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

Vincent Durlach, Dominique Bonnefont-Rousselot, Franck Boccara, Mathilde Varret, Mathilde Di-Filippo Charcosset, Bertrand Cariou, René Valero, Sybil Charriere, Michel Farnier, Pierre E Morange, et al.

Archives of Cardiovascular Disease xxx (xxxx) xxx—xxx

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

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)

Vincent Durlach[a], Dominique Bonnefont-Rousselot[b,c], Franck Boccara[d,e], Mathilde Varret[f,g], Mathilde Di-Filippo Charcosset[h,i], Bertrand Cariou[j], René Valero[k], Sybil Charriere[l], Michel Farnier[m,n], Pierre E. Morange[o], Olivier Meilhac[p,q], Gilles Lambert[p,q], Philippe Moulin[l], Philippe Gillery[r], Sophie Beliard-Lasserre[k], Eric Bruckert[s,t], Alain Carrié[u], Jean Ferrières[v], Xavier Collet[w], M. John Chapman[x], Eduardo Anglés-Cano[y,1,*]

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 ; KIV_2-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.

* Corresponding author.
Adresses e-mail : Eduardo.Angles-Cano@inserm.fr, Eduardo.Angles-Cano@parisdescartes.fr (E. Anglés-Cano).
[1] Twitter address: @AnglescanoE.

https://doi.org/10.1016/j.acvd.2021.10.009

Pour citer cet article : V. Durlach, D. Bonnefont-Rousselot, F. Boccara et al., Lipoprotein(a): Pathophysiology, measurement, indication and treatment in cardiovascular disease. A consensus statement from the Nouvelle Société Francophone d'Athérosclérose (NSFA), Arch Cardiovasc Dis, https://doi.org/10.1016/j.acvd.2021.10.009

[a] *Champagne-Ardenne University, UMR CNRS 7369 MEDyC & Cardio-Thoracic Department, Reims University Hospital, 51092 Reims, France*
[b] *Metabolic Biochemistry Department, Hôpital Pitié-Salpêtrière, AP—HP, 75013 Paris, France*
[c] *Université de Paris, CNRS, INSERM, UTCBS, 75006 Paris, France*
[d] *Sorbonne University, GRC n° 22, C²MV, INSERM UMR_S 938, Centre de Recherche Saint-Antoine, IHU ICAN, 75012 Paris, France*
[e] *Service de Cardiologie, Hôpital Saint-Antoine, AP—HP, 75012 Paris, France*
[f] *Laboratory for Vascular Translational Science (LVTS), INSERM U1148, Centre Hospitalier Universitaire Xavier Bichat, 75018 Paris, France*
[g] *Université de Paris, 75018 Paris, France*
[h] *Hospices Civils de Lyon, UF Dyslipidémies, 69677 Bron, France*
[i] *Laboratoire CarMen, INSERM, INRA, INSA, Université Claude-Bernard Lyon 1, 69495 Pierre-Bénite, France*
[j] *Université de Nantes, CHU Nantes, CNRS, INSERM, l'Institut du Thorax, 44000 Nantes, France*
[k] *Endocrinology Department, La Conception Hospital, AP—HM, Aix-Marseille University, INSERM, INRAE, C2VN, 13005 Marseille, France*
[l] *Hospices Civils de Lyon, INSERM U1060, Laboratoire CarMeN, Université Lyon 1, 69310 Pierre-Bénite, France*
[m] *PEC2, EA 7460, University of Bourgogne Franche-Comté, 21079 Dijon, France*
[n] *Department of Cardiology, CHU Dijon Bourgogne, 21000 Dijon, France*
[o] *Aix-Marseille University, INSERM, INRAE, C2VN, 13385 Marseille, France*
[p] *INSERM, UMR 1188 DéTROI, Université de La Réunion, 97744 Saint-Denis de La Réunion, Reunion*
[q] *CHU de La Réunion, CIC-EC 1410, 97448 Saint-Pierre, Reunion*
[r] *Laboratory of Biochemistry-Pharmacology-Toxicology, Reims University Hospital, University of Reims Champagne-Ardenne, UMR CNRS/URCA n° 7369, 51092 Reims, France*
[s] *Service d'Endocrinologie-Métabolisme, Hôpital Pitié-Salpêtrière, AP—HP, 75013 Paris, France*
[t] *IHU ICAN, Sorbonne University, 75013 Paris, France*
[u] *Sorbonne University, UMR INSERM 1166, IHU ICAN, Laboratory of Endocrine and Oncological Biochemistry, Obesity and Dyslipidaemia Genetic Unit, Hôpital Pitié-Salpêtrière, AP—HP, 75013 Paris, France*
[v] *Department of Cardiology and INSERM UMR 1295, Rangueil University Hospital, TSA 50032, 31059 Toulouse, France*
[w] *INSERM U1048, Institute of Metabolic and Cardiovascular Diseases, Rangueil University Hospital, BP 84225, 31432 Toulouse, France*
[x] *Sorbonne University, Hôpital Pitié-Salpêtrière and National Institute for Health and Medical Research (INSERM), 75013 Paris, France*
[y] *Université de Paris, INSERM, Innovative Therapies in Haemostasis, 75006 Paris, France*

Reçu le 15 juin 2021 ; reçu sous la forme révisée le 16 octobre 2021 ; accepté le 18 octobre 2021

KEYWORDS
Lipoprotein(a) ;
Atherothrombosis ;
Cardiovascular diseases ;
Apolipoprotein(a) ;
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.

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 structurelle 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 athérothrombotique 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 oligonucléotides 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 hypolipidémiant. En raison de sa pertinence clinique, le coût du test lipoprotéine(a) devrait être couvert par la sécurité sociale et les autorités sanitaires.

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 interethnic 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 KIV_1 to KIV_{10}) have been recognized in apo(a) [20], and at least one of them, KIV_{10}, contains a lysine-binding site similar to that of plasminogen KIV [21]. KIV_1 and KIV_3 to KIV_{10} are present in single copies. In contrast, the number of copies of KIV_2 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 KIV_2 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 KIV_2 copy number variation (KIV_2-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 KIV_2 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 KIV_2-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 KIV_2-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 KIV_2, Lp(a) immunoassays could result in underestimation of

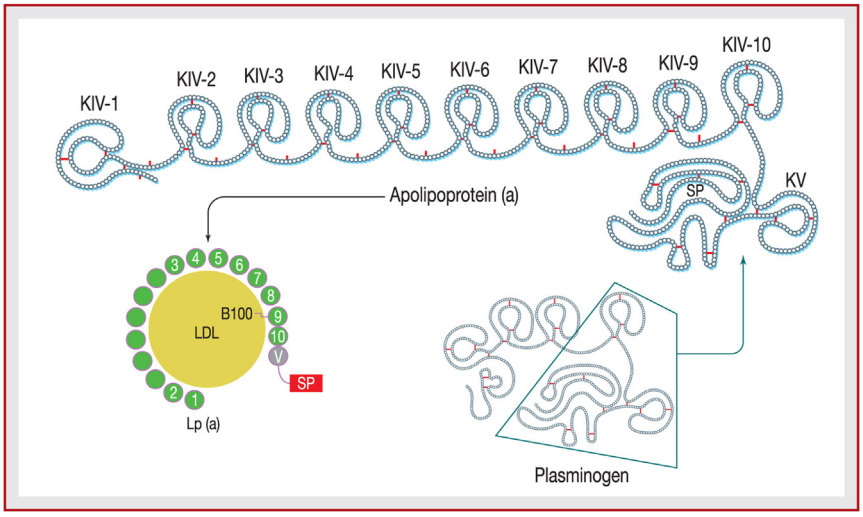

Figure 1. Lipoprotein(a)/apolipoprotein(a) (Lp(a)/apo(a)) structure. Lp(a) is a complex particle composed of a lipid core and two disulphide-linked apolipoproteins: apolipoprotein B-100 (low-density lipoprotein [LDL]) and apo(a). Apo(a) glycoprotein shows a high degree of homology with plasminogen, the 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 (≈ ≥ 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) × 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 concentrations											
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		0.53	0.59	0.38	0.35	[33]
(TTTTA)n[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 concentrations											
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; KIV_{6-9}: kringle IV type 6—9; KIV_2-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 KIV_2-CNV.

[b] SNP in linkage disequilibrium with the KIV_2-CNV in Mexicans.

[c] SNP associated with medium-size KIV_2 alleles in Africans, with large-size KIV_2 alleles in Europeans.

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

[e] SNP in linkage disequilibrium with KIV_2-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 $\geq$ 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 KIV_{10} [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 $\pm$ 0.3 nmol/L), regardless of apo(a) size, than the corresponding affinity of plasminogen (K_d 0.5—1 μmol/L)

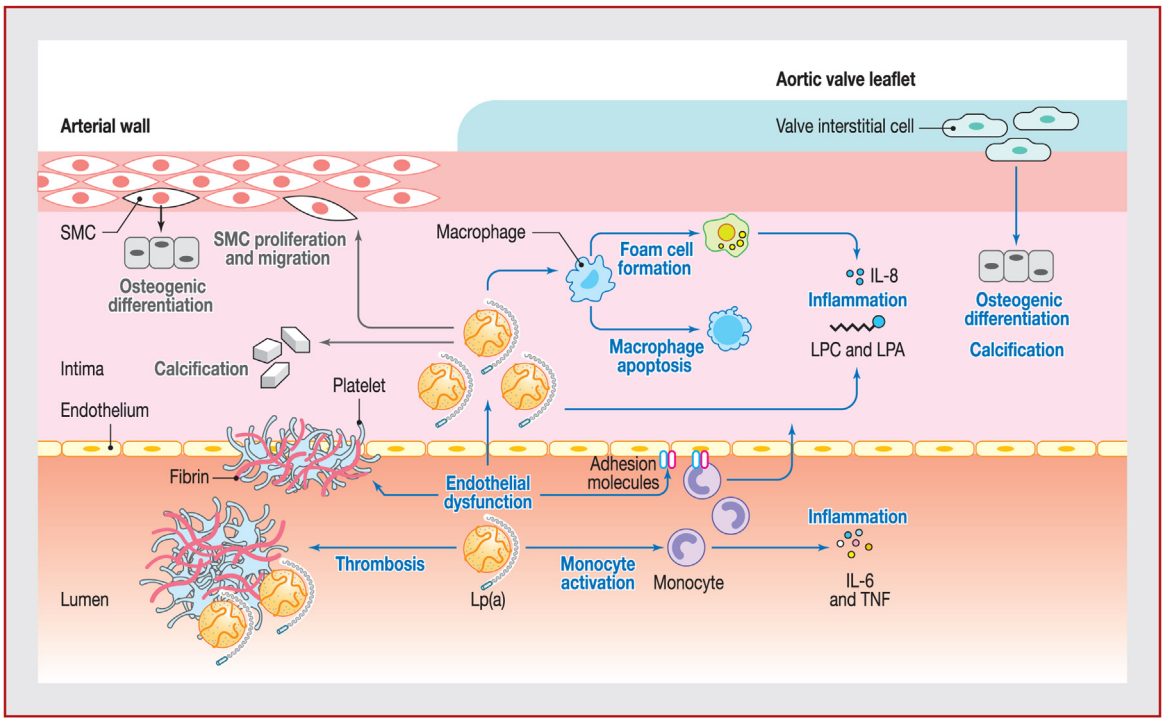

Figure 2. Cellular effects of lipoprotein(a) (Lp(a)) and Lp(a)-associated oxidized phospholipids (from [75]). Lp(a) promotes endothelial damage by inducing mural thrombosis and endothelial dysfunction; the latter promotes Lp(a) passage through the protective endothelial layer. Lp(a) can also activate 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.

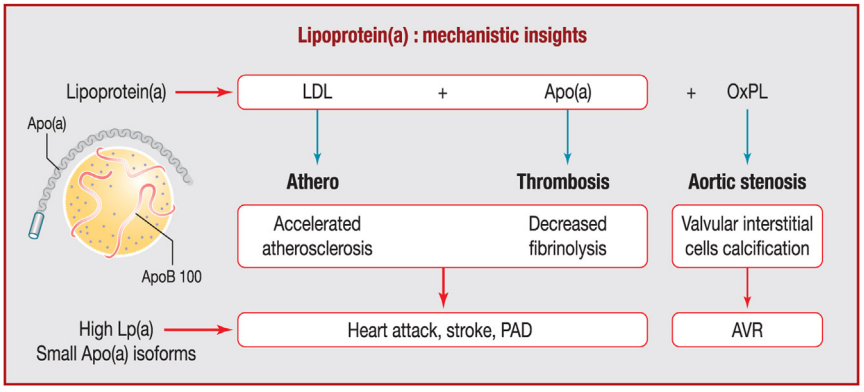

Figure 3. Lipoprotein(a) (Lp(a)): mechanistic insights. Pathophysiological pathways providing a causal link between high plasma concentrations of Lp(a) and atherosclerotic vascular disease and aortic stenosis. Clinical outcomes are related to atherosclerotic stenosis complicated by thrombosis (myocardial 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 KIV_{10} 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,

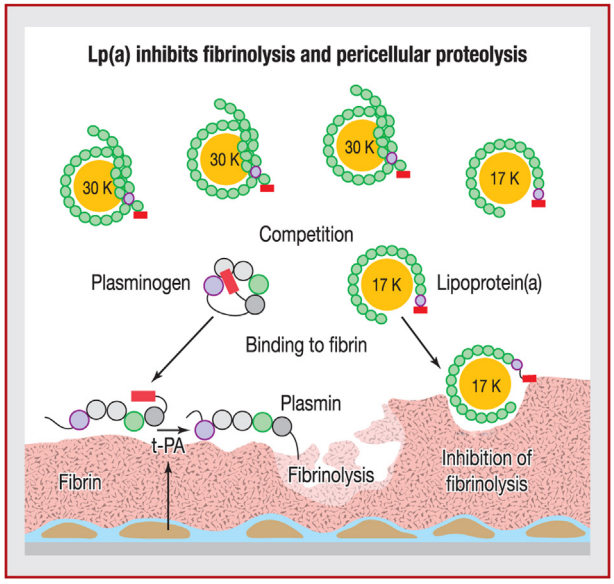

Figure 4. Contribution of apolipoprotein(a) (apo(a)) polymorphism to inhibition of fibrinolysis, a mechanism that may favour thrombus development. Lipoprotein(a) (Lp(a)) competes with plasminogen for binding to fibrin and cell plasminogen receptors. Inhibition of plasminogen binding and activation impairs 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 KIV_{10} 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 (≈ 1.17 g/L) than in individuals with Lp(a) < 12.5 nmol/L (≈ 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

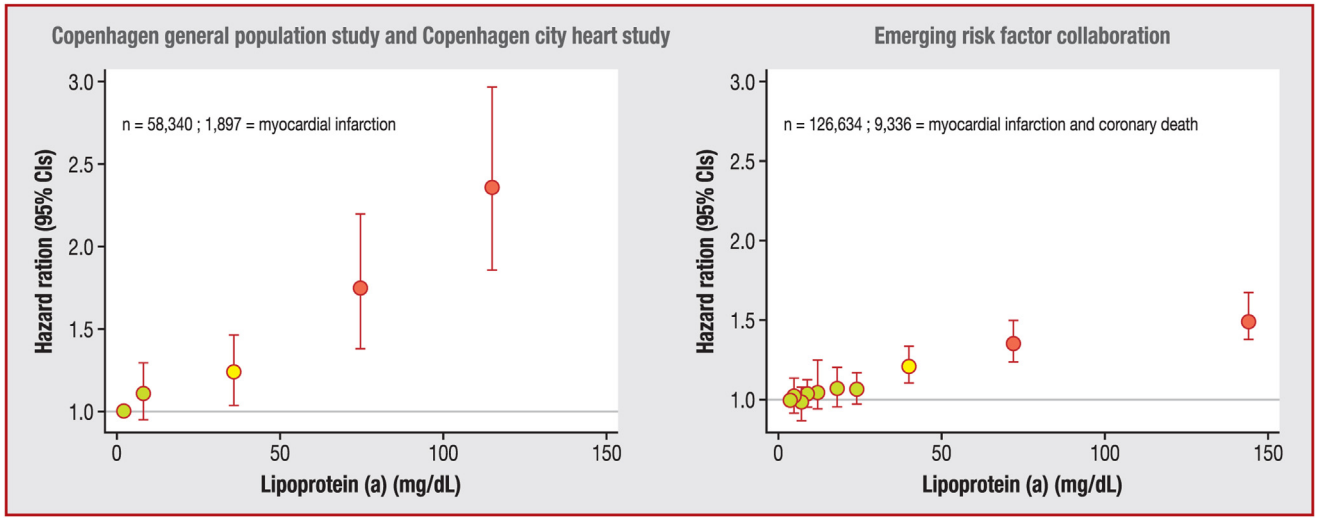

Figure 5. Observational associations between high plasma lipoprotein(a) concentrations and risk of cardiovascular disease in the Copenhagen City Heart Study and Copenhagen General Population Study combined (left panel) and in the Emerging Risk Factors Collaboration (right panel). Reproduced from [67].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

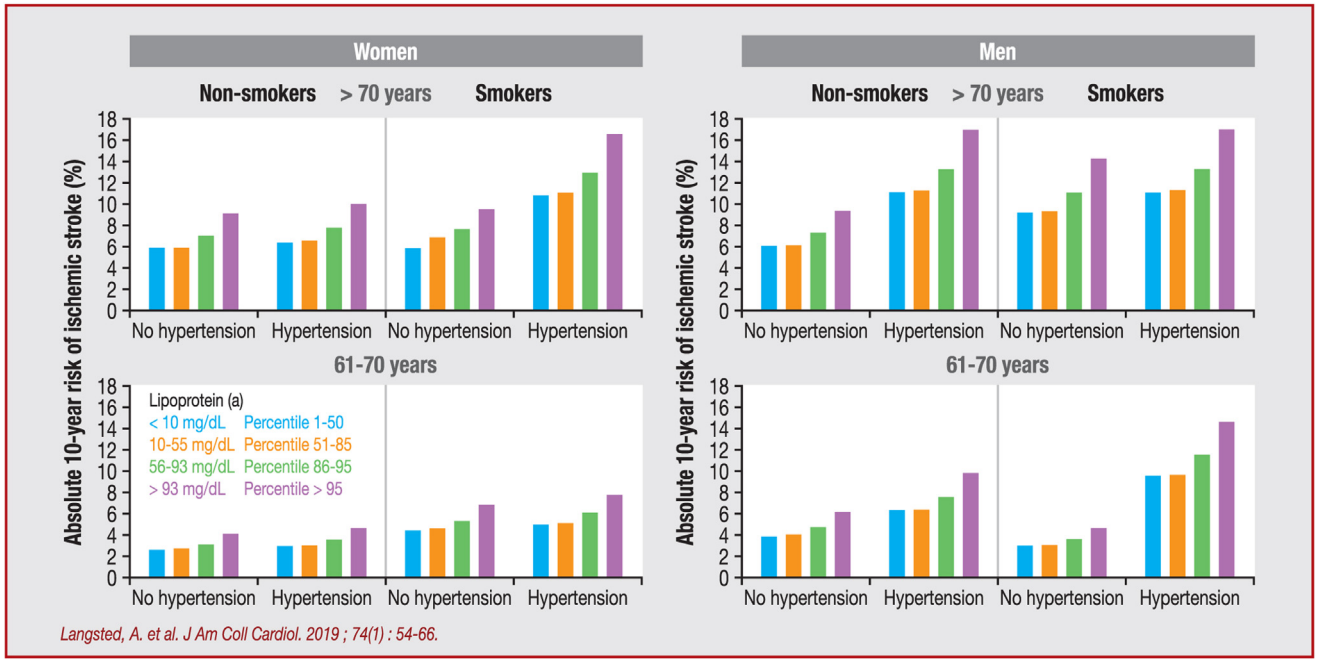

Figure 6. Lipoprotein(a) and risk of ischaemic stroke [104]. Predicted absolute 10-year risk of ischaemic stroke by concentrations of lipoprotein(a), sex, age, smoking and hypertension. Analyses were by binominal regression. Based on 49,699 individuals from the Copenhagen General Population Study. Reproduced 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) $\geq$ 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 ($\approx$ 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 ($\approx$ 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 (≈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—laropiprant 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 $\geq$ 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 baseline Lp(a), and for the first time will evaluate the clinical benefit of a targeted reduction in Lp(a) concentrations.

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

In patients with Lp(a) > 250 nmol/L ($\approx$ 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 ($\approx$ 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).

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 (~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) × 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).

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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.

Références

[1] Berg K. A new serum type system in Man — the Lp System. Acta Pathol Microbiol Scand 1963;59:369—82.
[2] Eaton DL, Fless GM, Kohr WJ, et al. Partial amino acid sequence of apolipoprotein(a) shows that it is homologous to plasminogen. Proc Natl Acad Sci U S A 1987;84:3224—8.
[3] McLean JW, Tomlinson JE, Kuang WJ, et al. cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. Nature 1987;330:132—7.
[4] Kronenberg F. Human genetics and the causal role of lipoprotein(a) for various diseases. Cardiovasc Drugs Ther 2016;30:87—100.
[5] Burgess S, Ference BA, Staley JR, et al. Association of LPA variants with risk of coronary disease and the implications for lipoprotein(a)-lowering therapies: a Mendelian Randomization Analysis. JAMA Cardiol 2018;3:619—27.
[6] Trinder M, Zekavat SM, Uddin MM, Pampana A, Natarajan P. Apolipoprotein B is an insufficient explanation for the risk of coronary disease associated with lipoprotein(a). Cardiovasc Res 2021;117:1245—7.
[7] Thanassoulis G, Campbell CY, Owens DS, et al. Genetic associations with valvular calcification and aortic stenosis. N Engl J Med 2013;368:503—12.
[8] Kotani K, Sahebkar A, Serban MC, et al. Lipoprotein(a) levels in patients with abdominal aortic aneurysm. Angiology 2017;68:99—108.
[9] Kronenberg F. Prediction of cardiovascular risk by Lp(a) concentrations or genetic variants within the LPA gene region. Clin Res Cardiol Suppl 2019;14:5—12.
[10] Rao F, Schork AJ, Maihofer AX, et al. Heritability of biomarkers of oxidized lipoproteins: twin pair study. Arterioscler Thromb Vasc Biol 2015;35:1704—11.
[11] Cobbaert C, Kesteloot H. Serum lipoprotein(a) levels in racially different populations. Am J Epidemiol 1992;136:441—9.
[12] Pare G, Caku A, McQueen M, et al. Lipoprotein(a) levels and the risk of myocardial infarction among 7 ethnic groups. Circulation 2019;139:1472—82.
[13] Lawn RM, Wade DP, Hammer RE, Chiesa G, Verstuyft JG, Rubin EM. Atherogenesis in transgenic mice expressing human apolipoprotein(a). Nature 1992;360:670—2.
[14] Malgaretti N, Acquati F, Magnaghi P, et al. Characterization by yeast artificial chromosome cloning of the linked apolipoprotein(a) and plasminogen genes and identification of the apolipoprotein(a) 5′ flanking region. Proc Natl Acad Sci U S A 1992;89:11584—8.
[15] Magnaghi P, Citterio E, Malgaretti N, Acquati F, Ottolenghi S, Taramelli R. Molecular characterisation of the human apo(a)-plasminogen gene family clustered on the telomeric region of chromosome 6 (6q26-27). Hum Mol Genet 1994;3:437—42.
[16] Guevara Jr J, Knapp RD, Honda S, Northup SR, Morrisett JD. A structural assessment of the apo[a] protein of human lipoprotein[a]. Proteins 1992;12:188—99.

[17] Longstaff C, Kolev K. Basic mechanisms and regulation of fibrinolysis. J Thromb Haemost 2015;13(Suppl. 1):S98—105.
[18] Xue Y, Bodin C, Olsson K. Crystal structure of the native plasminogen reveals an activation-resistant compact conformation. J Thromb Haemost 2012;10:1385—96.
[19] Fleury V, Angles-Cano E. Characterization of the binding of plasminogen to fibrin surfaces: the role of carboxy-terminal lysines. Biochemistry 1991;30:7630—8.
[20] Guevara Jr J, Jan AY, Knapp R, Tulinsky A, Morrisett JD. Comparison of ligand-binding sites of modeled apo[a] kringle-like sequences in human lipoprotein[a]. Arterioscler Thromb 1993;13:758—70.
[21] Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. J Clin Invest 1992;90:52—60.
[22] Haibach C, Kraft HG, Kochl S, Abe A, Utermann G. The number of kringle IV repeats 3—10 is invariable in the human apo(a) gene. Gene 1998;208:253—8.
[23] Hervio L, Brunner C, Sorell L, Kang C, Muller H, Angles-Cano E. Effect of plasminogen activators on human recombinant apolipoprotein(a) having the plasminogen activation cleavage site. Biochim Biophys Acta 1999;1434:124—34.
[24] Utermann G, Menzel HJ, Kraft HG, Duba HC, Kemmler HG, Seitz C. Lp(a) glycoprotein phenotypes. Inheritance and relation to Lp(a)-lipoprotein concentrations in plasma. J Clin Invest 1987;80:458—65.
[25] Berglund L, Ramakrishnan R. Lipoprotein(a): an elusive cardiovascular risk factor. Arterioscler Thromb Vasc Biol 2004;24:2219—26.
[26] Holmer SR, Hengstenberg C, Kraft HG, et al. Association of polymorphisms of the apolipoprotein(a) gene with lipoprotein(a) levels and myocardial infarction. Circulation 2003;107:696—701.
[27] Perombelon YF, Soutar AK, Knight BL. Variation in lipoprotein(a) concentration associated with different apolipoprotein(a) alleles. J Clin Invest 1994;93:1481—92.
[28] Mack S, Coassin S, Rueedi R, et al. A genome-wide association meta-analysis on lipoprotein (a) concentrations adjusted for apolipoprotein (a) isoforms. J Lipid Res 2017;58:1834—44.
[29] Zeng L, Mirza-Schreiber N, Lamina C, et al. Cis-epistasis at the LPA locus and risk of cardiovascular disease. Cardiovasc Res 2021, http://dx.doi.org/10.1093/cvr/cvab136 [518290].
[30] Puckey LH, Knight BL. Sequence and functional changes in a putative enhancer region upstream of the apolipoprotein(a) gene. Atherosclerosis 2003;166:119—27.
[31] Trommsdorff M, Kochl S, Lingenhel A, et al. A pentanucleotide repeat polymorphism in the 5′ control region of the apolipoprotein(a) gene is associated with lipoprotein(a) plasma concentrations in Caucasians. J Clin Invest 1995;96:150—7.
[32] Bopp S, Kochl S, Acquati F, et al. Ten allelic apolipoprotein[a] 5′ flanking fragments exhibit comparable promoter activities in HepG2 cells. J Lipid Res 1995;36:1721—8.
[33] Chretien JP, Coresh J, Berthier-Schaad Y, et al. Three single nucleotide polymorphisms in LPA account for most of the increase in lipoprotein(a) level elevation in African Americans compared with European Americans. J Med Genet 2006;43:917—23.
[34] Rainwater DL, Kammerer CM, VandeBerg JL, Hixson JE. Characterization of the genetic elements controlling lipoprotein(a) concentrations in Mexican Americans. Evidence for at least three controlling elements linked to LPA, the locus encoding apolipoprotein(a). Atherosclerosis 1997;128:223—33.
[35] Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med 2009;361:2518—28.
[36] Lu W, Cheng YC, Chen K, et al. Evidence for several independent genetic variants affecting lipoprotein (a) cholesterol levels. Hum Mol Genet 2015;24:2390—400.
[37] Ogorelkova M, Kraft HG, Ehnholm C, Utermann G. Single nucleotide polymorphisms in exons of the apo(a) kringles IV types 6 to 10 domain affect Lp(a) plasma concentrations and have different patterns in Africans and Caucasians. Hum Mol Genet 2001;10:815—24.
[38] Kraft HG, Haibach C, Lingenhel A, et al. Sequence polymorphism in kringle IV 37 in linkage disequilibrium with the apolipoprotein (a) size polymorphism. Hum Genet 1995;95:275—82.
[39] Kraft HG, Windegger M, Menzel HJ, Utermann G. Significant impact of the +93C/T polymorphism in the apolipoprotein(a) gene on Lp(a) concentrations in Africans but not in Caucasians: confounding effect of linkage disequilibrium. Hum Mol Genet 1998;7:257—64.
[40] Ogorelkova M, Gruber A, Utermann G. Molecular basis of congenital lp(a) deficiency: a frequent apo(a) 'null' mutation in caucasians. Hum Mol Genet 1999;8:2087—96.
[41] Parson W, Kraft HG, Niederstatter H, et al. A common nonsense mutation in the repetitive Kringle IV-2 domain of human apolipoprotein(a) results in a truncated protein and low plasma Lp(a). Hum Mutat 2004;24:474—80.
[42] Morgan BM, Brown AN, Deo N, et al. Non-synonymous SNPs in LPA homologous to plasminogen deficiency mutants represent novel null apo(a) alleles. J Lipid Res 2020;61:432—44.
[43] Zekavat SM, Ruotsalainen S, Handsaker RE, et al. Deep coverage whole genome sequences and plasma lipoprotein(a) in individuals of European and African ancestries. Nat Commun 2018;9:2606.
[44] Larsson SC, Gill D, Mason AM, et al. Lipoprotein(a) in Alzheimer, atherosclerotic, cerebrovascular, thrombotic, and valvular disease: Mendelian randomization investigation. Circulation 2020;141:1826—8.
[45] Trinder M, Uddin MM, Finneran P, Aragam KG, Natarajan P. Clinical utility of lipoprotein(a) and LPA Genetic Risk Score in risk prediction of incident atherosclerotic cardiovascular disease. JAMA Cardiol 2020;6(3):1—9.
[46] Lambert G, Thedrez A, Croyal M, et al. The complexity of lipoprotein (a) lowering by PCSK9 monoclonal antibodies. Clin Sci (Lond) 2017;131:261—8.
[47] Kronenberg F, Utermann G. Lipoprotein(a): resurrected by genetics. J Intern Med 2013;273:6—30.
[48] Marcovina SM, Albers JJ. Lipoprotein (a) measurements for clinical application. J Lipid Res 2016;57:526—37.
[49] Wilson DP, Jacobson TA, Jones PH, et al. Use of Lipoprotein(a) in clinical practice: a biomarker whose time has come. A scientific statement from the National Lipid Association. J Clin Lipidol 2019;13:374—92.
[50] Mackness MI, Bhatnagar D, Weiringa G, MBewu A, Haynes B, Durrington PN. A comparative study of six commercial lipoprotein(a) assays in seventeen laboratories within the British Isles. Ann Clin Biochem 1996;33(Pt 1):63—70.
[51] Clouet-Foraison N, Marcovina SM, Guerra E, et al. Analytical performance specifications for lipoprotein(a), apolipoprotein B-100, and apolipoprotein A-I using the biological variation model in the EuBIVAS population. Clin Chem 2020;66:727—36.
[52] Enkhmaa B, Anuurad E, Berglund L. Lipoprotein (a): impact by ethnicity and environmental and medical conditions. J Lipid Res 2016;57:1111—25.
[53] Hopewell JC, Haynes R, Baigent C. The role of lipoprotein (a) in chronic kidney disease. J Lipid Res 2018;59:577—85.
[54] Marcovina SM, Albers JJ, Gabel B, Koschinsky ML, Gaur VP. Effect of the number of apolipoprotein(a) kringle 4 domains on immunochemical measurements of lipoprotein(a). Clin Chem 1995;41:246—55.

[55] Marcovina SM, Albers JJ, Scanu AM, et al. Use of a reference material proposed by the International Federation of Clinical Chemistry and Laboratory Medicine to evaluate analytical methods for the determination of plasma lipoprotein(a). Clin Chem 2000;46:1956—67.
[56] Marcovina SM, Koschinsky ML, Albers JJ, Skarlatos S. Report of the National Heart, Lung, and Blood Institute Workshop on Lipoprotein(a) and Cardiovascular Disease: recent advances and future directions. Clin Chem 2003;49:1785—96.
[57] Scharnagl H, Stojakovic T, Dieplinger B, et al. Comparison of lipoprotein (a) serum concentrations measured by six commercially available immunoassays. Atherosclerosis 2019;289:206—13.
[58] Tsimikas S, Fazio S, Ferdinand KC, et al. NHLBI Working Group recommendations to reduce lipoprotein(a)-mediated risk of cardiovascular disease and aortic stenosis. J Am Coll Cardiol 2018;71:177—92.
[59] Stefanutti C, Pisciotta L, Favari E, et al. Lipoprotein(a) concentration, genetic variants, apo(a) isoform size, and cellular cholesterol efflux in patients with elevated Lp(a) and coronary heart disease submitted or not to lipoprotein apheresis: an Italian case-control multicenter study on Lp(a). J Clin Lipidol 2020;14 [487—97 e1].
[60] Ruhaak LR, Cobbaert CM. Quantifying apolipoprotein(a) in the era of proteoforms and precision medicine. Clin Chim Acta 2020;511:260—8.
[61] Marcovina SM, Clouet-Foraison N, Koschinsky ML, et al. Development of an LC-MS/MS proposed candidate reference method for the standardization of analytical methods to measure lipoprotein(a). Clin Chem 2021;67:490—9.
[62] Cobbaert CM, Althaus H, Begcevic Brkovic I, et al. Towards an SI-traceable reference measurement system for seven serum apolipoproteins using bottom-up quantitative proteomics: conceptual approach enabled by cross-disciplinary/cross-sector collaboration. Clin Chem 2021;67:478—89.
[63] Willeit P, Ridker PM, Nestel PJ, et al. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. Lancet 2018;392:1311—20.
[64] Yeang C, Witztum JL, Tsimikas S. 'LDL-C' = LDL-C + Lp(a)-C: implications of achieved ultra-low LDL-C levels in the proprotein convertase subtilisin/kexin type 9 era of potent LDL-C lowering. Curr Opin Lipidol 2015;26:169—78.
[65] Nordestgaard BG, Langlois MR, Langsted A, et al. Quantifying atherogenic lipoproteins for lipid-lowering strategies: consensus-based recommendations from EAS and EFLM. Atherosclerosis 2020;294:46—61.
[66] Yeang C, Witztum JL, Tsimikas S. Novel method for quantification of lipoprotein(a)-cholesterol: implications for improving accuracy of LDL-C measurements. J Lipid Res 2021;62:100053.
[67] Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. J Lipid Res 2016;57:1953—75.
[68] Lippi G, Guidi G. Lipoprotein(a): from ancestral benefit to modern pathogen? QJM 2000;93:75—84.
[69] O'Brien KD, Reichenbach DD, Marcovina SM, Kuusisto J, Alpers CE, Otto CM. Apolipoproteins B, (a), and E accumulate in the morphologically early lesion of 'degenerative' valvular aortic stenosis. Arterioscler Thromb Vasc Biol 1996;16:523—32.
[70] van der Valk FM, Bekkering S, Kroon J, et al. Oxidized phospholipids on lipoprotein(a) elicit arterial wall inflammation and an inflammatory monocyte response in humans. Circulation 2016;134:611—24.
[71] Gencer B, Kronenberg F, Stroes ES, Mach F. Lipoprotein(a): the revenant. Eur Heart J 2017;38:1553—60.
[72] Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. J Am Coll Cardiol 2017;69:692—711.
[73] Eckardstein AV. Lipoprotein(a). Eur Heart J 2017;38:1530—2.
[74] Zheng KH, Tsimikas S, Pawade T, et al. Lipoprotein(a) and oxidized phospholipids promote valve calcification in patients with aortic stenosis. J Am Coll Cardiol 2019;73:2150—62.
[75] Boffa MB, Koschinsky ML. Oxidized phospholipids as a unifying theory for lipoprotein(a) and cardiovascular disease. Nat Rev Cardiol 2019;16:305—18.
[76] Gendron N, Rosa M, Blandinieres A, et al. Human aortic valve interstitial cells display proangiogenic properties during calcific aortic valve disease. Arterioscler Thromb Vasc Biol 2021;41:415—29.
[77] Hervio L, Durlach V, Girard-Globa A, Angles-Cano E. Multiple binding with identical linkage: a mechanism that explains the effect of lipoprotein(a) on fibrinolysis. Biochemistry 1995;34:13353—8.
[78] Soulat T, Loyau S, Baudouin V, et al. Effect of individual plasma lipoprotein(a) variations in vivo on its competition with plasminogen for fibrin and cell binding: an in vitro study using plasma from children with idiopathic nephrotic syndrome. Arterioscler Thromb Vasc Biol 2000;20:575—84.
[79] Plow EF, Doeuvre L, Das R. So many plasminogen receptors: why? J Biomed Biotechnol 2012;2012:141806.
[80] Ezratty A, Simon DI, Loscalzo J. Lipoprotein(a) binds to human platelets and attenuates plasminogen binding and activation. Biochemistry 1993;32:4628—33.
[81] Hervio L, Girard-Globa A, Durlach V, Angles-Cano E. The antifibrinolytic effect of lipoprotein(a) in heterozygous subjects is modulated by the relative concentration of each of the apolipoprotein(a) isoforms and their affinity for fibrin. Eur J Clin Invest 1996;26:411—7.
[82] Rouy D, Koschinsky ML, Fleury V, Chapman J, Angles-Cano E. Apolipoprotein(a) and plasminogen interactions with fibrin: a study with recombinant apolipoprotein(a) and isolated plasminogen fragments. Biochemistry 1992;31:6333—9.
[83] Martinez C, Rivera J, Loyau S, et al. Binding of recombinant apolipoprotein(a) to human platelets and effect on platelet aggregation. Thromb Haemost 2001;85:686—93.
[84] Kang C, Dominguez M, Loyau S, Miyata T, Durlach V, Angles-Cano E. Lp(a) particles mold fibrin-binding properties of apo(a) in size-dependent manner: a study with different-length recombinant apo(a), native Lp(a), and monoclonal antibody. Arterioscler Thromb Vasc Biol 2002;22:1232—8.
[85] Hervio L, Chapman MJ, Thillet J, Loyau S, Angles-Cano E. Does apolipoprotein(a) heterogeneity influence lipoprotein(a) effects on fibrinolysis? Blood 1993;82:392—7.
[86] Leibundgut G, Scipione C, Yin H, et al. Determinants of binding of oxidized phospholipids on apolipoprotein (a) and lipoprotein (a). J Lipid Res 2013;54:2815—30.
[87] Boffa MB, Marar TT, Yeang C, et al. Potent reduction of plasma lipoprotein (a) with an antisense oligonucleotide in human subjects does not affect ex vivo fibrinolysis. J Lipid Res 2019;60:2082—9.
[88] Miles LA, Plow EF. Binding and activation of plasminogen on the platelet surface. J Biol Chem 1985;260:4303—11.
[89] Rouy D, Grailhe P, Nigon F, Chapman J, Angles-Cano E. Lipoprotein(a) impairs generation of plasmin by fibrin-bound tissue-type plasminogen activator. In vitro studies in a plasma milieu. Arterioscler Thromb 1991;11:629—38.
[90] Romagnuolo R, Marcovina SM, Boffa MB, Koschinsky ML. Inhibition of plasminogen activation by apo(a): role of carboxyl-terminal lysines and identification of inhibitory domains in apo(a). J Lipid Res 2014;55:625—34.
[91] Sandmark J, Tigerstrom A, Akerud T, et al. Identification and analyses of inhibitors targeting apolipoprotein(a) kringle domains KIV-7, KIV-10, and KV provide insight into kringle domain function. J Biol Chem 2020;295:5136—51.
[92] Rand ML, Sangrar W, Hancock MA, et al. Apolipoprotein(a) enhances platelet responses to the thrombin receptor

-activating peptide SFLLRN. Arterioscler Thromb Vasc Biol 1998;18:1393—9.
[93] Wu HD, Berglund L, Dimayuga C, et al. High lipoprotein(a) levels and small apolipoprotein(a) sizes are associated with endothelial dysfunction in a multiethnic cohort. J Am Coll Cardiol 2004;43:1828—33.
[94] Etingin OR, Hajjar DP, Hajjar KA, Harpel PC, Nachman RL. Lipoprotein (a) regulates plasminogen activator inhibitor-1 expression in endothelial cells. A potential mechanism in thrombogenesis. J Biol Chem 1991;266:2459—65.
[95] Bennet A, Di Angelantonio E, Erqou S, et al. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. Arch Intern Med 2008;168:598—608.
[96] Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J 2010;31:2844—53.
[97] Emerging Risk Factors C., Erqou S, Kaptoge S, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA 2009;302:412—23.
[98] CARDIoGRAMplusC4D Consortium, Deloukas P, Kanoni S, et al. Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet 2013;45:25—33.
[99] Nave AH, von Eckardstein A. Is lipoprotein(a) a risk factor for ischemic stroke and venous thromboembolism? Clin Res Cardiol Suppl 2019;14:28—32.
[100] Smolders B, Lemmens R, Thijs V. Lipoprotein (a) and stroke: a meta-analysis of observational studies. Stroke 2007;38:1959—66.
[101] Erqou S, Thompson A, Di Angelantonio E, et al. Apolipoprotein(a) isoforms and the risk of vascular disease: systematic review of 40 studies involving 58,000 participants. J Am Coll Cardiol 2010;55:2160—7.
[102] Nave AH, Lange KS, Leonards CO, et al. Lipoprotein (a) as a risk factor for ischemic stroke: a meta-analysis. Atherosclerosis 2015;242:496—503.
[103] Arora P, Kalra R, Callas PW, et al. Lipoprotein(a) and risk of ischemic stroke in the REGARDS Study. Arterioscler Thromb Vasc Biol 2019;39:810—8.
[104] Langsted A, Nordestgaard BG, Kamstrup PR. Elevated lipoprotein(a) and risk of ischemic stroke. J Am Coll Cardiol 2019;74:54—66.
[105] Boffa MB, Koschinsky ML. Lipoprotein (a): truly a direct prothrombotic factor in cardiovascular disease? J Lipid Res 2016;57:745—57.
[106] Nowak-Gottl U, Junker R, Hartmeier M, et al. Increased lipoprotein(a) is an important risk factor for venous thromboembolism in childhood. Circulation 1999;100:743—8.
[107] Revel-Vilk S, Chan A, Bauman M, Massicotte P. Prothrombotic conditions in an unselected cohort of children with venous thromboembolic disease. J Thromb Haemost 2003;1:915—21.
[108] Laschkolnig A, Kollerits B, Lamina C, et al. Lipoprotein (a) concentrations, apolipoprotein (a) phenotypes, and peripheral arterial disease in three independent cohorts. Cardiovasc Res 2014;103:28—36.
[109] Levin MG, Zuber V, Walker VM, et al. Prioritizing the role of major lipoproteins and subfractions as risk factors for peripheral artery disease. Circulation 2021;144:353—64.
[110] Kheirkhah A, Lamina C, Rantner B, et al. Elevated levels of serum PCSK9 in male patients with symptomatic peripheral artery disease: the CAVASIC study. Atherosclerosis 2021;316:41—7.
[111] Verweij SL, de Ronde MWJ, Verbeek R, et al. Elevated lipoprotein(a) levels are associated with coronary artery calcium scores in asymptomatic individuals with a family history of premature atherosclerotic cardiovascular disease. J Clin Lipidol 2018;12 [597—603 e1].
[112] Dasa O, Pepine CJ, Pearson TA. Aspirin in primary prevention: what changed? A critical appraisal of current evidence. Am J Cardiol 2021;141:38—48.
[113] Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. J Am Coll Cardiol 2014;63:470—7.
[114] Capoulade R, Yeang C, Chan KL, Pibarot P, Tsimikas S. Association of mild to moderate aortic valve stenosis progression with higher lipoprotein(a) and oxidized phospholipid levels: secondary analysis of a randomized clinical trial. JAMA Cardiol 2018;3(12):1212—7.
[115] Capoulade R, Chan KL, Yeang C, et al. Oxidized phospholipids, lipoprotein(a), and progression of calcific aortic valve stenosis. J Am Coll Cardiol 2015;66:1236—46.
[116] Bergmark BA, O'Donoghue ML, Murphy SA, et al. An exploratory analysis of proprotein convertase subtilisin/kexin type 9 inhibition and aortic stenosis in the FOURIER Trial. JAMA Cardiol 2020;5:709—13.
[117] Hojo Y, Kumakura H, Kanai H, Iwasaki T, Ichikawa S, Kurabayashi M. Lipoprotein(a) is a risk factor for aortic and mitral valvular stenosis in peripheral arterial disease. Eur Heart J Cardiovasc Imaging 2016;17:492—7.
[118] Hu P, Dharmayat KI, Stevens CAT, et al. Prevalence of familial hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. Circulation 2020;141:1742—59.
[119] Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide prevalence of familial hypercholesterolemia: meta-analyses of 11 million subjects. J Am Coll Cardiol 2020;75:2553—66.
[120] Farnier M, Bruckert E, Boileau C, Krempf M, Nouvelle societe francaise da. [Diagnostic and treatment of familial hypercholesterolemia (FH) in adult: guidelines from the New French Society of Atherosclerosis (NSFA)]. Presse Med 2013;42:930—50.
[121] Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34:3478a—90a.
[122] Alonso R, Andres E, Mata N, et al. Lipoprotein(a) levels in familial hypercholesterolemia: an important predictor of cardiovascular disease independent of the type of LDL receptor mutation. J Am Coll Cardiol 2014;63:1982—9.
[123] Tada H, Kawashiri MA, Yoshida T, et al. Lipoprotein(a) in familial hypercholesterolemia with proprotein convertase subtilisin/kexin type 9 (PCSK9) gain-of-function mutations. Circ J 2016;80:512—8.
[124] Kraft HG, Lingenhel A, Raal FJ, Hohenegger M, Utermann G. Lipoprotein(a) in homozygous familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 2000;20:522—8.
[125] Langsted A, Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Lipoprotein(a) and familial hypercholesterolaemia — Authors' reply. Lancet Diabetes Endocrinol 2016;4:730—1.
[126] Trinder M, DeCastro ML, Azizi H, et al. Ascertainment bias in the association between elevated lipoprotein(a) and familial hypercholesterolemia. J Am Coll Cardiol 2020;75:2682—93.
[127] Kinpara K, Okada H, Yoneyama A, Okubo M, Murase T. Lipoprotein(a)-cholesterol: a significant component of serum cholesterol. Clin Chim Acta 2011;412:1783—7.
[128] Langsted A, Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. High lipoprotein(a) as a possible cause of clinical familial hypercholesterolaemia: a prospective cohort study. Lancet Diabetes Endocrinol 2016;4:577—87.
[129] Vuorio A, Watts GF, Schneider WJ, Tsimikas S, Kovanen PT. Familial hypercholesterolemia and elevated lipoprotein(a):

double heritable risk and new therapeutic opportunities. J Intern Med 2020;287:2—18.
[130] O'Donoghue ML, Fazio S, Giugliano RP, et al. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. Circulation 2019;139:1483—92.
[131] Cegla J, Neely RDG, France M, et al. HEART UK consensus statement on Lipoprotein(a): a call to action. Atherosclerosis 2019;291:62—70.
[132] Waldeyer C, Makarova N, Zeller T, et al. Lipoprotein(a) and the risk of cardiovascular disease in the European population: results from the BiomarCaRE consortium. Eur Heart J 2017;38:2490—8.
[133] Jun JE, Kang H, Hwang YC, Ahn KJ, Chung HY, Jeong IK. The association between lipoprotein (a) and carotid atherosclerosis in patients with type 2 diabetes without pre-existing cardiovascular disease: a cross-sectional study. Diabetes Res Clin Pract 2021;171:108622.
[134] Saeed A, Sun W, Agarwala A, et al. Lipoprotein(a) levels and risk of cardiovascular disease events in individuals with diabetes mellitus or prediabetes: the Atherosclerosis Risk in Communities study. Atherosclerosis 2019;282:52—6.
[135] Jin JL, Cao YX, Zhang HW, et al. Lipoprotein(a) and cardiovascular outcomes in patients with coronary artery disease and prediabetes or diabetes. Diabetes Care 2019;42:1312—8.
[136] Paige E, Masconi KL, Tsimikas S, et al. Lipoprotein(a) and incident type-2 diabetes: results from the prospective Bruneck study and a meta-analysis of published literature. Cardiovasc Diabetol 2017;16:38.
[137] Gudbjartsson DF, Thorgeirsson G, Sulem P, et al. Lipoprotein(a) concentration and risks of cardiovascular disease and diabetes. J Am Coll Cardiol 2019;74:2982—94.
[138] Schwartz GG, Szarek M, Bittner VA, et al. Relation of lipoprotein(a) levels to incident type 2 diabetes and modification by alirocumab treatment. Diabetes Care 2021;44:1219—27.
[139] Littmann K, Wodaje T, Alvarsson M, et al. The association of lipoprotein(a) plasma levels with prevalence of cardiovascular disease and metabolic control status in patients with type 1 diabetes. Diabetes Care 2020;43:1851—8.
[140] Dentali F, Gessi V, Marcucci R, Gianni M, Grandi AM, Franchini M. Lipoprotein(a) as a risk factor for venous thromboembolism: a systematic review and meta-analysis of the literature. Semin Thromb Hemost 2017;43:614—20.
[141] Marcucci R, Liotta AA, Cellai AP, et al. Increased plasma levels of lipoprotein(a) and the risk of idiopathic and recurrent venous thromboembolism. Am J Med 2003;115:601—5.
[142] Wang CW, Su LL, Tao SB, Ma PJ, Chang HG, Ji SB. An increased serum level of lipoprotein(a) is a predictor for deep vein thrombosis in patients with spinal cord injuries. World Neurosurg 2016;87:607—12.
[143] Shi Z, Zhang M, Dong X, Xu J. Serum lipoprotein (a) on postoperative day 3: a strong predictor of portal and/or splenic vein thrombosis in cirrhotic patients with splenectomy. Clin Appl Thromb Hemost 2020;26 [1076029620912020].
[144] Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Genetic evidence that lipoprotein(a) associates with atherosclerotic stenosis rather than venous thrombosis. Arterioscler Thromb Vasc Biol 2012;32:1732—41.
[145] Schwartz GG, Steg PG, Szarek M, et al. Peripheral artery disease and venous thromboembolic events after acute coronary syndrome: role of lipoprotein(a) and modification by alirocumab: prespecified analysis of the ODYSSEY OUTCOMES Randomized Clinical Trial. Circulation 2020;141:1608—17.
[146] Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713—22.
[147] Helgadottir A, Gretarsdottir S, Thorleifsson G, et al. Apolipoprotein(a) genetic sequence variants associated with systemic atherosclerosis and coronary atherosclerotic burden but not with venous thromboembolism. J Am Coll Cardiol 2012;60:722—9.
[148] Kronenberg F. Causes and consequences of lipoprotein(a) abnormalities in kidney disease. Clin Exp Nephrol 2014;18:234—7.
[149] Bajaj A, Damrauer SM, Anderson AH, et al. Lipoprotein(a) and risk of myocardial infarction and death in chronic kidney disease: findings from the CRIC Study (Chronic Renal Insufficiency Cohort). Arterioscler Thromb Vasc Biol 2017;37:1971—8.
[150] Alessandri C, Basili S, Vieri M, et al. [Relationship between blood fibrinogen and plasma lipoproteins in patients with hypercholesterolemia]. Minerva Med 1994;85:287—92.
[151] Cimminiello C, Soncini M, Gerosa MC, Toschi V, Motta A, Bonfardeci G. Lipoprotein (a) and fibrinolytic system in liver cirrhosis. Coagulation Abnormalities in Liver Cirrhosis (CALC) Study Group. Biomed Pharmacother 1995;49:364—8.
[152] Lamina C, Kronenberg F, Lp(a)-GWAS Consortium. Estimation of the required lipoprotein(a)-lowering therapeutic effect size for reduction in coronary heart disease outcomes: a Mendelian randomization analysis. JAMA Cardiol 2019;4:575—9.
[153] Khera AV, Everett BM, Caulfield MP, et al. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). Circulation 2014;129:635—42.
[154] Yeang C, Hung MY, Byun YS, et al. Effect of therapeutic interventions on oxidized phospholipids on apolipoprotein B100 and lipoprotein(a). J Clin Lipidol 2016;10:594—603.
[155] Tsimikas S, Gordts P, Nora C, Yeang C, Witztum JL. Statin therapy increases lipoprotein(a) levels. Eur Heart J 2020;41:2275—84.
[156] Scanu AM, Bamba R. Niacin and lipoprotein(a): facts, uncertainties, and clinical considerations. Am J Cardiol 2008;101:44B—7B.
[157] Parish S, Hopewell JC, Hill MR, et al. Impact of apolipoprotein(a) isoform size on lipoprotein(a) lowering in the HPS2-THRIVE Study. Circ Genom Precis Med 2018;11:e001696.
[158] HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, et al. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med 2014;371:203—12.
[159] AIM-HIGH Investigators, Boden WE, Probstfield JL, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011;365:2255—67.
[160] Thomas T, Zhou H, Karmally W, et al. CETP (Cholesteryl Ester Transfer Protein) inhibition with anacetrapib decreases production of lipoprotein(a) in mildly hypercholesterolemic subjects. Arterioscler Thromb Vasc Biol 2017;37:1770—5.
[161] Bloomfield D, Carlson GL, Sapre A, et al. Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib as monotherapy and coadministered with atorvastatin in dyslipidemic patients. Am Heart J 2009;157 [352—60 e2].
[162] HPS3/TIMI55 Collaborative Group, Bowman L, Hopewell JC, et al. Effects of anacetrapib in patients with atherosclerotic vascular disease. N Engl J Med 2017;377:1217—27.
[163] Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet 2013;381:40—6.
[164] Santos RD, Raal FJ, Catapano AL, Witztum JL, Steinhagen-Thiessen E, Tsimikas S. Mipomersen, an antisense oligonucleotide to apolipoprotein B-100, reduces lipoprotein(a) in various populations with hypercholesterolemia: results of 4 phase III trials. Arterioscler Thromb Vasc Biol 2015;35:689—99.
[165] Merki E, Graham MJ, Mullick AE, et al. Antisense oligonucleotide directed to human apolipoprotein B-100 reduces lipoprotein(a) levels and oxidized phospholipids on human

apolipoprotein B-100 particles in lipoprotein(a) transgenic mice. Circulation 2008;118:743—53.
[166] Nandakumar R, Matveyenko A, Thomas T, et al. Effects of mipomersen, an apolipoprotein B100 antisense, on lipoprotein (a) metabolism in healthy subjects. J Lipid Res 2018;59:2397—402.
[167] Raal FJ, Giugliano RP, Sabatine MS, et al. Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolocumab (AMG 145): a pooled analysis of more than 1300 patients in 4 phase II trials. J Am Coll Cardiol 2014;63:1278—88.
[168] Gaudet D, Kereiakes DJ, McKenney JM, et al. Effect of alirocumab, a monoclonal proprotein convertase subtilisin/kexin 9 antibody, on lipoprotein(a) concentrations (a pooled analysis of 150 mg every two weeks dosing from phase 2 trials). Am J Cardiol 2014;114:711—5.
[169] Romagnuolo R, Scipione CA, Marcovina SM, et al. Roles of the low-density lipoprotein receptor and related receptors in inhibition of lipoprotein(a) internalization by proprotein convertase subtilisin/kexin type 9. PLoS One 2017;12:e0180869.
[170] Villard EF, Thedrez A, Blankenstein J, et al. PCSK9 modulates the secretion but not the cellular uptake of lipoprotein(a) ex vivo: an effect blunted by alirocumab. JACC Basic Transl Sci 2016;1:419—27.
[171] Croyal M, Tran TT, Blanchard RH, et al. PCSK9 inhibition with alirocumab reduces lipoprotein(a) levels in nonhuman primates by lowering apolipoprotein(a) production rate. Clin Sci (Lond) 2018;132:1075—83.
[172] Reyes-Soffer G, Pavlyha M, Ngai C, et al. Effects of PCSK9 inhibition with alirocumab on lipoprotein metabolism in healthy humans. Circulation 2017;135:352—62.
[173] Watts GF, Chan DC, Somaratne R, et al. Controlled study of the effect of proprotein convertase subtilisin-kexin type 9 inhibition with evolocumab on lipoprotein(a) particle kinetics. Eur Heart J 2018;39:2577—85.
[174] Chemello K, Beeske S, Trang Tran TT, et al. Lipoprotein(a) cellular uptake ex vivo and hepatic capture in vivo is insensitive to PCSK9 inhibition with alirocumab. JACC Basic Transl Sci 2020;5:549—57.
[175] Mahmood T, Minnier J, Ito MK, et al. Discordant responses of plasma low-density lipoprotein cholesterol and lipoprotein(a) to alirocumab: a pooled analysis from 10 ODYSSEY Phase 3 studies. Eur J Prev Cardiol 2021;28(8):816—22, http://dx.doi.org/10.1177/2047487320915803.
[176] Bittner VA, Szarek M, Aylward PE, et al. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. J Am Coll Cardiol 2020;75:133—44.
[177] Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL-cholesterol. N Engl J Med 2020;382:1507—19.
[178] Tsimikas S. RNA-targeted therapeutics for lipid disorders. Curr Opin Lipidol 2018;29:459—66.
[179] Tsimikas S, Viney NJ, Hughes SG, et al. Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study. Lancet 2015;386:1472—83.
[180] Viney NJ, van Capelleveen JC, Geary RS, et al. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. Lancet 2016;388:2239—53.
[181] Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, et al. Lipoprotein(a) reduction in persons with cardiovascular disease. N Engl J Med 2020;382:244—55.
[182] Waldmann E, Parhofer KG. Lipoprotein apheresis to treat elevated lipoprotein (a). J Lipid Res 2016;57:1751—7.
[183] Schettler VJJ, Neumann CL, Peter C, et al. Current insights into the German Lipoprotein Apheresis Registry (GLAR) — Almost 5 years on. Atheroscler Suppl 2017;30:50—5.
[184] Jaeger BR, Richter Y, Nagel D, et al. Longitudinal cohort study on the effectiveness of lipid apheresis treatment to reduce high lipoprotein(a) levels and prevent major adverse coronary events. Nat Clin Pract Cardiovasc Med 2009;6:229—39.
[185] Roeseler E, Julius U, Heigl F, et al. Lipoprotein apheresis for lipoprotein(a)-associated cardiovascular disease: prospective 5 years of follow-up and apolipoprotein(a) characterization. Arterioscler Thromb Vasc Biol 2016;36:2019—27.
[186] Tsimikas S, Fazio S, Viney NJ, Xia S, Witztum JL, Marcovina SM. Relationship of lipoprotein(a) molar concentrations and mass according to lipoprotein(a) thresholds and apolipoprotein(a) isoform size. J Clin Lipidol 2018;12:1313—23.