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SPECIAL ARTICLE
Miscellaneous

Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement

Florian Kronenberg [1], Samia Mora [2], Erik S.G. Stroes [3], Brian A. Ference[4], Benoit J. Arsenault [5], Lars Berglund[6], Marc R. Dweck [7], Marlys Koschinsky [8], Gilles Lambert [9], François Mach[10], Catherine J. McNeal [11], Patrick M. Moriarty[12], Pradeep Natarajan [13], Børge G. Nordestgaard [14,15], Klaus G. Parhofer [16], Salim S. Virani [17], Arnold von Eckardstein [18], Gerald F. Watts[19], Jane K. Stock[20], Kausik K. Ray[21], Lale S. Tokgözoğlu[22], and Alberico L. Catapano [23,24]

[1]Institute of Genetic Epidemiology, Medical University of Innsbruck, Innsbruck, Austria; [2]Center for Lipid Metabolomics, Division of Preventive Medicine, and Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA; [3]Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; [4]Centre for Naturally Randomized Trials, University of Cambridge, Cambridge, UK; [5]Centre de Recherche de l'Institut Universitaire de Cardiologie et de Pneumologie de Québec, and Department of Medicine, Faculty of Medicine, Université Laval, Québec City, QC, Canada; [6]Department of Internal Medicine, School of Medicine, University of California-Davis, Davis, Sacramento, CA, USA; [7]British Heart Foundation Centre for Cardiovascular Science, Edinburgh Heart Centre, University of Edinburgh, Chancellors Building, Little France Crescent, Edinburgh EH16 4SB, UK; [8]Robarts Research Institute, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada; [9]Inserm, UMR 1188 Diabète Athérothrombose Thérapies Réunion Océan Indien (DéTROI), Université de La Réunion, 97400 Saint-Denis de La Reunion, France; [10]Department of Cardiology, Geneva University Hospital, Geneva, Switzerland; [11]Division of Cardiology, Department of Internal Medicine, Baylor Scott & White Health, 2301 S. 31st St., USA; [12]University of Kansas Medical Center, Kansas City, KS, USA; [13]Cardiovascular Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, and Program in Medical and Population Genetics and Cardiovascular Disease Initiative, Broad Institute of Harvard and MIT, Cambridge, MA, USA; [14]Department of Clinical Biochemistry and the Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark; [15]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [16]Medizinische Klinik und Poliklinik IV, Ludwigs- Maximilians University Klinikum, Munich, Germany; [17]Section of Cardiovascular Research, Baylor College of Medicine & Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, USA; [18]Institute of Clinical Chemistry, University Hospital Zurich, University of Zurich, Zurich, Switzerland; [19]Medical School, University of Western Australia, and Department of Cardiology, Lipid Disorders Clinic, Royal Perth Hospital, Perth, Australia; [20]European Atherosclerosis Society, Mässans Gata 10, SE-412 51 Gothenburg, Sweden; [21]Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, School of Public Health, Imperial College London, London, UK; [22]Department of Cardiology, Hacettepe University Faculty of Medicine, Ankara, Turkey; [23]Department of Pharmacological and Biomolecular Sciences, University of Milano, Milano, Italy; and [24]IRCCS Multimedica, Milano, Italy

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* Corresponding author. Tel: +43 512 9003 70560, Fax: +43 512 9003 73560; Email: florian.kronenberg@i-med.ac.at
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Introduction

Since the 2010 European Atherosclerosis Society (EAS) consensus statement,[1] knowledge about the role of lipoprotein(a) [Lp(a)] in atherosclerotic cardiovascular disease (ASCVD) and aortic valve stenosis (AVS) has expanded substantially (Box 1 and *Graphical Abstract*). Strong evidence for causality for ASCVD prompted the development of novel drugs that specifically lower Lp(a) levels. New genetic, mechanistic, and imaging insights also suggest therapeutic potential in AVS,[2,3] arguably the last major cardiovascular condition lacking medical therapy for slowing disease progression. With AVS prevalence predicted to dramatically increase (>300%) by 2050, this remains an urgent unmet clinical need.

Box 1 What is new since the 2010 EAS consensus statement?

- Strong evidence for a causal association between Lp(a) concentration and cardiovascular outcomes in different ethnicities.
- This association is continuous even at low levels of low-density lipoprotein cholesterol.
- Lp(a) is a new risk factor for aortic valve stenosis.
- Evidence does not support Lp(a) as a risk factor for venous thromboembolism and impaired fibrinolysis.
- Lifelong very low Lp(a) concentrations may associate with diabetes mellitus.
- Lp(a) should be measured at least once in adults.
- A high Lp(a) concentration should be interpreted in the context of other risk factors and absolute global cardiovascular risk, and addressed through intensified lifestyle and risk factor management.
- Specific effective Lp(a)-lowering therapies are in Phase II/III clinical trials.

Despite affecting ≈1.4 billion people worldwide,[4] the contribution of elevated Lp(a) concentration to cardiovascular risk remains underappreciated. This second EAS statement highlights new evidence for Lp(a), identifies gaps requiring further study, and provides clinical guidance for testing and treating elevated Lp(a) levels. This statement should catalyze global action to improve the management of Lp(a).

What determines plasma Lp(a) concentration?

Genetics of Lp(a) concentration

Lp(a) concentration ranges between <0.1 mg/dL and >300 mg/dL (<0.2–750 nmol/L) and is predominantly (>90%) determined by genetic variability at the *LPA* locus. By age 2 years, the *LPA* gene is fully expressed; adult Lp(a) levels are usually attained by ∼5 years[5] but may increase until adulthood.[6,7] The Kringle-IV (K-IV) repeat polymorphism explains ∼30–70% of the variability in concentration (*Figure 1*).[8–10] Expression of a low number (<23) of K-IV repeats is characterized by small apolipoprotein(a) [apo(a)] isoforms and markedly higher Lp(a) concentration compared with those with only large isoforms. However, as levels for a given apo(a) isoform may vary up to 200-fold between unrelated individuals and up to 2.5-fold within families when alleles are identical-by-descent,[11] it is likely that other genetic variants with regulatory effects are also involved (*Figure 1*).[10]

Among known *LPA* variants, the single-nucleotide polymorphisms (SNPs) rs10455872 and rs3798220 are claimed as proxies for small apo(a) isoforms[12] but are only evident in 50% of small isoform carriers.[13] Up to 70% of the *LPA* gene are encoded by hypervariable K-IV Type-2 repeats which are not easily accessible for conventional sequencing technologies.[10] Of >500 genetic variants identified here, some have very pronounced effects on Lp(a) concentration.[14] Two of these, the splice site variants 4733G > A and 4925G > A (carried by 38 and 22% of the population, respectively) decrease Lp(a) concentration by ∼14 and 30 mg/dL, and associate with lower cardiovascular risk.[15,16] Beyond the wider *LPA* gene region, the *APOE, CETP*, and *APOH* loci have also been shown to associate with Lp(a) concentration.[17–19] Further information on the genetic control of Lp(a) concentration is provided in the Supplementary material online.

Impact of ethnicity and sex

Ethnicity also impacts Lp(a) concentration, as evident in the UK Biobank, in which median Lp(a) increased sequentially in Chinese, White, South Asian and Black individuals (16, 19, 31, and 75 nmol/L, respectively).[20,21] The ARIC study also showed that Lp(a) levels vary more widely among Black than White individuals, as the ∼50th percentile in Black people equated with the highest quintile in White people.[22] In addition, Lp(a) distribution was less skewed in Black people than in other ethnic groups (*Figure 2*).[23]

These ethnicity differences are mainly ascribed to Lp(a) isoform size and genetic variants within the *LPA* locus. In support, the Dallas Heart Study showed a linear correlation between the number of K-IV repeats and Lp(a) concentration for Black, White and Hispanic individuals, although Black people had higher Lp(a) levels for any given number of K-IV repeats.[24] However, different SNPs, including loss-of-function variants, effects on promoter activity by non-genetic influences, as well as other undefined mechanisms may also play a role.[25]

Although the strength of association between some SNPs and apo(a) isoform size and Lp(a) concentration varies with ethnicity,[26–28] it is uncertain whether these are true causal effects.[14–16] Indeed, over 20 functional variants explain >80% of Lp(a) variance, with consistent cross-ethnicity variability beyond K-IV Type-2 number, which implies that both SNPs and K-IV Type-2 number determine Lp(a) concentration regardless of ethnicity.[29]

Finally, there are sex differences, with Lp(a) concentration generally ∼5–10% higher in women than men, in both Black and White individuals.[22,25,30] In men, Lp(a) remains relatively constant, whereas in women levels tend to increase at menopause.[31]

Consensus key points: Influence of genetics and ethnicity on Lp(a)

- Lp(a) concentration is predominantly determined by genetics (>90%), more than any other lipoprotein.
- The K-IV repeat polymorphism explains most of the variability in Lp(a) concentration.
- Several frequent and rare functional SNPs profoundly modify the inverse correlation of isoform size and Lp(a) concentration.
- Lp(a) level varies with ethnicity (in increasing order: Chinese, White, South Asian, and Black individuals).

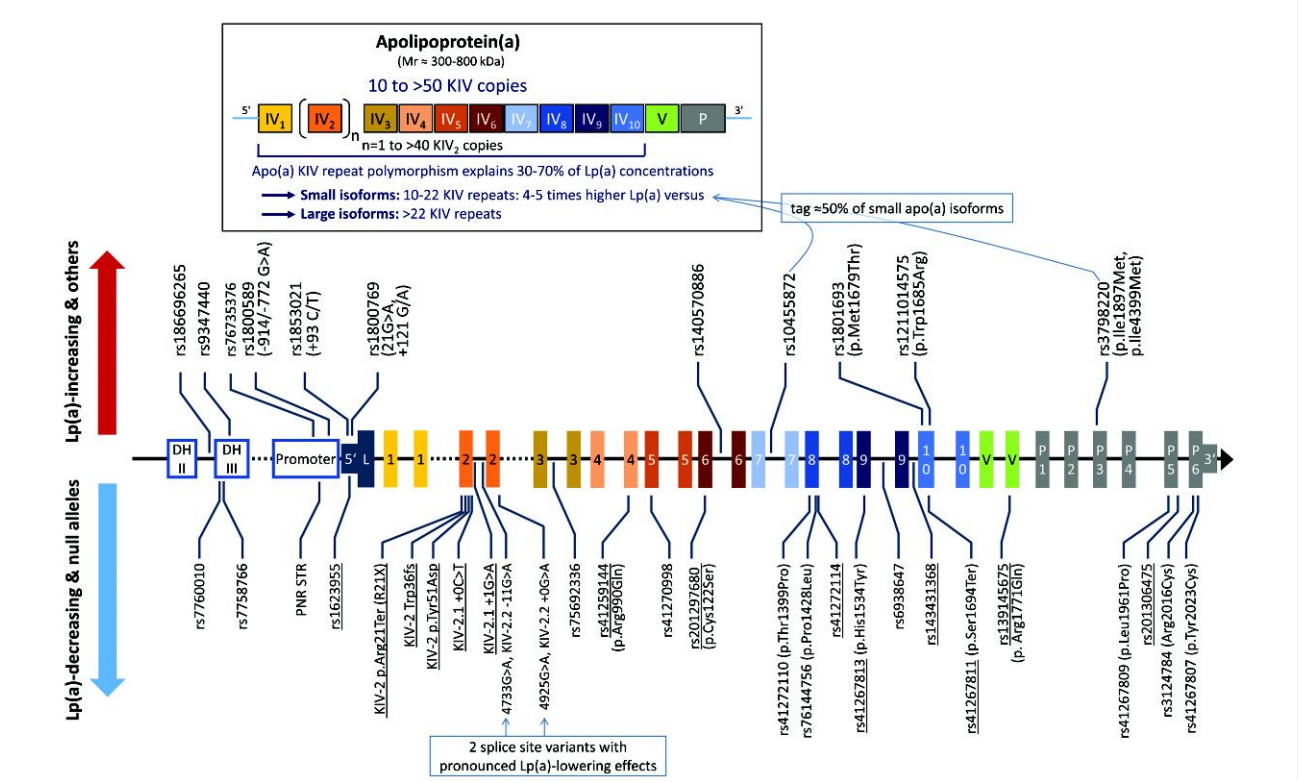


Figure 1 Structure and genetic variability of the *LPA* gene. The upper panel shows the topology of apolipoprotein(a) and the association of the Kringle-IV repeat polymorphism with lipoprotein(a) [Lp(a)] concentration, which explains 30%–70% of variation depending on ethnicity. The lower panel shows the structure of the *LPA* gene and the known single-nucleotide polymorphisms within the gene that have marked effects on Lp(a) concentration. The exons are numbered according to the domain that they encode (L. leader sequence, 1–10: KIV-1 to KIV-10, V: KV domain, P: protease domain, 5′: 5′UTR, 3′: 3′ UTR). Single-nucleotide polymorphisms associated with increased Lp(a) concentration are shown above the gene structure, and those associated with decreased Lp(a) concentrations (both causally or by association only) are shown below. Single-nucleotide polymorphisms that cause null alleles are underlined; however, Lp(a)-lowering single-nucleotide polymorphisms may cause null alleles if present on an allele already associated with low Lp(a) production. Single-nucleotide polymorphisms in the Kringle-IV Type-2 region are named according to their publication; they cannot be assigned a single rs-identifier as their location is not unique. Figure provided and adapted by Prof. Florian Kronenberg and Prof. Stefan Coassin based on reference.[10]

Influence of non-genetic factors

Although less well-characterized, non-genetic factors may also modulate Lp(a) concentration (*Table 1*, for extended discussion see Supplementary material online).[31–62] Lifestyle interventions have minimal impact, but a low carbohydrate/high fat diet may decrease levels by 10–15%.[31,32]

Several hormones, particularly those affecting lipoprotein metabolism, influence Lp(a) concentration.[36–40] Impaired kidney function may increase levels, possibly due to increased hepatic Lp(a) synthesis triggered by protein loss in urine (nephrotic syndrome) or peritoneal dialysate,[41,42,50,51,63] or impaired catabolism.[41,51,64] As Lp(a) production occurs in the liver, hepatic impairment may decrease Lp(a) levels.[44] Finally, while pre-clinical models showed that inflammation impacts Lp(a),[60] the effects in population studies were small or negligible.[34] Clinically, Lp(a) was lower in severe, life-threatening acute-phase conditions but higher in several acute and chronic inflammatory conditions.[45,46] Increases related to interleukin-6 concentration were reported[61] and decreases with tocilizumab.[47]

Novel insights from Lp(a) epidemiology

As most people have relatively low Lp(a) concentrations (*Figure 2A and B*), studies focus on the top-third of the population with (very) high Lp(a) who exhibit >20% increase in risk of cardiovascular morbidity and mortality (*Figure 2C–E*).[20,69]

Primary prevention

In the primary prevention setting, elevated Lp(a) associate with several ASCVD outcomes, as well as AVS and cardiovascular and all-cause mortality (*Figure 3*, *Figure 4A* and *Table 2*). Lp(a) levels above the 75th percentile increased the risk for AVS and myocardial infarction, whereas higher levels (>90th percentile) were associated with increased risk for heart failure.[70] The risk for cardiovascular mortality and ischaemic stroke[71–73] only increased at very high levels (>95th percentile).

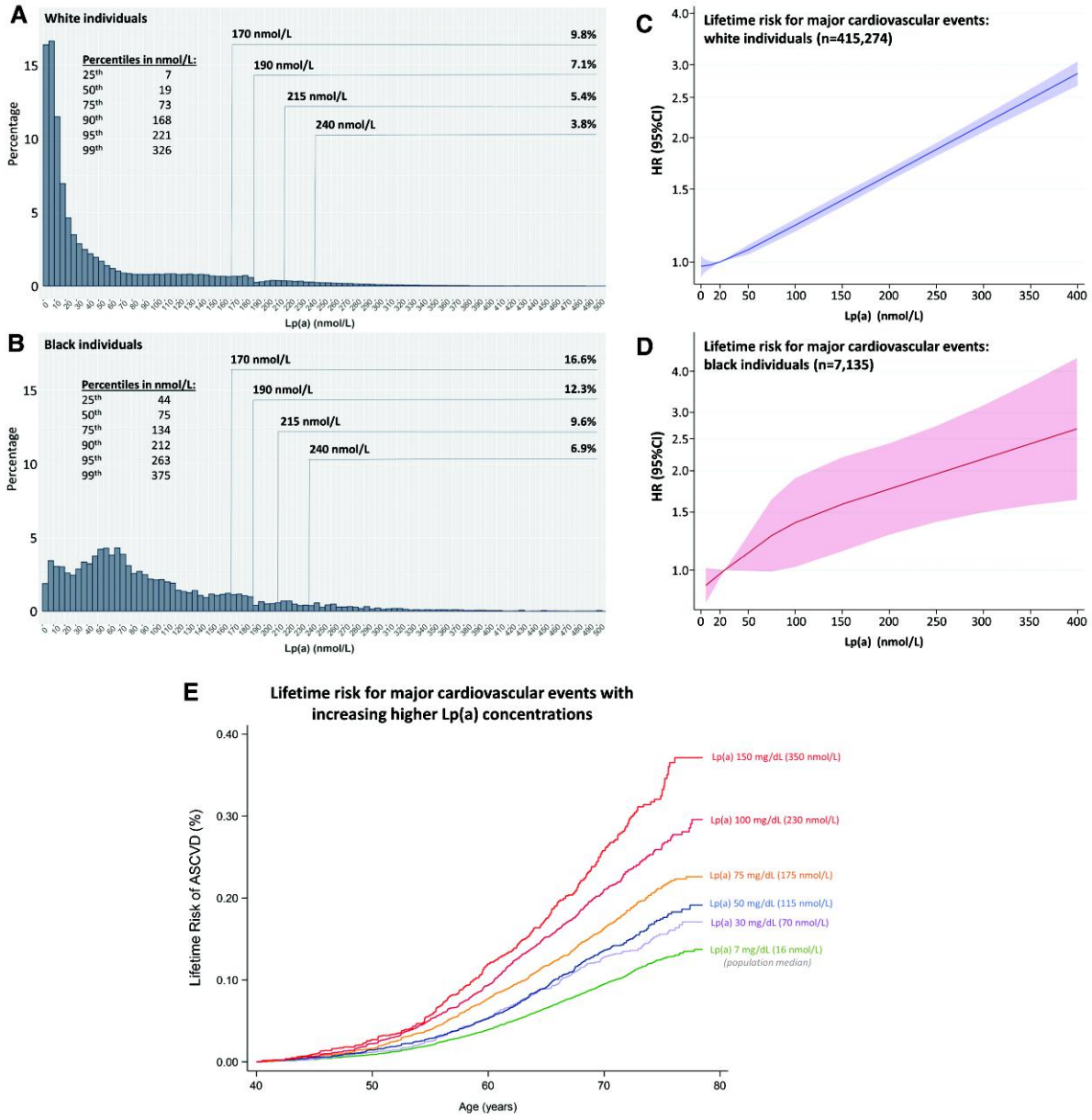


Figure 2 Distribution of lipoprotein(a) [Lp(a)] concentration and association with risk for major cardiovascular events. Data from the UK Biobank show the typical distribution of Lp(a) concentrations in White (*Panel A*) and Black people (*Panel B*) and the linear relationship of Lp(a) concentration with risk for major cardiovascular events in White (*Panel C*), and Black people (*Panel D*). Panels A and B give the percentage of the population with an Lp(a) of 170, 190, 215, and 240 nmol/L or higher, respectively. Panels C and D show the smoothed adjusted hazard ratio (HR) and 95% confidence interval (95% CI) for lifetime risk for major cardiovascular events for a given Lp(a) concentration relative to the median Lp(a) in the population (19.7 nmol/L). These data were estimated using a Cox proportional hazards regression model adjusted for age at enrolment, sex, and the first 10 principle components of ancestry and modelled using cubic natural splines. Confidence intervals are wider in Black people due to the smaller sample size. *Panel E* shows the lifetime risk of major cardiovascular events with increasing Lp(a) concentrations among men of European ancestry in the UK Biobank (results were similar for women but with lower absolute event rates). Participants were partitioned into categories with increasingly greater median Lp(a) plasma concentrations; and the cumulative major cardiovascular event rates were plotted for each group up to age 80 years. *Panel A* and *B* are provided by Prof. Florian Kronenberg and Silvia Di Maio; *Panel C-E* are provided by Prof. Brian Ference and Prof. Alberico L. Catapano. For detailed methodological description, see Supplementary material online.

Secondary prevention

In secondary prevention patients, elevated Lp(a) associated with an increased risk of major adverse cardiovascular events (MACEs) although there was some heterogeneity among studies.[105] In a meta-analysis, Lp(a) levels >80th percentile were significantly predictive of recurrent events in statin-treated patients with coronary artery disease [odds ratio (OR): 1.40, 95% confidence interval (CI): 1.15–1.71] but not when baseline low-

Table 1 Non-genetic influences on lipoprotein(a) concentration

Condition/intervention	Effect on Lp(a) levels
Lifestyle	
Replacement of dietary saturated fat with carbohydrate or unsaturated fat[32]	~10%–15% increase
Low carbohydrate diet high in saturated fat[33]	~15% decrease
Fasting[34]	None
Physical activity[35]	None/minimal
Hormones and related conditions	
Hyperthyroidism[36]	Decrease; 20%–25% increase with thyrostatic treatment or radioactive iodine therapy
Hypothyroidism[36]	Increase; 5%–20% decrease with replacement therapy
Growth hormones[37]	2x increase with therapy
Endogenous sex hormones[31]	None/minimal
Pregnancy[38,39]	2x increase
Menopause[31]	None/minimal
Postmenopausal hormonal replacement therapy[40]	~25% decrease
Surgical or biochemical castration in males[48]	Small increase
Ovariectomy, oestrogen receptor antagonist[49]	Small increase
Chronic kidney disease[41,42]	
Nephrotic syndrome[50,63]	3–5 x increase (vs. control)
Peritoneal dialysis patients[51]	2 x increase (vs. control)
Haemodialysis treatment and chronic kidney disease[51,52,64]	Increases in large apo(a) isoform carriers
Kidney transplantation[43]	~Normalization of levels
Hepatic impairment[44,59]	Decrease, depending on cause
Liver transplantation[53]	Changes of apo(a) isoform to that of the donor, with corresponding changes in Lp(a) levels
Inflammation and related conditions[55,60]	
Severe, life-threatening acute-phase conditions (sepsis, severe burns)[46]	Decrease
Several inflammatory conditions[45]	Increase
Tocilizumab (interleukin-6 inhibitor)[47,61]	~30%–40% decrease
Protease inhibitors or antiretroviral therapy[56,57]	Increase
Statins[65–68]	May slightly increase Lp(a) (but reports are heterogeneous)
Air pollution (fine particulate, PM2.5)[58]	Slight increase

Changes are based on limited data; studies referenced are representative examples.

density lipoprotein cholesterol (LDL-C) was <130 mg/dL.[106] In the Copenhagen General Population Study, however, the risk for incident MACE was higher at Lp(a) ≥50 mg/dL vs. <10 mg/dL, even when LDL-C levels were <70 mg/dL.[107] AIM-HIGH also showed ~90% higher risk for MACE at baseline Lp(a) >75th percentile (>125 nmol/L) vs. lower levels even with comparable low LDL-C (~65 mg/dL).[108] In addition, in a patient-level meta-analysis, elevated Lp(a) at baseline and on-statin showed an independent approximately linear relationship with cardiovascular disease risk.[65]

Lp(a) and aortic valve stenosis

Since 2013, the *LPA* locus is established as a major contributor to AVS risk,[89] supported by numerous epidemiologic and genetic studies.[90–98] High Lp(a) is associated with both microcalcification and macrocalcification of the aortic valve,[109,110] especially in relatively young healthy individuals (45–54 years), in whom risk is increased three-fold at an Lp(a) >80th percentile vs. lower levels (15.8% vs. 4.3%, respectively).[111] High Lp(a) may also promote faster progression of aortic stenosis, culminating in earlier aortic valve replacement or death.[109,112]

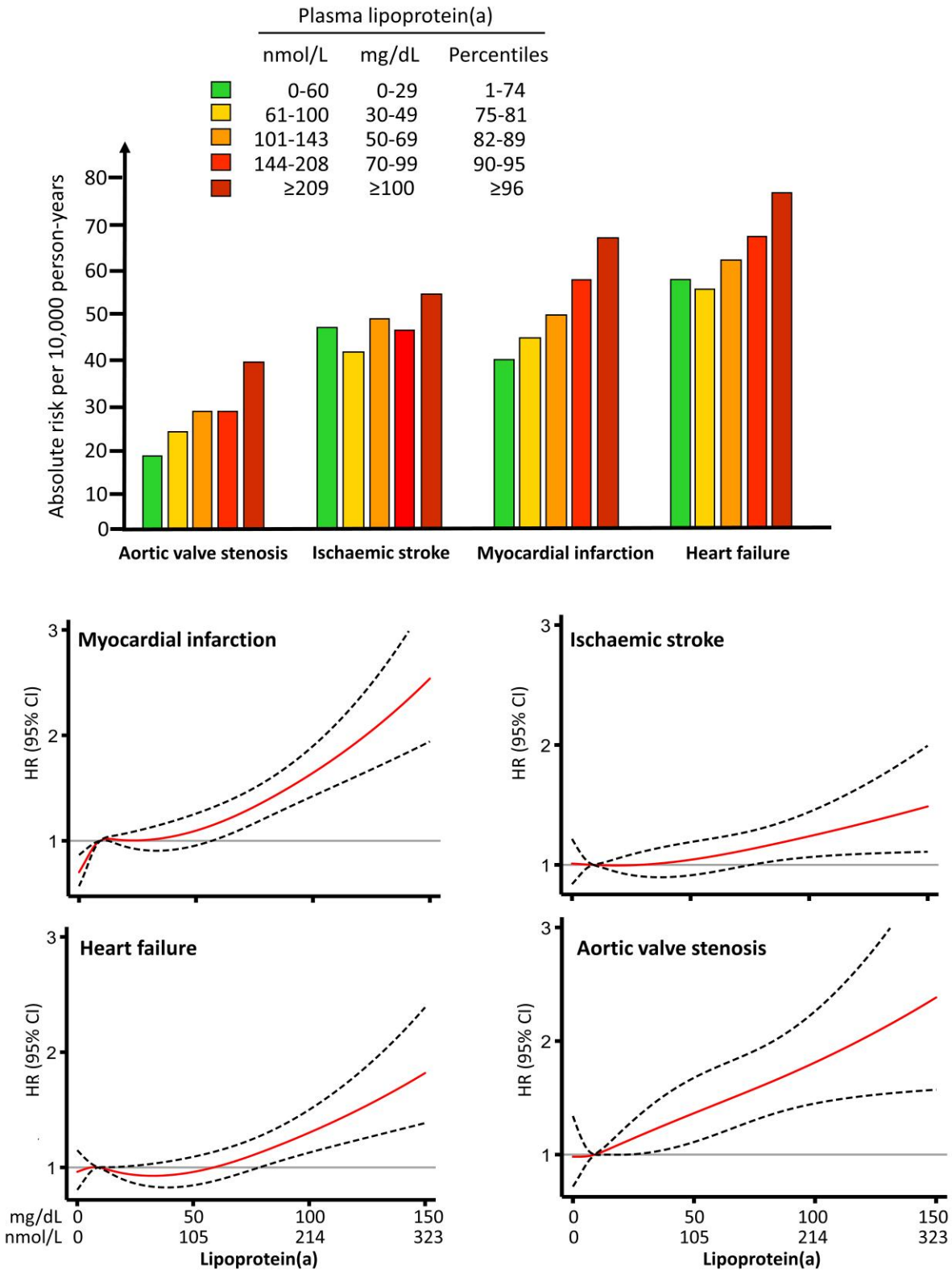


Figure 3 Risk of clinical outcomes with Lp(a) concentration. Absolute and relative risks of aortic valve stenosis, ischaemic stroke, myocardial infarction and heart failure as a function of increasing plasma Lp(a) concentration in the general population. Top panel shows the absolute risk per 10000 person-years, and the lower panel shows hazard ratios as solid red line with 95% confidence intervals as dotted black lines; when the lower 95% confidence interval no longer overlap the hazard ratios reference value of 1.0 for the median Lp(a) concentration, risk is significantly elevated. Based on data from 70 286 White individuals in the Copenhagen General Population Study with a median 7.4 years of follow-up. Data provided by Prof. Børge G. Nordestgaard and Dr. Anne Langsted.

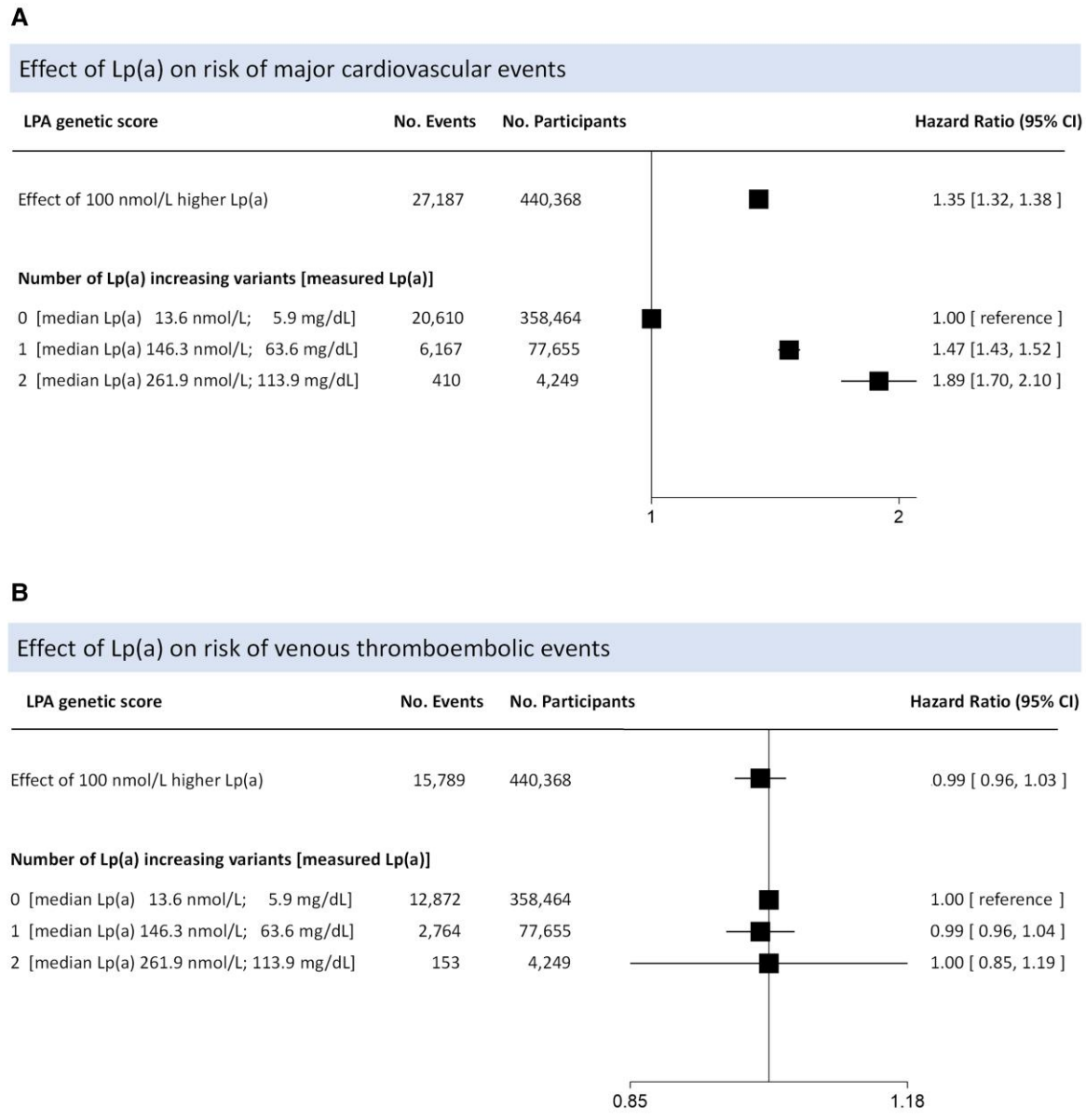


Figure 4 Effect of Lp(a) concentration and *LPA* score copies on risk for major cardiovascular events and venous thrombotic events. Data are from 440 368 UK Biobank participants of European ancestry. The *LPA* score is defined as the number of minor alleles of *LPA* variants rs10455872 or rs3798220 inherited by each participant, with the reference group defined as participants with no copies of either minor allele. The measured median Lp(a) concentration is provided for each group. *Panel A* shows the effect of higher Lp(a) among participants who inherit one minor allele [median Lp(a) 146.3 nmol/L] or two minor alleles [median Lp(a) 261.9 nmol/L] on the risk of major cardiovascular events [defined as the composite of the first occurrence of fatal or non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery)] vs. the reference group [median Lp(a) 13.6 nmol/L]. *Panel B* shows the effect on the risk of venous thromboembolic events (VTE, defined as deep venous thrombosis or pulmonary embolism). Higher Lp(a) levels were strongly associated with increased risk of atherosclerotic cardiovascular disease but not VTE. The solid boxes represent point estimates for effect and the lines 95% confidence intervals. Data provided by Prof. Brian Ference and Prof. Alberico L. Catapano. For detailed methodological description, see Supplementary material online.

Lp(a) and other cardiovascular outcomes

Studies implicate elevated Lp(a) with stroke risk dependent on aetiology. In the ARIC study and a large Mendelian randomization study, Lp(a) concentration and *LPA* genotype, respectively, associated with risk for non-cardioembolic stroke.[80,81] In addition, in the BIOSIGNAL study, Lp(a) >100 nmol/L associated with recurrent stroke in patients with large artery stroke, but not in those with atrial fibrillation,[82] possibly explaining why elevated Lp(a) is more relevant for risk for stroke in those aged <60 years.[77,82,83]

Table 2 Summary of epidemiological and genetic evidence for the association of lipoprotein(a) concentration with clinical outcomes

	Case–control or cross-sectional studies	Large prospective observational studies	Meta-analyses of prospective observational studies	Large genome-wide association studies	Large Mendelian randomization studies	Clinical trials of Lp(a)-lowering therapy
Myocardial infarction[12,21,65,73–76]	Yes	Yes	Yes	Yes	Yes	Trial ongoing
Angina pectoris/coronary stenosis [77–79]	Yes	Yes	Data lacking	Yes	Yes	—
Ischaemic stroke[21,71–73,75,77,80–83]	Yes	Yes	Yes	Yes	Yes	Trial ongoing
Carotid stenosis[77,78,84,85]	Yes	Yes	Data lacking	Yes	Yes	—
Peripheral arterial disease[75,77,78,86–88]	Yes	Yes	Data lacking	Yes	Yes	—
Aortic valve stenosis [21,89–98]	Yes	Yes	Data lacking	Yes	Yes	—
Heart failure[21,70]	Yes	Yes	Data lacking	Yes	Yes	—
Cardiovascular mortality[21,71,75,99,100]	Yes	Yes	Data lacking	Yes	Yes	Trial ongoing
All-cause mortality[71,99,101,102]	Data lacking	Yes	No	Yes	Yes	Trial ongoing
Venous thromboembolism[77,103,104]	No	No	No	No	No	—

Numerous studies have been published. The Table above lists only some representative examples without following a formalized selection protocol.
Yes = association between Lp(a) and outcome has been described; No = no association between Lp(a) and outcome has been reported; Data lacking means there are no studies available.

The *LPA* gene locus is also the strongest genetic predictor of peripheral arterial disease (PAD).[86] In population-based studies, higher Lp(a) and small apo(a) isoforms associated with PAD risk, and among secondary prevention patients, the rs10455872 SNP was associated with reduced Ankle-Brachial Index.[87]

Finally, while recent large-scale epidemiological and genetic studies indicated an association between elevated Lp(a) and atrial fibrillation, the magnitude of effect was relatively small and partly mediated by ASCVD and AVS.[113,114]

Is Lp(a) a causal risk factor for atherosclerotic cardiovascular disease and aortic valve stenosis?

Extensive genetic evidence supports a causal association between elevated Lp(a) and ASCVD and AVS.[1,8,9,12,71,72,74,77,115–118] This was largely derived from Mendelian randomization studies which used genetic tools that strongly predict Lp(a) levels, including apo(a) isoforms determined by the number of K-IV repeats on Western blots,[118,119] the number or sum of K-IV repeats,[74,120] and SNPs (notably rs10455872 and rs3798220).[12,75] Overall, genetic variants that associated with high Lp(a) are more common in individuals with prevalent and incident cardiovascular events (*Figure 4A*).[8] In contrast, rare loss-of-function variants[121] and very common splice site variants within the K-IV Type-2 region that associated with marked decreases in Lp(a) are protective against cardiovascular events.[15,16]

While these data predominantly relate to White populations, there is evidence that elevated Lp(a) is also a risk factor for ASCVD in other ethnic groups.[20,22,23,122–125] The UK Biobank showed very similar relationships between Lp(a) and ASCVD risk in White, Black, and South Asian individuals[20] (*Figure 2C and D*), consistent with findings from the ARIC study,[22] MESA study,[122] and INTERHEART study.[23] Given limited data in non-White populations, however, further study is needed. Finally, differences in the oxidized phospholipid component of apoB-containing particles may also modify Lp(a)-mediated ASCVD risk.[123]

Is the association between Lp(a) concentration and atherosclerotic cardiovascular disease outcomes discrete or linear?

Recent findings from the UK Biobank challenge the concept of an Lp(a) threshold associated with ASCVD risk. Risk increases continuously with increasing Lp(a) concentration,[20] already at levels below reported thresholds (*Figure 2C*), and across different ethnic groups (*Figure 2D*). Despite this, Lp(a) thresholds remain pragmatic tools in clinical practice (see below). Very high Lp(a) levels (>180 mg/dL or >430 nmol/L) also identify individuals with lifetime ASCVD risk equivalent to untreated heterozygous familial hypercholesterolaemia (FH).[126]

Is Lp(a) a risk factor at (very) low low-density lipoprotein cholesterol concentrations?

In a large primary prevention study,[127] the association between Lp(a) and cardiovascular risk was abrogated at LDL-C <100 mg/dL. This

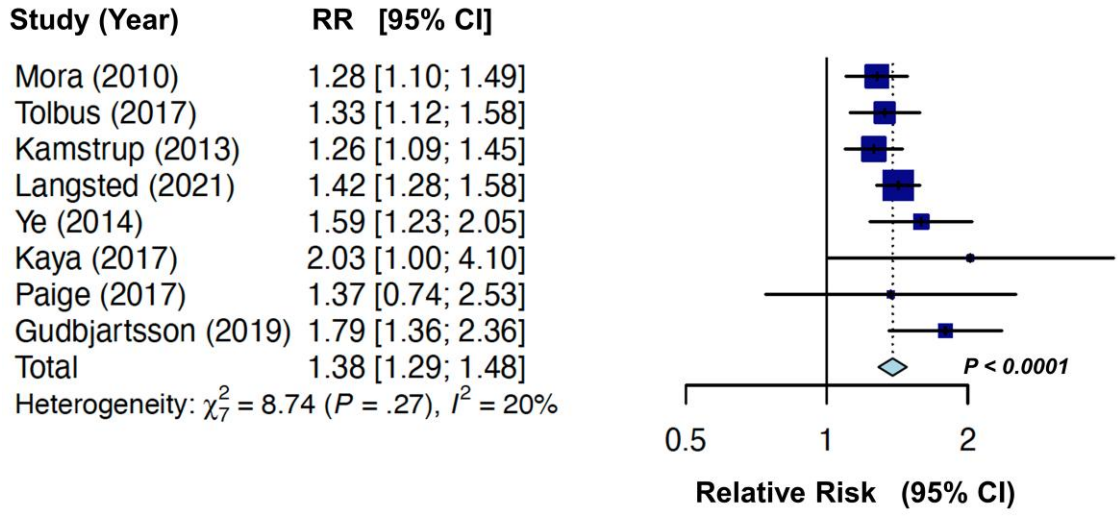


Figure 5 Association of Lp(a) concentration with diabetes mellitus. Random effects meta-analysis of seven prospective studies[135–141] and one case–control study[76] examining the association of lipoprotein(a) with risk of diabetes. Summary relative risks comparing bottom vs. top quintile were adjusted for clinical risk factors, with the size of the squares proportional to the number of cases in each study. Results were similar when excluding the Kamstrup *et al.* study[137] (for potential overlap with the Tolbus *et al.*[136] and Langsted *et al.*[138] studies; Supplementary material online, *Figure S1A*) or when excluding the case–control study by Gudbjartsson *et al.*[76] (Supplementary material online, *Figure S1B*). The summary relative risk *P*-values were all <0.001. (See also Supplementary material online). Data provided by Prof. Samia Mora, Dr. Olga Demler and Dr. Yanyan Liu.

finding should be interpreted cautiously, however, given limited patient numbers and potential over-correction of LDL-C for Lp(a) cholesterol.[128] In contrast, the JUPITER trial showed that the association between baseline Lp(a) and first incident cardiovascular event was similar above and below median LDL-C (110 mg/dL),[54] and even at low LDL-C levels (54 mg/dL), reinforcing high Lp(a) as a contributor to residual cardiovascular risk. Similar findings have been reported in the secondary prevention setting (see above).[65,107,108]

Is Lp(a) a risk factor for thromboembolic events?

Lp(a) was discussed controversially as risk factor for thrombotic events given high homology with plasminogen[103,129] and hypothetically mediated via impaired fibrinolysis based on *in vitro* data.[130] Observational studies in humans, however, showed only a slightly increased risk for venous thromboembolism at very high Lp(a) (>95th percentile).[77] Most importantly, causality was not supported by Mendelian randomization studies[77,131] (*Figure 4B*).

Paediatric perspectives

In children, elevated Lp(a) is clinically silent, with the rare exception of arterial ischaemic stroke, although this differs in risk factors and aetiology compared with that in adults. Limited data suggest an association between Lp(a) and incident arterial ischaemic stroke in children, somewhat stronger for recurrent events,[132–134] with risk more than doubling at Lp(a) levels >30 mg/dL.[132] While some studies indicated that thrombophilic risk factors and Lp(a) >30 mg/dL amplify the risk of ischaemic stroke and venous thromboembolism/sinus venous thrombosis,[5] such findings should be interpreted with caution due to the small sample sizes.

Consensus key points: Lp(a) and clinical outcomes

- Observational and genetic evidence convincingly demonstrates that high Lp(a) concentration is causal for ASCVD, AVS and cardiovascular and all-cause mortality in men and women and across ethnic groups.
- The relation between Lp(a) concentration and these outcomes is continuous; elevated Lp(a) is a risk factor even at very low LDL-C concentration.
- The risk of ischaemic stroke and heart failure increases at higher Lp(a) levels than those associated with the risk of myocardial infarction and AVS.
- In children, an Lp(a) >30 mg/dL (>75 nmol/L) is associated with increased risk of (recurrent) arterial ischaemic stroke.
- Lp(a) is not a risk factor for venous thromboembolism.

Lp(a) concentration and diabetes

Multiple studies over the last decade showed that very low Lp(a) levels associate with an increased risk of incident Type 2 diabetes mellitus. In an initial study, risk increased by 28% for the lowest vs. highest quintile.[135] Our meta-analysis of all available studies[76,135–141] showed a 38% (95% CI 29–48%, $P < 0.0001$) higher risk for the bottom quintile (thresholds <3 to 5 mg/dL) vs. top quintile of Lp(a) (thresholds >27 to 55 mg/dL) with no significant heterogeneity across studies (*Figure 5* and Supplementary material online, *Table S1*). A large cross-sectional Chinese study also showed that low Lp(a) associated with increased risk of pre-diabetes, insulin resistance, and hyperinsulinaemia.[142]

The mechanisms underlying this association are uncertain and not explained by established risk factors or known diabetes variants.[143–145] It is also unclear whether this risk relates to Lp(a) concentration or other factors. Mendelian randomization studies yielded mixed results depending on the genetic instrument used.[76,136–139] Loss-of-function variants might be preferable for identifying individuals with very low Lp(a) levels; in support, an Icelandic study demonstrated a causal association with this type of variant.[76]

Whether potent Lp(a)-lowering therapies might increase risk of incident diabetes has been raised as potential issue. At high baseline levels (>70 mg/dL) required for trial entry, however, it is unlikely that patients will attain very low Lp(a) concentration (e.g. <5 mg/dL). Whether this diabetes risk is causal, or whether it may be exacerbated by aggressive Lp(a) lowering, is uncertain. Both remain considerations for future risk–benefit analyses with novel therapeutics under investigation.

Metabolic insights

Apo(a), a key component of Lp(a), is exclusively synthesized in hepatocytes.[53] Compared with small apo(a) isoforms, large isoforms are more susceptible to proteasomal degradation in the endoplasmic reticulum, resulting in lower Lp(a) concentrations in carriers.[146] Kinetic studies also showed higher apo(a) production rates in subjects with smaller vs. larger apo(a) isoforms.[147] Taken together, these findings reinforce apo(a) production as a principal target for therapy.[148]

Lp(a) is predominantly metabolized in the liver, with a minor contribution from the kidney. Multiple putative pathways implicate the scavenger receptor BI, plasminogen receptors, and members of the LDL receptor (LDLR) family (Supplementary material online, Figure S2),[149] but genome-wide association studies failed to identify candidate receptor genes involved in Lp(a) removal.[17,18] Given important structural similarities between LDL and Lp(a), the LDLR has received most attention although its role remains elusive.[149,150] Both statins and proprotein convertase subtilisin/kexin Type 9 (PCSK9) inhibitors increase LDLR expression; however, statins increase (slightly, if at all) and PCSK9 inhibitors decrease (by 15–30%) Lp(a) concentration.[66,151] Some (but not all) *in vitro* studies indicate that PCSK9 inhibitors decrease hepatic uptake of Lp(a) via the LDLR.[150,152–155] The impact of PCSK9 inhibition on Lp(a) kinetics in humans is unclear, as both unchanged or slightly increased fractional catabolic rates were reported.[156–158]

What mechanisms contribute to the pathogenicity of Lp(a)?

Similar to LDL, Lp(a) is an apoB-containing lipoprotein but the number of circulating particles is much lower. Given that risk associated with Lp(a) on a per particle basis may exceed that of LDL,[159] cell signalling effects mediated by Lp(a) rather than Lp(a) accumulation *per se* may mainly contribute to atherogenicity. Imaging studies revealed that Lp(a) initiates inflammation in the arterial wall,[160] and in advanced coronary artery disease, high Lp(a) levels were associated with accelerated progression of coronary calcium[161] and the necrotic core volume.[162] Similarly in AVS, high Lp(a) and proteins transported by Lp(a) (e.g. autotaxin) induces the expression of inflammatory and calcification genes in valvular interstitial cells and associates with increased incidence and progression of AVS.[112,163,164]

Oxidized phospholipids (OxPLs), preferentially carried by Lp(a) in the plasma, have been proposed as major players in the pro-inflammatory and pro-calcific effects of Lp(a).[165] Identification of key genes regulating glycolytic processes in endothelial cells exposed to high Lp(a) levels implicates glycolysis as a driver of Lp(a)-induced inflammation.[166] Studies also indicate that the OxPL component of Lp(a) particles promotes secretion of chemo-attractants and cytokines, upregulation of adhesion molecules, and transendothelial migration of monocytes (Supplementary material online, Figure S3). In patients with elevated Lp(a), immune cells demonstrate increased migration into atherosclerotic plaques.[160] OxPLs also induce expression of key genes regulating osteoblastic processes in valvular interstitial cells,[112] with effects attenuated by OxPL-blocking antibodies.

Whether Lp(a) plays a role in thrombotic processes in humans (enhanced coagulation or impaired fibrinolysis) is uncertain.[167] Apo(a) contains a protease-like domain similar to that in plasminogen, but inactive, suggesting that Lp(a) could promote impaired fibrinolysis. Human studies, however, failed to show any effect of substantial Lp(a) lowering on *ex vivo* fibrinolytic activity.[168] Epidemiological and genetic evidence also do not support a role for elevated Lp(a) in venous thrombosis (*Figure 4B*).[77,131]

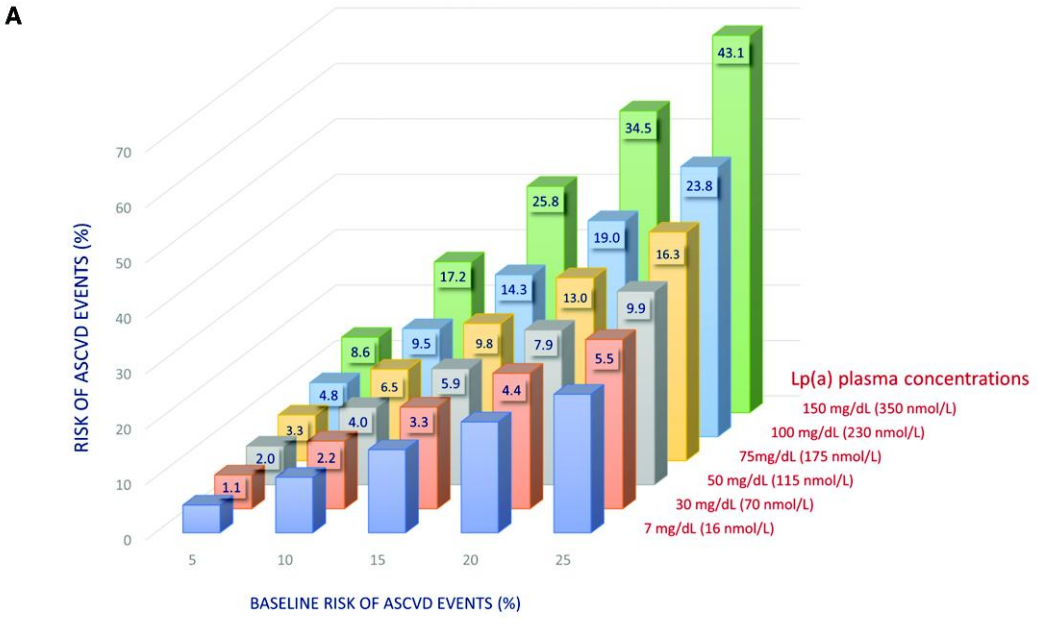
Consensus key points: Proposed mechanisms for the pathogenicity of Lp(a) in ASCVD and AVS

- Lp(a) has pro-inflammatory and pro-atherosclerotic properties, which may partly relate to the OxPLs carried by Lp(a).
- A potential role for Lp(a) in pro-thrombotic and anti-fibrinolytic activity *in vivo* remains unproven.
- High Lp(a) induces the expression of inflammatory and calcification genes in vascular and valvular cells and associates with increased incidence and progression of AVS.

How to incorporate Lp(a)-associated atherosclerotic cardiovascular disease risk in risk estimation?

The 2010 EAS statement[1] provided a basis for European and US guidelines to recommend the use of an Lp(a) threshold (50 mg/dL) as a 'risk enhancer' to refine interpretation of an individual's estimated 10-year risk of ASCVD.[116,126] This merits reconsideration, however, with evidence of a continuous relationship between Lp(a) concentration and absolute ASCVD risk.[169] As adding Lp(a) to risk algorithms only marginally improves risk discrimination[170–172] (as is the case for most biomarkers), an alternative approach is to estimate how much the Lp(a) level increases the individual's overall risk of ASCVD, taking into account both Lp(a) and baseline absolute global risk of ASCVD. As shown in *Figure 6A*, an Lp(a) level of 100 mg/dL (~250 nmol/l) approximately doubles the risk of ASCVD

A

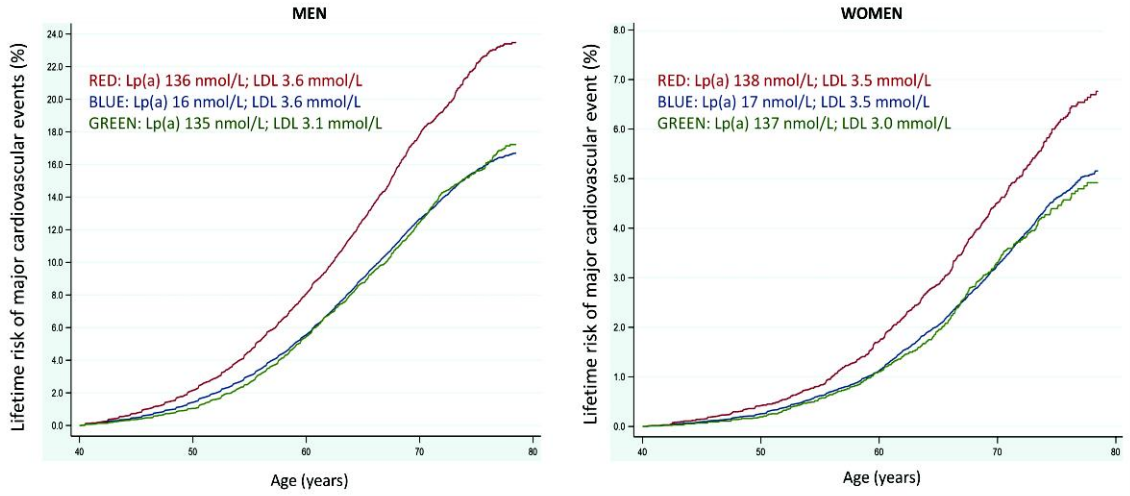


B

	Total CV risk (SCORE) %	Untreated Lp(a) concentrations < 10 mg/dL < 25 nmol/L	10 to <30 mg/dL 25 to <75 nmol/L	30 to <50 mg/dL 75 to <125 nmol/L	50 to <75 mg/dL 125 to <188 nmol/L	75 to <100 mg/dL 188 to <250 nmol/L	≥100 mg/dL ≥250 nmol/L
Primary Prevention	< 1 low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
Primary Prevention	≥1 to <5, or moderate-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
Primary Prevention	≥5 to <10, or high- risk	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
Primary Prevention	≥10, or at very-high risk due to a risk condition	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
Secondary Prevention	Very-high-risk	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)

Figure 6 Effect of increasing Lp(a) levels and estimated baseline absolute risk for major cardiovascular events. *Panel A* shows the estimated remaining lifetime risk of a major cardiovascular event [defined as the composite of the first occurrence of fatal or non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery)] among 415 274 participants of European ancestry in the UK Biobank for whom measured Lp(a) values were available. Participants are divided into categories of baseline estimated lifetime risk (5%, 10%, 15%, 20%, and 25%) calculated using the Joint British Societies (JBS3) Lifetime Risk Estimating algorithm (derived from a similar UK population). Within each baseline risk category, participants are then further divided into categories defined by baseline measured Lp(a) concentration. The incremental increase in risk caused by higher Lp(a) concentrations from 30 to 150 mg/dL (70 from 350 nmol/L) was estimated by adding Lp(a) as an independent exposure to the JBS3 risk estimating algorithm. The numbers at the upper end of each bar represent the increment of increased absolute risk above the estimated baseline risk caused by Lp(a). This information is presented in tabular form in Supplementary material online, *Table S2*. For example, for a person with a baseline risk of 5%, an Lp(a) concentration of 30 mg/dL increases the absolute remaining lifetime risk of a major cardiovascular event by 1.1% to 6.1% (vs. a person with an Lp(a) of 7 mg/dL). By contrast, for a person with a baseline risk of 25%, an Lp(a) concentration of 30 mg/dL increases the absolute risk of a major cardiovascular event by 5.5% to 30.5% (vs. a person with an Lp(a) of 7 mg/dL). For individuals with an Lp(a) concentration of 75 mg/dL, the corresponding absolute increases in risk are 3.3% and 16.3%, respectively. The figure illustrates that failure to consider a person's Lp(a) level can lead to a substantial underestimate of their absolute risk of a major cardiovascular event. Data provided by Prof. Brian Ference and Prof. Alberico L. Catapano. Further details are provided in the Supplementary material online. *Panel B* provides the intervention strategies as a function of total cardiovascular risk and untreated Lp(a) concentration. In the absence of specific Lp(a)-lowering therapy, these focus on management of other cardiovascular risk factors. For detailed methodological description, see Supplementary material online, *Table S3*.

A Lifetime risk of major cardiovascular events with higher lifetime exposure to Lp(a) and lower lifetime exposure to LDL-C



B Intensification of LDL-C reduction needed to reduce the global cardiovascular risk to a similar extent as the risk attributable to elevated Lp(a) depending on age at which LDL-C reduction is initiated

Lp(a) nmol/L	Δ Lp(a) compared to median	Lp(a) percentile	HR for MCVE due to increased Lp(a)	Intensification of LDL-C reduction (nmol/L) needed to mitigate the increased risk caused by Lp(a)			
				Begin age 30y	Begin age 40y	Begin age 50y	Begin age 60 y
320	300	99	2.56	1.2 mmol/L	1.4 mmol/L	1.7 mmol/L	2.3 mmol/L
270	250	97.5	2.19	1.0 mmol/L	1.2 mmol/L	1.5 mmol/L	1.9 mmol/L
220	200	93.5	1.87	0.8 mmol/L	0.9 mmol/L	1.2 mmol/L	1.5 mmol/L
170	150	90	1.60	0.6 mmol/L	0.7 mmol/L	0.9 mmol/L	1.1 mmol/L
120	100	82.5	1.37	0.4 mmol/L	0.5 mmol/L	0.6 mmol/L	0.8 mmol/L
70	50	75	1.17	0.2 mmol/L	0.2 mmol/L	0.3 mmol/L	0.4 mmol/L
20	ref.	50	ref.	ref.	ref.	ref.	ref.

Figure 7 Low-density lipoprotein cholesterol reduction needed to reduce global cardiovascular risk to a similar extent as the risk attributable to high Lp(a). *Panel A* shows the cumulative absolute lifetime risk of a major cardiovascular event (defined as the composite of the first occurrence of fatal or non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or coronary revascularization [percutaneous coronary intervention or coronary artery bypass graft surgery]) among 440 368 UK Biobank participants of European descent. For each sex, these were divided into three groups: a reference group with population average Lp(a) [16–17 nmol/L] and low-density lipoprotein cholesterol levels [3.5–3.6 mmol/L] who had no copies of either the rs10455872 or rs3798220 Lp(a)-increasing alleles; a group with higher lifetime exposure to Lp(a) [136–138 nmol/L) due to inheriting one copy of either the rs10455872 or rs3798220 Lp(a)-increasing alleles, but with population average low-density lipoprotein cholesterol levels [3.5–3.6 mmol/L]; and a group with BOTH higher lifetime exposure to Lp(a) [136–138 nmol/L) due to inheriting one copy of either the rs10455872 or rs3798220 Lp(a)-increasing alleles AND lifetime exposure to 0.5 mmol/L lower low-density lipoprotein cholesterol [3.0-3.1 mmol/L) due to inheriting a combination of low-density lipoprotein cholesterol lowering genetic variants. The Figure demonstrates that the increased risk of major cardiovascular event caused by lifetime exposure to approximately 120 nmol/L higher Lp(a) can be mitigated at all ages by a lifetime exposure to approximately 0.5 mmol/L lower LDL-C. This finding illustrates the potential to estimate how much intensification of risk factor modification, in this case low-density lipoprotein cholesterol lowering, is needed to mitigate the increased risk of major cardiovascular events caused by a person's Lp(a) level. *Panel B* provides a quantitative estimate of the intensification of low-density lipoprotein cholesterol lowering needed to mitigate the increased risk of major cardiovascular event caused by increasingly higher Lp(a) levels, and the age at which low-density lipoprotein cholesterol lowering is initiated. Because the proportional reduction in risk produced by lowering low-density lipoprotein cholesterol decreases with decreasing duration of exposure, greater intensification of low-density lipoprotein cholesterol lowering is needed to mitigate a given Lp(a) level if low-density lipoprotein cholesterol lowering is started at a later

Continued

irrespective of baseline absolute risk. For individuals with a higher baseline risk, the magnitude of absolute increase in ASCVD risk is greater (e.g. from 20% to 40% risk) than for those with lower baseline risk (from 5% to 10% risk).

On this basis, the panel recommends more intensive risk factor management with increasing Lp(a) concentration and increasing baseline risk to personalize cardiovascular risk management (*Figure 6B*). This approach is also consistent with observational data showing that the risk of developing a cardiovascular event for individuals with high Lp(a) but a healthy 'Cardiovascular Health Score' is only a third of that for those with high Lp(a) but an unhealthy score (for details see Supplementary material online, Figure S4).[173,174] It is also possible to estimate how much additional LDL-C-lowering, as recommended by the guidelines, is needed to reduce the global cardiovascular risk by a similar extent as the increased risk caused by high Lp(a) concentration (*Figure 7*). Similar calculations can be performed for blood pressure lowering or other interventions. However, where the major component of global risk is substantial and mainly attributable to elevated Lp(a), lowering traditional risk factors could be insufficient to mitigate this increased risk. In these cases specific Lp(a)-lowering therapies are urgently awaited.

Lipoprotein(a) testing

Who should get an Lp(a) test?

Consistent with epidemiological and genetic evidence and recent European[126] and Canadian guidelines,[175] Lp(a) should be measured at least once in adults, preferably in the first lipid profile, to identify those with high cardiovascular risk. Incorporating Lp(a) in global risk assessment may also improve risk stratification, especially for individuals with very high Lp(a); in one study, 31%–63% of those with Lp(a) levels >99th percentile were reclassified from moderate to higher risk.[176] With some exceptions (e.g. kidney or liver disease, acute infections), repeated measurement is not required as it does not improve risk prediction.[67]

In youth, Lp(a) measurement is recommended when there is a history of ischaemic stroke, or a parent has premature ASCVD and no other identifiable risk factors.[115] Multiple testing may be required as Lp(a) levels may increase until adulthood.[6,7]

Is there a role for cascade testing for Lp(a)?

Given its potential for risk enhancement, it seems reasonable to measure Lp(a) if a parent or sibling has markedly elevated Lp(a), using systematic or opportunistic approaches.[177] For example, where services already exist for cascade testing for FH, these could be extended to cascade testing for high Lp(a).[178–180] Cascade testing should be also considered in models of care for diabetes, hypertension, obesity, and secondary prevention of ASCVD.

Consensus panel recommendations for Lp(a) testing

- Lp(a) should be measured at least once in adults to identify those with high cardiovascular risk.
- Screening is also recommended in youth with a history of ischaemic stroke or a family history of premature ASCVD or high Lp(a) and no other identifiable risk factors.
- Cascade testing for high Lp(a) is recommended in the settings of FH, family history of (very) high Lp(a), and personal or family history of ASCVD.

Measurement issues related to Lp(a)

Lp(a) measurement is challenging.[181] There is substantial variability in assays, in part relating to apo(a) structure and variability in K-IV repeats.[182] Ideally, clinical assays should use an antibody for a unique non-repetitive epitope in apo(a), recognizing each Lp(a) particle once and reporting levels as nmol/L. In practice, as raising such antibodies is difficult, most assays incorporate polyclonal antibodies which recognize different epitopes, and therefore potentially underestimate or overestimate Lp(a) levels depending on the presence of small or large isoforms, respectively. Incorporating multiple calibrators spanning a range of sizes in the assay can at least partly address this issue (see Supplementary material online, Figure S5 for further explanation). Working groups for standardization of Lp(a) measurement are in progress, aiming to provide improved reference materials as a major step forward in Lp(a) measurement.[183,184]

Figure 7 Continued
age. For example, a person with an elevated Lp(a) level of 220 nmol/L has a 1.87-fold increased risk of major cardiovascular event as compared to a person with an Lp(a) level of 20 nmol/L (assuming all other risk factors are equal). This increased risk of major cardiovascular event can be mitigated by lowering low-density lipoprotein cholesterol by 0.8 mmol/L if started at age 30 years, but would require more intense low-density lipoprotein cholesterol lowering by 1.5 mmol/L if started at age 60 years. The data in the table of panel B elaborates on current clinical practice guidelines that recommend more intense risk factor modification among persons with elevated Lp(a) levels by providing specific quantitative guidance for how much low-density lipoprotein cholesterol lowering should be intensified to mitigate the increased risk of major cardiovascular event caused by increasingly higher Lp(a) levels. An easy-to-use online Lp(a) risk and benefit algorithm can provide convenient and specific guidance on how much intensification of low-density lipoprotein cholesterol lowering is needed to mitigate the risk caused by a person's Lp(a) level depending on the age at which low-density lipoprotein cholesterol lowering is initiated. However, where the main part of the risk is substantial and mainly attributable to Lp(a), a lowering of traditional risk factors such as low-density lipoprotein cholesterol will be insufficient to mitigate this increased risk. In these cases specific Lp(a)-lowering therapies are urgently required. This information should motivate testing of Lp(a) and inform the clinical use of measured Lp(a) levels. The online Lp(a) risk and benefit algorithm is available at the European Atherosclerosis Society website (www.eas-society.org/LPA_risk_and_benefit_algorithm). Further details are provided in the Supplementary material online. For detailed methodological description, see Supplementary material online. Data provided by Prof. Brian Ference and Prof. Alberico L. Catapano.

Can Lp(a) concentrations be converted from mass units to molar units and vice versa?

Strictly speaking, assays based on polyclonal antibodies cannot report in molar units.[181] As a compromise, they approximate their findings by comparison with apo(a) isoform-insensitive reference methods that use molar units;[183–185] if this is not possible, reporting should be in mg/dL. Manufacturers should strive to ensure that assays are apo(a) isoform-insensitive and provide an appropriate conversion factor if both measures are given.

This panel does not recommend using a standard factor to convert between mg/dL and nmol/L, as assays vary extensively.[186] Where both units are used in clinical practice, 2–2.5 is only a 'best guess' for a conversion factor (mg/dL to nmol/L).[183,184] In this statement, units are given as in the original publications, and for general statements relating to Lp(a) concentration, in both mg/dL and nmol/L with an approximated 'interim' conversion factor of 2.5.

Consequences for risk thresholds

While the association between Lp(a) and cardiovascular outcomes is linear, in clinical practice threshold levels identify values expected to translate to a clinically significant increase in risk, although analytical issues may raise questions about their validity. One solution is to define assay specific cut-offs, analogous to those used in different cardiac troponin assays.[187] This consensus panel suggests a pragmatic approach, with Lp(a) cut-offs to 'rule out' (<30 mg/dL or <75 nmol/L) or 'rule-in' (>50 mg/dL or >125 nmol/L) risk. The interim grey zone (i.e. 30–50 mg/dL; 75–125 nmol/l) is relevant when considering Lp(a)-attributable risk in the presence of other risk factors and in risk stratification.[181] Laboratories should include in reports the assay name to allow for tracking of discrepant results in patient follow-up.

Should Lp(a)-cholesterol be used to correct low-density lipoprotein cholesterol?

Cholesterol contained in Lp(a) particles cannot be separated from that in LDL particles and is therefore collectively reported as LDL-C concentration. Previous analyses of isolated Lp(a) particles suggested cholesterol accounted for 30%–45% of Lp(a) mass concentration.[188,189] Thus, Lp(a)-cholesterol [Lp(a)-C] was estimated by multiplying Lp(a) mass (mg/dL) by 0.3 and used to correct LDL-C (=Lp(a)-C-corrected LDL-C).

However, this approach has limitations. Direct measurement of Lp(a) cholesterol relative to Lp(a) mass showed inter- and intraindividual variation ranging from 6% to 60%,[128] which may impact risk prediction. Therefore, this panel does not recommend routine correction of LDL-C for Lp(a)-C. One exception may be patients with clinically suspected FH[190] and elevated Lp(a) levels, where correction may refine or exclude diagnosis and avoid unnecessary genetic sequencing;[191,192] in previous studies, 15%–25% of those with probable/definite FH were reclassified with this approach.[191,192] In addition, with the *LPA* locus identified as a cause of statin resistance and Lp(a)-C considered a statin-resistant fraction of LDL-C,[193] correcting LDL-C for Lp(a)-C may differentiate patients with higher baseline Lp(a) levels associated with reduced statin responsiveness.

Is there a role for genetic testing?

Measurement of Lp(a) concentration is sufficient for Lp(a)-related risk estimation without the need for genotyping, polygenic risk scores, or investigation of expressed apo(a) isoform sizes.[194]

Consensus panel recommendations for Lp(a) measurement

- Laboratories should use an Lp(a) assay that is insensitive to apo(a) isoform and traceable to official reference materials.
- Measurement of Lp(a) should be in molar units if available. If not, the units in which the assay is calibrated should be used for reporting.
- Rather than absolute values, clinical guidelines should consider using risk thresholds with 'grey' zones (e.g., 30–50 mg/dL or 75–125 nmol/L) to either rule-in (≥50 mg/dL; 125 nmol/L) or rule-out (<30 mg/dL; 75 nmol/L) cardiovascular risk.

Clinical guidance: What to do with the patient with high Lp(a)?

In the absence of approved specific Lp(a)-lowering drugs, this panel recommends early, intensive management of other risk factors for individuals with elevated Lp(a) levels, consistent with most guidelines.[126,175] Personalized management of LDL-C, blood pressure, glucose, and lifestyle factors, taking into account baseline cardiovascular risk and the untreated Lp(a) level, is recommended to reduce ASCVD risk sufficiently to mitigate increased risk caused by an elevated Lp(a) level (*Figure 6B*).

LDL-C management should be in accordance with current guidelines.[126,175] Although statins may slightly increase Lp(a) levels,[65–68] treatment should not be discontinued as the cardiovascular benefits in patients with high Lp(a) far outweigh any potential risk associated with modest increases in Lp(a) levels.[65,195] Lipoprotein apheresis can be considered in patients with very high Lp(a) and progressive ASCVD despite optimal treatment of other risk factors as uncontrolled data indicate benefit.[196,197]

In major studies with PCSK9 inhibitors, the absolute cardiovascular risk reduction with this treatment was higher at higher baseline Lp(a) levels. In FOURIER, the absolute risk reduction was 2.41% vs. 1.41% with an Lp(a) >50 vs. <50 mg/dL[198] and in ODYSSEY OUTCOMES, 3.7% at Lp(a) >60 mg/dL vs. 0.5% in the lowest Lp(a) quartile.[199] However, PCSK9 inhibitors are not registered for Lp(a) lowering.

Niacin is not recommended given the lack of clinical benefit in two outcomes studies.[200,201] Current data also do not support targeting aspirin use based on Lp(a) levels.[202] Whether aspirin might be beneficial among individuals with markedly elevated Lp(a) is uncertain (see Supplementary material online).

Emerging therapies

Novel antisense and small interfering RNA (siRNA) treatments that target apo(a) production in the hepatocyte lower Lp(a) concentration.[203] In early trials, mean decreases of 80 and 72% were reported

Table 3 Suggested recommendations for implementing better care of elevated lipoprotein(a)

Healthcare professionals involved in screening and testing for high Lp(a)
• Measurement of Lp(a) should be routinely included as part of an initial lipid profile • Offer training in the interpretation of results and family counselling • Notify close relatives about risk; offer cascade testing for high Lp(a) and pre- and post-test counselling to close relatives of the index case • Include Lp(a) in ASCVD risk stratification strategies
Patient-clinician interaction
• Base on shared decision making, with coaching methods if required • Assess absolute risk of ASCVD • Offer initial cascade testing of first-degree relatives • Address behavioural risk factors with lifestyle counselling • Discuss risks and benefits of drug therapies for cardiovascular risk factors, accounting for patient values and preferences • Refer more complex patients to lipid specialists.
Advice from a lipid specialist
• Review by a specialist should be offered to all patients with elevated Lp(a) and a higher risk of ASCVD.
Laboratory reporting
• Alert clinicians to the importance of the extent of elevation in Lp(a) concentration. • Interpretive comments should address the need for ASCVD risk assessment, consideration of cascade testing, and potential referral to a lipid specialist.
Worldwide implementation of ICD codes
• Promote the use of ICD codes for elevated Lp(a) in hospital and primary care records and clinical registries • ICD-10-CM Diagnosis Code E78.41: Elevated Lp(a) • ICD-10-CM Diagnosis Code Z83.430: Family history of elevated Lp(a)
Clinical registries and codification
• All patients with extremely high Lp(a) and affected relatives should be consented for inclusion in a quality clinical registry.
Cardiovascular risk prediction calculators
• Elevated Lp(a) should be incorporated as a predictor variable in country-specific risk equations for primary and secondary prevention of ASCVD.
Engagement with consumer groups
• Partner with consumer groups to advocate for improvement in the care of people with high Lp(a): this should include raising public and government awareness, implementation of cost-effective testing strategies, and access to new therapies. • Employ several modalities to engage with consumers and other key stakeholders, including social media, health apps, websites and webinars

ASCVD, atherosclerotic cardiovascular disease; ICD, International Classification of Diseases; Lp(a), lipoprotein(a).

with the antisense oligonucleotide pelacarsen [formerly TQJ230 and AKCEA-APO(a)-LRx] given 20 mg weekly and 60 mg every 4 weeks, respectively, with 98% and 81% of participants attaining Lp(a) levels <125 nmol/L at the end of the study.[204] Reductions ranging between 71% and 97% were observed with olpasiran (formerly AMG 890), a *N*-acetylgalactosamine (GalNAc)-conjugated siRNA, which were sustained for over 6 months.[205] Both treatments showed a favourable safety profile. Another GalNAc-conjugated siRNA (SLN360, Silence Therapeutics) is in early development.[206]

How much should Lp(a) be lowered for benefit?

Although estimates vary, several Mendelian randomization studies suggested that large absolute reductions in Lp(a) concentration (>50–100 mg/dL) are needed for a clinically meaningful reduction in the risk of ASCVD events in a 'short-term' (<5 years) clinical trial.[107,169,207] How much Lp(a) needs to be lowered to produce a clinically meaningful benefit remains uncertain. Data are awaited from the Lp(a)HORIZON trial in patients with ASCVD and elevated Lp(a) (>70 mg/dL) (NCT04023552).

Promise of Lp(a) lowering in aortic valve disease

There is robust evidence that high Lp(a) concentrations are likely causal in the initiation of aortic valve disease and also associate with increased disease activity and progression (*Table 2*).[93,112] Randomized controlled trial of Lp(a) lowering in AVS are now required. While tempting to speculate about the impact of Lp(a) lowering on AVS progression, defining the most appropriate patient population and selecting appropriate trial endpoint in aortic stenosis is a challenge.[110]

Consensus panel recommendations for managing high Lp(a) concentration

- In the absence of specific Lp(a)-lowering therapies, early risk factor management is recommended for individuals with elevated Lp(a), taking into account their absolute global cardiovascular risk and Lp(a) level.
- Among patients with high Lp(a), all cardiovascular risk factors should be comprehensively addressed as per guideline recommendations.
- Lipoprotein apheresis can be considered in patients with very high Lp(a) and progressive cardiovascular disease despite optimal management of risk factors.
- Niacin is not recommended for Lp(a) lowering.

Clinical implementation and challenges

Although implementing clinical care of elevated Lp(a) can be challenging, models proposed for patients and families with FH offer a basis.[179] Increasing general awareness and training a wide spectrum of healthcare and laboratory practitioners regarding the importance of managing elevated Lp(a) are essential (*Table 3* and Supplementary material online, *Figure S6*).[208]

Conclusions

This 2022 EAS consensus statement updates evidence relating to the associations of Lp(a) and ASCVD, strongly reinforcing recommendations from clinical guidelines and its inclusion in global risk estimation. Improved standardization of Lp(a) measurement, together with implementation using models of care possibly based on those of FH, are key.

However, gaps in our knowledge about Lp(a) remain (Box 2). A critical question is whether lowering elevated Lp(a), against a background of well controlled LDL-C levels, reduces cardiovascular events; insights from the Lp(a) HORIZON trial are crucial. Finally, investigating the potential of Lp(a) lowering to reduce AVS progression is a priority, given the urgent and escalating unmet clinical need in this setting.

Box 2. Critical knowledge gaps in the Lp(a) field

- Many aspects of the genetic regulation of Lp(a) are not fully understood. Identification of causal variants and the mechanisms by which they modulate Lp(a) concentration or enhance Lp(a) pathogenicity require further research.
- Better understanding of the pathogenicity of the various moieties of Lp(a) particles is a priority.
- Investigation of the mechanisms underlying the link between very low Lp(a) concentration and the development of diabetes mellitus is needed.
- Standardization and harmonization of Lp(a) measurement needs to be improved.
- Studies in larger samples of different ethnicities are needed.
- Whether Lp(a) lowering reverses accelerated atherogenesis and AVS progression and reduces cardiovascular events has to be tested. The extent of Lp(a) lowering required for clinical benefit is also not known.

Author contributions

This consensus panel appraised and discussed evidence for Lp(a) during two closed virtual meetings in September and December 2021. The panel was co-chaired by F.K., S.M., and E.S.G.S. All authors contributed to drafting the manuscript, which was reviewed and edited by the writing group, comprising F.K., S.M., E.S.G.S., A.L.C., L.S.T., K.K.R., and J.K.S. A revised draft was reviewed by all members of the panel, and the final manuscript was approved by all authors before submission to the journal.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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