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ORIGINAL ARTICLE

Lipoprotein(a): Pathophysiology, measurement, indication and treatment in cardiovascular disease. A consensus statement from the Nouvelle Société Francophone d'Athérosclérose (NSFA)[☆]

Lipoprotéine (a) : physiopathologie, indication de dosage et traitement dans les MCV. Déclaration de consensus de la Nouvelle Société Francophone d'Athérosclérose (NSFA)

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Abbreviations: apo(a), apolipoprotein(a); ASO, antisense oligonucleotide; AVS, aortic valve stenosis; CETP, cholesteryl ester transfer protein; CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease; GWAS, genome-wide association study; HR, hazard ratio; KIV₂-CNV, kringle IV type 2 copy number variation; LDL, low-density lipoprotein; LDLR, LDL receptor; Lp(a), lipoprotein(a); LOE/Class, level of evidence and class of recommendation; OxPL, oxidized phospholipids; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin/kexin type 9; RNA, ribonucleic acid; SNP, single nucleotide polymorphism; VTE, venous thromboembolism.

[☆] Tweet: In this consensus statement we present evidence for a causal role of Lp(a) in the pathophysiology of atherothrombosis from prospective epidemiological and genetic studies, as well as the partial homology of apo(a) with plasminogen, which underlies its ability to attenuate fibrinolysis and promote the development of thrombosis.

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Plasminogen

Summary Lipoprotein(a) is an apolipoprotein B100-containing low-density lipoprotein-like particle that is rich in cholesterol, and is associated with a second major protein, apolipoprotein(a). Apolipoprotein(a) possesses structural similarity to plasminogen but lacks fibrinolytic activity. As a consequence of its composite structure, lipoprotein(a) may: (1) elicit a prothrombotic/antifibrinolytic action favouring clot stability; and (2) enhance atherosclerosis progression via its propensity for retention in the arterial intima, with deposition of its cholesterol load at sites of plaque formation. Equally, lipoprotein(a) may induce inflammation and calcification in the aortic leaflet valve interstitium, leading to calcific aortic valve stenosis. Experimental, epidemiological and genetic evidence support the contention that elevated concentrations of lipoprotein(a) are causally related to atherothrombotic risk and equally to calcific aortic valve stenosis. The plasma concentration of lipoprotein(a) is principally determined by genetic factors, is not influenced by dietary habits, remains essentially constant over the lifetime of a given individual and is the most powerful variable for prediction of lipoprotein(a)-associated cardiovascular risk. However, major interindividual variations (up to 1000-fold) are characteristic of lipoprotein(a) concentrations. In this context, lipoprotein(a) assays, although currently insufficiently standardized, are of considerable interest, not only in stratifying cardiovascular

risk, but equally in the clinical follow-up of patients treated with novel lipid-lowering therapies targeted at lipoprotein(a) (e.g. antiapolipoprotein(a) antisense oligonucleotides and small interfering ribonucleic acids) that markedly reduce circulating lipoprotein(a) concentrations. We recommend that lipoprotein(a) be measured once in subjects at high cardiovascular risk with premature coronary heart disease, in familial hypercholesterolaemia, in those with a family history of coronary heart disease and in those with recurrent coronary heart disease despite lipid-lowering treatment. Because of its clinical relevance, the cost of lipoprotein(a) testing should be covered by social security and health authorities.

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MOTS CLÉS

Lipoprotéine(a) ;
Lipoprotéines (LDL) ;
Athérosclérose ;
Maladies
cardiovasculaires ;
Calcification de la
valve aortique ;
Plasminogène

Résumé La lipoprotéine(a) est une lipoprotéine de basse densité riche en cholestérol, contenant de l'apolipoprotéine B100, associée à une deuxième protéine majeure, l'apolipoprotéine(a). L'apolipoprotéine(a) présente une similitude structurale avec le plasminogène mais n'a pas d'activité fibrinolytique. En raison de sa structure composite, la lipoprotéine(a) peut : (1) exercer une action prothrombotique/antifibrinolytique favorisant la stabilité du caillot ; et (2) favoriser la progression de l'athérosclérose par sa propension à la rétention dans l'intima artérielle avec dépôt de sa charge en cholestérol aux sites de formation de la plaque. De même, la lipoprotéine(a) peut induire une inflammation et une calcification dans l'interstitium de la valve du feuillet aortique, entraînant une sténose calcifiante de la valve aortique. Des preuves expérimentales, épidémiologiques et génétiques soutiennent l'affirmation selon laquelle des niveaux élevés de lipoprotéine(a) sont liés de manière causale au risque athérotrombotique et également à la sténose calcifiante de la valve aortique. La concentration plasmatique de lipoprotéine(a) est principalement déterminée par des facteurs génétiques, n'est pas influencée par les habitudes alimentaires, reste essentiellement constante tout au long de la vie pour un individu donné et constitue le paramètre le plus puissant pour prédire le risque cardiovasculaire associé à la lipoprotéine(a). Cependant, des variations interindividuelles majeures (jusqu'à 1000 fois) sont caractéristiques des niveaux de lipoprotéine(a). Dans ce contexte, les dosages de la lipoprotéine(a), bien qu'actuellement insuffisamment standardisés, présentent un intérêt considérable non seulement pour la stratification du risque cardiovasculaire, mais également pour le suivi clinique des patients traités par de nouvelles thérapies hypolipémiantes ciblées sur la lipoprotéine(a) (par exemple les oligonucleotides antisens anti-apolipoprotéine(a) et les petits acides ribonucléiques interférents) qui réduisent sensiblement les concentrations circulantes de la lipoprotéine(a). Nous recommandons que la lipoprotéine(a) soit mesurée une fois chez les sujets à haut risque cardiovasculaire présentant une maladie coronarienne prématurée, dans l'hypercholestérolémie familiale, chez ceux ayant des antécédents familiaux de maladie coronarienne et chez ceux présentant une maladie coronarienne récurrente malgré un traitement hypolipédémiant. En raison de sa pertinence clinique, le coût du test lipoprotéine(a) devrait être couvert par la sécurité sociale et les autorités sanitaires.

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Background

Lipoprotein(a) (Lp(a)) was initially described by Kare Berg in 1963 [1]; it has a complex structure that combines a cholesterol-rich low-density lipoprotein (LDL)-like particle and apolipoprotein(a) (apo(a)), a glycoprotein of variable size. Apo(a) shares a high degree of sequence homology with plasminogen (75–94%) but lacks fibrinolytic activity [2,3]. The structure of Lp(a) led to the suggestion of a possible link between high circulating concentrations of Lp(a) and atherothrombotic risk. After many years of debate, Mendelian randomization studies established a causal role for elevated Lp(a) concentrations in atherosclerotic cardiovascular disease (CVD) and, more specifically, in coronary heart disease (CHD) and stroke [4–6]. Lp(a) is also an independent

risk factor for calcific aortic stenosis [7] and abdominal aortic aneurysms [8].

Lp(a) is characterized by a spectacularly wide range of plasma concentrations (0.01 to > 3 g/L; ≈ 25 to 750 nmol/L) [4] that are mostly influenced by genetic factors, but not by age, sex or lifestyle [9]. Variations in the *LPA* gene, which encodes apo(a), account for 91% of the variability in the plasma concentration of Lp(a) [10], and explain differences in circulating concentrations between different populations. The highest average concentrations of Lp(a) are found in African populations, and are followed in descending order by those of South Asian, Caucasian, Hispanic and East Asian populations [11], raising the question about possible inter-ethnic variability in the relationship between circulating concentrations and clinical thresholds [12].

Considerable progress has been made in our understanding of the pathophysiological role of Lp(a) in atherothrombotic CVD in recent years. The goals of this Nouvelle Société Francophone d'Athérosclérose (NSFA) expert consensus statement are therefore:

- to critically appraise the current status of Lp(a) as a causal cardiovascular risk factor;
- to assess the status of assays for Lp(a) quantitation;
- to report on recent progress in the development of innovative therapeutics to substantially lower Lp(a) concentrations in subjects at risk;
- to provide recommendations to clinicians with respect to high-risk patient groups who may be considered a priority for Lp(a) screening and ultimately preventive treatment targeted at Lp(a) itself.

Lp(a) structure and genetic variations

Lp(a) combines two distinct components: an LDL-like particle and apo(a) linked to apolipoprotein B100 by a disulphide bridge (Fig. 1). Apo(a) is encoded by *LPA* (MIM#15220), located on chromosome 6q26-q27, which evolved from the plasminogen gene (*PLG*) by duplications, deletions, gene conversions and point mutations [3,13]. These two genes are separated by about 50,000 base pairs and are flanked by other extremely similar genes or pseudogenes [14,15]. The molecular weight of apo(a) varies from 250 to 800 kDa, depending on both the number of “kringle” molecular domains (pretzel-shaped helical structures), similar to those of plasminogen, and the degree of glycosylation [2,3,16]. Plasminogen, which is a major line of defence against thrombosis [17], is a single-chain molecule consisting of an N-terminal region, five kringle domains and a serine-proteinase region [18]. Plasminogen kringle domains 1 and 4 – KIV in apo(a) – each contain a lysine-binding site that ensures binding of plasminogen to fibrin [19]. Ten types of plasminogen-like KIV copies (hereafter referred to as KIV₁ to KIV₁₀) have been recognized in apo(a) [20], and at least one of them, KIV₁₀, contains a lysine-binding site similar to that of plasminogen KIV [21]. KIV₁ and KIV₃ to KIV₁₀ are present in single copies. In contrast, the number of copies of KIV₂ varies from two to > 40, resulting in > 40 isoforms and thus > 40 different sizes of Lp(a) [22]. Apo(a) also contains a copy of KV and a non-functional copy of the serine-proteinase region mutated at the plasminogen cleavage site [23]. Such size polymorphism is inversely related to the plasma concentration of Lp(a), such that apo(a) isoforms with a low number of KIV₂ copies are associated with elevated concentrations of Lp(a) [24].

Most individuals carry two differently sized apo(a) alleles, and the degree of heterozygosity at the genetic level is very high (> 95%) [25]. However, the degree of heterozygosity at the protein level is much lower (70–80%), because not all apo(a) alleles are expressed as protein. Smaller isoforms are three times more likely to be expressed than larger ones. This dominance pattern is more common in Caucasians than in Africans. However, the KIV₂ copy number variation (KIV₂-CNV) alone explains only part (19–77%) of the variation in Lp(a) concentrations, depending on the population and assay used [26]. Some single nucleotide polymorphisms (SNPs) within KIV₂ have been reported, and may help to explain

why Lp(a) circulating concentrations can vary by 200-fold, even for alleles of the same size [27]. Many additional SNPs in *LPA* also influence the plasma concentrations of Lp(a), either by increasing them (activating SNPs) [28–38] or by reducing them (inhibiting SNPs) [30,33,37,39] (Table 1). For most of these SNPs, the effect on the plasma concentration of Lp(a) relies on linkage disequilibrium (i.e. transmitted jointly) with KIV₂-CNV. Other SNPs are null alleles, and cause a total lack of apo(a) expression, resulting in congenital deficiency of Lp(a) (MIM#618807) and a benign phenotype [40,41]. Interestingly, non-synonymous SNPs present in null Lp(a) individuals are in an equivalent position to mutations in the *PLG* gene that cause plasminogen deficiency [42].

LPA genetic scores

Several meta-analyses of genome-wide association studies (GWAS) have identified variants both within and outside the *LPA* region that are significantly associated with concentrations of Lp(a) or Lp(a)-cholesterol. Genetic risk scores identified in GWAS, consisting of 1 to > 300 variants, have demonstrated anticipated associations with incident CVD [5,43,44]. The association of genetically predicted Lp(a) concentrations with CHD risk appeared to be independent of changes in LDL-cholesterol concentrations [5]. However, to our knowledge, no comparison between GWAS is available to decide how these studies should be used in clinical practice. Thus, although it is known that the concentration of circulating Lp(a) is determined by a complex interplay between the KIV₂-CNV and different SNPs in all parts of the gene, the best predictor of CVD risk remains the circulating concentration of Lp(a) [45].

Lp(a) measurement in clinical practice

Interest in Lp(a) assays was reignited by the arrival of new therapies with the potential to significantly reduce the circulating concentration of Lp(a) [46]. The isoform size, which is highly polymorphic in humans, as described above, explains 30–70% of Lp(a) concentration variability [47]. Low-molecular-weight isoforms (< 23 KIV) are associated with markedly higher median Lp(a) concentrations (≈ 100 nmol/L; 0.4 g/L) than high-molecular-weight isoforms (≥ 23 KIV; median Lp(a) of ≈ 25 nmol/L; 0.1 g/L). Moreover, even in carriers of the same isoform, Lp(a) can vary by > 100-fold, but only by 2- to 3-fold for isoforms that are identical by descent (i.e. within families) [27]. These unique features of Lp(a) underpin the major hurdle to setting up accurate Lp(a) assays. Extensive reviews of the issues affecting the measurement of Lp(a) have been published recently [48,49]. Importantly, intraindividual biological variation in Lp(a) concentrations over time is of the order of 7–10% [50,51]. The principal physiological and pathological causes of variation in Lp(a) concentrations are summarized in Table A.1 [47,49,52,53].

Lp(a) concentrations should be determined by an immunoassay not affected by apo(a) size variation using a monoclonal antibody specific for a unique apo(a) epitope. Indeed, if antibodies are directed to an epitope present in KIV₂, Lp(a) immunoassays could result in underestimation of

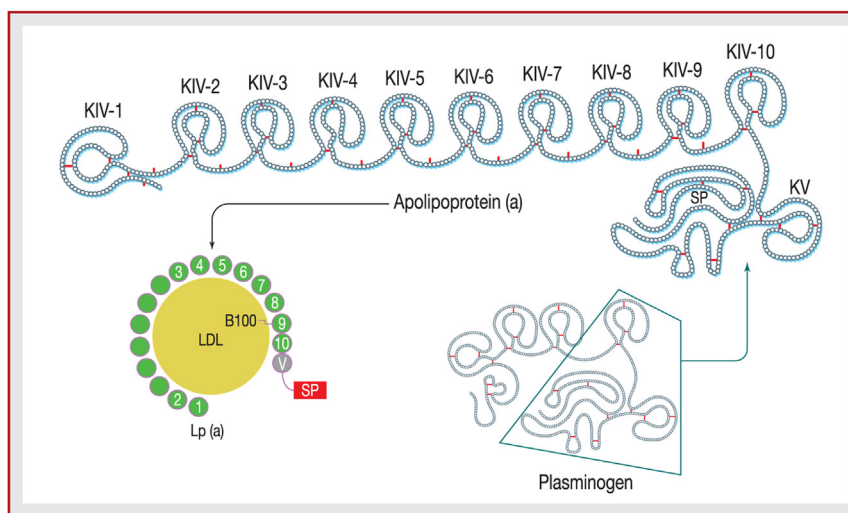


Figure 1. Lipoprotein(a)/apolipoprotein(a) (Lp(a)/apo(a)) structure. Lp(a) is a complex particle composed of a lipid core and two disulphide-linked apolipoproteins: apolipoprotein B-100 (low-density lipoprotein [LDL]) and apo(a). Apo(a) glycoprotein shows a high degree of homology with plasminogen, the precursor of plasmin, the fibrinolytic enzyme. By amino acid sequence analysis and complementary deoxyribonucleic acid (cDNA) cloning it has been established that apo(a) consists of 10 different types of kringle IV (KIV) repeats (green circles), one of which, KIV type 2 (KIV-2), is present in variable numbers. In addition, apo(a) shares single copies of plasminogen kringle 5 (KV) and an inactive serine-proteinase domain (SP). KV: plasminogen kringle V.

the concentrations of small Lp(a) isoforms and overestimation of large Lp(a) isoforms [48,54–56]. Some commercially available assays minimize this bias by using a 5-point calibrator, consisting of a range of Lp(a) isoforms [48].

The absence of harmonization between calibration of Lp(a) assays has led to significant concentration-dependent biases [50,57,58]. Lp(a) assays are based on two approaches:

- assignment of target values to the assay calibrators in terms of total Lp(a) mass, with expression in g/L (or mg/dL) and no traceability of the calibrators to any established reference material;
- or assignment of target values to calibrators traceable to the secondary reference material PRM-2B [55], with expression in nmol/L of apo(a), reflecting the number of circulating Lp(a) particles.

The second approach is considered the “gold standard” [54]. There is no conversion factor that accurately converts the values from one unit to the other [48]. In addition, reporting Lp(a) concentration in mass units (g/L) is metrologically inappropriate, and should be discontinued, given that only apo(a) with its highly variable mass is measured by the antibodies. Furthermore, use of accurate technology, such as mass spectrometry, is required to provide unequivocal molecular characterization and accurate quantitation of apo(a) in molar units, whatever the size polymorphism [59–61]. To guarantee that this approach fits with clinical applications, a working group (Apolipoproteins by Mass Spectrometry) has been created by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) to settle issues on commutability of peptide-based compared with recombinant apo(a)-based reference material. The obvious goal is to develop a next-generation protein test that measures apo(a) in a kringle-independent manner using liquid chromatography, with tandem mass spectrometry quantification of Lp(a) in plasma (<http://www.ifcc.org/ifcc-scientific-division/sd-working-groups/wg-apo-ms/>) [62].

Reference values for plasma Lp(a) concentrations assayed by immunoturbidimetry have been reported as < 75–125 nmol/L (or < 0.30–0.50 g/L) [55], although these concentrations are known to vary from ≈ 25 nmol/L to 750 nmol/L (or ≈ 0.01 to > 3 g/L), with a highly asymmetrical distribution [4]. Moreover, the distribution of Lp(a) concentrations differs between ethnic groups [49], and the interpretation of Lp(a) concentrations should take into account specific risk thresholds [48]. For identification of individuals at risk of CVD or for treatment assignment, a tentative cut-off point of ≥ 125 nmol/L ($\approx \geq 0.50$ g/L) has been proposed from meta-analyses in a range of populations [63]. This cut-off point is reasonable to use, as these concentrations suggest an increased risk of atherosclerotic CVD in Caucasian patients.

High plasma Lp(a) concentrations can also influence the value of LDL-cholesterol. Indeed, the equations used to calculate LDL-cholesterol include the cholesterol content of Lp(a), and this is also true for most LDL-cholesterol assays [64,65]. Given that about 30–45% of an Lp(a) particle is composed of cholesterol by weight, an overestimation of LDL-cholesterol concentration is observed in subjects with high Lp(a) concentrations.

When Lp(a) concentration is expressed in g/L, the empirical correction is as follows: Lp(a)-corrected LDL-cholesterol (g/L) = LDL-cholesterol (g/L) – [Lp(a) (g/L) \times 0.30]. However, recent data indicate that the percentage of Lp(a) cholesterol relative to its mass may vary from 6–57% between individuals [66].

Recommendations for Lp(a) measurement in clinical practice

Grading and assigning of levels of evidence and classes of recommendation (LOE/Class) for lipid-lowering therapy were based on the criteria in the European Society

Table 1 Single nucleotide polymorphisms modulating circulating concentrations of lipoprotein(a).

SNP	Domain	Genomic position (NC_000006.12, GRCh38)	cDNA position (NM_005577.4)	Protein position (NP_005568.2)	Functional activity	Association with CAD risk	Frequency in				Ref.
							Europeans	Africans	Latinos	Asians	
Activating SNPs, associated with higher Lp(a) circulating concentra- tions											
rs186696265	Enhancer	g.160690668C>T				Yes, +73%	0.0170	0.0036	0.0024	0.0038	[31]
rs9458001	Enhancer	g.160694967G>A				Yes, if combined with rs1800769, OR = 1.42	0.22	0.19	0.17	0.18	[32]
rs9347440	Enhancer	g.160685089A>G			70% increase in Lp(a) in EU	No	0.53	0.59	0.38	0.35	[33]
(TTTTA) ^a	Promoter					No	–	–	–	–	[34,35]
rs1800769 ^{b,c}	Promoter	g.160664235C>T	c.-21G>A			No, OR = 0.99; yes, if combined with rs9458001, OR = 1.42	0.15	0.45	0.47	0.32	[36,37]
rs10455872 ^a	KIV ₇	g.160589086A>G	c.3947+467T>C		Higher LPA expression	Yes, OR = 1.92	0.064	0.013	0.026	6.4 × 10 ⁻⁴	[38,39]
rs140720828	KIV ₉	g.160577245G>A	c.4522C>T	p.(Arg1508Trp)			0	0	0	2.0 × 10 ⁻⁵	[40]
rs1801693 ^a	KIV ₉	g.160548597A>G	c.5036T>C	p.(Met1679Thr)	No		0.68	0.86	0.55	0.53	[41]
rs3798220 ^a	Protease- like domain	g.160540105T>C	c.5673A>G	p.(Ile1891Met)		Yes, OR = 1.70	0.017	0.008	0.277	0.038	[38]
Inhibiting SNPs, associated with lower Lp(a) circulating concentra- tions											
rs7760010 ^d	Enhancer	g.160685571G>T					2.3 × 10 ⁻³	0.132	0.015	0	[33]
s7758766 ^e	Enhancer	g.160685476C>A			Yes		0.148	0.213	0.114	0.003	[33]
rs1853021 ^{a,f}	Promoter	g.160664263A>G	c.-49T>C				0.77	0.95	0.86	0.68	[42]
rs121912503	KI	g.160650438G>A	c.109C>T	p.(Arg37Ter)	Congenital deficiency		7.4 × 10 ⁻⁶	0	0	0	[43]
rs200561706	KIV ₆	g.160594009G>A	c.3578C>T	p.(Ser1193Phe)			2.6 × 10 ⁻⁵	0.0046	0.0002	0	[40]
rs41272110	KIV ₈	g.160585140T>G	c.4195A>C	p.(Thr1399Pro)			0.138	0.024	0.096	0.061	[36]
rs41272114	KIV ₈	g.160585045C>T	c.4289+1G>A		Congenital deficiency	Protective effect	0	0	0	9.9 × 10 ⁻⁵	[44]

CAD: coronary artery disease; cDNA: complementary deoxyribonucleic acid; EU: Europeans; KI: kringle I; KIV₆₋₉: kringle IV type 6–9; KIV₂-CNV: kringle IV type 2 copy number variation; LPA: lipoprotein(a) gene; Lp(a): lipoprotein(a); OR: odds ratio; Ref.: reference number; SNP: single nucleotide polymorphism.

^a SNP in linkage disequilibrium (transmitted jointly) with the KIV₂-CNV.

^b SNP in linkage disequilibrium with the KIV₂-CNV in Mexicans.

^c SNP associated with medium-size KIV₂ alleles in Africans, with large-size KIV₂ alleles in Europeans.

^d SNP associated with Lp(a) concentrations in Europeans.

^e SNP in linkage disequilibrium with KIV₂-CNV, leading to no effect on Lp(a) concentrations.

^f SNP associated with Lp(a) concentrations in Africans but not in Europeans.

Box 1 : Recommendations for lipoprotein(a) measurement in clinical practice.

Use assays expressing Lp(a) concentration in nmol/L (LOE B/Class I) [49]

In the absence of Lp(a) standardization, use a 5-point calibration against the WHO/IFCC secondary reference (LOE B/Class I) [49]

Do not use a single conversion factor between assays (LOE C/Class III) [49,186]

Use a tentative cut-off point of ≥ 125 nmol/L ($\approx \geq 0.5$ g/L), as these concentrations suggest an increased risk of atherosclerotic CVD in Caucasian patients (LOE B/Class IIa)

Do not measure Lp(a) in case of inflammation or intercurrent illness; if the Lp(a) concentration was determined in the absence of inflammation or intercurrent illness, a second determination is not recommended (LOE C/Class III)

Class: class of recommendation; CVD: cardiovascular disease; IFCC: International Federation of Clinical Chemistry and Laboratory Medicine; LOE: level of evidence; Lp(a): lipoprotein(a); WHO: World Health Organization.

of Cardiology/European Atherosclerosis Society guidelines (<http://www.escardio.org/guidelines/>), and are summarized in Fig. A.1. Recommendations for Lp(a) measurement in clinical practice are summarized in Box 1.

Lp(a) pathophysiology: inflammatory and atherogenic properties

The physiological role of Lp(a) remains unknown. Individuals without measurable concentrations of plasma Lp(a) manifest no identifiable disease [40,41], but high concentrations of plasma Lp(a) are associated with atherothrombosis and elevated cardiovascular risk [67]. It is possible that the pathophysiological effects of Lp(a) derive from ancestral functions in tissue repair/wound healing and fibrinolysis modulation that are no longer of physiological relevance [68].

Lp(a) and apo(a) have been found within lesioned intima of animal and human arteries, and within early to end-stage lesions of human aortic valve stenosis (AVS) [67,69]. These observations indicate that Lp(a) can enter and accumulate in the intima of arteries and aortic valve leaflets (Fig. 2). In vivo kinetic studies in animals and humans suggest that Lp(a) and LDL enter and are removed from the intima at similar rates in normal arteries, but that Lp(a) may be preferentially trapped in injured arterial intima, which is potentially related to the greater capacity of Lp(a) to bind to fibrin or glycosaminoglycans [67]. Fibrin-bound Lp(a) may be transported to and accumulate in vulnerable plaques (coronary, carotid and femoral arteries) or at turbulent flow sites of minor injury (AVS and atherosclerotic stenosis) [49,67].

Lp(a) promotes endothelial damage and dysfunction, leading to Lp(a) passage through the protective endothelial layer (Fig. 2). Lp(a) can also activate circulating monocytes

and induce monocyte trafficking to the arterial wall [70]. Furthermore, Lp(a) can be taken up by monocyte-derived macrophages to produce foam cells; equally, it elicits smooth muscle cell proliferation and migration [67,71–73]. In agreement with data showing that Lp(a) is an independent risk factor for both atherosclerotic CVD and calcific aortic valve disease, Lp(a) promotes similar actions (lipid deposition, inflammation and calcification) in the arterial intima and the valve interstitium in the aortic leaflet (Fig. 2) [74,75]. The osteogenic cells responsible for calcification are differentiated from vascular smooth muscle cells in arterial plaques, and from valve interstitial cells in calcific aortic valve disease [75]. Human valve interstitial cells from human calcified aortic valves have perivascular differentiation ability and a vascular endothelial growth factor A (VEGF-A) paracrine effect, allowing endothelial cell migration, proliferation and sprouting that may be relevant in aortic valve calcification [76]. Oxidized phospholipids (OxPL), which modify Lp(a) primarily by covalent binding to apo(a), are implicated directly in Lp(a) pathogenicity, and provide a mechanistic link between atherosclerotic CVD and calcific aortic valve disease [75]. Indeed, and as distinct from LDL, OxPL specifically colocalizes with Lp(a) in arterial and aortic valve lesions, activates intracellular signalling pathways to promote proatherosclerotic, proinflammatory and/or pro-osteogenic effects on endothelial cells, macrophages and valve interstitial cells, and thus directly promotes endothelial dysfunction, lipid deposition, inflammation and osteogenic differentiation.

Apo(a) pathophysiology: mechanisms underlying the link between apo(a) and atherothrombosis

In addition to mechanisms related to OxPL, the structural similarity of apo(a) and plasminogen is argued to be a key factor explaining the causal relationship between Lp(a) and atherothrombosis (Fig. 3). Here, we discuss experimental evidence in support of this argument.

Despite the high degree of sequence homology shared by apo(a) and plasminogen, apo(a) cannot be transformed into an active proteolytic enzyme, and therefore, unlike plasminogen, is not considered a zymogen [23]. Apo(a) isoforms may therefore be of pathophysiological relevance by virtue of binding to fibrin and cell surfaces, and hence inhibiting plasmin formation (Fig. 4) [77,78]. Indeed, a number of experimental in vitro studies have provided convincing evidence that Lp(a) binds to fibrin surfaces and to a variety of plasminogen receptors [79,80], thereby competing with plasminogen and inhibiting its activation [81]. Such unique behaviour has been attributed to the lysine-binding function of apo(a) conferred by KIV₁₀ [82].

Plasminogen receptors are heterogeneous cell surface proteins expressed by platelets [83] and different cell types, including endothelial cells, monocytes and epithelial cells [79]. A non-exclusive list of plasminogen receptors is shown in Table A.2. The affinity of recombinant apo(a) for fibrin and plasminogen receptors was shown to be higher (affinity constant, K_d 3.6 ± 0.3 nmol/L), regardless of apo(a) size, than the corresponding affinity of plasminogen (K_d 0.5 – 1 μ mol/L)

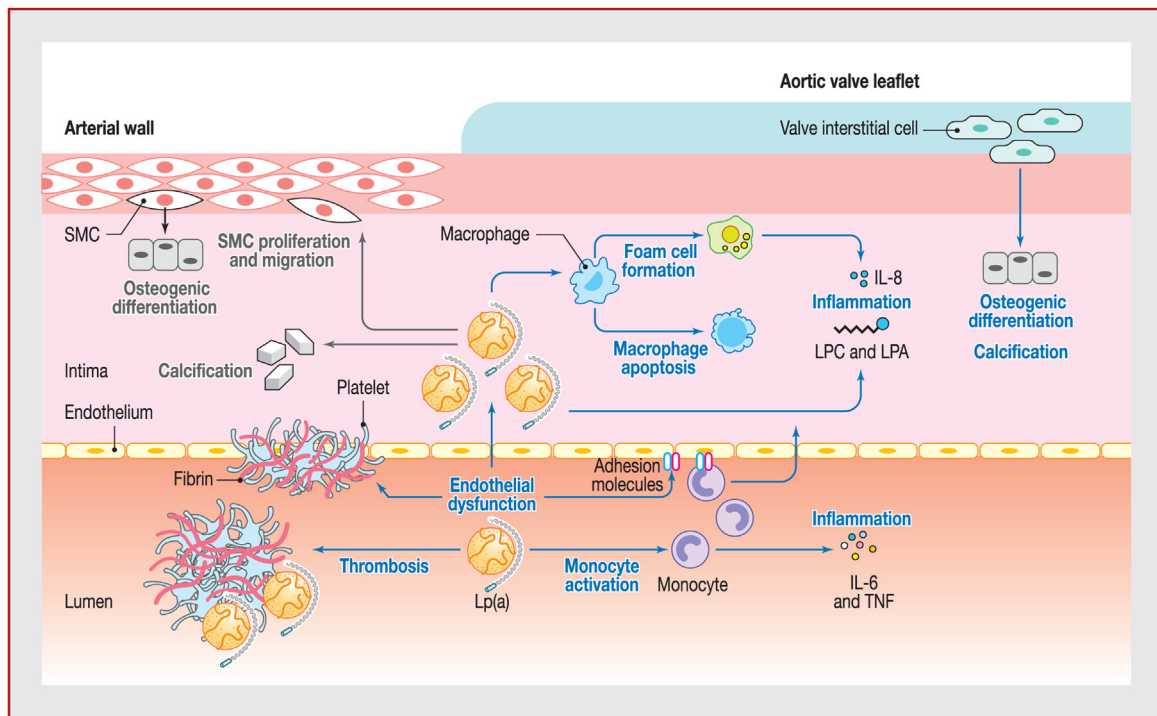


Figure 2. Cellular effects of lipoprotein(a) (Lp(a)) and Lp(a)-associated oxidized phospholipids (from [75]). Lp(a) promotes endothelial damage by inducing mural thrombosis and endothelial dysfunction; the latter promotes Lp(a) passage through the protective endothelial layer. Lp(a) can also activate monocytes in the blood. The roles of Lp(a) in arterial intima in atherosclerosis and in the valve interstitium in the aortic leaflet overlap, and involve promotion of lipid deposition, inflammation and calcification. The activities shown in blue are mediated by oxidized phospholipids on apolipoprotein(a) and Lp(a). IL: interleukin; LPA: lysophosphatidic acid; LPC: lysophosphatidylcholine; SMC: smooth muscle cell; TNF: tumour necrosis factor.

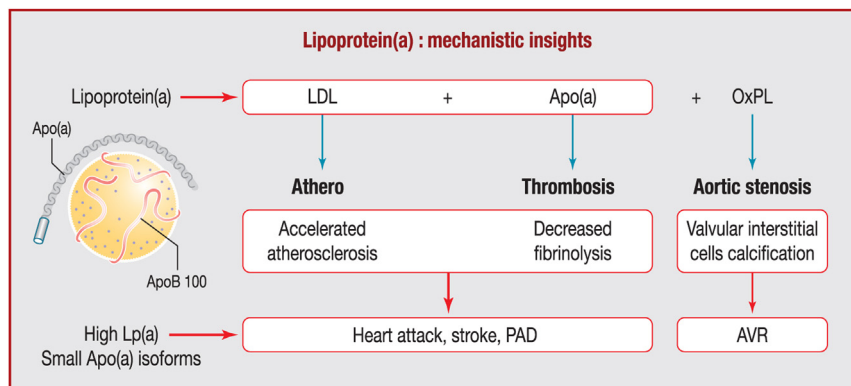


Figure 3. Lipoprotein(a) (Lp(a)): mechanistic insights. Pathophysiological pathways providing a causal link between high plasma concentrations of Lp(a) and atherosclerotic vascular disease and aortic stenosis. Clinical outcomes are related to atherosclerotic stenosis complicated by thrombosis (myocardial infarction, stroke), peripheral artery disease (PAD) or aortic valve replacement (AVR) caused by valve calcification and aortic stenosis. Apo(a): apolipoprotein(a); LDL: low-density lipoprotein; OxPL: oxidized phospholipids.

[84]. Fibrin affinities of native Lp(a) particles are inversely related to apo(a) kringle number, with the low-molecular-weight isoforms (< 22 KIV copies) having the highest affinity for fibrin [85]. Fibrin-binding is therefore an intrinsic property of apo(a), modulated by the composite structure of the Lp(a) particle. The high affinity binding of apo(a) to plasminogen receptors in small Lp(a) particles may interfere with many different pathophysiological responses, including fibrinolysis, thrombus lysis, vascular wall inflammation or inflammation in the atheroma plaque (Fig. 4). Recent studies suggest that the lysine-binding site of KIV₁₀ influences

the covalent binding of OxPL to apo(a) [86]. A recent pilot trial in a small number of patients with highly elevated Lp(a) concentrations showed that a potent reduction in Lp(a) following treatment with an antisense oligonucleotide (ASO) did not modify variables of ex vivo fibrinolysis [87]. However, it is unlikely that a decrease in Lp(a) would modify the normal equilibrated response of fibrinolysis either in terms of fibrinolytic variables or in vitro clot lysis.

In fibrinolysis, for instance, plasminogen is rate limiting for plasmin formation on fibrin and the surface of platelets and cells of the injured vascular wall [88]. Thus,

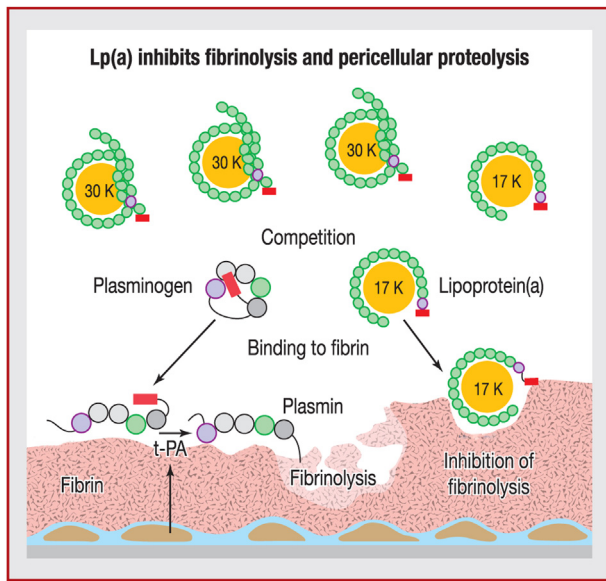


Figure 4. Contribution of apolipoprotein(a) (apo(a)) polymorphism to inhibition of fibrinolysis, a mechanism that may favour thrombus development. Lipoprotein(a) (Lp(a)) competes with plasminogen for binding to fibrin and cell plasminogen receptors. Inhibition of plasminogen binding and activation impairs fibrinolysis/pericellular proteolysis, and is related to high Lp(a) concentrations and small apo(a) isoforms (<22 kringles [K]; 17 K in the figure), but not to large apo(a) isoforms (30 K in the figure). t-PA: tissue plasminogen activator.

the fibrinolytic potential (i.e. lysis of thrombi) is controlled by the accessibility of plasminogen to its binding sites on fibrin or cell membranes, where it is transformed into plasmin by tissue plasminogen activator or urokinase released by endothelial cells or inflammatory cells, respectively. The accumulation of Lp(a) rather than plasminogen at the surface of fibrin might not only interfere with clot lysis, but also favour the accumulation of cholesterol in thrombi of the vessel wall (Fig. 3). Indeed, decreased fibrinolysis, with accumulation of Lp(a) at sites of vascular injury, may represent the link between elevated Lp(a) concentrations and the development of atherothrombosis. The kringle domains of apo(a) may therefore play an important inhibitory role in fibrinolysis. Similar functional analogies in the binding of Lp(a) to cellular receptors for plasminogen or to proteins with affinity for plasminogen have been demonstrated recently [89,90]. Interestingly, small-molecule inhibitors have been developed, which target the lysine-binding site of KIV₁₀ and are able to attenuate the pathophysiological effects of Lp(a) [91].

The binding of distinct recombinant apo(a) isoforms (10, 18 and 30 kringle domains) and native Lp(a) to platelets promotes an aggregation response in the platelets to low doses of arachidonic acid [83]. Purified Lp(a) and recombinant apo(a) also enhance the response of platelets via stimulation of the thrombin receptor by the activating peptide SFLLRN [92]. Overall, these results suggest that the prothrombotic action of Lp(a) may, in part, be mediated by modulating platelet function through the interaction of its apo(a) subunit with a specific receptor at the platelet surface.

Other potential prothrombotic effects of Lp(a) have been proposed, including endothelial dysfunction [93] and

stimulation of expression of plasminogen activator inhibitor type 1 and its ability to inactivate tissue-type plasminogen activator as well as tissue factor pathway inhibitor [94].

The role of Lp(a) in disease

Lp(a) and clinical atherothrombotic outcomes

CHD

A substantial body of evidence links high Lp(a) concentrations with premature CVD. The largest prospective analysis of the association between elevated Lp(a) concentrations and incident CHD (in 2047 patients and 3921 controls) showed an odds ratio of 1.60 (95% confidence interval [CI]: 1.38–1.85) between the upper and lower thirds of baseline Lp(a) concentrations after adjustment for traditional cardiovascular risk factors, and a continuous association between Lp(a) concentrations and risk of future CHD in a broad range of individuals [95]. Equally, the Copenhagen City Heart Study found that the risk of myocardial infarction was 2.6-fold higher in individuals with plasma Lp(a) concentrations > 292 nmol/L (\approx 1.17 g/L) than in individuals with Lp(a) < 12.5 nmol/L (\approx 0.05 g/L) [96]. An earlier report in 2009 by the Emerging Risk Factor Collaboration, involving a meta-analysis of more than 120,000 participants in 36 prospective studies, found that the association between Lp(a) and CHD event risk was continuous, and that the rates of CHD were 5.6 and 4.4 per 1000 person-years in the top and bottom thirds of baseline Lp(a) distribution, respectively. After adjustment for multiple traditional risk factors, the risk ratio for CHD events per 3.5-fold higher usual Lp(a) concentration was 1.13 (95% CI: 1.09–1.18) [97] (Fig. 5). Consistent with the above findings, the CardiogramPlus4CD Consortium showed that LPA is one of the strongest (if not the strongest) monogenic risk factors for CHD [98]. Finally, in a recent analysis of individual level data from the UK Biobank and Jackson Heart Study, the age- and sex-adjusted odds ratio for coronary artery disease was 1.42 (95% CI: 1.40–1.45) for a 120 nmol/L increase in Lp(a) [6].

Ischaemic stroke

The evidence for Lp(a) as a risk factor for stroke is not as robust as the relationship with CHD. The ischaemic and haemorrhagic aetiology and the lack of distinction of subgroups of ischaemic stroke (atherothrombotic, cardioembolic, lacunar stroke) may be confounding factors [99]. However, a significant and independent association of increased risk of ischaemic stroke with elevated Lp(a) has been found in both case-control studies and prospective cohort studies [97,100–102].

Recently, the REGARDS (REasons for Geographic And Racial Differences in Stroke) cohort study confirmed that Lp(a) is a risk factor for ischaemic stroke [103]. Although Lp(a) concentrations were higher in black participants than white participants, elevated Lp(a) was associated with increased risk of ischaemic stroke among all participants. This relationship was stronger for black than white participants, but the difference was not statistically significant.

A large genetic sample size from the Copenhagen General Population Study and the Copenhagen City Heart Study

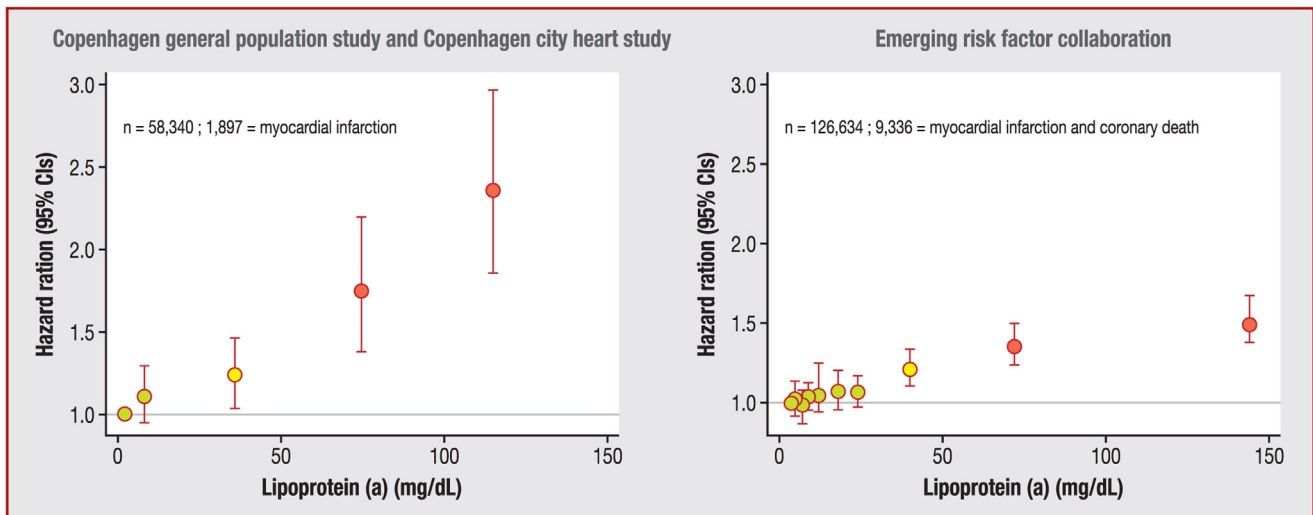


Figure 5. Observational associations between high plasma lipoprotein(a) concentrations and risk of cardiovascular disease in the Copenhagen City Heart Study and Copenhagen General Population Study combined (left panel) and in the Emerging Risk Factors Collaboration (right panel). Reproduced from [67]. CI: confidence interval.

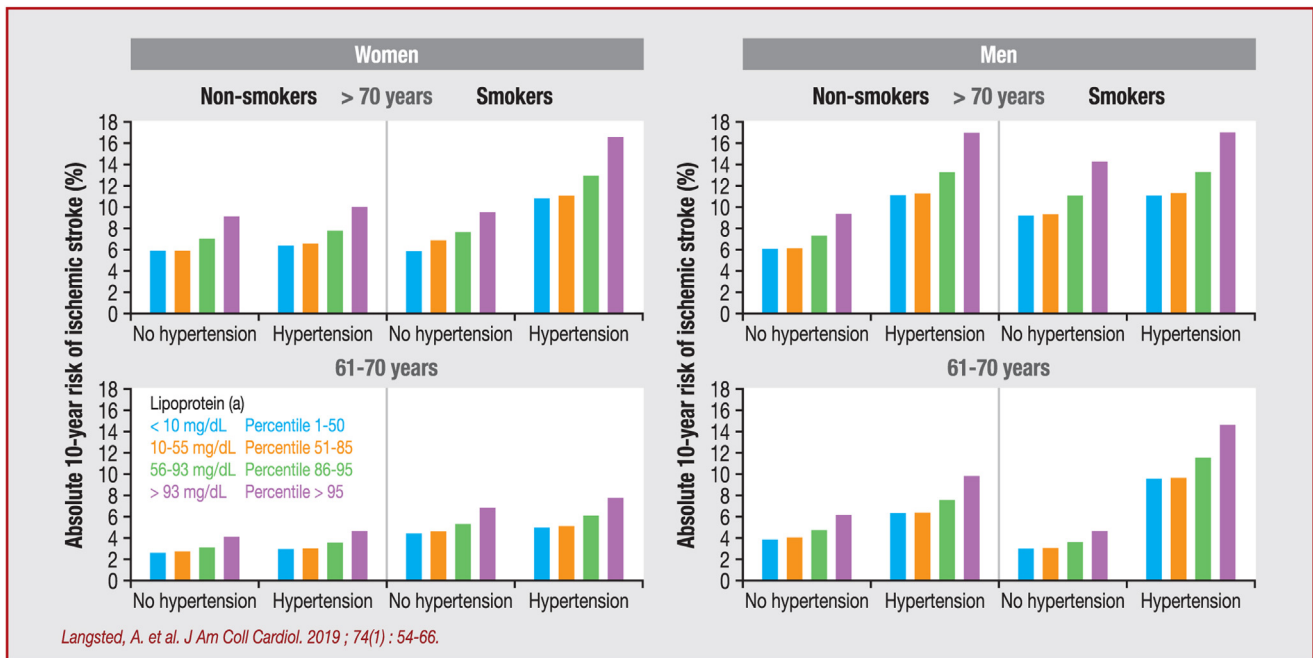


Figure 6. Lipoprotein(a) and risk of ischaemic stroke [104]. Predicted absolute 10-year risk of ischaemic stroke by concentrations of lipoprotein(a), sex, age, smoking and hypertension. Analyses were by binominal regression. Based on 49,699 individuals from the Copenhagen General Population Study. Reproduced from [104].

demonstrated that high concentrations of lipoprotein(a) and corresponding genetic LPA variants are associated with an increased risk of ischaemic stroke [104]. However, risk estimates are less pronounced than those reported previously for CHD and AVS. The absolute 10-year risks of ischaemic stroke according to lipoprotein(a) concentration, sex, age, smoking status and hypertension are shown in Fig. 6 [104].

Elevated Lp(a) concentrations have also been associated with stroke, particularly in youths and children [105–107]. In line with these reports, in a meta-analysis of both prospective and observational studies, elevated Lp(a) was an

independent risk factor for ischaemic stroke that may be especially relevant for young stroke patients [102].

Peripheral artery disease

Peripheral artery disease (PAD) represents another common manifestation of atherosclerotic CVD that is also associated with significant morbidity and mortality. However, the relative contribution of Lp(a) to the risk of PAD has not been well defined. A causal relationship between Lp(a) and PAD has been proposed, as the genetically determined apo(a) phenotypes and SNP alleles are indeed associated

with PAD [108]. Recently, GWAS summary statistics were used in Mendelian randomization analyses to define the most likely causal major lipoprotein risk factors for PAD [109]. Increases in genetically predicted Lp(a) were associated with an increased risk of PAD (odds ratio 1.04 per 10 mg/dL increase in Lp(a), 95% CI: 1.03–1.04). This modest, but significant association between Lp(a) and PAD was independent of apolipoprotein B. The Cardiovascular Disease in Intermittent Claudication (CAVASIC) study has shown that high Lp(a) and high proprotein convertase subtilisin/kexin type 9 (PCSK9) add cumulatively and independently to PAD risk, which supports the independent but additive association of both PCSK9 and Lp(a) concentrations with prevalent PAD [108,110].

Lp(a) and aspirin in the primary prevention of atherothrombosis

High concentrations of Lp(a) ≥ 250 nmol/L (1 g/L) are associated with subclinical atherosclerosis (i.e. coronary artery calcium score > 400 Agatston units or significant carotid stenosis $> 50\%$), and current evidence appears sufficient to recommend low-dose aspirin (< 100 mg/day) for primary prevention in carefully selected patients, after outweighing the bleeding risks and assessing the most favourable risk–benefit profile [111,112].

Lp(a) and aortic valve calcifications and stenosis

Large genetic studies and Mendelian randomization studies have documented a strong association between elevated circulating Lp(a) concentrations and the presence of valvular calcifications and AVS [113]. Indeed, elevated Lp(a) is associated with a higher incidence of AVS, faster haemodynamic progression of AVS and increased risk of aortic valve replacement, especially in younger patients [114]. The OxPL-apo(a) content within Lp(a) appears to mediate the progression of AVS, leading to the hypothesis that the use of therapies to lower Lp(a) and OxPL-apo(a) might be an interesting option in patients with AVS [115]. The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk) trial showed that decreased Lp(a) concentrations could reduce incidence of AVS [116]. Finally, elderly individuals with Lp(a) > 225 nmol/L (≈ 0.9 g/L) have a threefold increased risk of AVS [115].

Data on the association of Lp(a) with calcification of other valves have been reported only for the mitral valve, which is in the continuum of the left haemodynamic circulation [117]. This selected aortic valve localization could be related to mechanical shear stress on aortic valve interstitial cells, leading to proangiogenic and paracrine properties of interest in valve calcification [76].

Lp(a) and familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is an inherited autosomal dominant monogenic disease caused by mutations in *LDLR* (LDL receptor), *APOB* (apolipoprotein B) and *PCSK9*, genes encoding proteins involved in the catabolism of LDL. FH exists in a frequent heterozygous form, prevalence 1/311 [118] and 1/313 [119], and a rarer homozygous disorder

resulting from biallelic pathogenic variants. It is characterized by a significant rise in LDL-cholesterol from birth, leading to the early development of atherosclerosis and a high-risk of CVD, especially if untreated [120,121]. Several studies have shown that Lp(a) concentrations are high in patients with either the heterozygous [122,123] or homozygous [124] forms of FH, leading to the suggestion that Lp(a) is, at least partly, catabolized by the LDLR, which is often dysfunctional in patients with FH. However, these clinical observations are currently being questioned, as they could result from an ascertainment bias [125,126]. Evidence in support of the argument is presented below.

Cholesterol in Lp(a) accounts for up to 30% of LDL-cholesterol, as calculated by the Friedewald formula (and even directly measured), and up to 45% if plasma Lp(a) concentrations are high [127]. However, in most cases, the diagnosis of FH is made clinically, and is based on elevated LDL-cholesterol measurements and premature CVD. Thus, a proportion of patients with a clinical diagnosis of FH are, in fact, patients with elevated Lp(a) rather than LDL concentrations.

Two recent studies involving large biobanks of unselected populations with a clinical and genetic diagnosis of FH (Copenhagen General Population Study and UK Biobank) showed that:

- high Lp(a) concentrations are involved in 25% of clinical FH diagnoses;
- *LPA* genotypes conferring elevated Lp(a) are more frequent in patients with a clinical FH diagnosis;
- Lp(a) concentrations are similar in patients with genetically determined FH and those without FH [126,128].

The authors conclude that the observation of elevated Lp(a) in patients with FH is therefore the result of ascertainment bias, and that LDLR dysfunction in FH does not lead to an increase in plasma Lp(a).

FH and elevated Lp(a) concentrations are two common genetic disorders, both of which increase atherothrombotic risk, and in which CVD risk is cumulative [129]. The coexistence of these two pathologies is therefore not uncommon, and increases CVD risk. For example, compared with patients without FH and without high Lp(a) concentrations, the risk of myocardial infarction is 1.4 times higher for patients with isolated Lp(a) > 125 nmol/L (≈ 0.50 g/L), 3.2 times higher for patients with isolated FH and 5.3 times higher for patients with FH and Lp(a) > 125 nmol/L [128]. High Lp(a) increases the penetrance of FH, i.e. patients with FH with high Lp(a) have the most severe disease and are therefore more often diagnosed. It is therefore important to perform an Lp(a) assay in all patients suspected of having FH, to differentiate between patients with FH, patients with high Lp(a) and patients with both conditions. This makes it possible to:

- clarify the diagnosis;
- stratify the CVD risk;
- adapt the treatment;
- carry out family screening for FH, Lp(a) or both;
- check for peripheral vascular disease more specific to elevated Lp(a) (aortic valve calcifications are also more frequent in the homozygous form of FH).

Therapeutic management differs depending on whether the patient has FH, high Lp(a) or a combination of the two,

as high-dose statins, which are ineffective in lowering Lp(a) concentrations, are used to treat FH. Treatment with PCSK9 inhibitors and LDL apheresis are effective both in patients with FH and in those with high Lp(a), so should be considered in patients with both genetic disorders [121,130]. For the same reasons, an Lp(a) assay should probably be performed in patients with other genetic dyslipidaemias, such as familial combined hyperlipidaemia and dysbetalipoproteinaemia [131].

Lp(a) and diabetes

Association of Lp(a) with cardiovascular risk in type 2 diabetes and prediabetes

A meta-analysis reported that elevated Lp(a) concentrations are associated with a higher risk of major coronary events and incident CVD events in individuals with type 2 diabetes (hazard ratio [HR] for major coronary events 1.31, 95% CI: 1.15–1.50; HR for CVD 1.22, 95% CI: 1.08–1.38) compared with those without diabetes (HR for major coronary events 1.15, 95% CI: 1.08–1.21; HR for CVD 1.13, 95% CI: 1.07–1.19) [132]. Elevated Lp(a) was significantly associated with the presence of carotid atherosclerosis in patients with type 2 diabetes, independent of conventional cardiometabolic risk factors. Even when target LDL-C concentrations were achieved, an elevated Lp(a) concentration was still associated with the presence of carotid atherosclerosis [117,133].

Two large cohort studies have shown increased rates of incident cardiovascular events in individuals with prediabetes and diabetes. In Caucasians in primary prevention with Lp(a) \geq 125 nmol/L (\approx 0.5 g/L) vs. 25 nmol/L (\approx 0.1 g/L) [134], the prediabetes HR was 1.35 (95% CI: 1.07–1.69; $P=0.03$) and the diabetes HR was 1.42 (95% CI: 1.10–1.84; $P<0.01$) [134]. In Chinese patients in secondary prevention with stable coronary artery disease with Lp(a) \geq 0.3 to $<$ 0.5 g/L or \geq 125 nmol/L (\approx 0.5 g/L) vs. Lp(a) \leq 25 nmol/L (\approx 0.1 g/L) the prediabetes HRs were 2.18 (95% CI: 1.10–4.33) and 2.67 (95% CI: 1.38–5.42), and the diabetes HRs were 3.09 (95% CI: 1.54–5.90) and 3.47 (95% CI: 1.80–6.69) (all $P<0.05$) [135].

Lp(a) concentrations are inversely associated with risk of type 2 diabetes

In a meta-analysis including four prospective cohorts ($n=74,575$ subjects), the risk of incident type 2 diabetes was significantly higher in the first two quintiles of Lp(a) concentration – mean Lp(a) 7.5 nmol/L (\approx 0.03 g/L) and 17.5 nmol/L (\approx 0.07 g/L), respectively – compared with quintile 5 (155 nmol/L; \approx 0.63 g/L): quintile 1 HR: 1.28 (95% CI: 1.14–1.43); quintile 2 HR: 1.14 (95% CI: 1.01–1.28) [136]. This finding was replicated recently in a very large case-control study, with a greater risk of type 2 diabetes in the 10% of subjects with Lp(a) $<$ 3.5 nmol/L (\approx 0.014 g/L) (odds ratio: 1.44; $P<0.0001$) [137]. The mechanisms underlying this association are unknown. However, a causal risk is suspected, as the risk of type 2 diabetes is higher in homozygous carriers of an *LPA* mutation responsible for Lp(a) deficiency (odds ratio: 1.45; $P=0.022$) and in subjects with low genetically imputed Lp(a) molar concentrations

($<$ 3.5 nmol/L) (odds ratio: 1.16; $P=0.0012$), independent of body mass index [137,138].

Lp(a) concentrations are associated with complications in type 1 diabetes

A recent large study in type 1 diabetes (1860 patients) showed that patients in the higher Lp(a) quartiles exhibited a higher risk of complications [139]. Relative risk ratios (adjusted for sex and smoking status, but not LDL-cholesterol) were: 1.51 (95% CI: 1.01–2.28; $P=0.048$) for macrovascular disease; 1.70 (95% CI: 0.97–3.00; $P=0.063$) for CHD; 1.68 (95% CI: 1.12–2.50; $P=0.01$) for albuminuria; and 2.03 (95% CI: 1.03–4.03; $P=0.042$) for calcified aortic valve disease. This study also showed that Lp(a) concentrations are related to metabolic control (glycated haemoglobin [HbA1c]) [139].

Lp(a) and venous thromboembolism

The question of whether Lp(a) concentrations are causally related to venous thromboembolism (VTE) remains a matter of debate. Some studies suggest that increased Lp(a) concentrations are an independent risk factor for VTE [140,141]. Associations between Lp(a) concentrations and VTE are strong in patients at very high-risk of VTE, such as those with a spinal cord injury or a postoperative condition that makes them prone to portal and/or splenic vein thrombosis [142,143]. Data from prospective studies are less clear, and a significant association between Lp(a) concentration and incidence of VTE was not observed in the Copenhagen City Heart Study, despite the large number of patients that experienced VTE (735 out of 8960 patients over a 15–18-year follow-up) [144].

In the recent ODYSSEY OUTCOMES randomized trial, the risk of VTE was assessed in patients with recent acute coronary syndrome receiving maximal-tolerated statin treatment, who were randomized to either the PCSK9 inhibitor alirocumab or placebo. Despite a 23.5% decrease in Lp(a) concentration in the intervention group, the reduction in risk of VTE was small, and did not reach statistical significance [145]. In the FOURIER study, involving intervention with evolocumab, 128 of 27,564 patients developed VTE, with a non-significant decreased event rate in the treatment group relative to placebo group (0.45% vs. 0.63%; $P=0.05$) [146].

Overall, these data agree with genetic studies showing no direct association of elevated Lp(a) with VTE [144,147]. Lp(a) may therefore be a predisposing factor for VTE that is particularly relevant in patients at high-risk and in combination with other thrombophilic factors [99].

Lp(a) and renal diseases and liver insufficiency

Lp(a) concentrations are inversely associated with glomerular filtration rate; concentrations begin to increase in the early stage of kidney impairment, before glomerular filtration rate starts to decrease. Interestingly, this increase is only observed in individuals with large apo(a) isoforms. Lp(a) concentrations decrease without normalization in patients on haemodialysis or continuous ambulatory peritoneal dialysis, and return to normal after renal transplantation [148].

Box 2 : Recommendations for performing lipoprotein(a) assays in familial hypercholesterolaemia and other diseases.

In any patient diagnosed with FH, it is imperative to perform an Lp(a) assay (LOE B/Class I)

The combination of FH and Lp(a) > 125 nmol/L (\approx 0.5 g/L) requires aggressive cholesterol-lowering therapy; treatment with PCSK9 inhibitors and/or LDL apheresis should be discussed (LOE C/Class IIb)

Perform an Lp(a) assay, at least once, in any patient suspected of atherogenic dyslipidaemia (LOE C/Class IIb)

Perform an Lp(a) assay, at least once, in patients with type 1 or 2 diabetes (LOE B/Class I).

Perform an Lp(a) assay, at least once, in patients with chronic kidney disease (LOE B/Class IIb).

An Lp(a) measurement is not recommended in liver insufficiency (LOE B/Class III).

Class: class of recommendation; FH: familial hypercholesterolaemia; LDL: low-density lipoprotein; LOE: level of evidence; Lp(a): lipoprotein(a); PCSK9: proprotein convertase subtilisin/kexin type 9.

Nephrotic syndrome is also associated with a marked increase in serum Lp(a) (Fig. A.2). A major proportion of LDL-cholesterol is derived from Lp(a) in nephrotic patients, mostly in patients with small apo(a) isoforms, and may contribute to the thrombotic/atherogenic risk in this syndrome. Plasma Lp(a) decreases with remission of nephrotic syndrome or in response to antiproteinuric therapies [78]. Abnormal Lp(a) concentrations are attributed to increased hepatic Lp(a) production in nephrotic syndrome, but to decreased Lp(a) clearance in chronic kidney disease and haemodialysis [148].

In the CRIC (Chronic Renal Insufficiency Cohort) study, the highest quartile of Lp(a) was associated with an increased risk of myocardial infarction (HR: 1.49, 95% CI: 1.05–2.11) and death (HR: 1.28, 95% CI: 1.05–1.57) [149]. Several studies have suggested that higher Lp(a) concentrations and smaller apo(a) isoforms are independent risk factors for CVD in haemodialysis [53].

Lp(a) concentrations are lower during liver insufficiency, progressively decreasing with impaired liver function as a result of reduced hepatic synthesis; such concentrations correlate well with prothrombin plasma activity, apolipoprotein B100 and albumin concentrations in serum [150,151].

Recommendations for performing Lp(a) assays

Recommendations for performing Lp(a) assays in FH and other diseases are summarized in Box 2.

Therapeutic options to lower Lp(a)

No commercially available pharmacological therapy that specifically lowers Lp(a) concentrations currently exists. Results from dedicated ongoing cardiovascular outcome trials of new drugs with specific Lp(a)-lowering activity are required to confirm that lowering Lp(a) decreases

cardiovascular events. Importantly, recent Mendelian randomization studies suggested that a Lp(a)-lowering effect size of 0.657 to 1 g/L (164 to 250 nmol/L) might produce an effect equivalent to a reduction of 0.386 g/L (1.0 mmol/L) in LDL-cholesterol [5,152]. However, Mendelian randomization estimates must be transferred to the real percentage of Lp(a) cholesterol relative to its mass among individuals, as estimated with a specific assay (from 6–57% instead of the conventional 30%) [66].

The effect of statin treatment on Lp(a) concentrations remains an area of controversy [72]. Whereas most studies report that statins do not affect Lp(a) concentrations [96], recent data suggest that statins can increase Lp(a) concentrations [153,154]. Yeang et al. [154] reported that statins alone or in combination with ezetimibe led to an 11% increase in Lp(a) concentrations and a 24% increase in OxPL-apoB. The mechanisms by which statins raise Lp(a) concentrations remain to be determined [155].

Oral lipid-lowering drugs to lower Lp(a)

Niacin

Niacin is the most effective oral drug to decrease Lp(a) concentrations; it decreases Lp(a) in a dose-dependent manner, and by approximately 30–40% on average [96,156]. The underlying mechanism involves inhibition of Lp(a) synthesis rather than increased catabolism. In HPS2-THRIVE (Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events), the niacin–laropirant combination induced a mean proportional reduction in Lp(a) concentration of 31%. However, this reduction varied strongly with apo(a) isoform size, and was attenuated in the quintile with the highest baseline Lp(a) concentrations and low isoform size [157]. Niacin failed to show cardiovascular benefit in either the HPS2-THRIVE [158] or AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) [159] cardiovascular outcomes trials, but showed an increased rate of adverse events, such as new-onset type 2 diabetes, bleeding and infections. Therefore, niacin is not a suitable therapeutic option for decreasing Lp(a) concentrations in subjects at high-risk of CVD, and no medication containing niacin is currently approved in Europe.

Others

Ezetimibe and fibrates have no or small effects on Lp(a) concentrations [72,96]. Cholesteryl ester transfer protein (CETP) inhibitors have shown promising Lp(a)-lowering effects, involving a decrease in hepatic apo(a) production rate [160]. In the DEFINE (Determining the Efficacy and Tolerability of CETP INhibition with AnacEtrapib) study, anacetrapib given in combination with statins decreased Lp(a) by 17% [161]. However, CETP inhibitors were either without effect or led to a minor reduction in Lp(a) concentrations [162], and they are not approved for clinical use. Lomitapide, a microsomal triglyceride transfer protein inhibitor, was shown to decrease Lp(a) concentrations by 15–19% [163], but its use is restricted to patients with homozygous FH.

Injectable lipid-lowering drugs

Mipomersen

Mipomersen is an apoB ASO that blocks apoB synthesis. In clinical trials, mipomersen has been shown to significantly decrease Lp(a) concentrations by about 30% (range: 21–39%) [164]. The mechanism appears to involve a decrease in the availability of apoB for Lp(a) assembly [165]. However, an in vivo kinetic study performed in healthy subjects indicates that mipomersen increases the catabolism of Lp(a) rather than its production rate [166]. Mipomersen is approved in the USA, but not in Europe, and is restricted to the treatment of subjects with homozygous FH.

PCSK9 inhibitors

The fully human anti-PCSK9 monoclonal antibodies, evolocumab and alirocumab, decrease Lp(a) concentrations by 20–30% [167,168]. The mechanism by which PCSK9 inhibitors decrease Lp(a) remains unclear [46], with studies showing either an increase in LDLR-mediated uptake or a decrease in the production of Lp(a) particles [169–174]. However, a discordant LDL-cholesterol/Lp(a) response was frequently observed with alirocumab in phase 3 studies, further suggesting that PCSK9 inhibition reduces Lp(a) concentrations through alternative pathways to LDLR clearance [175]. The reduction in Lp(a) concentration has been confirmed in two cardiovascular prevention trials: the FOURIER trial with evolocumab and the ODYSSEY OUTCOMES trial with alirocumab [145,146]. Complementary analyses of the ODYSSEY OUTCOMES trial have shown that Lp(a) lowering by alirocumab:

- is an independent contributor to the reduction of major cardiovascular events, notably when LDL-cholesterol is at guideline-recommended goal [176];
- contributes to the reduction of PAD and VTE [145].

In addition, inclisiran, a small interfering ribonucleic acid (RNA) targeting intracellular PCSK9, which is under development in phase 3, has been shown to decrease Lp(a) by around 20% [177].

Lp(a) inhibitors

The most promising future treatment options for decreasing Lp(a) concentrations involve the use of molecules that directly target the hepatic synthesis of apo(a) – either an ASO or a small interfering RNA [178]. A dose-dependent reduction in Lp(a) with the first generation of antisense therapy was observed in a phase 1 study [179], and was confirmed in two phase 2 studies conducted in patients with elevated Lp(a) [180], and with the second generation of antisense therapy. AKCEA-APO(a)-LRX, a second-generation hepatocyte-directed ASO, was administered at a range of doses (20, 40 or 60 mg every 4 weeks, 20 mg every 2 weeks or 20 mg every week) to patients with established CVD and Lp(a) concentrations ≥ 150 nmol/L (0.6 g/L) [181]. Significant Lp(a) reductions were observed with all the tested strategies, the maximum reduction (80%) being observed with the dose of 20 mg every week. A phase 3 cardiovascular outcome trial (Lp(a)HORIZON) with pelacarsen is now ongoing in patients with elevated

Box 3 : Recommendations for the treatment of patients with a high lipoprotein(a) concentration.

In patients with Lp(a) > 250 nmol/L (≈ 1 g/L), cardiovascular risk is elevated, and therefore lipid-lowering treatment should be intensified (LOE B/Class IIb)

A discrete rise in Lp(a) under statin treatment does not limit the use of statins, given the net overall cardiovascular benefit of the treatment, even in patients with high Lp(a) (LOE A/Class I)

In primary prevention, aspirin treatment should be considered in patients with Lp(a) > 250 nmol/L (≈ 1 g/L) and subclinical atherosclerosis (i.e. coronary artery calcium score > 400 Agatston units) or significant carotid stenosis > 50% (LOE B/Class IIa)

Class: class of recommendation; LOE: level of evidence; Lp(a): lipoprotein(a).

baseline Lp(a), and for the first time will evaluate the clinical benefit of a targeted reduction in Lp(a) concentrations.

Lipoprotein apheresis

Lipoprotein apheresis is highly efficient at decreasing Lp(a) concentrations, with reductions of approximately 60–75% after a single apheresis session [182]. Because of a quick rebound, concentrations return to baseline within about 7 days, and apheresis performed weekly or biweekly results in a mean interval reduction of 25–40%. Lp(a) apheresis is expensive, time consuming and invasive, but data from a German registry show that it is associated with a low rate of side effects ($\sim 5\%$) [183].

There is no randomized trial showing a reduction in cardiovascular endpoints by treating high Lp(a) concentrations with apheresis. However, two retrospective analyses indicate that regular apheresis is associated with a decrease in the annual rate of major cardiovascular events [184,185].

Recommendations for the treatment of patients with high Lp(a)

Recommendations for the treatment of patients with high Lp(a) are summarized in Box 3.

Conclusions

Evidence for a causal role for Lp(a) in the pathophysiology of atherosclerotic CVD is now indisputable, and is principally derived from prospective epidemiological studies in large cohorts and genetic studies involving Mendelian randomization analyses. Indeed, the circulating concentrations of Lp(a), determined primarily by the size of genetically determined apo(a) isoforms, are central to its impact on cardiovascular risk and atherosclerosis progression. The partial homology of apo(a) with plasminogen underlies its capacity to attenuate fibrinolysis, thereby favouring enhanced

thrombus size and stability, and the development of thrombotic accidents. Despite difficulties in standardizing and calibrating Lp(a) assays, each validated immunoassay can differentiate subjects possessing low Lp(a) concentrations from elevated concentrations associated with increased cardiovascular risk, thereby allowing atherothrombotic risk stratification. Exciting developments in innovative therapeutics are ongoing, aiming to substantially and specifically lower Lp(a) concentrations in subjects at high CVD risk with ASOs and small interfering RNA molecules. Indeed, these developments open new horizons for the clinical community, with the hope that a marked reduction in Lp(a) may lower cardiovascular risk.

Key messages

What is Lp(a)?

Lp(a) is an LDL-like particle associated with apo(a), an apolipoprotein structurally similar to plasminogen that interferes with fibrinolysis

Lp(a) concentration is genetically determined and is not influenced by diet

Why should Lp(a) be measured?

Lp(a) concentration is linked to antifibrinolytic activity, atherothrombotic risk and calcific valvular aortic stenosis

The most powerful variable for prediction of Lp(a)-associated risk remains its circulating concentration

When and how to measure Lp(a)?

Lp(a) must be measured once in subjects at high cardiovascular risk or with a family history of premature CHD, familial hypercholesterolaemia, type 1 or 2 diabetes or chronic kidney disease.

Lp(a) concentrations should be determined by an immunoassay not affected by apo(a) size variation using a monoclonal antibody specific for a unique apo(a) epitope

Do not measure Lp(a) in case of inflammation or intercurrent illness

What concentration of Lp(a) is considered high?

In patients with Lp(a), a cut-off point of ≥ 125 nmol/L ($\approx \geq 0.5$ g/L) suggests increased risk of atherothrombotic disease in Caucasian patients

In case of high Lp(a), LDL-cholesterol must be calculated as follows:

Lp(a)-corrected LDL-cholesterol (g/L) = LDL-cholesterol (g/L) – [Lp(a) (g/L) \times 0.30]

In patients with Lp(a) > 250 nmol/L (≈ 1 g/L), lipid-lowering treatment should be intensified

apo(a): apolipoprotein A; CHD: coronary heart disease; LDL: low-density lipoprotein; Lp(a): lipoprotein(a).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.acvd.2021.10.009>.

Disclosure of interest

The authors declare that they have no competing interest.

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