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Global Spotlights

Eight reasons why lipoprotein(a) should be measured in everyone at least once in a lifetime

Benoit J. Arsenault [1,2] and Pia R. Kamstrup [3,4]*

[1]Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec, Canada; [2]Department of Medicine, Faculty of Medicine, Université Laval, Québec, QC, Canada; [3]Department of Clinical Biochemistry, Copenhagen University Hospital—Herlev and Gentofte, Borgmester Ib Juuls Vej 73, DK-2730 Herlev, Denmark; and [4]The Copenhagen General Population Study, Copenhagen University Hospital—Herlev and Gentofte, Borgmester Ib Juuls Vej 73, DK-2730 Herlev, Denmark

Lipoprotein(a) [Lp(a)] is a highly atherogenic lipoprotein particle that may be found in high concentrations in the blood of individuals who inherited Lp(a)-raising genetic variants.[1] Genetically determined high or very high Lp(a) levels are thus present in ∼20% of the general population. A series of large-scale Mendelian randomization studies published over the past 15 years have revealed a strong, linear, and likely causal effect of Lp(a) on a wide range of cardiovascular and valvular diseases including coronary artery disease, peripheral artery disease, and aortic valve stenosis, as well as an effect on all-cause and cardiovascular mortality.[2,3] Despite the large scientific consensus on the causal and actionable role of Lp(a) in atherosclerotic cardiovascular disease (ASCVD), Lp(a) levels remain infrequently measured in high-risk individuals. As an example, the Lp(a)HERITAGE investigators recently revealed that in a large sample of patients with ASCVD from 48 countries, Lp(a) levels were available in <14% of patients.[4] One of the reasons why Lp(a) is not routinely measured is lack of empowerment by healthcare professionals. Clinicians often don't know what to do if an Lp(a) level comes back elevated in the absence of targeted Lp(a)-lowering therapies and are unsure whether or not an Lp(a) result will change the management of their patients. In order to challenge medical inertia and to promote a culture of proactive precision medicine, we hereby present eight reasons why Lp(a) should be measured in everyone at least once in a lifetime as recommended in an increasing number of guidelines and consensus statements (*Figure 1*).[5]

(1) To provide answers to patients who develop cardiovascular diseases despite having zero or few conventional risk factors.

Up to 15% of individuals who present with a first myocardial infarction have zero conventional risk factors. Lp(a) may explain why individuals without or with few conventional risk factors may still develop ASCVD.[1] A diagnosis of high Lp(a) may help patients understand that their cardiovascular event may be due to a genetic risk factor that they have no control over and not necessary by poor lifestyle choices as it is often suggested in the public discourse.

(2) To identify individuals who may benefit from earlier and more aggressive management of conventional risk factors.

As suggested in the latest Canadian Cardiovascular Society guidelines for the prevention of ASCVD, identification of high levels of Lp(a) is a useful consideration for shared decision making in individuals across all ASCVD risk categories.[6] In individuals with high Lp(a), reductions in modifiable ASCVD risk factors by targeting blood cholesterol levels, blood pressure, and promoting heart healthy diets, physical activity/exercise, etc. will lower their absolute risk of having a cardiovascular event, as recently demonstrated in a UK Biobank analysis presented in the latest European Atherosclerosis Society consensus statement on Lp(a)[1] and previously in the EPIC-Norfolk study.[7]

(3) To identify individuals at very high genetic risk of ASCVD.

There is clinical consensus about the importance of detecting familial hypercholesterolaemia (a genetic condition strongly predisposing to ASCVD and found in ∼1 in 250 individuals) for the optimal prevention of ASCVD. A recent analysis from the Copenhagen General Population Study (69 644 individuals followed for 42 years) found that people in the top percentiles of the Lp(a) distribution had a very high ASCVD risk which was comparable to that of patients with familial hypercholesterolaemia.[8] On a per-particle basis, estimates from Mendelian randomization studies revealed that Lp(a) particles could be six times more atherogenic compared to low-density lipoprotein particles.[9] High Lp(a) is one of the most common genetic disorders and should be diagnosed to identify individuals who may be at very high risk of premature cardiovascular events.

* Corresponding author. Email: pia.roerbaek.kamstrup@regionh.dk

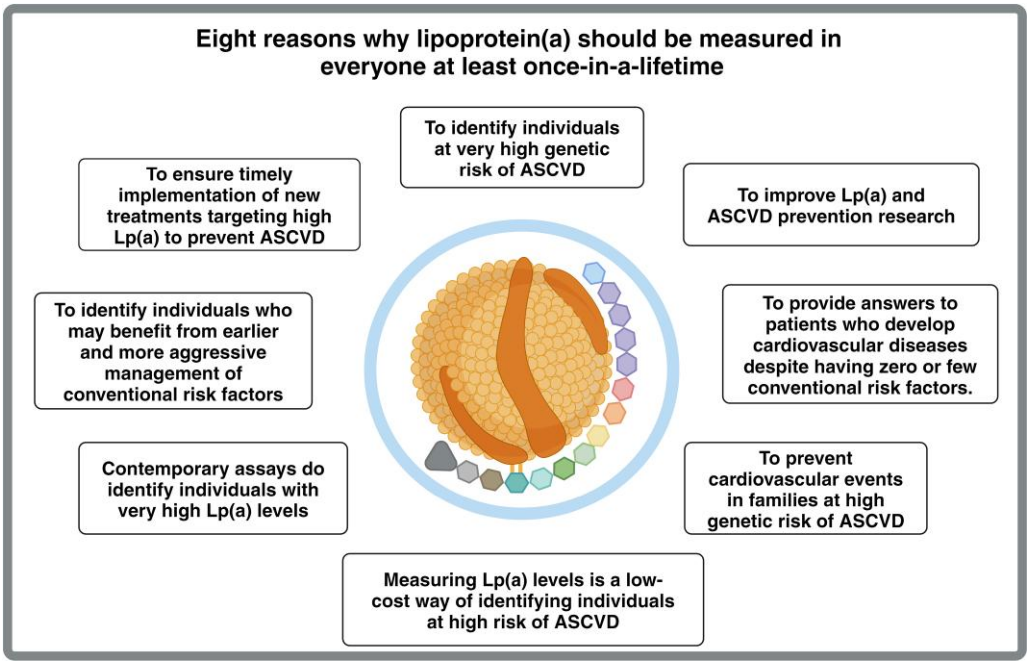

Figure 1 Eight reasons why Lp(a) should be measured in everyone at least once in a lifetime

(4) To prevent cardiovascular events in families at high genetic risk of ASCVD.

Identifying individuals with high Lp(a) and screening their families for high Lp(a) (i.e. cascade screening) effectively identifies high-risk individuals in need of aggressive targeting of modifiable ASCVD risk factors to prevent cardiovascular events. In a study of adult probands with Lp(a) concentrations ≥ 100 mg/dL (~≥250 nmol/L), one new case of elevated Lp(a) ≥ 50 mg/dL (~≥125 nmol/L) was identified for every 1.5 relatives tested and one new case of elevated Lp(a) ≥100 mg/dL was identified for every 2.8 relatives tested.[10]

(5) Measuring Lp(a) levels is a low-cost way of identifying individuals at high risk of ASCVD.

Lp(a) measurements have several advantages over other more invasive and more costly risk stratification tools such as cardiovascular imaging which are also required to be repeated periodically, and not broadly available. In contrast to, for instance, coronary artery calcium, which estimates subclinical atherosclerosis, the measurement of Lp(a), if done early in life, can be useful to target more aggressively other risk factors before the development of subclinical atherosclerosis. Ideally, Lp(a) measurement should be carried out in connection with the first lipid profile in early adulthood in all without the need for additional blood sampling and at a very low cost. Repeat Lp(a) measurement will rarely be needed as levels are relatively stable over time.

(6) Contemporary assays do identify individuals with high Lp(a) levels.

While some Lp(a) assays may perform better than others, and Lp(a) measurements from different assays may not be directly comparable due the present lack of international standardization, the majority of assays available can readily identify individuals with an Lp(a) level that puts them in a high-risk category. Lp(a) measurements expressed in nmol/L, as opposed to mg/dL, are preferable as they better estimate the number of atherogenic Lp(a) particles in the blood, however, assays also expressing levels in mg/dL can be used. An Lp(a) level of 125 nmol/L (~50 mg/dL) found in ~1 in 5 usually identifies a subgroup of the population that carries an elevated risk of ASCVD. While the risk of ASCVD can be observed at lower Lp(a) levels (~75 nmol/L or 30 mg/dL), the importance of aggressively targeting modifiable risk factors may here depend on the presence/absence of other risk factors and patients' preferences and motivation.[1]

(7) To improve Lp(a) and ASCVD prevention research.

Presently, most studies on Lp(a) and ASCVD are based on data from predominantly white populations while Lp(a) levels are known to vary with ancestry. To better understand the association of Lp(a) levels with risk of disease, widespread Lp(a) measurements are needed in different ethnic groups, sexes, and in individuals with a range of co-morbidities from all regions of the world. Several mechanistic, basic, pre-clinical, and clinical studies on Lp(a) need to be performed and collaborative research and resource sharing from diverse groups with complementary skills and expertise need to be set in place to better understand the role of Lp(a) in ASCVD and help healthcare professionals provide state-of-the-art care for people and families affected by elevated Lp(a) levels. While there are many unanswered questions on the biological or clinical role of Lp(a) in ASCVD, the definitive answer to these questions is not required to support widespread measurements of Lp(a).

(8) To ensure timely implementation of new treatments targeting high Lp(a) to prevent ASCVD.

Presently, potent and specific Lp(a) lowering therapies are being tested in large cardiovascular outcome trials with first results expected in 2025. In the HORIZON (NCT04023552) and OCEAN(a)—outcomes (NCT05581303) trials, respectively, the antisense oligonucleotide (ASO) pelacarsen and the small interfering RNA (siRNA) olpasiran, both targeted against the *LPA* gene in the liver and thus Lp(a) production. Several other targeted therapies against

Lp(a) are under development. While demonstration that specific reductions in Lp(a) levels provides cardiovascular benefits, and future availability of specific Lp(a) lowering treatments, will obviously represent additional reasons for why Lp(a) should be measured in everyone at least once, final results from these cardiovascular outcomes trials are not required prior to implementing widespread Lp(a) measurement.

In conclusion, despite several national guidelines and consensus statements on the prevention of ASCVD recommending that Lp(a) should be measured in everyone at least once,[1,6,11] most clinicians and healthcare professionals do not routinely measure Lp(a) as part of the first lipid profile in early adulthood or in patients with established ASCVD. We hope that the eight reasons why Lp(a) should be measured in everyone at least once listed above will help address some of their concerns and that implementing routine Lp(a) measurements will empower both patients and their healthcare providers to better use Lp(a) for optimal prevention and treatment of ASCVD.

Declarations

Disclosure of Interest

B.J.A. is a consultant for Novartis, Eli Lilly, Editas Medicine, and Silence Therapeutics and has received research contracts from Pfizer, Eli Lilly, and Silence Therapeutics. P.R.K. has received lecture honoraria or consultancy fees from Physicians Academy for Cardiovascular Education, Novartis, Silence Therapeutics, Eli Lilly, and Amgen.

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