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Lipoprotein(a) and its Significance in Cardiovascular Disease
A Review

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IMPORTANCE Lipoprotein(a) (Lp[a]) is a low-density lipoprotein (LDL) cholesterol–like particle bound to apolipoprotein(a). This novel marker of cardiovascular disease acts through induction of vascular inflammation, atherogenesis, calcification, and thrombosis. While an absolute risk threshold remains to be universally accepted, an estimated 20% to 25% of the global population have Lp(a) levels of 50 mg/dL or higher, a level noted by the European Atherosclerosis Society to confer increased cardiovascular risk.

OBSERVATIONS Compelling evidence from pathophysiological, observational, and genetic studies suggest a potentially causal association between high Lp(a) levels, atherosclerotic cardiovascular disease, and calcific aortic valve stenosis. Additional evidence has demonstrated that elevated Lp(a) levels are associated with a residual cardiovascular risk despite traditional risk factor optimization, including LDL cholesterol reduction. These findings have led to the formulation of the Lp(a) hypothesis, namely that Lp(a) lowering leads to cardiovascular risk reduction, intensifying the search for Lp(a)-reducing therapies. The ineffectiveness of lifestyle modification, statins, and ezetimibe to lower Lp(a); the modest Lp(a) reduction with proprotein convertase subtilisin/kexin type 9 inhibitors; the adverse effect profile and unclear cardiovascular benefit of pharmacotherapies such as niacin and mipomersen; and the impracticality of regular lipoprotein apheresis represent major challenges to currently available therapies. Nevertheless, emerging nucleic acid–based therapies, such as the antisense oligonucleotide pelacarsen and the small interfering RNA olpasiran, are generating interest because of their potent Lp(a)-lowering effects. Assessment of new-onset diabetes in patients achieving very low Lp(a) levels will be important in future trials.

CONCLUSIONS AND RELEVANCE Epidemiologic and genetic studies suggest a potentially causal association between elevated Lp(a) levels, atherosclerotic cardiovascular disease, and aortic valve stenosis. Emerging nucleic acid–based therapies have potent Lp(a)-lowering effects and appear safe; phase 3 trials will establish whether they improve cardiovascular outcomes.

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Supplemental content

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Lipoprotein(a) (Lp[a]) is a low-density lipoprotein (LDL) cholesterol–like particle that was first identified by Kåre Berg, MD, in 1963.[1] Its concentration is largely genetically determined, with marked variations across populations.[2] Epidemiologic and observational studies suggest a potential causal association between elevated Lp(a) and an increased risk of atherosclerotic cardiovascular disease (ASCVD)[3,4] and calcific aortic valve stenosis (AS).[5,6] These findings have been recently supported by genetic studies.[7,8] While no universally accepted absolute risk threshold exists, approximately 20% to 25% of the global population have an Lp(a) level of 50 mg/dL (to convert to milligrams per liter, multiply by 10) or greater,[2] which according to the European Atherosclerosis Society (EAS) confers an increased cardiovascular risk[9] despite traditional risk factor optimization.[10]

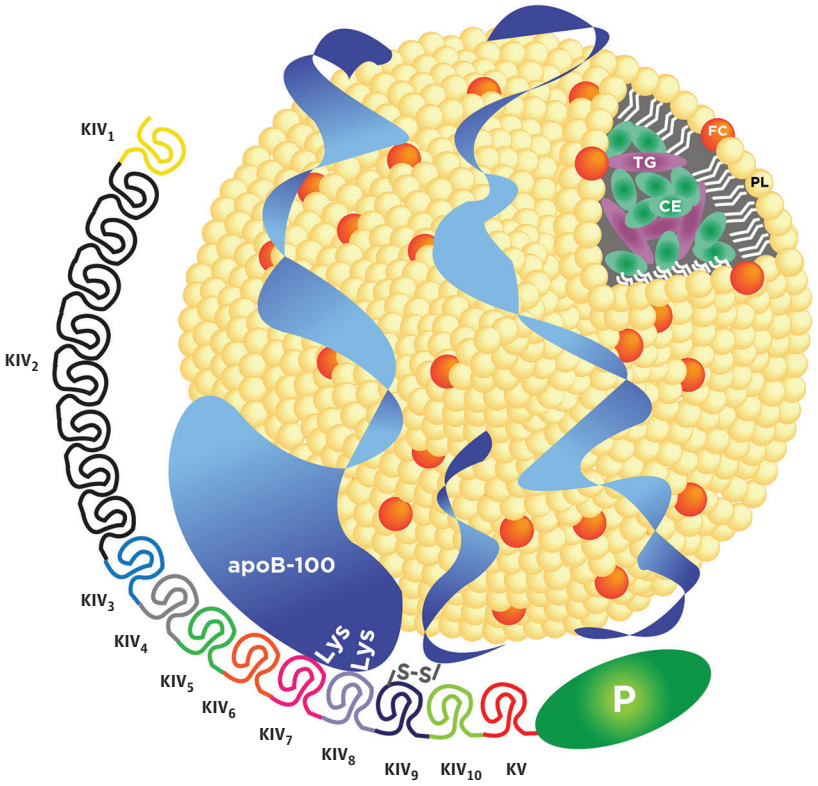
This article aims to review Lp(a) biology and pathophysiology, data with current therapies, and novel therapies under development.

Structure and Metabolism

Lp(a) assembly occurs either on the hepatocyte surface or in the space of Disse. Its core composition resembles LDL and consists of triglycerides and cholesteryl esters surrounded by an outer membrane of phospholipids and free cholesterol. Its protein moiety comprises a single copy of apolipoprotein B-100 (apoB) bound to a single apolipoprotein(a) (apo[a]) particle through covalent and noncovalent bonds (**Figure 1**).[11]

Lp(a) synthesis is primarily determined through the *LPA* gene, which codes for 2 kringle domains (kringles IV-V [KIV-KV]). KIV expands into 10 subtypes (KIV_1-KIV_{10}), while KV is attached to both KIV_{10} and an inactive protease domain. Expansion of KIV_2 results in a variable intragenic copy number variation resulting in 1 to more than 40 identically repeated copies. This leads to heterogeneous apo(a) isoform sizes, a unique occurrence among proteins. The other KIV

Figure 1. Lipoprotein(a) Structure



Lipoprotein(a) is a low-density lipoprotein–like particle covalently bound to apolipoprotein(a) via a disulfide linkage. Apolipoprotein(a) consists of 10 subtypes of kringle domain IV (KIV_{1-10}), kringle domain V (KV), and an inactive protease domain (P). KIV_2 can expand into more than 40 identically repeated copies. apoB-100 indicates apolipoprotein B-100; CE, cholesterol ester; FC, free cholesterol; Lys, lysine residue; PL, phospholipid; TG, triglyceride.

domains (KIV_1 and KIV_3-KIV_{10}) are present as single copies, with KIV_{10} containing a site to which oxidized phospholipids are covalently attached.[11] Lp(a) is eventually removed as separate units from the blood and may have a hepatic, kidney, or combined mechanism of clearance.[12]

Pathogenicity

Lp(a) promotes ASCVD and calcific aortic valve stenosis (AS) via 4 mechanisms: vascular inflammation, atherogenesis, calcification, and thrombosis. Lp(a) enters the arterial intima through molecular pores, where it undergoes oxidation, resulting in the formation of reactive oxygen species that induce inflammation through augmented endothelial permeability, diapedesis, cytokine production, apoptosis, and vascular wall remodeling. The oxidized LDL portion is avidly taken up by macrophages to generate foam cells and promote atherosclerotic plaque formation.[12] Lp(a) is the only apoB-containing lipoprotein that carries oxidized phospholipids, which are delivered to injured vessels and aortic valve leaflets when Lp(a) concentrations are high, and cause endothelial dysfunction, lipid accumulation, calcification, and inflammation. Lp(a) kringles are believed to attach to fibrin to form the quaternary complex that prevents plasminogen activation, thus promoting thrombus formation.[11] Lp(a) may therefore represent the missing link between atherosclerosis, AS, and thrombosis.

Challenges in Measurement

The size heterogeneity of apo(a) impairs the accuracy of antibody-mediated immunoassays to measure the true Lp(a) burden. Because each Lp(a) particle consists of 1 mole of apo(a) and 1 mole of apoB, regardless of the apo(a) size, measuring molar concentrations circumvents the heterogeneity of mass measurement[13] (eFigure 1 in the Supplement).

The International Federation of Clinical Chemistry (IFCC), in conjunction with the World Health Organization (WHO) Committee of Biological Standards, created a proposed reference material with the measurement of Lp(a) in nanomoles per liter.[14] A list of manufacturers and relative instruments certified by the Northwest Research Lipid Laboratory, University of Washington, Seattle, whose assays meet the WHO/IFCC proposed reference material standards has been published.[13] Importantly, direct conversion between Lp(a) mass (milligrams per deciliter) and concentration (nanomoles per liter) is an imprecise approximation since all conversion factors are inherently isoform dependent.

Cut Points

Lp(a) plasma levels are 90% genetically determined, inversely related to the number of KIV_2 repeats, and remain stable

Box. When to Measure Lipoprotein(a) (Lp[a]) and Thresholds for Treatment

2018 American College of Cardiology/American Heart Association Cholesterol Guidelines[19]
- ASCVD not explained by major risk factors
- Family history of premature ASCVD[a]
- Lp(a) levels ≥125 nmol/L (≥50 mg/dL) are considered an ASCVD risk-enhancing factor

2019 National Lipid Association Scientific Statement[20]
- Personal or family history of premature ASCVD[a]
- Personal or family history of severe hypercholesterolemia (LDL-C ≥190 mg/dL) or suspected familial hypercholesterolemia
- Family history of elevated Lp(a)
- Borderline (5% to 7.4%) and intermediate (7.5% to 19.9%) 10-year ASCVD risk (for statin consideration)
- At very high risk of ASCVD (for PCSK9 consideration)[b]
- Partial response to LDL-C–lowering therapy
- Recurrent or progressive ASCVD, despite optimal lipid-lowering therapy
- Calcific aortic valve stenosis
- Lp(a) levels ≥100 nmol/L (≥50 mg/dL) are considered an ASCVD risk-enhancing factor

2019 European Society of Cardiology/European Atherosclerosis Society Guidelines for the Management of Dyslipidaemias[21]
- Measure at least once in each adult person's lifetime (universal screening)
- Lp(a) levels >430 nmol/L (>180 mg/dL) are considered very high risk

2019 HEART UK Consensus Statement[22]
- Personal or family history of premature ASCVD[c]
- First-degree relatives with serum Lp(a) levels >200 nmol/L
- Familial hypercholesterolemia or other genetic dyslipidemias
- Calcific aortic valve stenosis
- Borderline increased (but <15%) 10-year ASCVD risk
- Lp(a) levels >90 nmol/L are considered high risk

2020 Endocrine Society Lipid Management Guidelines[23]
- Family history of premature ASCVD or high Lp(a)
- Personal history of ASCVD
- Lp(a) levels ≥125 nmol/L (≥50 mg/dL) are considered an ASCVD risk-enhancing factor

2021 Canadian Guidelines for the Management of Dyslipidemia[24]
- Measure at least once in each adult person's lifetime (universal screening)
- Lp(a) levels ≥100 nmol/L (≥50 mg/dL) are considered high risk

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

[a] Younger than 55 years in men and younger than 65 years in women.

[b] Individuals with multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

[c] Younger than 60 years.

throughout an individual's lifetime.[15] Lp(a) levels have a direct linear relationship with ASCVD risk as opposed to a threshold effect causing a sharp rise in risk at the highest concentrations.[3] Challenges to the establishment of a universal risk cut point include: (1) differences in measurement units and techniques, (2) heterogeneity of reported values across different studies, and (3) pronounced variation in Lp(a) concentrations among different racial groups[16] and among those with comorbidities (eg, chronic kidney disease, liver disease, and hypothyroidism).[17]

The Multi-Ethnic Study of Atherosclerosis found that Lp(a) concentrations of 50 mg/dL or greater had a stronger association with CAD in Chinese American, Hispanic, and White individuals compared with concentrations of 30 mg/dL or greater in Black individuals.[18] The 2021 UK Biobank study demonstrated that when using a race-specific cut point of the 90th percentile or higher or an absolute threshold of 150 nmol/L or greater, the ASCVD risk was similar among Black, South Asian, and White individuals.[3] These observations have potential implications in redefining whether race-specific percentiles or absolute thresholds are better predictors of cardiovascular risk and treatment candidacy. The current Lp(a) thresholds determined by guideline committees are summarized in the **Box**.[19-24]

Evidence Linking Lp(a) to Atherosclerosis

Data from key studies in a variety of populations supporting a strong association between elevated Lp(a) levels and ASCVD risk are summarized in **Table 1**.[3-6,8,25-28]

Cohort Studies

The Copenhagen City Heart Study (CCHS) observed 9330 individuals from the general Danish population for 10 years. An increased risk of myocardial infarction (MI) proportional to Lp(a) levels was found.[25] Levels of 120 mg/dL or greater conferred up to a 4-fold increased relative risk and a 35% higher absolute 10-year risk of MI. A meta-analysis by the Emerging Risk Factors Collaboration[4] from 36 prospective studies involving 126 634 participants without prior cardiovascular disease (CVD) revealed a broadly continuous increased risk for CAD (relative risk per 1-SD rise in Lp[a], 1.13; 95% CI, 1.09-1.18) that was only slightly attenuated after adjustment for established cardiovascular risk factors.

Analysis of 460 506 middle-aged individuals from the UK Biobank database observed for a median of 11.2 years revealed a linear association between Lp(a) and the risk of ASCVD (hazard ratio [HR] per 50 nmol/L rise in Lp[a], 1.11; 95% CI, 1.10-1.12).[3] In 283 540 healthy adults from the UK Biobank cohort, both Lp(a) levels and a genetic risk score comprising 43 variants at the *LPA* gene modestly improved the risk discriminatory ability of the Pooled Cohort Equations or QRISK3,[29] consistent with other contemporary primary prevention studies.[30,31]

Genetic Data

Two large genetic studies provided evidence of a potential causal association between Lp(a) and CAD.[7,8] A classic mendelian randomization study in 40 486 individuals from 3 sources: the CCHS, the Copenhagen General Population Study (CGPS), a cross-sectional general population study, and the Copenhagen Ischemic Heart Disease Study, a case-control study, showed a 22% increase in the risk of MI per doubling of genetically determined Lp(a) levels and an increase in the adjusted HRs with high Lp(a) and low KIV_2 repeats.[8] A case-control study of 3145 patients with CAD and 3352 controls from the Precocious Coronary Artery Disease cohort in Europe analyzed 48 742 single-nucleotide variants and

Table 1. Landmark Studies Linking Lipoprotein(a) (Lp[a]) to Cardiovascular Disease

Source	Design	Population	Key findings
Association between Lp(a) and ASCVD			
CCHS[25]	Prospective	9330 Individuals from the general population in Denmark	Adjusted HR for incident myocardial infarction with Lp(a) levels ≥120 mg/dL (≥95th percentile) vs levels <5 mg/dL (<22nd percentile) were 3.6 (95% CI, 1.7-7.7) in women and 3.7 (95% CI, 1.7-8.0) in men
Emerging Risk Factors Collaboration[4]	Meta-analysis	126 634 Individuals with no prior history of coronary heart disease or stroke from 36 cohorts	Adjusted RR of 1.13 (95% CI, 1.09-1.18) for incident coronary heart disease per 1-SD rise in Lp(a)
Kamstrup et al,[8] 2009	Mendelian randomization	40 486 Patients from 3 large Danish cohorts: CCHS, CGPS, and CIHS	Causal association between increasing genetically determined Lp(a) levels and the risk of myocardial infarction (HR per doubling of Lp[a] levels, 1.22; 95% CI, 1.09-1.37)
O'Donoghue,[26] 2014	Meta-analysis	18 978 Individuals with coronary artery disease	OR for MACE was 1.40 (95% CI, 1.15-1.71) for the highest vs lowest Lp(a) quantile
UK Biobank[3]	Prospective	460 506 Middle-aged individuals with and without ASCVD	Incident or recurrent ASCVD events had an overall HR of 1.11 (95% CI, 1.10-1.12) per 50-nmol/L increment in Lp(a) concentrations
Association between lipoprotein(a) and calcific aortic valve stenosis			
CCHS and CGPS[5]	Mendelian randomization	77 680 Danish participants from the general population	When combining all genotypes, a genetic RR for aortic stenosis of 1.6 (95% CI, 1.2-2.1) for a 10-fold increase in Lp(a) concentration was reported
EPIC-Norfolk[6]	Prospective	17 553 Adults from the general UK population	Participants in the top Lp(a) tertile had an adjusted HR for aortic stenosis of 1.57 (95% CI, 1.02-2.42) compared with participants in the bottom tertile
FOURIER[27]	Clinical trial	27 564 Individuals with stable ASCVD taking statins	The adjusted HR for aortic stenosis events was 1.55 (95% CI, 1.17-2.05) per 1-SD increase in Lp(a) levels; LDL-C levels had no association with aortic stenosis
Association between Lp(a) and ischemic stroke			
Emerging Risk Factors Collaboration[4]	Meta-analysis	126 634 Individuals with no prior history of coronary heart disease or stroke from 36 cohorts	Adjusted RR for ischemic stroke was 1.10 (95% CI, 1.02-1.18) per 1-SD rise in Lp(a)
CCHS and CGPS[28]	Prospective	60 512 Individuals from the general Danish population	The HR for ischemic stroke was 1.60 (95% CI, 1.24-2.05) for individuals with Lp(a) >93 mg/dL compared with individuals with Lp(a) <10 mg/dL

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; CIHS, Copenhagen Ischemic Heart Disease Study; EPIC, European Prospective Investigation into Cancer; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; OR, odds ratio; RR, relative risk.

SI conversion factor: To convert Lp(a) to mg/L, multiply by 10.

identified 2 *LPA* variants (rs10455872 and rs3798220) that were associated with high levels of Lp(a), a reduced copy number of KIV_2 repeats, and the strongest association with CAD risk compared with other polymorphisms.[7]

Data in individuals with loss-of-function *LPA* variants also suggest a potential causal association between Lp(a) and ASCVD risk.[32,33] Genomewide analysis studies in 63 746 individuals with CAD and 130 681 controls from the Coronary Artery Disease Genome-Wide Replication and a Meta-analysis Consortium showed that the *LPA* locus has a more robust genetic association with CAD than the LDL, PCSK9, and 9p21 loci.[34]

Clinical Trial Populations

A meta-analysis of 18 978 individuals from 3 large clinical trial populations of patients with CAD revealed that Lp(a) levels in the highest quantile were associated with a 40% higher risk of major adverse cardiovascular events (MACE) compared with the lowest quantile.[26] The data for secondary prevention populations, however, are mixed. Some studies suggest an attenuated association between Lp(a) and cardiovascular outcomes at lower LDL-C levels while others show an independent association.[35] The residual cardiovascular risk attributed to high Lp(a) levels, independent of LDL-C, has been reported across multiple secondary prevention studies[36,37] and landmark clinical trials.[10,38,39]

Lp(a) and Calcific Aortic Valve Stenosis

There is an increasing body of evidence identifying Lp(a) as a strong, independent, and potentially causal risk factor for AS (Table 1), making LPA the only monogenetic risk factor for AS reported to date.[40] A mendelian randomization study in 77 680 participants from the CCHS and CGPS cohorts showed that elevated Lp(a) levels were positively associated with a higher risk of AS in a concentration-dependent manner. When combining all Lp(a)-related genotypic variants, a 10-fold increase in genetically determined Lp(a) values resulted in a significantly higher risk of AS.[5] Similar results were reported thereafter using a multidirectional mendelian randomization design of the same cohorts.[41] Analysis of 17 553 participants from the European Prospective Investigation into Cancer-Norfolk cohort found that individuals in the top vs bottom Lp(a) tertile had a 57% higher risk of AS.[6] The rs10455872 variant of the *LPA* gene was associated with both higher Lp(a) levels and an increased risk of AS in the same data set.

In a secondary analysis of the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial including 27 564 individuals with stable ASCVD taking statins, increasing Lp(a) levels but not LDL-C levels (despite Lp[a] correction) were associated with a higher risk of subsequent AS events (either progression of AS or need for aortic valve replacement).[27] Finally, a systematic

review of 21 studies including case-control, observational, and genetic studies found convincing evidence to suggest a potential causal association between elevated Lp(a) and AS.[42]

Lp(a) and Other Cardiovascular Conditions

Limited data from observational studies reveal an independent association between elevated Lp(a) levels and ischemic stroke (Table 1). Large prospective epidemiologic and genetic studies demonstrate strong associations of high Lp(a) concentrations with heart failure and peripheral arterial disease.[43]

When to Measure Lp(a)

The indications for measurement of Lp(a) concentrations from expert panels are heterogeneous (Box). Currently, the European Society of Cardioloy/European Atherosclerosis Society guidelines,[21] Canadian Cardiovascular Society guidelines,[24] and Indian Expert Consensus guidelines[44] support universal routine measurement to improve cardiovascular risk classification, while the 2021 European guidelines on CVD prevention[45] acknowledge that the reclassification potential of Lp(a) remains limited and that further studies are needed. Guidelines and expert statements all encourage Lp(a) measurement in individuals with strong family history of premature ASCVD. While cascade screening for individuals with elevated Lp(a) has not been widely supported, systematic screening from patients with index cases with both high Lp(a) and familial hypercholesterolemia appears effective in identifying relatives with elevated Lp(a).[46] Given their stable values throughout an individual's lifetime, recent data favor one-time measurement of Lp(a) instead of repeated measurements.[47]

Inclusion of Lp(a) *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification*, codes (E78.41: elevated Lp[a]; Z83.430: family history of elevated Lp[a]) introduced in 2018 now provide more research opportunities to systematic studies using billing databases and also permit standardized billing and reimbursement. In fact, elevated Lp(a) became the first laboratory testing abnormality that achieved the status of a clinical diagnosis.[48] A study assessing the trends in Lp(a) testing between 2003 and 2016 at an academic medical center in California showed that Lp(a) measurement was infrequent, variable, and unpredictable (315 patients in 2003, 104 in 2008, 270 in 2009, and 409 in 2015).[49] Furthermore, a 2021 American College of Cardiology poll indicated that Lp(a) is not routinely measured.[50] Major barriers include (1) underappreciation of Lp(a) as an ASCVD risk factor, (2) absence of approved Lp(a)-lowering medications, (3) inconsistent insurance coverage for Lp(a) testing, and (4) lack of clinical trial data demonstrating MACE reduction.[51]

Rationale for Lp(a) Reduction —The Lp(a) Hypothesis

Strong, independent, and causal associations between elevated Lp(a) levels, ASCVD, and AS, coupled with a residual cardiovascular risk associated with Lp(a) despite statin therapy, form the backbone of the Lp(a) hypothesis—that reducing Lp(a) will prevent future cardiovascular events. Since a robust Lp(a) reduction (eg, 100 nmol/L) would be necessary to significantly prevent cardiovascular events,[52,53] patients with very high Lp(a) levels (well above those considered elevated in current guidelines) would be most suitable for specific Lp(a)-lowering therapies.

Current options to reduce Lp(a) are limited. Dietary interventions and exercise have yielded inconsistent results,[54] and to our knowledge, no pharmacotherapies (**Table 2**)[10,55-60] are yet approved to specifically lower Lp(a).

Ineffective Treatments

Although statins and ezetimibe do not effectively lower Lp(a) and are generally well tolerated, they may paradoxically increase its concentrations up to 30% (eFigure 2 in the Supplement), which has inconsequential effects on incident CAD.[47,55,56] It is thus reasonable to intensify therapy with these agents in patients with elevated Lp(a) to minimize the risk attributed to LDL-C; recent guidelines recommend that in patients without diabetes aged 40 to 75 years who have a borderline (5% to 7.4%) or intermediate (7.5% to 19.9%) 10-year ASCVD risk, initiation of a statin should be considered if there is presence of a risk-enhancing factor, such as Lp(a) of 50 mg/dL or greater.[19,20] In situations where the cardiovascular risk remains uncertain, including when an elevated Lp(a) is the sole remaining untreated risk factor, assessment of the coronary artery calcium score may reclassify risk and inform shared decision-making.[19] In fact, recent data suggest that an elevated Lp(a) and a coronary artery calcium score of 100 or more are independently associated with ASCVD risk, which supports a complementary role in risk stratification for these 2 factors.[61]

Other pharmacologic therapies that have been studied for their Lp(a)-lowering effects, include niacin, ascorbic acid, mipomersen, fibrates, and sex-hormone therapies. These are less-appealing options because of their adverse effect profile and lack of evidence to support a reduction in cardiovascular events.

Modestly Effective Treatments

In an analysis of the FOURIER trial, the PCSK9 inhibitor (PCSK9i) evolocumab lowered Lp(a) by a median of 27% at 48 weeks.[10] In individuals with baseline Lp(a) levels greater than the median (37 nmol/L), evolocumab reduced risk of CAD mortality, MI, or urgent revascularization by 23% (HR, 0.77; 95% CI, 0.67-0.88) compared with placebo and by 7% (HR, 0.93; 95% CI, 0.80-1.08) in those with levels lower than the median (*P* for interaction = .07). FOURIER trial data also showed that evolocumab may reduce AS progression (new or worsening AS or need for aortic valve replacement) after 1 year.[27]

A prespecified analysis of the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES) trial of 18 924 patients with recent acute coronary syndrome who were taking high-intensity statin demonstrated that the PCSK9i alirocumab reduced Lp(a) by 23% after 4 months.[57] A higher baseline Lp(a) level was correlated with a higher magnitude of Lp(a) reduction, which, in turn, was associated with a greater reduction in the risk of MACE, independent of LDL-C levels.

Table 2. Landmark Studies of the Most Relevant Lipoprotein(a) (Lp[a])–Lowering Therapies

Source	Design	Population	Key findings
Statins			
Willeit et al,[55] 2018	Meta-analysis	29 069 Patients with established cardiovascular disease with and without statin therapy	Statins reduced LDL-C concentrations without a significant change in Lp(a) levels
Tsimikas et al,[56] 2020	Meta-analysis	5256 Patients (1371 taking placebo and 3885 taking different statins) from 6 clinical trials	The Lp(a) concentration mean percentage change from baseline ranged from 8.5% to 19.6% in the statin groups and from −0.4% to −2.3% in the placebo group
PCSK9 inhibitors			
FOURIER[10]	Clinical trial	25 096 Patients with ASCVD already receiving intensive statin therapy with or without ezetimibe	Evolocumab reduced Lp(a) by a median percentage of 26.9% from baseline at 48 weeks and was associated with a 23% reduction in the risk of MACE in patients with a baseline Lp(a) above the median (37 nmol/L) compared with placebo
ODYSSEY OUTCOMES[57]	Clinical trial	18 924 Patients who had a prior ACS event and were taking high-intensity statin	Alirocumab reduced Lp(a) by a median percentage of 23% from baseline at 4 mo; a higher baseline Lp(a) was correlated with a higher magnitude of Lp(a) reduction, which was associated with more significant reductions in the risk of MACE, independent of LDL-C levels
Nucleic acid–based therapies			
siRNA			
Olpasiran (AMG 890)[58]	1	64 Healthy adults with Lp(a) ≥70 nmol/L	Olpasiran resulted in dose-dependent mean percentage reductions of 71% to 97% from baseline in patients with Lp(a) ≥70 to ≤199 nmol/L and of 76% to 91% in those with Lp(a) ≥200 nmol/L
ASO			
$APO(a)_{Rx}$[59]	2	64 Healthy individuals with baseline Lp(a) ≥125 nmol/L	$APO(a)_{Rx}$ significantly reduced Lp(a) concentration by a mean percentage of 70% from baseline at day 85
Pelacarsen (TQJ230)[59]	1/2a	58 Healthy participants with Lp(a) ≥75 nmol/L	Significant dose-dependent mean percentage reductions in Lp(a) levels from baseline, up to 92% with the highest dose, were noted in all single and multiple dose groups at day 30 and 36, respectively
Pelacarsen (TQJ230)[60]	2	286 Patients with established cardiovascular disease and baseline Lp(a) ≥150 nmol/L	Pelacarsen administration resulted in significant dose-dependent mean percentage reductions from baseline in Lp(a) levels of up to 80% at 6 mo

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; ASO, antisense oligonucleotide; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; siRNA, small interfering RNA.

Both studies suggested that Lp(a) lowering is an independent contributor to MACE reduction and that the main benefits are in patients who have higher baseline levels and/or large reductions in Lp(a). While PCSK9i reduce Lp(a) by approximately 15% to 25% from baseline (eFigure 2 in the Supplement), it is difficult to quantify the reduction in cardiovascular events attributed to Lp(a) lowering, since these drugs also reduce LDL-C by 50% to 60%.[62,63] A post hoc analysis of the ODYSSEY OUTCOMES trial revealed a 30% reduction in the risk for MACE associated with alirocumab in patients with an LDL-C less than 70 mg/dL only when Lp(a) levels were greater than the median (13.7 mg/dL).[64] These results suggest that Lp(a) reduction may contribute to added cardiovascular benefit or that high Lp(a) identifies patients that are more susceptible to the plaque-stabilizing properties of PCSK9i. Overall, these drugs are well tolerated and may cause mild local injection site reactions infrequently without promoting an excess in drug discontinuation.[62,63]

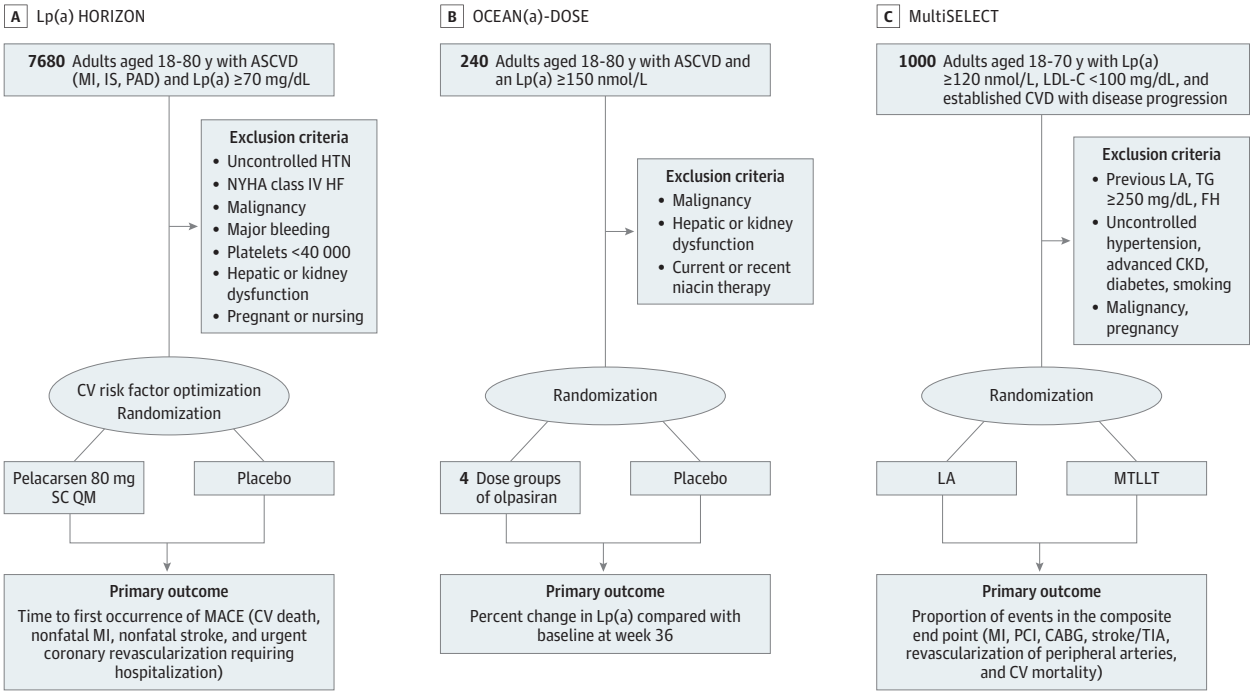
Of note, observational and trial data have revealed a potential association between low Lp(a) levels and type 2 diabetes (T2D) prevalence and incidence.[65] In the ODYSSEY OUTCOMES trial, each 10-mg/dL reduction in Lp(a) with alirocumab was associated with a higher incidence of T2D compared with placebo (HR 1.07; 95% CI 1.03-1.12).[66] Mendelian randomization studies, however, do not support causality, and a clear increased cardiovascular risk with high Lp(a) in patients with T2D persists.[67]

Lipoprotein Apheresis

Lipoprotein apheresis (LA) is highly effective in transiently reducing Lp(a) but impractical (weekly to biweekly sessions of 2 to 3 hours each for life), limiting its broad-scale application. LA lowers Lp(a) levels by 53% to 73% from baseline and is associated with a 53% to 90% reduction in MACE.[68] LA is approved in Germany and Turkey (not in the US) for patients with Lp(a) levels higher than 60 mg/dL who have CVD progression despite maximally tolerated lipid-lowering therapy. Expert panels including the European Atherosclerosis Society,[9] HEART UK,[22] National Lipid Association,[20] and American Society for Apheresis[69] have provided recommendations for LA.

The Effect of Lipoprotein(a) Elimination by Lipoprotein Apheresis on Cardiovascular Outcomes (MultiSELECT) trial is an ongoing prospective 2-arm matched-pair observational study comparing weekly LA with maximally tolerated lipid-lowering therapy in ap-

Figure 2. Designs of Ongoing Lipoprotein(a) (Lp[a]) Clinical Studies



Three ongoing clinical studies of lipoprotein(a)–lowering therapies include (1) the Assessing the Impact of Lipoprotein(a) Lowering With TQJ230 on Major Cardiovascular Events in Patients With CVD (Lp[a]HORIZON) trial (pelacarsen, phase 3); (2) Olpasiran Trials of Cardiovascular Events And LipoproteiN(a) Reduction (OCEAN[a]-DOSE) trial (olpasiran, phase 2); and (3) the Effect of Lipoprotein(a) Elimination by Lipoprotein Apheresis on Cardiovascular Outcomes (MultiSELECT) trial (prospective study of lipoprotein apheresis on the risk of major adverse cardiovascular events [MACE]). ASCVD indicates atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; FH, familial hypercholesterolemia; HF, heart failure; IS, ischemic stroke; LA, lipoprotein apheresis; MI, myocardial infarction; MTLLT, maximally tolerated lipid-lowering therapy; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SC QM, subcutaneous every month; TG, triglyceride; TIA, transient ischemic attack.

proximately 1000 patients aged 18 to 70 years with Lp(a) levels of 120 nmol/L or greater, corrected LDL-C levels less than 100 mg/dL, and ASCVD progression (**Figure 2**).[70] The primary objective of this trial is to determine the clinical benefit of LA on the occurrence of MACE (MI, percutaneous coronary intervention, coronary artery bypass graft surgery, ischemic stroke, transient ischemic attack, peripheral arterial revascularization, or cardiovascular death).

Novel Treatments

Nucleic acid–based therapies target the messenger RNA (mRNA) product of the *LPA* gene and include the antisense oligonucleotide (ASO) and small-interfering RNA (siRNA) drugs (eFigure 3 in the Supplement). ASOs are single-stranded nucleic acid sequences that promote RNase H-mediated mRNA destruction. siRNA are double-stranded molecules that lead to target mRNA destruction via the RNA-induced silencing complex (eFigure 3 in the Supplement).[71]

ASOs

The first study using ASO for Lp(a) reduction in humans included 47 healthy adults who had an Lp(a) concentration of 25 nmol/L or higher. Serial doses of increasing concentrations of IONIS-APO $(a)_{Rx}$ (Ionis Pharmaceuticals) resulted in significant Lp(a) reductions, up to 78% from baseline, and no severe adverse events.[72] Pelacarsen (TQJ230 or IONIS-APO(a)-L_{Rx}) is a variant of IONIS-APO$(a)_{Rx}$ that has a triantennary *N*-acetyl-galactosamine (GalNAc) complex attached, allowing specific uptake via the asialoglycoprotein receptor in hepatocytes yielding a 30-fold higher potency.[59]

Results of 2 trials, one comparing IONIS-APO$(a)_{Rx}$ with placebo (phase 2) and another comparing pelacarsen with placebo (phase 1/2a), were published simultaneously.[59] In the IONIS-APO $(a)_{Rx}$ vs placebo trial, mean Lp(a) reductions of 67% in cohort A (n = 51; Lp[a] of 125 to 437 nmol/L) and 72% in cohort B (n = 13; Lp[a] of 438 nmol/L or greater) at day 85 ($P < .001$) were observed.

The pelacarsen trial enrolled 58 healthy participants with Lp(a) levels of 75 nmol/L (30 mg/dL) or greater into single ascending dose, multiple ascending dose, and placebo cohorts. Significant dose-dependent reductions in Lp(a) levels, up to 92% with the highest doses, were noted in all single dose and multiple dose groups compared with the placebo group at day 30 and 36, respectively. A phase 2 multicenter trial in 286 patients with established CVD and baseline Lp(a) levels of 150 nmol/L (60 mg/dL) or greater compared pelacarsen with placebo.[60] Pelacarsen significantly reduced Lp(a), in a dose-dependent fashion, by up to 80% compared with placebo at 6 months (eFigure 2

in the Supplement). Adverse effects included myalgias (12%), headaches (11%), and influenzalike symptoms (7%). Similarly, significant reductions in oxidized phospholipids, LDL-C, and apoB have been reported with Lp(a)-specific ASOs.[27,60]

The Assessing the Impact of Lipoprotein(a) Lowering With TQJ230 on Major Cardiovascular Events in Patients With CVD (Lp[a]HORIZON) trial, an ongoing phase 3, randomized, placebo-controlled trial, is assessing the clinical efficacy and safety of monthly subcutaneous pelacarsen (80 mg) in approximately 7680 patients with established ASCVD (prior MI, ischemic stroke, and/or symptomatic peripheral arterial disease) who are taking optimized LDL-C–lowering therapy with an Lp(a) level of 70 mg/dL (175 nmol/L) or greater observed for 2.5 or more years (Figure 2).[73] The primary end point is a composite of cardiovascular death, nonfatal MI, nonfatal ischemic stroke, and urgent coronary revascularization requiring hospitalization. Two coprimary outcome measures will be assessed depending on the baseline Lp(a) levels (70 mg/dL or greater or 90 mg/dL or greater), each with a 1-sided α level of 2.45%. The study is projected to accrue the targeted 993 primary cardiovascular events in June 2024.

siRNAs

Olpasiran (AMG 890; Amgen) is an siRNA that has been designed specifically to target *LPA* mRNA. Single-dose administration in 48 adults with Lp(a) levels of 70 nmol/L or greater effectively reduced mean Lp(a) levels in a dose-dependent manner compared with placebo. Maximal reductions greater than 90% from baseline were attained between days 43 and 71, and no serious adverse events were reported.[58] An ongoing phase 2 trial of olpasiran (Olpasiran Trials of Cardiovascular Events And LipoproteiN[a] Reduction [OCEAN(a)-DOSE]; TIMI 67) in 240 patients with ASCVD and Lp(a) levels greater than 150 nmol/L began in July 2020 (Figure 2).[74] The study has 4 arms of escalating doses of the drug and 1 placebo arm. Its primary outcome is the percent change in Lp(a) from baseline at week 36 and has an estimated completion of April 2023.

The phase 1 APOLLO trial of SLN360, a GalNAc-conjugated siRNA that targets *LPA* mRNA, included 32 participants with no known CVD and a plasma Lp(a) level of 150 nmol/L (60 mg/dL) or greater who were randomized to single doses of the SLN360 vs placebo.[75] Increasing doses of SLN360 resulted in significant dose-dependent reductions in Lp(a) levels and nadir concentration lasting 150 days or more after administration. Maximal median percentage reductions in Lp(a) greater than 95% were achieved with the highest doses (eFigure 2 in the Supplement), and the drug was well tolerated.

Future Directions

A more complete understanding of Lp(a) physiology, metabolism, and pathogenicity is desirable as Lp(a)-lowering therapies are being developed and may be available for clinical use in the near future. Widespread standardization of commercial Lp(a) immunoassays would help interpret the results of future studies and establish treatment thresholds. Additional data assessing the role of Lp(a) in secondary prevention populations could help clarify the prognostic value of Lp(a). Clinical trials assessing the clinical benefits of Lp(a) reduction on ASCVD and AS are underway, with siRNA and ASO therapies leading the way.

Conclusions

The epidemiologic burden of Lp(a) is substantial, with approximately 20% to 25% estimated to have elevated concentrations (although the definition of elevated is somewhat arbitrary). Epidemiologic and genetic studies strongly support a potentially causal association between elevated Lp(a) concentrations and an increased risk of ASCVD and, to a lesser degree, AS. The residual cardiovascular risk of elevated Lp(a) levels, independent of LDL-C optimization and statin use, has intensified interest in lowering Lp(a). Emerging gene-silencing approaches have demonstrated substantial Lp(a)-reducing properties and safety.

The Family Heart Foundation is an organization created in 2011 that has expanded to promote scientific awareness of the consequences of elevated Lp(a). It is a valuable resource that provides useful information and support to those with high Lp(a), their relatives, and clinicians.

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Correction: This article was corrected on July 13, 2022, to fix the SI conversion factor for lipoprotein (a), 2 typographical errors in the population column of Table 1 and 2 typographical errors in the main text, and the key findings cell in the CCHS row in Table 1.

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