Lipoprotein (a): epidemiology, pathophysiology, measurement issues and clinical management

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ABSTRACT

Lipoprotein (a) [Lp(a)], a circulating low-density lipoprotein particle, was discovered in 1963. Since then, knowledge about the Lp(a) pathophysiology and its role on atherosclerotic cardiovascular disease and aortic valve stenosis have progressively expanded. Lp(a) measurement is recommended once in a patient's lifetime, particularly in Familial Hypercholesterolemia subjects, but also as part of the initial lipid screening to assess cardiovascular risk. The apo(a) size polymorphism represents a challenge for Lp(a) measurement in plasma, but advancements in diagnostic testing are overcoming these difficulties. In clinical practice, high Lp(a) concentration should be interpreted as an independent cardiovascular risk factor, also useful for absolute global cardiovascular risk assessment. Until now, no pharmacological treatments were available to selectively lower Lp(a), only LDL plasma apheresis moderately reduce Lp(a) levels in conjunction with PCSK9 inhibitor treatment. The antisense oligonucleotide directed to apo(a) configures as a new therapeutic promise.

Key words: *Apo(a) polymorphism, Lp(a) testing, risk factor management*

INTRODUCTION

Lipoprotein (a) [Lp(a)], a circulating low-density lipoprotein particle, was discovered in 1963 (1). In recent years, Lp(a), the most complex and polymorphic of the lipoprotein particles, became an attractive target for intervention in cardiovascular disease (ASCVD) and aortic valve stenosis (AVS) (2). According to the latest consensus statement (2), Lp(a) should be considered an independent cardiovascular risk factor and its measurement is particularly recommended in subjects with familial hypercholesterolemia (FH), but also, once in the patient's lifetime, as part of initial lipid screening to evaluate cardiovascular risk.

However, a couple of issues made difficult and slowed down the use of Lp(a) in clinical practice: their structural heterogeneity (observed between different individuals and within the same subject) and the lack of pharmacological treatments to selectively lower Lp(a). Nowadays, the Lp(a) structural polymorphism still represents a challenge for Lp(a) measurement in plasma, but the latest advancements in diagnostic testing are almost overcoming these difficulties (3). New drug treatments may become available in the next years, adjusting the therapeutic gap currently filled only by LDL plasma apheresis in conjunction with PCSK9 inhibitor tretment.

The aim of this review is to point out the Lp(a) epidemiology, pathophysiology, measurement issues and clinical management.

LIPOPROTEIN (a): EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Lp(a) consists by one apolipoprotein(a) [apo(a)] molecule, a glycoprotein characterized by loop-like repeated structures named kringles, and a lipoprotein closely resembling to a low-density lipoprotein (LDL). These two components are joined together by non-covalent bindings and by a disulfide bridge between the apoB100 of the LDL-like particle and the apo(a) molecule (Figure 1).

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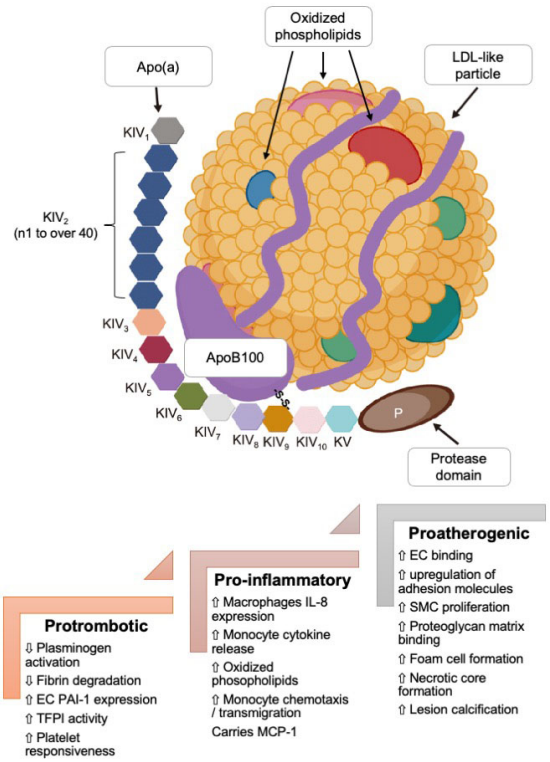

Figure 1

Structure of Lp(a) molecule and atherogenicity categories of Lp(a).

apoB-100, apolipoprotein B-100; apo(a), apolipoprotein (a); EC, endothelial cell; IL, interleukin; KIV, kringle IV; KV, kringle V; MCP, monocyte chemoattractant protein; P, protease domain; PAI, plasminogen activator inhibitor; SMC,smooth muscle cell; TFPI, tissue factorpathway inhibitor.

Adapted from Tsimikas et al. J Am Coll Cardiol 2017;69:692-711..

The human gene encoding for apo(a) is located in chromosome 6 and possibly evolved from the plasminogen gene (4). Kringle IV, present in plasminogen in a single copy, expanded and differentiated in the apo(a) gene in ten subtypes. Of those, subtype 2 further expanded in a variable number of copies, from 1 to over 40, explaining the wide size polymorphism of the encoded apo(a) in humans, which spans from 300 to 800 kDa (5).

The similarity with LDL, together with its ability to carry oxidized phospholipids, are considered the main features making Lp(a) harmful for cardiovascular health (6).

Plasma Lp(a) concentrations vary over 1000-folds in humans, about 90% of plasma Lp(a) levels are genetically determined, hereditary and are quite stable throughout life.

Caucasian population ancestry shows a skewed frequency distribution of Lp(a) plasma concentrations, with most of the subjects presenting very low levels, a similar distribution is observed in Arabian and Asian populations, while Blacks present a more homogeneous distribution with higher number of subjects exhibiting elevated Lp(a) levels (7).

The main genetic determinant is a copy number variation, based on the number of kringle-IV (K-IV) encoding repeats in the *LPA* gene. This results in a remarkable size polymorphism of the encoded apo(a), with an inverse correlation between the apo(a) isoform size and Lp(a) plasma concentration. Individuals carrying a low number of K-IV repeats (≤22 K-IV repeats) have 4-5 times higher median Lp(a) concentrations than those with a large number of K-IV repeats (>22 repeats) (8), probably due to the higher synthesis rate of molecules with low number of repeats.

Non-genetic factors may weakly modulate Lp(a) concentration. Dietary habits that increase LDL cholesterol, such as high saturated/polyunsaturated fatty acid ratio, minimally affect Lp(a) level (9), and no significant difference was found between fed/fasting conditions (10). Other conditions can alter Lp(a) concentrations:

- hormones levels, particularly those affecting lipoprotein metabolism (11-13);
- impaired kidney function may increase Lp(a) levels (14);
- liver dysfunction may decrease Lp(a) levels (15);
- Lp(a) was lower in severe life-threatening acute-phase conditions, but higher in several acute and chronic inflammatory conditions (16,17).

There is probably more than one mechanism linking Lp(a) levels to increased cardiovascular risk. Like an LDL particle, Lp(a) molecules can enter in the vessel wall and become oxidized, stimulating inflammatory cell recruitment and uptake by monocyte/macrophages (18). Moreover, Lp(a) had a high content of oxidized phospholipids, proinflammatory molecules that can enhance the inflammatory cascade by cytokines and adhesion molecules secretion in endothelial cells, promoting smooth muscle cell proliferation and monocyte/macrophage activation, inducing valve cell calcification (19,20) (Figure 1). Furthermore, the prothrombotic and antifibrinolytic properties of apo(a) could contribute to the vulnerability of atherosclerotic plaques (21).

LIPOPROTEIN (a): MEASUREMENT ISSUES

For many years, the need to standardize Lp(a) measurement has been recognized and many efforts have been made, leading to the preparation of primary reference standard (IFCCPRM1), followed by secondary reference standard (WHO/IFCC SRM-2B), used by different companies to assign value to the calibrators of their Lp(a) assays. A couple of years ago, the development of a liquid chromatography-mass spectrometry methodology has been proposed as candidate reference method for the standardization of Lp(a) measurement (22). Nevertheless, the structural heterogeneity of the apo(a) still represent a major problem to manage, as does the transition to the new measurement units, but this is a necessary step that cannot be longer delayed.

Unfortunately, traditional Lp(a) methods of measurement are conditioned by apo(a) isoform sizes, due to the variability of the number of K-IV (23). The apo(a) size can determine a significant reduction in the accuracy of immunoassays using polyclonal antibodies (24) that bind with high affinity to the repetitive K-IV (Figure 2).

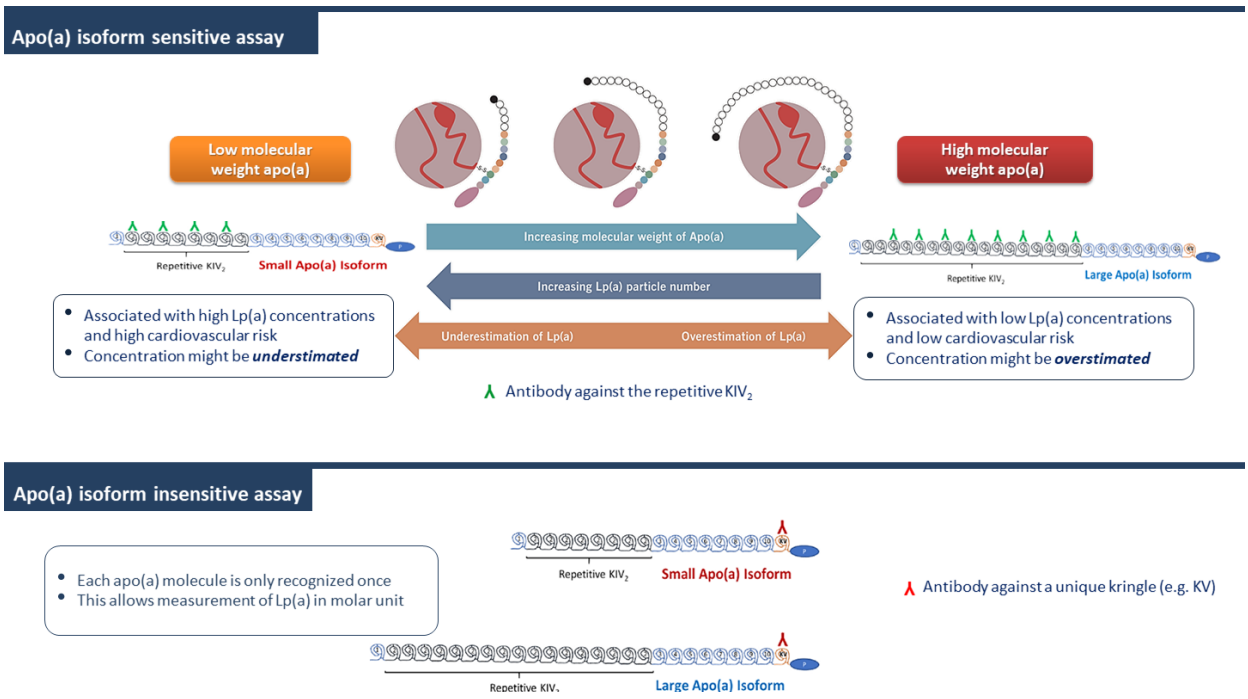

Figure 2
Apo(a) sensitive or insensitive assay and possible measurements errors related to Apo(a) molecular weight. Adapted from Kronenberg et al. Atheroscelrosis 2022;349:123-35 and Cegla et al. Ann Clin Biochem 2021;58:16-21.

To date, two types of assays are available for measuring Lp(a), classified as sensitive and insensitive to the apo(a) isoform.

The apo (a) isoform-sensitive assays use polyclonal antibodies that, recognizing various apo(a) epitopes, bind to repeat motif of the apo(a) and can cause bias measurement (25):
- small isoforms with fewer K-IV repeats, usually associated with elevated Lp(a) levels, are underestimated;
- large isoforms with numerous K-IV repeats, usually associated with low Lp(a) levels, are overestimated.

Another crucial aspect that can made Lp(a) measurement inaccurate is the choice of calibrator, required in any assay. A single calibrator, used in different dilutions, is made with only one isoform of apo(a) and can therefore worsen the analytical performance of an isoform-sensitive assay. For this reason, the use of different calibrators, each with a different isoform composition directly correlated to the different concentrations of Lp(a), is recommended (25).

The apo(a) isoform-insensitive assays use antibodies that recognize "unique" parts (non-variable epitopes) of apo(a), therefore, each apo(a) molecule is recognized only once. This assay has better specificity as it detects Lp(a) molecules; for this reason the measurement is expressed in nmol/L (25). The calibrator isoforms are not that critical, as long as they meet the requirements for an appropriate calibrator widely discussed by the IFCC Working Group for Standardization of Apolipoproteins by Mass Spectrometry (22,26,27).

The most recent European Atherosclerosis Society (EAS) consensus statement underlines the use of a method insensitive to the apo(a) dimensional heterogeneity (2), that is, assays that measure Lp(a) molecules (the number of lipoproteins per volume - nmol/L) (3), rather than their mass (mg/dL). Unfortunately, the lack of an accurate conversion factor to easily switch between the two measurement units, makes the results understanding less immediate for clinicians who have been handling Lp(a) levels expressed in mg/dL for a long time, increasing resistance to adopting of the "new" assay. Anyway, to help clinicians compare the patient's historical Lp(a) values in the transition phase, an approximate conversion factor has been proposed: to convert Lp(a) nmol/L to mg/dL, multiply the nmol/L value by 0.4. (or divide by 2.5).

The introduction of the apo(a) isoforms non-sensitive test requires the adoption of new decisional levels for Lp(a) risk assessment (2,25) (Figure 3):
- low-risk <75 nmol/L (≲30 mg/dL);
- intermediate risk 75-125 nmol/L also called "gray-zone" (~30-50 mg/dL);
- high-risk >125 nmol/L (≳50 mg/dL).

Thanks to the lifetime stability of Lp(a) concentrations, it is recommended to measure Lp(a) in the all population at least once to evaluate the additive cardiovascular risk (28), avoiding non-necessary multiple measurements (2,29).

LIPOPROTEIN (a): CLINICAL MANAGEMENT

In the last decades, observational studies have indicated a linear direct correlation between cardiovascular disease and Lp(a) plasma levels (2) with a causal role of Lp(a) in ASCVD and AVS, as also suggested by mendelian randomization studies.

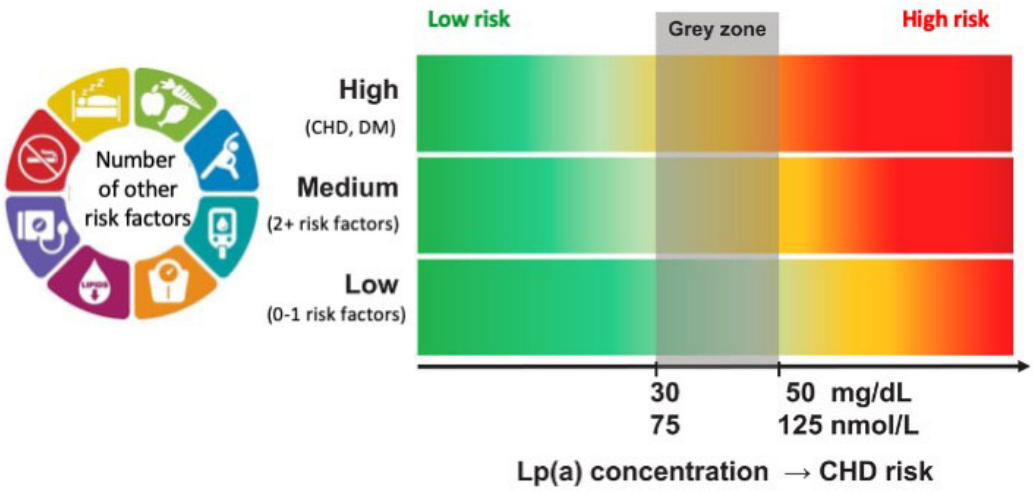

Figure 3
Relationship between Lp(a) concentrations and risk of coronary heart disease respect to concomitant cardiovascular risk factors. CHD, coronary heart disease; DM, diabetes.
Adapted from Kronenberg et al. Atherosclerosis 2023;374:107-20.

Based on this evidence, the 2010 EAS statement drafted the European and US guidelines recommended an Lp(a) threshold of 125 nmol/L (corresponding to the 80th percentile of the Lp(a) distribution in Caucasian population) as a 'risk enhancer' to improve the 10-year ASCVD risk estimation (30). When Lp(a) concentrations double (250 nmol/L; ~100 mg/dL), the ASCVD risk also approximately doubles, irrespective of baseline absolute risk (2).

Nowadays, in absence of specific Lp(a)-lowering therapies, early risk factor management is recommended for individuals with elevated Lp(a). The use of the new algorithm to estimate the risk of having a heart attack or stroke up to age of 80 evaluates the additive effect of Lp(a) levels respect to traditional cardiovascular risks factors (31).

Moreover, it is worth remembering that extremely high Lp(a) values are associated to premature coronary heart disease as shown in the pedigree of a family reported in Figure 4. For this reason, all cardiovascular risk factors should be comprehensively addressed according to guidelines. FH for example, has an important joint role with Lp(a) in accelerating ASCVD, but there is little awareness for this role. Cascade screening of close family members of an index case, is a cost-effective approach for identifying new cases of FH and elevated Lp(a), particularly when the proband has both FH and elevated Lp(a) (32).

In recent years, recommendations for Lp(a) measurement have changed based on new information regarding the role of Lp(a) in estimating and stratifying for ASCVD's risk. The 2020 EAS/EFLM recommendations proposed the evaluation of Lp(a) only in selected cases such as: early ASCVD, FH, family history of early ASCVD and/or elevated Lp(a), recurrent ASCVD despite statin treatment, patients with aortic valve stenosis (29). Instead, the 2022 EAS consensus recommends measuring Lp(a), as a clinical practice, in all adults at least once with the goal of interpreting the result in the context of the patient's absolute global CV risk.

Early screening is mostly recommended recommended in young people with a history of ischemic stroke or a family history of premature ASCVD or elevated Lp(a) levels and no other identifiable risk factors. The 2022 consensus also introduces the Lp(a) measurement test for cascade screening in the context of: FH, family history of (very) elevated Lp(a), and personal or family history of ASCVD (2).

Therapeutic strategy

The choice of a therapeutic strategy (Table 1) to reduce Lp(a) concentrations should take into account some important considerations:

Table 1
Effect on Lp(a) plasma levels by current available hypolipemic drugs (3,36).

Hypolipemic drug	Effect on Lp(a) levels
Lipoprotein apheresis	70% acute reduction 35% time-average reduction
Antisense Oligonucleotide*	70-99% reduction
Nicotinic acid	20-40% reduction
PCSK9 inibitors	15-30% reduction
Lomitapide**	17% reduction
Ezetimibe	7% reduction
Bempedoic acid	No variation
Statins	10-20% increase***

**Data from phase 2 and 3 randomized trial;*
***approved only for Homozygous Familial Hypercholesterolemia;*
****especially with simvastatin (38) but reports are heterogeneous.*

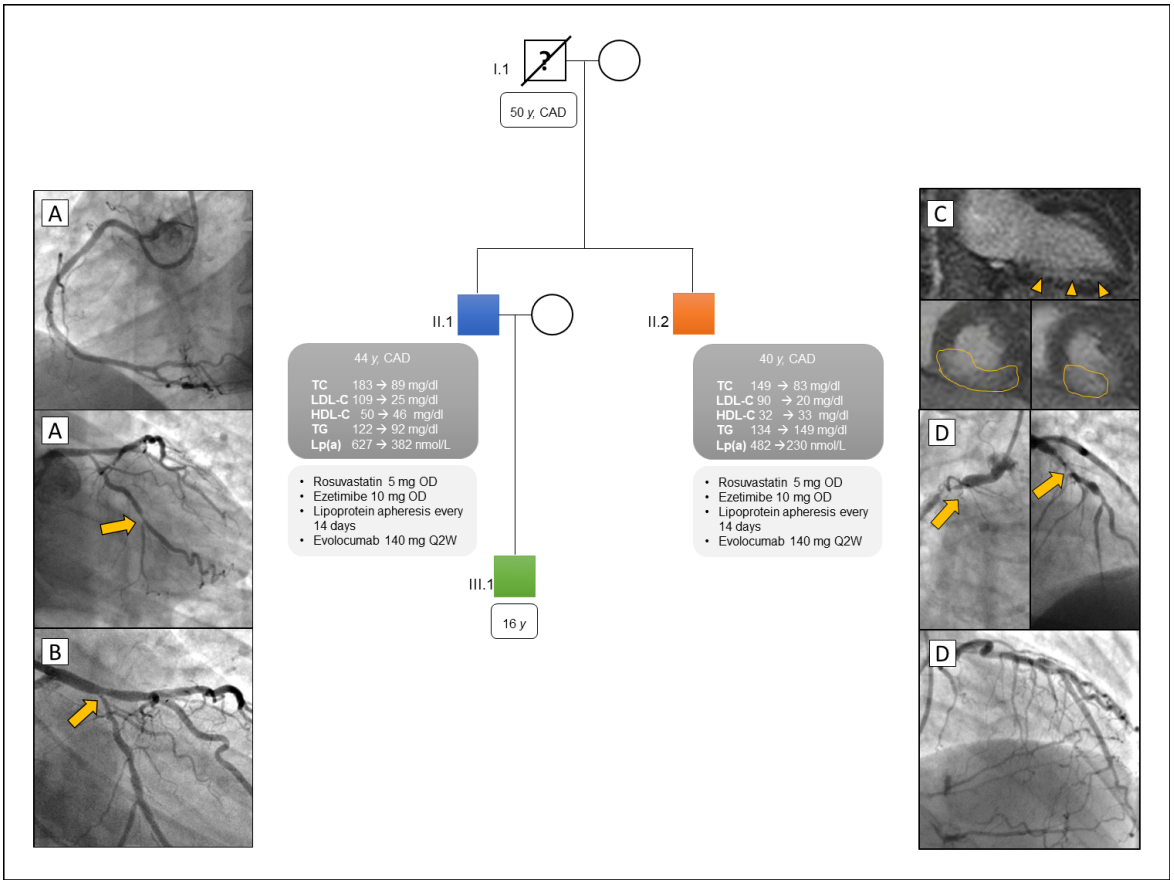

Figure 4

Pedigree of a family with high Lp(a) concentrations and premature CAD.
Subject II.1: (44 years-old) had a history of percutaneous coronary intervention on circumflex coronary (middle segment – arrow in Panel A). After 10 months he had risen of effort angina. Coronary angiography was repeated and reveal the atherosclerotic progression on circumflex coronary ostium (arrow in Panel B). He was referred to our Center showing a condition of hyper-Lp(a) (627 nmol/L). Lipid lowering therapy was maximized (statin plus PCSK9i and ezetimibe) and lipoprotein apheresis was started.
The cascade screening showed that his father died at 50 years-old for acute coronary syndrome and was identified his brother (subject II.2) who had, at 30 years-old, an inferior wall ST-Elevation myocardial infarction. The cardiac magnetic resonance reveals transmural fibrotic areas on the inferior wall of the left ventricle (yellow areas and arrowheads in delayed enhancement sequences Panel C). When subject II.2 came to our attention hyper-Lp(a) was identified (482 nmol/L) and he had effort angina. Coronary angiography reveals significant stenosis on anterior descending coronary and chronic occlusion of the right coronary artery with flow through collateral circulation (Panel D). Patient was scheduled for surgical bypass intervention and the same lipid lowering therapeutic strategy as his brother was undertaken.
CAD, coronary artery disease; HDL-C, high density lipoprotein cholesterol (mg/dL); LDL-C, low density lipoprotein cholesterol (mg/dL); Lp(a), lipoprotein(a) (mg/dL); OD, once a day; Q2W, every two weeks; TC, total cholesterol (mg/dL); TG, triglycerides (mg/dl); y, years.

Lipoprotein apheresis

It should be reserved for patients with very high Lp(a) concentrations (>250 nmol/L; ~100 mg/dL) and progressive cardiovascular disease, despite optimal management of risk factors.

PCSK9 inhibitors

These are an option to reach low density lipoprotein cholesterol goal with the additional cardiovascular risk reduction in patients with high Lp(a) concentrations, despite a modest Lp(a)-lowering, as revealed by FOURIER (33) and ODYSSEY trials (34).

Advanced options

Development of antisense oligonucleotides (ASOs) or small interfering RNA (siRNA) for a selective modulation of Lp(a) levels are ongoing and the results are expected in 2025 [HORIZON; gal-nac apo(a)-antisense pelacarsen] and 2026 [OCEAN(a); gal-nac silencing RNA olpasiran].

Statins treatment

Discontinuation of statins treatment in ASCVD patients is not justified by the potential risk of a small increase in Lp(a) levels, the events reduction achieved by statins is clinically essential (35).

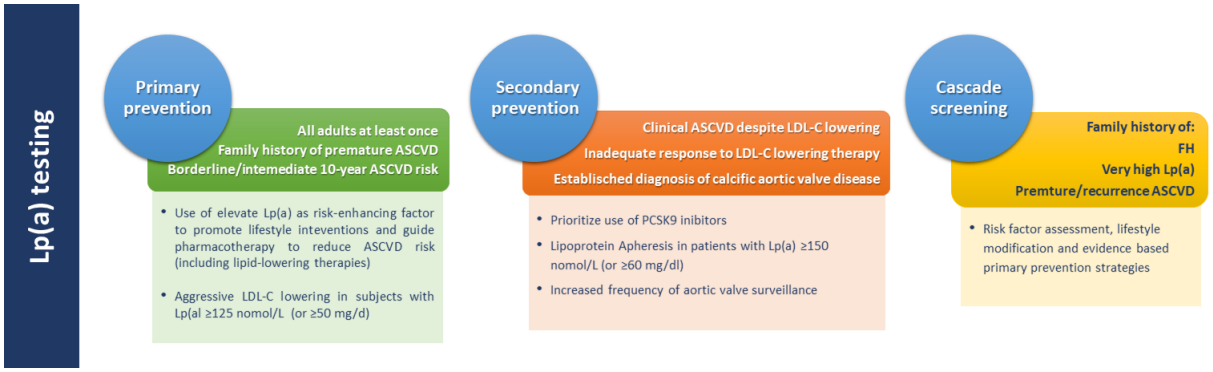

Figure 5
Recommendations of Lp(a) testing in primary prevention, secondary prevention and cascade screening. ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol;

CONCLUSION

Lp(a) causes atherosclerotic cardiovascular disease and aortic valve stenosis. Cardiovascular risk increases linearly with Lp(a) levels and the plasma values are generally stable during lifetime so Lp(a) measurement is strongly recommended once in a patient's lifetime.

Awaiting the approval of selective Lp(a)-lowering drugs, the current Lp(a)-lowering therapies are lipoprotein apheresis and PCSK9 inhibitors, in association with a strongly recommended intensive management of the other risk factors In light of these observations, the Lp(a) treatment as a risk factor in primary and secondary prevention should follow the proposed scheme, and cascade screening could be also considered (Figure 5).

CONFLICT OF INTEREST

None

REFERENCES

1. Berg K. A new serum type system in man--the LP system. Acta Pathol Microbiol Scand 1963;59:369-82.
2. Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J 2022;43:3925-46.
3. Chiesa G, Zenti MG, Baragetti A, Barbagallo CM, Borghi C, Colivicchi F, et al. Consensus on Lipoprotein(a) from the Italian Society for the Study of Atherosclerosis (SISA). Nutr Metab Cardiovasc Dis 2023;33:1866-77.
4. Frank SL, Klisak I, Sparkes RS, Mohandas T, Tomlinson JE, McLean JW, et al. The apolipoprotein(a) gene resides on human chromosome 6q26-27, in close proximity to the homologous gene for plasminogen. Hum Genet 1988;79:352-6.
5. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. J Clin Invest 1992;90:52-60.
6. Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, et al. Frequent questions and responses on the 2022 lipoprotein(a) consensus statement of the European Atherosclerosis Society. Atherosclerosis 2023;374:107-20.
7. Mehta A, Jain V, Saeed A, Saseen JJ, Gulati M, Ballantyne CM, et al. Lipoprotein(a) and ethnicities. Atherosclerosis 2022;349:42-52.
8. Utermann G, Menzel HJ, Kraft HG, Duba HC, Kemmler HG, Seitz C. Lp(a) glycoprotein phenotypes: inheritance and relation to Lp(a)-lipoprotein concentrations in plasma. J Clin Invest 1987;80:458-65.
9. Enkhmaa B, Petersen KS, Kris-Etherton PM, Berglund L. Diet and Lp(a): Does dietary change modify residual cardiovascular risk conferred by Lp(a)? Nutrients 2020;12:2024.
10. 10. Langsted A, Nordestgaard BG. Nonfasting versus fasting lipid profile for cardiovascular risk prediction. Patholog 2019;51:131-41.
11. Kotwal A, Cortes T, Genere N, Hamidi O, Jasim S, Newman CB, et al. Treatment of thyroid dysfunction and serum lipids: a systematic review and meta-analysis. J Clin Endocrinol Metab 2020;105:dgaa672.
12. Edén S, Wiklund O, Oscarsson J, Rosén T, Bengtsson B-Å. Growth hormone treatment of growth hormone-deficient adults results in a marked increase in Lp(a) and HDL cholesterol concentrations. Arterioscler Thromb 1993;13:296–301.
13. Zechner R, Desoye G, Schweditsch MO, Pfeiffer KP, Kostner GM. Fluctuations of plasma lipoprotein(a) concentrations during pregnancy and postpartum. Metabolism 1986;35:333-6.
14. Kronenberg F. Causes and consequences of lipoprotein(a) abnormalities in kidney disease. Clin Exp Nephrol 2014;18:234–7.
15. Feely J, Barry M, Keeling PW, Weir DG, Cooke T. Lipoprotein(a) in cirrhosis. BMJ 1992;304:545-6.
16. Missala I, Kassner U, Steinhagen-Thiessen E. A systematic literature review of the association of lipoprotein(a) and autoimmune diseases and atherosclerosis. Int J Rheumatol 2012;2012:480784.
17. Mooser V, Berger MM, Tappy L, Cayeux C, Marcovina SM, Darioli R, et al. Major reduction in plasma Lp(a) levels during sepsis and burns. Arterioscler Thromb Vasc Biol 2000;20:1137-42.
18. Boren J, Chapman MJ, Krauss RM, Packard CJ, Bentzon JF, Binder CJ, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2020;41:2313-30.

19. Koschinsky ML, Boffa MB. Oxidized phospholipid modification of lipoprotein(a): epidemiology, biochemistry and pathophysiology. Atherosclerosis 2022;349:92-100.
20. Di Fusco SA, Maggioni AP, Scicchitano P, Zuin M, D'Elia E, Colivicchi F. Lipoprotein (a), Inflammation, and Atherosclerosis. J Clin Med 2023;12:2529.
21. Boffa MB. Beyond fibrinolysis: the confounding role of Lp(a) in thrombosis. Atherosclerosis 2022;349:72-81.
22. Marcovina SM, Clouet-Foraison N, Koschinsky ML, Lowenthal MS, Orquillas A, Boffa MB, et al. Development of an LC-MS/MS proposed candidate reference method for the standardization of analytical methods to measure lipoprotein(a). Clin Chem 2021;67:490-9.
23. Scharnagl H, Stojakovic T, Dieplinger B, Dieplinger H, Erhart G, Kostner GM, et al. Comparison of lipoprotein(a) serum concentrations measured by six commercially available immunoassays. Atherosclerosis 2019;289:206-13.
24. Marcovina SM, Albers JJ, Gabel B, Koschinsky ML, Gaur VP. Effect of the number of apolipoprotein(a) kringle 4 domains on immunochemical measurements of lipoprotein(a). Clin Chem 1995;41:246-55.
25. Kronenberg F. Lipoprotein(a) measurement issues: Are we making a mountain out of a molehill? Atherosclerosis 2022:349:123-35.
26. Lassman ME, McLaughlin TM, Zhou H, Pan Y, Marcovina SM, Laterza O, et al. Simultaneous quantitation and size characterization of apolipoprotein(a) by ultra-performance liquid chromatography/mass spectrometry. Mass Spectrom 2014;28:1101-6.
27. Cobbaert CM, Althaus H, Begcevic Brkovic I, Ceglarek U, Coassin S, Delatour V, et al. Towards an SI-traceable reference measurement system for seven serum apolipoproteins using bottom-up quantitative proteomics: conceptual approach enabled by cross-disciplinary/cross-sector collaboration. Clin Chem 2021;67:478-89.
28. Trinder M, Paruchuri K, Haidermota S, Bernardo R, Zekavat SM, Gilliland T, et al. Repeat Measures of Lipoprotein(a) Molar Concentration and Cardiovascular Risk. J Am Coll Cardiol 2022;79:617-28.
29. Langlois MR, Nordestgaard BG, Langsted A, Chapman MJ, Aakre KM, Baum H, et al. Quantifying atherogenic lipoproteins for lipid-lowering strategies: consensus-based recommendations from EAS and EFLM. Clin Chem Lab Med 2020;58:496-517.
30. Nordestgaard BG, Chapman MJ, Ray K, Borén J, Andreotti F, Watts GF, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J 2010;31:2844-53
31. http://www.lpaclinicalguidance.com (last access: december 2023)
32. Ellis KL, Perez de Isla L, Alonso R, Fuentes F, Watts GF, Mata P. Value of measuring lipoprotein(a) during cascade testing for familial hypercholesterolemia. J Am Coll Cardiol 2019;73:1029-39.
33. O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I, et al. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. Circulation 2019;139:1483-92.
34. Bittner VA, Szarek M, Aylward PE, Bhatt DL, Diaz R, Edelberg JM, et al. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. J Am Coll Cardiol 2020;75:133-44.
35. Cholesterol Treatment Trialists' (CTT) Collaboration; Baigent C, Blackwell L, Emberson J, Blackwell L, Reith C, Solbu MD, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.
36. Tsimikas S. A Test in Context: Lipoprotein(a): Diagnosis, prognosis, controversies, and emerging therapies. J Am Coll Cardiol 2017;69:692-711.
37. Cegla J, France M, Marcovina SM, Neely RDG. Lp(a): When and how to measure it. Ann Clin Biochem 2021;58:16-21.
38. Galetta F, Sampietro T, Basta G, Giannasi G, Bionda A. Effects of simvastatin on blood levels of lipoprotein (a)). Minerva Med 1995;86:299-303.