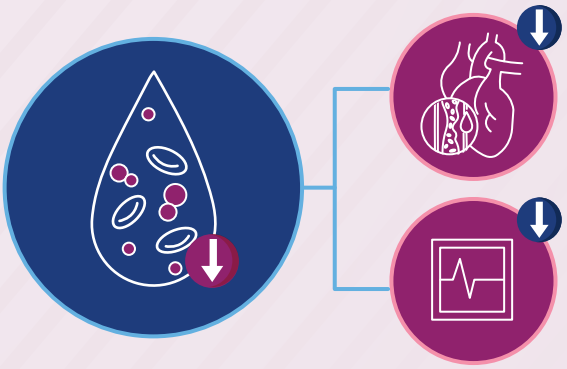
WILEY

Lipoprotein(a) in Atherosclerotic Cardiovascular Disease: Current Perspectives on Prevalence, Risk Assessment, and Management

Insights into screening and therapeutic management of elevated lipoprotein(a)

Lipid-lowering therapies (LLTs) significantly reduce the levels of low-density lipoprotein-cholesterol (LDL-C) and apolipoprotein B—the key drivers of atherosclerotic cardiovascular disease (ASCVD)[1,2]



However, the residual risk of ASCVD remains high despite the use of intensive LLTs[2]

Targeting alternative lipid factors holds promise in addressing the residual risk of ASCVD[2]

- Lipoprotein(a) (Lp(a)) is an LDL-like particle formed by the covalent binding of apolipoprotein(a) and apolipoprotein B-100[2]
- Elevated Lp(a) is a risk factor associated with ASCVD, stroke, peripheral artery disease, calcific aortic stenosis, and heart failure[3,4]
- Lp(a) plays a role in atherosclerosis progression and plaque vulnerability[5]

Mechanisms by which elevated Lp(a) leads to ASCVD[6]

- Proatherogenic
- Calcification
- Prothrombotic
- Lipid deposition
- Proinflammatory
- Endothelial dysfunction

One in five individuals has an Lp(a) concentration ≥50 mg/dL, associated with an increased risk of ASCVD[3,6]

Lp(a) level nmol/L	Lp(a) level approximately in mg/dL	Impact on CV risk
32–90	18–40	Minor
90–200	40–90	Moderate
200–400	90–180	High
>400	>180	Very high

Recommendation from the European Society of Cardiology 2025[7]
Lp(a) levels >50 mg/dL (105 nmol/L) should be considered in all adults as a CV risk-enhancing factor, with higher Lp(a) levels associated with a greater increase in risk

Majority of individuals with elevated Lp(a) remain unaware of their increased risk for ASCVD[6]

About one fourth of the global population with ASCVD has elevated Lp(a) levels[8]

Most patients with ASCVD continue to be managed without Lp(a) assessment[8]

Despite its profound impact on ASCVD, Lp(a) testing remains as low as 1–2%[3]

Specific guidelines regarding the management of elevated Lp(a) and targeted therapies are lacking[3]

Visit https://ascvd-lipidology.knowledgehub.wiley.com/ for additional resources

Global variations in Lp(a) levels

>80% of elevated Lp(a) is determined by genetic variants[3]

Prevalence of elevated Lp(a) varies substantially[6]

Factors affecting Lp(a) levels[3,6,8,9]

Geographic, ethnic, and racial

Europeans | South East Asians (lowest) | Hispanics and Whites | Middle Eastern | South Asians | Blacks (highest)

Genetic

- Number of kringle IV repeats
- Splice site variants
- Single nucleotide polymorphisms

Clinical

↑ Lp(a) ∞ ↑ LDL-C → higher risk of ASCVD

Intraindividual variations

Median Lp(a) levels[10]

- **Highest in Africa: 62 nmol/L**
- **Lowest in Western Pacific: 22 nmol/L**

Europe
- Portugal: 59 nmol/L
- Poland: 19.5 nmol/L

South America
- Colombia: 46 nmol/L
- Argentina: 32 nmol/L

Western Pacific
- Malaysia: 39.5 nmol/L
- Philippines: 14 nmol/L

Global clinical guidelines for Lp(a) measurement[3,11]

Indications for Lp(a) testing

When to be tested?

- Once in a lifetime testing

Who should be tested?

- Personal history of premature ASCVD
- Family history of premature ASCVD
- Family history of elevated Lp(a)
- Familial hypercholesterolemia

Why get tested?

- Identification of high-risk individuals
- Reclassification of risk level
- Treatment optimization and intensification
- Risk mitigation
- Prevention and lifestyle modifications
- Hereditary risk assessment

Clinicians should check for specific Lp(a) levels instead of standard lipid panels for thorough CVD risk evaluation[11]

Visit https://ascvd-lipidology.knowledgehub.wiley.com/ for additional resources

Management of elevated Lp(a)[2,11]

Measurement and risk assessment | Imaging interpretations – coronary artery calcium | Assessment of inflammatory markers | Lifestyle modifications | Cardiovascular risk-lowering therapies or procedures | Management of comorbidities

Approved LLTs that affect Lp(a) levels[2,11,12]

Therapeutic strategy	Apheresis	Statins	Ezetimibe	Niacin	Proprotein convertase subtilisin/kexin type 9 inhibitors (inclisiran)
Effect on Lp(a)	↓ 30–35%	↑ 9–20%	↓ 0–7%	↓ 21%	↓ 19–27%

Emerging Lp(a)-lowering therapies[2,11,12]

Therapeutic	Mean/median Lp(a) reduction	Current clinical trial stage
Antisense oligonucleotides • Pelacarsen • Mipomersen	 35–80% Up to 25%	**Phase 3** [Lp(a) HORIZON]/ NCT04023552 RADICHOL I and II
RNA interference – small interfering RNAs • Olpasiran • Zerlasiran • Lepodisiran	 70–97% 46–98% 41–97% Reduced mean serum concentrations from 60 to 180 days[13]	**Phase 3** (OCEAN(a) – Outcomes) NCT05581303 **Phase 2** NCT05537571 **Phase 2** NCT05565742
Small molecule inhibitor • Muvalaplin	 Up to 65%	**Phase 2** (KRAKEN) NCT05563246
CRISPR/Cas9 gene editing (CTX320)	Up to 90% in non-human primates	Preclinical

Aspirin and Lp(a)

Population	Total participants	Lp(a) measurement	Outcomes with aspirin use
MESA[14]	2,183	Lp(a) >50 mg/dL vs. ≤50 mg/dL	HR: 0.54 (95% CI: 0.32–0.94) for CHD in Lp(a) >50 mg/dL
NHANES III[14]	2,990	Lp(a) ≥50 mg/dL vs. <50 mg/dL	HR: 0.48 (95% CI: 0.28–0.83) for ASCVD mortality in Lp(a) ≥50 mg/dL
ARIC[15]	13,085	Lp(a) ≥50 mg/dL vs. <50 mg/dL	HR: 1.12 (95% CI: 0.96–1.31) for CVD in Lp(a) ≥50 mg/dL
CHS[15]	3,956		HR: 1.04 (95% CI: 0.96–1.13) for CVD in Lp(a) <50 mg/dL
MESA[15]	6,621		No evidence to suggest that the association between aspirin and the incidence of CVD may differ by Lp(a) levels

MESA: Multi-Ethnic Study of Atherosclerosis; CHD: coronary heart disease; NHANES III: third National Health and Nutrition Examination Survey; ARIC: Atherosclerosis Risk in Communities; CHS: Cardiovascular Health Study

Lp(a) is not associated with all-cause or cardiovascular death in patients with acute coronary syndrome on optimized statin treatment[16]

Visit https://ascvd-lipidology.knowledgehub.wiley.com/ for additional resources

Integrating Lp(a) measurement in clinical practice[3,11,12]


Screening of elevated Lp(a)


Use of digital health technologies


Direct-to-consumer Lp(a) assays


Insurance coverage of the tests


Assay standardization – Lp(a) size, isoform, and measurement unit


Use of diagnostic codes


Polygenic risk scores


Personalized medicine

Challenges and barriers[3,11]


Lack of a universal Lp(a) threshold


Perceived lack of Lp(a) targeted therapies


Selection bias and diverse patient cohorts


Limited actionable recommendations


Lack of awareness


Inconsistent Lp(a) measurements


Small sample size


Variable outcome measures

Key message

- **Screening and management of elevated Lp(a) can help address the residual cardiovascular risk in patients with ASCVD receiving intensive LLTs**
- **Clinical guidelines should be considered to screen individuals patients for high Lp(a) levels**
- **Integrating Lp(a) assessment in routine clinical practice can improve screening and enable targeted treatment**

Await results of ongoing and planned cardiovascular outcome trials

References:

1. Xie, S., Galimberti, F., Olmastroni, E., Carugo, S., Catapano, A. L., & Casula, M. (2025). Effect of lipid-lowering therapies on lipoprotein(a) levels: a comprehensive meta-analysis of randomized controlled trials. *Atherosclerosis, 408*, 120420.
2. Nicholls, S. J. (2024). Therapeutic potential of lipoprotein(a) inhibitors. *Drugs, 84*(6), 637–643.
3. Kronenberg, F., Bedlington, N., Ademi, Z., Geantă, M., Silberzahn, T., Rijken, M., ... and Daccord, M. (2025). The Brussels international declaration on lipoprotein(a) testing and management. *Atherosclerosis*,119218.
4. Markus, M. R. P., Ittermann, T., Mariño Coronado, J., Schipf, S., Bahls, M., Könemann, S., ... & Dörr, M. (2025). Low-density lipoprotein cholesterol, lipoprotein (a) and high-sensitivity C-reactive protein are independent predictors of cardiovascular events. *European Heart Journal*, ehaf281.
5. Erlinge, D., Tsimikas, S., Maeng, M., Maehara, A., Larsen, A. I., Engstrøm, T., ... & Stone, G. W. (2025). Lipoprotein (a), cholesterol, triglyceride levels, and vulnerable coronary plaques: a PROSPECT II substudy. *Journal of the American College of Cardiology, 85*(21), 2011–2024.
6. Kamstrup, P. R., Neely, R. D. G., Nissen, S., Landmesser, U., Haghikia, A., Costa-Scharplatz, M., Abbas, C., & Nordestgaard, B. G. (2024). Lipoprotein(a) and cardiovascular disease: sifting the evidence to guide future research. *European Journal of Preventive Cardiology, 31*(7), 903–914.
7. Mach, F., Koskinas, K. C., Roeters van Lennep, J. E., Tokgözoğlu, L., Badimon, L., Baigent, C., ... & Sabatine, M. S. (2025). 2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias: developed by the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *European Heart Journal*, ehaf190.
8. Nissen, S. E., Wolski, K., Cho, L., Nicholls, S. J., Kastelein, J., Leitersdorf, E., ... & Nordestgaard, B. G. (2022). Lipoprotein(a) levels in a global population with established atherosclerotic cardiovascular disease. *Open Heart, 9*(2), e002060.
9. Harb, T., Ziogos, E., Blumenthal, R. S., Gerstenblith, G., & Leucker, T. M. (2024). Intra-individual variability in lipoprotein (a): the value of a repeat measure for reclassifying individuals at intermediate risk. *European Heart Journal Open, 4*(5), oeae064.
10. Barkas, F., Brandts, J., De Bacquer, D., Jennings, C., De Backer, G. G., Kotseva, K., ... & Ray, K. K. (2025). Global variation in lipoprotein (a) levels among patients with coronary heart disease: insights from the INTERASPIRE study and implications for emerging Lp (a)-lowering therapies. *Journal of the American College of Cardiology, 85*(21), 2028–2042.
11. Reyes-Soffer, G., Yeang, C., Michos, E. D., Boatwright, W., & Ballantyne, C. M. (2024). High lipoprotein(a): actionable strategies for risk assessment and mitigation. *American Journal of Preventive Cardiology, 18*, 100651.
12. Fujino, M., Di Giovanni, G., & Nicholls, S. J. (2025). New approaches to lipoproteins for the prevention of cardiovascular events. *Journal of Atherosclerosis and Thrombosis, 32*(3), 265–280.
13. Nissen, S. E., Ni, W., Shen, X., Wang, Q., Navar, A. M., Nicholls, S. J., ... & Krege, J. H. (2025). Lepodisiran—a long-duration small interfering RNA targeting lipoprotein (a). *New England Journal of Medicine, 392*(17), 1673–1683.
14. Rikhi, R.R. and Bhatia H. (2024). An update on Lp(a) and aspirin in primary prevention. Expert analysis. https://www.acc.org/Latest-in-Cardiology/Articles/2024/07/17/14/02/An-Update-on-Lpa-and-Aspirin-in-Primary-Prevention
15. Colantonio, L. D., Wang, Z., Ghazi, L., Alanaeme, C. J., Christenson, A., Dubal, M., ... & Bittner, V. (2025). Aspirin use and the risk for cardiovascular disease by lipoprotein(a) levels: a multi-cohort study. *European Journal of Preventive Cardiology*, zwaf547.
16. Steg, P. G., Szarek, M., Jukema, J. W., Bhatt, D. L., Bittner, V. A., Diaz, R., ... & Schwartz, G. G. (2025). Relation of low-density lipoprotein cholesterol, high-sensitivity C-reactive protein, and lipoprotein (a) each to future cardiovascular events and death after acute coronary syndrome on high-intensity statin therapy: an analysis of the placebo arm of ODYSSEY OUTCOMES. *Circulation, 151*(14), 1047–1050.

Published by WILEY

Visit https://ascvd-lipidology.knowledgehub.wiley.com/ for additional resources