHD risk and all cause deaths, even when LDL-C <1.8 mmol/L
Verbeek R, et al. 2018 (41)	Observational: EPIC Norfolk + Copenhagen City Heart Study (CCHT)	26,102	≥80 <sup>th</sup> percentile cohort (≥45.4 mg/dL in EPIC Norfolk and ≥84 mg/dL in CCHT)	<ul style="list-style-type: none"> <li>● only modestly associated with risk when LDL-C &lt;2.5 mmol/L</li> <li>● CVD risk increase conveyed by Lp(a) appeared to diminish at lowest LDL-C levels</li> </ul>
Willeit P, et al. 2018 (42)	Meta-analysis of randomized, placebo controlled statin outcome	29,069	≥30 mg/dL (baseline) ≥50 mg/dL (on statin)	● baseline (≥30 mg/dL) and on statin (≥50 mg/dL) Lp(a) level associated with CVD event risk approximately

	trials in patients with established CVD			linearly <ul style="list-style-type: none"> <li>● Lp(a) <math>\geq 50</math> mg/dL associated with CVD risk even when baseline or on statin LDL-C <math>\leq 3.0</math> mmol/L</li> </ul>
Hippe DS, et al. 2018 (43)	Interventional: AIM-HIGH (intensive lipid-lowering therapy) - carotid artery magnetic resonance imaging	152	1-SD increase in median baseline Lp(a) (32 nmol/L)	associated with increase of % wall volume (% WV) when LDL-C $< 1.8$ mmol/L
O'Donoghue MI, et al. 2019 (3)	Interventional: FOURIER - established ASCVD (statin, ezetimibe, evolocumab)	25,096	doubling of median baseline Lp(a) (37 mg/dL)	<ul style="list-style-type: none"> <li>● associated with increased risk independently of LDL-C level</li> <li>● reduction of Lp(a) level on evolocumab therapy associated with decreased risk independently of LDL-C lowering</li> </ul>
Bittner VA, et al. 2020 (4)	Interventional: ODYSSEY OUTCOMES - after ACS (statin, ezetimibe, alirocumab)	18,924	quartiles: $< 6.7$ mg/dL, 6.7 to $< 21.2$ mg/dL, 21.2 to $< 59.6$ mg/dL, $> 59.6$ mg/dL	<ul style="list-style-type: none"> <li>● higher baseline Lp(a) quartile associated with increased risk independently of LDL-C level</li> <li>● reduction of Lp(a) levels on alirocumab therapy associated with decreased risk independently of LDL-C lowering</li> </ul>

ABBREVIATIONS: CVD – cardiovascular disease, CHD – coronary heart disease, LDL-C – low density lipoprotein cholesterol, ACS – acute coronary syndrome, SD – standard deviation.

**FIGURE'S LEGEND:**

**Figure 1.** The relationship between plasma concentrations of Lp(a) and relative risk of CVD. Approximate values summarised from the studies cited in this paper. Text in arrows indicates factors for elevating [LP(a)] and promising therapeutic strategies to reduce [Lp(a)] The grey shaded area shows the approximate distribution of [Lp(a)] in the population.

Abbreviations: ACS, acute coronary syndromes; CV, cardiovascular; FH, familial hypercholesterolaemia; Lp(a), Lipoprotein(a); PCSK9 Proprotein convertase subtilisin/kexin type 9; SNP, single nucleotide polymorphism.



