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Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease:

A Scientific Statement From the American Heart Association

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The International Atherosclerosis Society endorses this statement.

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Abstract

High levels of lipoprotein(a) [Lp(a)], an apoB100-containing lipoprotein, are an independent and causal risk factor for atherosclerotic cardiovascular diseases through mechanisms associated with increased atherogenesis, inflammation, and thrombosis. Lp(a) is predominantly a monogenic cardiovascular risk determinant, with ≈70% to ≥90% of interindividual heterogeneity in levels being genetically determined. The 2 major protein components of Lp(a) particles are apoB100 and apolipoprotein(a). Lp(a) remains a risk factor for cardiovascular disease development even in the setting of effective reduction of plasma low-density lipoprotein cholesterol and apoB100. Despite its demonstrated contribution to atherosclerotic cardiovascular disease burden, we presently lack standardization and harmonization of assays, universal guidelines for diagnosing and providing risk assessment, and targeted treatments to lower Lp(a). There is a clinical need to understand the genetic and biological basis for variation in Lp(a) levels and its relationship to disease in different ancestry groups. This scientific statement capitalizes on the expertise of a diverse basic science and clinical workgroup to highlight the history, biology, pathophysiology, and emerging clinical evidence in the Lp(a) field. Herein, we address key knowledge gaps and future directions required to mitigate the atherosclerotic cardiovascular disease risk attributable to elevated Lp(a) levels.

Keywords

AHA Scientific Statements; apolipoprotein B100; atherosclerotic cardiovascular disease; cholesterol, low-density lipoprotein; lipoprotein(a)

Cardiovascular disease (CVD) is the leading cause of death and disability worldwide.[1] Advances over the past 70 years have led to the identification of common and novel CVD risk factors, and the introduction of many pharmacological interventions for use in primary and secondary prevention, as well. Despite significant progress, there remains substantial residual CVD risk, even among well-treated groups.[2] The role of apolipoprotein B100 (apoB) containing lipoproteins as the central determinants of atherogenesis and risk for CVD is well established.[3] The apoB concentration in plasma is a marker of both cardiovascular risk and disease severity.[4] Lipoprotein(a) [Lp(a)] is an apoB-containing lipoprotein bound to a hydrophilic, highly glycosylated protein called apolipoprotein(a) [apo(a)][5,6] (Figure, see location a).

Epidemiological, genome-wide association, and Mendelian randomization data[7–11] provide clear support for a causal role for elevated Lp(a) in the development of atherosclerotic cardiovascular disease (ASCVD).[12] What is defined as high Lp(a) levels can differ, depending on (1) the assay and units of measurement (milligrams per deciliter versus nanomoles per liter) used; (2) the population ancestry; and (3) the underlying disease and clinical characteristics of the cohort. These factors have made it difficult to establish

universal thresholds for clinical use.[13,14] Our current ability to lower Lp(a) with approved apoB and low-density lipoprotein cholesterol (LDL-C)–lowering therapies[15] may not be optimal for reducing the cardiovascular risk associated with high Lp(a) levels.[16]

Novel therapies for Lp(a) lowering that target hepatic synthesis of apo(a) are in various phases of clinical trials (NCT04606602-SLN360, NCT04023552-TQJ230, and NCT04270760-AMG890). In addition, outcome studies using lipoprotein apheresis to remove Lp(a) and other apoB-containing lipoproteins from plasma are ongoing (NCT02791802). The completion of these studies will provide critical insight into the cardiovascular benefits of lowering Lp(a) and provide further evidence supporting or refuting its role as a causal risk factor.

This consensus statement, written by a multidisciplinary group of experts, will highlight the established and emerging biology, pathophysiology, and clinical epidemiology of Lp(a). It will identify key gaps in our understanding of the role of Lp(a) in ASCVD. The overall goal is to provide a rationale for targeted research efforts that can provide clinical direction for risk reduction, encourage appropriate screening strategies, and highlight the need for further studies of Lp(a) biology.

HISTORICAL PERSPECTIVE

In 1963, the geneticist Kåre Berg identified a unique antigen in the low-density lipoprotein (LDL) fraction of human serum that he called apolipoprotein(a).[5] Studying families, Berg soon determined the strong genetic control of Lp(a) levels, and by 1974, he had linked the presence of Lp(a) to coronary heart disease (CHD).[17] Confirmation of the association of Lp(a) with CHD required improvements in the assays to measure Lp(a),[18] but by the mid-1980s, results from numerous small to modest retrospective and cross-sectional studies supported Berg's initial observation.[19] Results from some early prospective studies suggested a central role for Lp(a) in CVD,[20,21] whereas others did not.[22] Strong genetic evidence supporting Lp(a) as an independent and potentially causal risk factor for ASCVD was reported in large studies published in 2009,[9,23] in support of earlier smaller studies demonstrating associations of Lp(a) phenotypes/genotypes with CVD.[24,25]

In parallel with the early population-based studies, efforts by several groups resulted in the isolation and purification of Lp(a),[26] which provided key insights into the structural and biochemical characteristics of this lipoprotein. In the late 1980s, the cloning and sequencing of a cDNA corresponding to the gene encoding apo(a) (now designated *LPA*) demonstrated that *LPA* had evolved through duplication of the plasminogen (*PLG*) gene, providing important clues to some of the proposed pathophysiological mechanisms of Lp(a).[27,28] Although *PLG* encodes 5 kringles (80–90 amino acid–long triple-looped protein structures) and a fibrinolytic protease region, *LPA* in humans lacks sequences encoding *PLG* kringles I to III and encodes 10 kringle IV subtypes (KIV1 through KIV10) similar to *PLG* kringle IV, followed by 1 *PLG* kringle V–like domain, and an inactive protease region (Figure, locations a and d).[28]

DETERMINANTS OF PLASMA Lp(a) LEVELS: GENETICS, PRODUCTION, AND CLEARANCE

Plasma Lp(a) levels arise from codominant expression of 2 *LPA* alleles. As such, in any given individual, the Lp(a) plasma level represents the sum of levels contributed by each *LPA* allele. Most individuals have 2 detectable circulating Lp(a) isoforms, each arising from a differently sized apo(a); the smaller isoform is usually present at higher levels in plasma. Small amounts of non–apoB-bound apo(a) fragments in plasma and in urine have been reported, and their physiological relevance remains unknown.[29–33]

Lp(a) levels are ≈70% to ≥90% genetically determined. The KIV2 copy number variant is inversely related to the Lp(a) concentration and is estimated to associate with 19% to 69% of interindividual heterogeneity in Lp(a) concentrations.[34] In addition, numerous single nucleotide polymorphisms (SNPs) in the *LPA* locus strongly associate with Lp(a) levels.[16] Although some are in linkage disequilibrium with the KIV2 copy number variant, SNPs independently associated with both high and low levels of Lp(a) have been reported.[35]

Outside the *LPA* gene locus, the *APOE*ε2 allele associates with lower Lp(a) levels, explaining an estimated 0.5% of the Lp(a) concentration variation.[35] Recent genome-wide association studies have also pointed to additional relationships of Lp(a) levels with *APOH*[36]; this gene codes (β_2-glycoprotein 1 that has been found to be associated with PCSK9 (proprotein convertase subtilisin kexin type 9) and binds to apo(a) KIV2.[37] β_2-Glycoprotein 1 is a known participant in coagulation.[36,38] The contribution of other genes to the regulation of Lp(a) levels requires further investigation. In the absence of various clinical conditions,[39] levels of Lp(a) have not been shown to substantially change across the life course, although some variability occurs, as documented by intraindividual temporal variability in serial measurements from placebo-treated subjects in clinical trials.[40] Results from the latter study demonstrate intraindividual biological variability of Lp(a) up to 20% suggesting that, for some patients, a mean of 2 Lp(a) determinations be obtained at different times to refine ASCVD risk stratification. The distribution of Lp(a) levels reported in large cohorts varies >100-fold,[16] with the highest variation observed in populations of European descent in which Lp(a) levels are highly positively skewed. In general, population Lp(a) levels are reported as median values because they are not normally distributed.

It is well established that Lp(a) levels differ across self-reported racial and ethnic groups. Black individuals of African descent and South Asian populations have higher median Lp(a) levels than White or East Asian individuals.[39] The difference between Black individuals of African descent and White individuals may result primarily from higher levels of Lp(a) associated with medium apo(a) alleles in people of African descent compared with White individuals. In White individuals, high Lp(a) levels are associated with small alleles.[41,42] For several SNPs that are in linkage disequilibrium with *LPA* allele sizes, the associations with Lp(a) levels in plasma differ between different ancestry groups.[43,44] Recently published data from diverse cohorts, such as the ARIC study (Atherosclerosis Risk in Communities),[45,46] the MESA study (Multi-Ethnic Study of Atherosclerosis),[47] and the MASALA study (Mediators of Atherosclerosis in South Asians Living in America),[48] link high plasma Lp(a) levels to increased ASCVD risk in various populations. However, there is large variability

between studies in the methods used to measure Lp(a), making it difficult to compare findings across different populations.

The assembly of Lp(a) from apo(a) and apoB expressed in hepatocytes and the pathways for Lp(a) removal from the circulation are not completely defined. Several mechanisms may contribute to the efficiency of Lp(a) synthesis.[49] The best studied is apo(a) isoform size-dependent variation in the secretion rate of apo(a). Large apo(a) isoforms are retained longer in the endoplasmic reticulum, despite being folded at the same rate as smaller isoforms and are subjected to increased degradation by the proteasome. This mechanism contributes to the general inverse correlation between apo(a) isoform size and plasma Lp(a) levels.[49] However, other mechanisms may contribute to plasma Lp(a) levels through isoform-dependent or independent mechanisms, including the modulation of *LPA* expression, mRNA stability of differently sized *LPA* transcripts, and isoform size–dependent regulation of apo(a) translation efficiency. The assembly of Lp(a) particles involves a 2-step process whereby initial lysine-dependent noncovalent interactions between apo(a) and apoB precede the formation of covalent disulfide bonds between apo(a) and apoB that result in Lp(a) particles.[49] The covalent bonding of apo(a) to apoB-containing lipoproteins occurs extracellularly (on, or proximal to, the plasma membrane), possibly using an oxidase-like enzyme secreted from the cells.[50,51] The domains involved in the noncovalent association between apo(a) and apoB have been identified: respectively, weak lysine binding sites in apo(a) and lysine-containing sequences in the N-terminal domain of apoB, suggesting the potential for inhibition of this first step in Lp(a) assembly using small molecules targeted to the lysine-binding domains of apo(a).[49] There is also ongoing controversy about the nature of the apoB-containing lipoprotein particle that binds to apo(a) to create Lp(a): whether apo(a) during its lifespan in circulation may exchange between more than 1 apoB-containing lipoprotein particle, and the role of internalized and recycled apo(a) and apoB-containing lipoproteins.[52] However, to date, a significant measurable pool of free apo(a) in plasma has not been identified, which suggests that free circulating apo(a) and recycling of apo(a) within the circulation may have a minor role in Lp(a) metabolism.[52]

Initial metabolic studies in humans to elucidate the regulation of Lp(a) were performed by various laboratories using radiolabeled apo(a).[6] Combined with recent studies using stable isotopes, human studies show evidence for both clearance and production of apo(a) contributing to plasma levels of Lp(a).[52] The liver has been identified as the primary site of Lp(a) catabolism; however, the receptors involved await definitive identification.[53,54] The LDL receptor may play a role in Lp(a) uptake under certain circumstances, such as the use of statins with a PCSK9 inhibitor in patients with elevated Lp(a).[55] However, results from earlier turnover studies showed similar rates of radiolabeled Lp(a) clearance in homozygous LDL receptor deficiency compared to those with normal LDL receptor activity.[56] A role for plasminogen receptors including Plg-R_{KT} has also been suggested,[57] although human data are lacking. Additional hepatic receptors such as SR-B1 (scavenger receptor class B type 1), LRP1, and LRP8 (low-density lipoprotein receptor–related protein-1 and -8)[54] could also play a role in Lp(a) clearance, although their relative contributions to Lp(a) catabolism in humans are unknown. Nonetheless, levels of circulating Lp(a), apo(a) isoform size, Lp(a)-associated proteins, and Lp(a) lipid content may modulate selectivity for particular receptors. Data from recently published studies suggest that additional proteins associated

with Lp(a) (ApoH, ApoCIII, ApoE) may also play a role in the clearance of the Lp(a) particle.[36,58,59]

The restricted species distribution of Lp(a) (orthologues of apo(a) are only found in humans, Old World monkeys, apes, and hedgehogs) poses challenges to the design and interpretation of animal model data. Of note, only human Lp(a) contains a strong lysine binding site in apo(a) KIV10 which may limit the applicability of findings about the assembly of Lp(a) from other species. The lack of a proper animal model has hindered elucidation of the true pathophysiological mechanisms of Lp(a) and, hence, the identification of therapeutic targets. In Table 1, we highlight some priorities for ongoing knowledge gaps.

QUANTIFICATION OF Lp(a) IN HUMAN PLASMA

Determination of Lp(a) levels in clinical chemistry laboratories is performed by immunoassays using antibody specific to apo(a) with 2 major problems affecting the accuracy of Lp(a) results and their clinical interpretation. The first problem, related to the size variability of apo(a), results in under- or overestimation of Lp(a) levels measured by different immunoassays as clearly elucidated using an ELISA method based on a monoclonal antibody that does not recognize the variably repeated KIV2 motifs of apo(a).[60] However, recent commercially available methods based on the use of 5 independent calibrators with a large range of Lp(a) levels and a suitable distribution of apo(a) isoforms are able to quantify Lp(a) with a reduced impact of apo(a) size if the values of the assay calibrators are well validated.[18] The use of this methodology on automated analyzers results in high precision although the assays are not able to fully eliminate the impact of apo(a) size variability in all evaluated samples. However, considering the large distribution of Lp(a) levels in populations, the use of Lp(a) levels measured by these assays for risk stratification should not result in high numbers of misclassifications. Studies specifically addressing this issue need to be performed.

The second problem is that, at present, there are 2 approaches to immunoassay calibration resulting in 2 different units for reporting Lp(a) results. The first highly sensitive assay for measuring Lp(a) was reported in the 1970s by Albers et al[61] before the structure of Lp(a) was elucidated. The authors purified Lp(a) from plasma of a single donor and the protein, lipid, and carbohydrate components were individually measured. The sum of all the components of this purified Lp(a) were assigned a value in milligrams per deciliter and used as the assay calibrator. All the subsequently developed immunoassays were calibrated in milligrams per deciliter of total Lp(a) mass although the assays only measured the apo(a) component of Lp(a). This historic approach to assay calibration, which assumed that the mass of the individual Lp(a) components was constant in all the individuals, is unacceptable, in particular, considering the well-known extreme size variability of apo(a).

The gold standard ELISA method[60] was calibrated in nanomoles per liter of apo(a), thus reflecting the number of Lp(a) particles. Recognizing the scientific validity of this approach, a value in nanomoles per liter was assigned to the reference material SRM-2B developed by the International Federation of Clinical Chemistry. Following the National Heart, Lung, and Blood Institute recommendations for expressing Lp(a) results in nanomoles per liter,[12,62]

several commercially available methods have been introduced with values in nanomoles per liter traceable to the International Federation of Clinical Chemistry reference material. Several Lp(a) guidelines and statements have recommended reporting Lp(a) values in nanomoles per liter.[63–65] The existence of 2 different units for expressing Lp(a) levels is confusing to clinicians and patients and there is no unbiased conversion factor from milligrams per deciliter to nanomoles per liter or vice versa. Improvements in methods for measuring Lp(a), the traceability of the measured value to a common reference material, and the reporting of values in nanomoles per liter are essential steps toward crucially needed harmonization of Lp(a) assays. A recently published article[66] describes the development and validation of a mass spectrometry method as a proposed candidate reference method for Lp(a) standardization. The high correlation of values with those obtained by the gold standard ELISA and the excellent recovery of the reference material indicate that no significant changes in calibration are expected for methods that are traceable to the World Health Organization/International Federation of Clinical Chemistry Reference Material SRM-2B.

The cholesterol content of Lp(a) is included in all clinical assays that quantify LDL-C, including the reference method β-quantification.[18] Therefore, some studies have tried to account for this by subtracting, from LDL-C, 30% of the mass concentration (milligrams per deciliter) of Lp(a). Results from a recent study in a small population of subjects with high Lp(a) demonstrated a significant variability in the amount of cholesterol in isolated Lp(a) particles.[67] These recent data confirm that estimating the cholesterol content of Lp(a) by a fixed percentage of measured Lp(a) in milligrams per deciliter requires several assumptions that limit its use in clinical practice. Lp(a) is measured by immunochemical methods and therefore even assays reporting Lp(a) values in milligrams per deciliter only estimate the total mass of the particle. The concentration of apoB and apoB-containing lipoprotein particles, including LDL, are more highly associated with ASCVD risk than mass of LDL-C or size of LDL particles.[3] Moreover, a recently completed study showed that, in statin-treated patients, elevated apoB and non–high-density lipoprotein cholesterol, but not LDL-C, were associated with residual risk of all-cause mortality and myocardial infarction.[68] Additional work is needed to encourage the use of standardized methods to measure Lp(a). In Table 2, we provide clinical use considerations for Lp(a) measurements, and in Table 3, we provide insight on the impact of Lp(a) to the plasma pool of apoB. It is important to note that Lp(a) is an ASCVD risk modifier and contributes to residual ASCVD risk at all levels of LDL-C and ApoB.

GENETIC APPROACHES TO ASCERTAINING Lp(a) ATTRIBUTABLE RISK

Its highly genetically determined levels make Lp(a) an excellent candidate for Mendelian randomization studies. In recent years, studies examining associations of *LPA* genotypes with Lp(a) levels and disease risk have provided supporting evidence for a causal relationship between high Lp(a) levels and ASCVD.[16] Large genetic epidemiological studies have documented strong, graded associations of high Lp(a) levels and corresponding *LPA* risk genotypes with increased risk of CHD and calcific aortic valvular disease (CAVD). In key studies including a large classic Mendelian randomization study (N>40000) with data on Lp(a) levels and KIV2 genotypes, each 2-fold higher level of genetically determined

Lp(a) levels was associated with 22% greater risk of myocardial infarction.[23] In a large case-control study including 3100 CHD cases genotyped for ≈49000 genetic variants in 2100 candidate genes, 2 *LPA* SNPs had the strongest association with risk of CHD of all SNPs tested; SNP carriers versus noncarriers had higher Lp(a) levels and a lower number of KIV2 repeats.[9] Of note, *LPA* SNPs associated with Lp(a) levels independently of apo(a) isoform size have been associated with CHD.[35]

In 2013, a genome-wide association study demonstrated an association of a particular SNP in the *LPA* locus with CAVD with an odds ratio of 2.05 per allele,[70] an even greater risk than that reported for CHD.[9] Subsequent prospective data from 2 combined Danish Mendelian randomization studies[71] and the EPIC-Norfolk study (European Prospective Investigation into Cancer Norfolk)[72] cohorts supported these results. A post hoc analysis of the ASTRONOMER randomized controlled trial (Effects of Rosuvastatin on Aortic Stenosis Progression), in which statin therapy did not slow progression of aortic stenosis, found accelerated progression of aortic stenosis in the top tertile of Lp(a) levels.[73] *LPA* remains the only monogenic risk factor identified for aortic stenosis.

Associations of Lp(a) with cerebrovascular disease and stroke are less clear. Although a recent Mendelian randomization analysis of data from 2 combined Danish cohorts suggests that Lp(a) is a risk factor for stroke (albeit not nearly as strong as for coronary disease or CAVD),[74] previous analyses of smaller cohorts have not found an association.[75] However, a role for Lp(a) in risk for stroke is further supported by a large genetic study (N>100000) in which 4 *LPA* SNPs, associated with low Lp(a) levels, were associated with 13% lower risk of stroke per 1 SD genetically lower Lp(a) levels. This same study observed ≈30% to 40% lower risk of CHD, peripheral artery disease, and CAVD.[76] In other studies, Lp(a) has been suggested as an independent risk factor for prevalent lower extremity atherosclerotic disease,[75,77] with risk alleles predictive of peripheral artery disease as well.[76,78] Recent studies have also described a greater risk of cardiovascular and all-cause mortality for the highest Lp(a) levels/lowest number of *LPA* KIV2 repeats.[79]

The association of *LPA* genotypes that determine circulating Lp(a) levels with risk of ASCVD represents strong evidence of causality, because genotype-disease associations in homogeneous populations, in general, are unconfounded and cannot result from reverse causality. Nonetheless, final proof of causality awaits randomized cardiovascular outcome trial data. In Table 4, we provide some priorities to address our existing gaps in knowledge.

CARDIOVASCULAR RISKS ASSOCIATED WITH Lp(a) AND ISSUES OF EFFECT MODIFICATION BY apo(a) SIZE AND ANCESTRY

Some *LPA* SNPs have been associated with apo(a) size and ASCVD risk.[35] Although the evidence of an association between Lp(a) levels and ASCVD is robust, as underscored in a large population-based study of ancestry groups with different Lp(a) level distributions that showed similar ASCVD risks by a given incremental increase in Lp(a) levels,[69] the question whether apo(a) sizes might be associated with ASCVD has attracted much interest. Several early studies reported that the presence of a small apo(a) or the combination of a high Lp(a) level and a small apo(a) isoform was associated with ASCVD. The close association

between high Lp(a) levels and small apo(a) sizes in samples from non-Black individuals, and the methodological difficulties in assessing allele-specific apo(a) levels, as well, have made it challenging to dissect this issue. In many recent studies, assessment of either the sum of the 2 combined apo(a) allele sizes or the dominant apo(a) size in a given individual have been used. Studies have collectively reported both the presence and the absence of any association of apo(a) size with ASCVD.[11,80] Although a large Mendelian randomization study in a South Asian cohort identified an independent causal role in ASCVD for both Lp(a) levels and apo(a) isoform size,[11] a definitive role for apo(a) size independent of Lp(a) levels in conveying ASCVD risk remains to be firmly established. For the latter, appropriate genetic tools in a variety of cohorts must be used, as up to now studies have used analytical techniques that might not necessarily be appropriate to answer this question. If smaller isoform sizes are independently associated with increased risk, this implies that certain pathogenic mechanisms mediated by apo(a) (see later in this scientific statement) are influenced by isoform size. At present, measurements of the Lp(a) molar concentration are believed to be sufficient for clinical assessment of ASCVD risk because the addition of apo(a) size data does not further discriminate risk in most patients.

A recent analysis from the UK Biobank provided the largest study to date examining the risk of ASCVD associated with Lp(a) in a broad and diverse sample of 460 000 individuals.[69] Patel et al[69] reported Lp(a) levels measured in nanomoles per liter using an immunoturbidometric assay with excellent concordance with the World Health Organization/International Federation of Clinical Chemistry reference material. Median Lp(a) levels were 19.6 nmol/L overall, and were 19, 31, 75, and 16 nmol/L among self-identified White, South Asian, Black, and Chinese participants. Lp(a) levels were also somewhat higher among women (22 nmol/L) than among men (17 nmol/L). The risk of ASCVD associated with Lp(a) levels was log-linear for levels above the median, with increasing risk for higher Lp(a) levels. The standardized risk for ASCVD was 11% higher for each increment of 50 nmol/L (hazard ratio 1.11 per 50 nmol/L [95% CI, 1.10–1.12]), independent of adjustment for traditional risk factors, and with similar effect estimates in all race and ethnicity groups. These findings support the current American College of Cardiology/American Heart Association cholesterol and primary prevention guidelines' recommendation to use Lp(a) as a risk-enhancing factor that, if measured, would favor statin initiation among individuals at borderline (5%–7.4%) or intermediate (7.5%–19.9%) 10-year predicted risk for ASCVD. Further guidance on how to use the risk information from Lp(a) levels is provided in Table 5.

CURRENT UNDERSTANDING OF THE PATHOPHYSIOLOGY OF Lp(a) AND ASCVD

Initial hypotheses based on Lp(a) composition suggested that it could contribute to both atherosclerosis (through the lipoprotein moiety) and thrombosis (through the plasminogen-like apo(a) moiety; Figure, locations a–d). However, results from recent studies have yielded appreciation of the unique roles that confer specific pro-inflammatory and procalcific effects to Lp(a). The apoB moiety of Lp(a) is expected to be atherogenic because of its similarity to LDL. Furthermore, although there are many fewer circulating plasma Lp(a) particles than

LDL particles, even in the presence of very high Lp(a) levels, Lp(a) may be selectively retained in the arterial wall through binding of apo(a) to extracellular matrix proteins.[16,83] Lp(a) also carries oxidized phospholipids (OxPLs) (Figure [b and c]), which are covalently bound to apo(a) and present in the lipid phase of Lp(a). OxPLs are endogenous danger-associated molecular patterns recognized by the innate immune system, triggering sterile inflammation and calcification[84] with relevance to ASCVD and CAVD pathogenesis. As a consequence of these effects, the OxPL content of Lp(a) may modulate the atherogenicity of Lp(a). Increased[18] fluorodeoxyglucose-positron emission tomography imaging demonstrates enhanced arterial wall inflammation in patients with elevated Lp(a) and supports the role of Lp(a) in promoting atherosclerosis.[85]

Apo(a) interacts with fibrin/fibrinogen and endothelial cells through its strong lysine-binding site and is found in human atheromas and calcified aortic valves.[86–88] Lp(a), through its OxPL component, upregulates endothelial adhesion molecule and cytokine expression and facilitates monocyte transmigration in vitro.[89] Moreover, Lp(a) is a strong chemoattractant for monocytes and upregulates monocyte cytokine expression.[85] Although inflammation is a key feature of atherosclerosis and early CAVD, progression of the latter is primarily dependent on aortic valve mineralization and ossification. Patients with elevated Lp(a) or OxPL-apoB have enhanced[18] F-NaF aortic valve uptake representative of calcifying activity, faster aortic valve calcification progression on serial computed tomography scans, and worse clinical outcomes.[73,90] Lp(a) components, including apo(a), OxPL, and autotaxin, colocalize in diseased human CAVD adjacent to valvular calcification.[88] Upregulation of procalcific and osteogenic genes in human valvular interstitial cells by Lp(a) and apo(a) were partially dependent on OxPL.90 Moreover, Lp(a)-treated valvular interstitial cells resulted in hydroxyapatite mineral deposition.[91] Autotaxin and its enzymatic product lysophosphatidic acid have been also implicated in the procalcific Lp(a) phenotype in vitro and in an animal model of CAVD, respectively.[88]

Whether Lp(a) contributes to atherothrombotic disease by directly inhibiting fibrinolysis, promoting thrombosis, or because of its role in atherogenesis remains the subject of investigation.[92] Apo(a) inhibits plasmin-mediated fibrinolysis in vitro. However, ex vivo clot lysis times were unchanged after Lp(a) lowering with apo(a) antisense oligonucleotide treatment.[93] The extensive homology between apo(a) and plasminogen has prompted investigation of a possible link between elevated Lp(a) levels and venous thromboembolism. Although some early reports suggested a positive association of Lp(a) level and risk of venous thromboembolism,[94,95] other data are mixed[96,97] and genetic data do not support a meaningful association,[78,98] except at very high Lp(a) levels. Therefore, the antifibrinolytic properties of apo(a) may be masked when covalently associated with apoB in the Lp(a) particle. Even if Lp(a) is not inherently antifibrinolytic, the impact of Lp(a) on formation of thrombosis, that is, through effects on platelets and the coagulation cascade, has yet to be thoroughly investigated. The need remains to develop in vivo models of elevated Lp(a) levels that can be translated to humans.

Lp(a)-LOWERING THERAPIES: EXISTING AND INVESTIGATIONAL

We currently lack definitive proof that specific pharmacological lowering of Lp(a) reduces adverse cardiovascular outcomes. However, data from several lines of genetic evidence support this notion.[16,99,100] Accordingly, many clinicians have the secondary goal of lowering Lp(a) in addition to lowering LDL-C and apoB in high-risk patients, in particular, when recurrent ASCVD events occur despite aggressive LDL-C lowering. Results from studies of dietary intervention show very modest effects on Lp(a) levels.[101]

The most effective clinically available intervention for Lp(a) lowering is lipoprotein apheresis. It is typically done every 2 weeks as Lp(a) levels return to their high levels over this interval.[102] It is performed every 2 weeks in the United States, but often weekly in Germany. Lipoprotein apheresis is Food and Drug Administration approved for lowering LDL in patients with functional familial hypercholesterolemia and coronary artery disease who have LDL-C >100 mg/dL [regardless of the level of Lp(a)], while also receiving maximally tolerated lipid-lowering treatments and lifestyle intervention. The Food and Drug Administration approval specifically for Lp(a) lowering requires Lp(a) >60 mg/dL. During the course of a single 3- to 4-hour treatment, the Lp(a) concentration is acutely lowered by ≈50% to 85%, in association with comparable reductions in oxidized phospholipids. In addition to lowering Lp(a), lipoprotein apheresis lowers LDL concentrations by 60% to 85%.[103,104] Limited clinical trial data suggest that Lp(a) lowering with lipoprotein apheresis may reduce the risk of ASCVD events,[105] but definitive studies are needed.

Standard LDL-C and apoB lowering treatments have minimal Lp(a)-lowering efficacy, with some statins minimally increasing Lp(a) levels.[106,107] Of note, data from trials of monoclonal antibodies directed against PCSK9 demonstrated dramatic LDL-C lowering by an average of 50% to 60%, but also modest Lp(a) lowering of 25% to 30%. The results of a recent analysis suggested that alirocumab-mediated Lp(a) lowering independently contributed to major adverse cardiovascular event reduction.[108]

Moreover, in patients with recent acute coronary syndrome on optimized statin therapy and LDL-C <70 mg/dL, alirocumab only lowered major adverse cardiovascular events in patients with mildly elevated (>13.7 mg/dL) Lp(a); there was no such interaction between Lp(a) levels and alirocumab benefit when LDL-C was ≥70 mg/dL.[109] Niacin may dose-dependently lower Lp(a) up to 25% to 40%, but the cardiovascular benefit of this intervention is unknown, and the adverse side effect profile of niacin in the setting of statins may be a concern.[110,111]

Several experimental therapies targeting the apo(a) moiety of Lp(a) are in development. An antisense oligonucleotide for apo(a), pelacarsen (formerly known as IONIS-APO(a)-LRx, AKCEA-APO(a)-LRx, and TQJ230), lowers Lp(a) 80% at a dose of 20 mg subcutaneously weekly, with seemingly good tolerance.[112] The administration of potent and specific Lp(a)-lowering antisense oligonucleotides to patients reduces the inflammatory gene expression profile in circulating monocytes and their ex vivo transendothelial migration capacity.[113] A 7682-person placebo-controlled randomized clinical outcomes trial to assess the effects of pelacarsen on ASCVD outcomes is in progress. Two investigational small interfering

ribonucleic acid molecules targeting apo(a) RNA are in phase II (ARO-LPA [AMG890]) and phase I (SLN-360) testing as of 2020.

SUMMARY

Epidemiological data consistently indicate a direct and dose-dependent risk association of Lp(a) with ASCVD and calcific aortic valvular disease. On the basis of mechanistic, observational, and genetic data, a strong case can be made that elevated Lp(a) is causal for ASCVD. Lp(a) levels are largely determined by genetic factors, with minimal influence from dietary or other behavioral factors. Further work is needed to understand the mechanistic links between apo(a) isoforms and risk for ASCVD; pathways for Lp(a) synthesis, regulation, and metabolism; and Lp(a)-associated risk in diverse genetic and environmental contexts. Although Lp(a) is a common, genetically inherited, and clinically important ASCVD risk factor that can be measured with a simple blood test, Lp(a) is not measured in most patients before or even after they have an ASCVD event. International standards for measurement of Lp(a) need to be established and codified to allow for consistent measurement, using assays expressing results in nanomoles per liter, and a common protocol is needed for monitoring of assay performance to ensure comparable results between laboratories. This will be especially important because targeted Lp(a)-lowering trials are conducted with different agents and repeated measurement of Lp(a) as a biomarker of therapeutic efficacy becomes possible.

At present, the evidence in favor of screening for Lp(a) is the strongest for those with a family or personal history of ASCVD, with consideration of cascade screening in appropriate individuals. Various organizations have proposed to obtain a level once in every adult.[64,65,114] Once the issues with Lp(a) measurement are resolved, which should be in the near future, a reassessment of broader population-based screening should be considered. The current best approach to lower overall ASCVD risk in patients with high Lp(a) is to target LDL-C/apoB with statin and adjunctive medications as initial therapy to lower risk for ASCVD. Additional information is needed on whether newer therapies for apoB lowering reduce ASCVD risk in part through effects on Lp(a).[108,115,116] Novel therapeutics that directly target apo(a) production are in clinical development. Further trials will indicate whether these therapies not only potently lower Lp(a), but also reduce ASCVD events. Positive results of such trials would firmly establish Lp(a) as modifiable causal risk factor and add to our therapeutic armamentarium to combat ASCVD and potentially CAVD.

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*Modest.

†Significant.

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*Modest.

†Significant.

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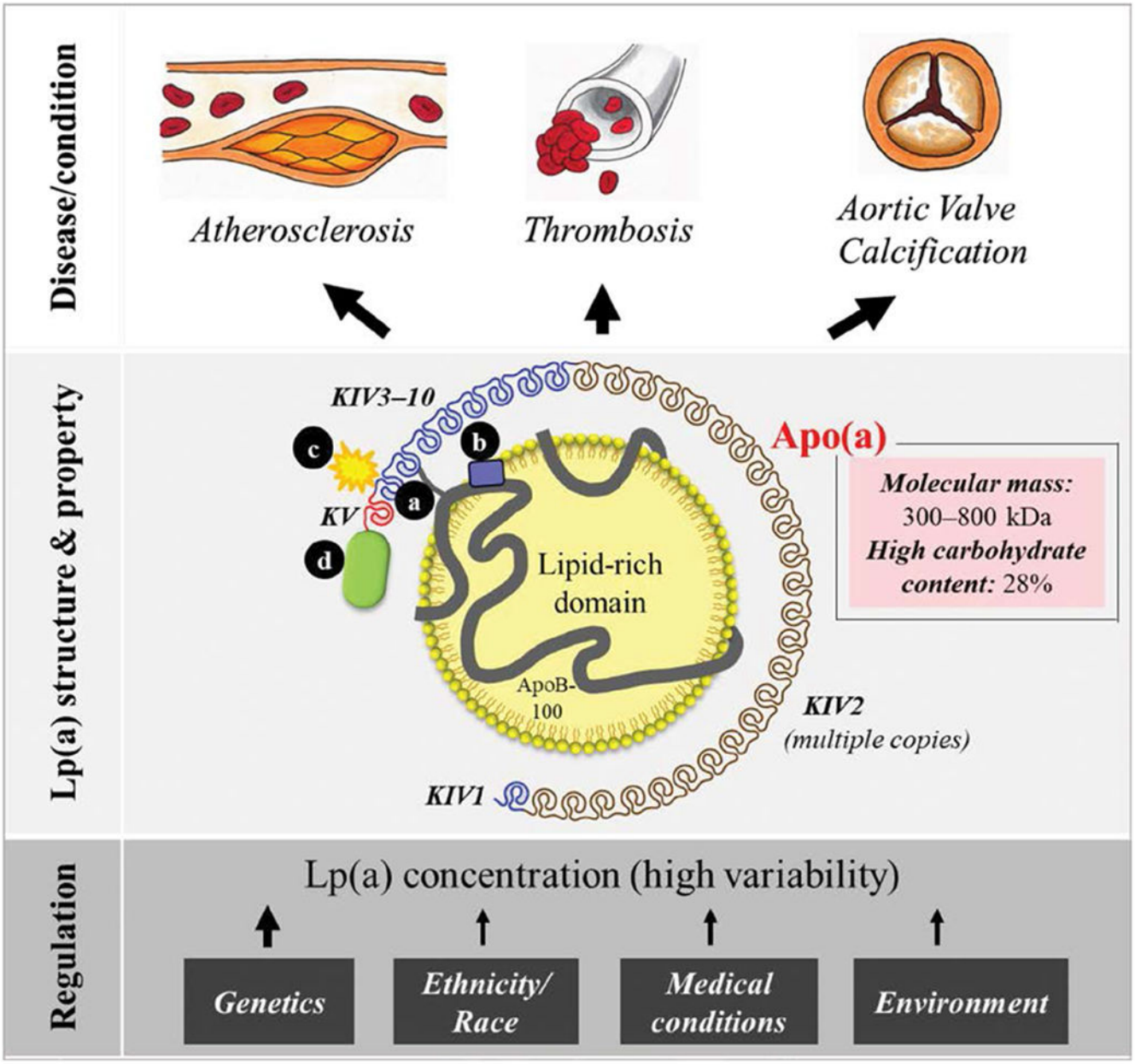

Figure. Lp(a) structure, properties, regulation, and relation to disease.

Lipoprotein(a) [Lp(a)] consists of a lipid-rich domain, primarily cholesteryl esters, and apolipoprotein(a) [apo(a)]. Apo(a) binds to apolipoprotein B100 (apoB) via a single disulfide bond (**a**) at a location close the low-density lipoprotein receptor binding site of apoB (**b**). Apo(a) contains repeated kringle (K) structures (KIV and KV), comparable with those in plasminogen. There are 10 different subtypes of apo(a) KIV, where type 2 is present in multiple copies, resulting in a highly variable molecular mass (300–800 kDa). Apo(a) is compositionally unique among apolipoproteins with a high carbohydrate content (≈28%). Proinflammatory and proatherogenic oxidized phospholipids bind to apo(a) KIV type 10 (**c**) and can also be found in the lipid phase. Apo(a) contains a protease domain (**d**) that

lacks enzymatic activity. The Lp(a) concentration is heterogeneous and, to a major extent, controlled by genetics, inversely related to the copy number variation in the *LPA* gene. Other factors such as ethnicity and race and medical and environmental conditions also play roles in Lp(a) regulation. Lp(a) has been associated with increased risks of atherosclerosis, thrombosis, and aortic valve calcification.

Table 1.

Priorities to Address Current Gaps in Knowledge

Determine how the genetic architecture of *LPA* accounts for differences in Lp(a) levels in different ancestry groups. Studies using properly processed samples and reliable methods for determining Lp(a) levels and apolipoprotein(a) isoform size will be required for this purpose.
Develop a complete understanding of apolipoprotein(a) synthesis and Lp(a) particle assembly by using sophisticated technologies, such as cryogenic electron microscopy.
Determine the mechanism(s) of Lp(a) clearance from the circulation and identify the key liver and extrahepatic receptors that are relevant to humans.

Lp(a) indicates lipoprotein(a).

Table 2.

Clinical Use of Lipoprotein(a) Measurements

Why would a clinician measure Lp(a)?
Elevated Lp(a) is a common independent atherosclerotic cardiovascular disease risk factor that is not measured in the majority of affected patients.
The only currently available method to know if someone has elevated Lp(a) is to measure Lp(a) with a simple blood test that is relatively inexpensive.
Awareness of the presence of elevated Lp(a) is important, because high Lp(a) increases atherosclerotic cardiovascular disease risk and could inform clinical decision-making regarding risk management.
Cascade screening of family members of patients with elevated Lp(a) may identify additional individuals with elevated Lp(a) because of its autosomal codominant inheritance pattern.
How should one measure Lp(a)?
Lp(a) should be measured with:
An isoform-insensitive assay
Assay that is traceable to the internationally accepted calibrator (World Health Organization/International Federation of Clinical Chemistry Reference Material SRM-2B)
Assay that is reported in nanomoles per liter (nmol/l).
If measurements are not uniformly calibrated, one cannot compare measurements generated by different assays.

Lp(a) indicates lipoprotein(a).

Table 3.

How Can a Clinician Gauge the Proportion of apoB-Containing Lipoproteins That Is Actually Lp(a)?

1. ApoB levels have been shown to be better predictors than low-density lipoprotein cholesterol to estimate incident and residual cardiovascular risk.[3,68]
2. By measuring total apoB in blood, the clinicians can calculate the proportion of apoB-containing lipoproteins attributable to Lp(a).
3. Unlike Lp(a), it is easy to convert apoB levels from milligrams per deciliter (mg/dL) to nanomoles per liter (nmol/L).
4. When apoB levels are available, clinicians can calculate how much of the plasma apoB is Lp(a) by converting the total apoB levels from milligrams per deciliter to nanomoles per liter by multiplying by 20.
The clinician can then divide the plasma Lp(a) levels in nanomoles per liter by the plasma apoB levels in nanomoles per liter and derive the percent of apoB that is in Lp(a). **This conversion allows the clinician to understand the contribution of Lp(a) to apoB levels.**
Example: If apoB is 100 mg/dL, this is ≈2000 nmol/L of apoB. Therefore, if the reported Lp(a) concentration is 20 nmol/L (the median level in the UK BioBank[69]), Lp(a)-apoB comprises 1% of total plasma apoB.
If the Lp(a) concentration is 200 nmol/L, Lp(a) is 10% of total apoB. If Lp(a) is 600 nmol/L, Lp(a)-apoB is 30% of total apoB.
If total apoB is lowered by treatments without a change in Lp(a), the latter comprises a greater percent of total apoB.

apo(B) indicates apolipoprotein B100; and Lp(a), lipoprotein(a).

Table 4.

Priorities to Address Current Gaps in Knowledge

Decode mechanisms by which genes outside *LPA* regulate Lp(a) levels (eg, *APOE, APOH*).
Fully characterize the role of single nucleotide polymorphisms not associated with KIV2.
Identify bona fide quantitative trait locuses in *LPA* and determine their mechanism of action.
Determine the role of ancestry on the magnitude of risk associated with Lp(a) including examination of the role of apolipoprotein(a) size, independent of Lp(a) levels, in different ancestry groups.
Develop tools to identify which patients with elevated Lp(a) levels may not have increased atherosclerotic cardiovascular disease risk, and elucidate potential mechanisms, as well.

Lp(a) indicates lipoprotein(a).

Table 5.

Clinical Implementation of Lp(a) Levels in Risk Assessment for Primary Prevention of Atherosclerotic Cardiovascular Disease

Current American College of Cardiology/American Heart Association guidelines[15,81,82] recommend that risk assessment for primary prevention of atherosclerotic cardiovascular disease should begin with 10-y risk estimation using the Pooled Cohort Equations (or similar well-validated equation for the patient population).
If the patient is in the borderline (5%–7.4%) or intermediate (7.5%–19.9%) 10-y risk group, personalization and recalibration of the risk estimate should be attempted during a patient-clinician discussion that considers risk-enhancing factors, including family history of premature atherosclerotic cardiovascular disease, chronic kidney disease, and other chronic conditions.
If measured, the Lp(a) level can be used as a risk-enhancing factor in this scenario. Based on the data from Patel et al,[69] the clinician could adjust the 10-y risk estimate based on the following formula to provide an approximate updated 10-y risk estimate: Predicted 10-y risk×[$1.11^{(\text{patient's Lp(a) level in nmol/L}/50)}$]
Patient example: For a patient with 10-y risk estimate of 10.0%, who has an Lp(a) level of 250 nmol/L, the updated predicted risk estimate would be 16.9%: 10.0 %×$1.11^{(250/50)}$=10.0%×1.115=10.0%×1.69=16.9%

Lp(a) indicates lipoprotein(a).