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CARDIOPULSE

# Lipoprotein(a)

## A refractory risk factor for atherosclerotic and thrombotic vascular diseases discussed by Arnold von Eckardstein

Epidemiology, intervention trials, human genetics, animal experiments, and mechanistic studies provide consistent and conclusive evidence that low density lipoproteins (LDL) play a causal role in the pathogenesis of atherosclerosis. LDL-cholesterol (LDL-C) has therefore become a prime target for prevention of atherosclerotic cardiovascular diseases. However, even patients nowadays reaching recommended target levels of LDL-C continue to suffer from cardiovascular events. The main strategies to lower this residual risk aim at more aggressive lowering of LDL-C and better control of other pathogenetic risk factors.[1] Among the latter, lipoprotein(a) (*spoken as* 'lipoprotein small a'; Lp(a)), has attracted special attention because it aggravates the risk associated with other risk factors including LDL-C,[2,3] limits the LDL-C lowering efficacy of statins,[4] and likely plays a causal role in other cardiovascular diseases beyond atherosclerosis.[5,6]

Lp(a) resembles LDL by the presence of one molecule of apolipoprotein B (ApoB) and its high content of cholesterol. It differs from LDL by the presence of an additional apolipoprotein named apo(a) which renders this particle several unique functional and metabolic features (*Figure 1*):[5–7]

- Apo(a) is only expressed in primates including humans, as well as in the hedgehog.[5,7]
- It is encoded by the LPA gene on chromosome 6 which evolved from the plasminogen gene by intragenic duplications and which was one of the first loci discovered by hypothesis-free genome-wide association studies (GWAS) as a genetic determinant for risk of coronary heart disease (CHD) as well as aortic valve calcification.[7–9]
- As with plasminogen, apo(a) contains a kringle V domain and a protease domain which however is catalytically inactive so that apo(a)

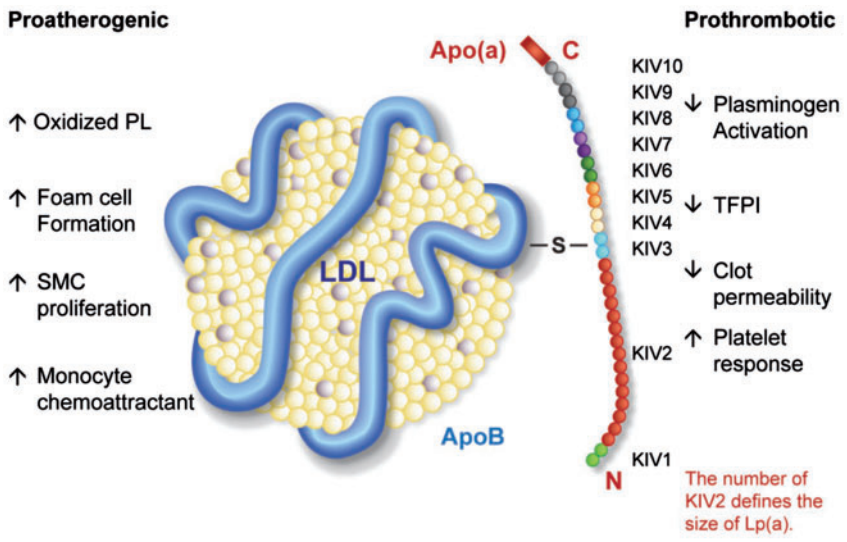


**Figure 1** Structure of lipoprotein(a). Lipoprotein(a) is composed of an LDL-like particle and an additional apolipoprotein called apolipoprotein(a) [apo(a)] that is bound to apolipoprotein B (apoB) by a disulfide bridge. Apo(a) protein is formed of cysteine-rich ≪kringles≫ with a variable number of KIV repeats, a KV kringle, and a protease domaine. KIV repeats are available in 10 different types and the number of kringle-IV type 2 repeats is highly variable, resulting in different isoforms. KIV, kringle IV type; LDL, low-density lipoprotein; PL, phospholipids; SMC, smooth muscle cell; TFPI, tissue factor pathway inhibitor. Reproduced from reference 5.

does not exert any fibrinolytic activity.[5–7] The kringle IV domain of plasminogen is also present, however as a variable number of repeat polymorphism ranging from 10 to 50 repeats (*Figure 1*).[5–7]

- The genetically determined number of so-called Kringle IV-2 repeats is the strongest determinant of Lp(a) plasma concentrations which range from 0 to a few g/L.[5–7,10]
- The presence of a variable number of Kringle IV repeats makes standardization and tracing of Lp(a) immunoassays difficult.[11] As a result, cut-offs for the definition of elevated Lp(a) differ widely and range between 200 mg/L and 500 mg/L depending on the assay used. Ideal assays use antibodies which are specific for a defined kringle-IV which is present once in every apo(a) isoform. Currently, the reference method for Lp(a) assays is such an isoform-insensitive immunoassay developed by Santica Marcovina. Efforts are being undertaken to use mass spectrometry as a more independent reference method.[11]
- Lp(a) is enriched with oxidized phospholipids.[6]
- Lp(a) is exclusively produced in the liver which secretes apo(a) and apoB-containing lipoproteins separately, so that the final assembly of Lp(a) takes place extracellularly by covalent linkage of apo(a) with apoB.[12]
- The catabolism of Lp(a) is not entirely resolved. Notably, the endocytic receptor removing Lp(a) from the circulation is a matter of debate.[13] The presence of apo(a) and perhaps also PCSK9 in Lp(a) hinders and limits, respectively, the removal of Lp(a) by the LDL-receptor. Several other endocytic receptors have been implicated to mediate the removal of Lp(a), namely LDL-receptor related protein 1, very low density lipoprotein receptor, scavenger receptor B1, and most recently plasminogen receptor KT ($PlgR_{KT}$).[13,14] By contrast to the lipoprotein receptors which shuttle Lp(a) into a route which leads to the lysosomal degradation of the entire particle, $PlgR_{KT}$ was reported to direct Lp(a) into a pathway which leads to the degradation of the lipids and apoB but to the re-secretion of apo(a) which then associates with another LDL-particle to form a new Lp(a) particle.

Several lines of evidence indicate that Lp(a) is a causal risk factor of atherosclerotic cardiovascular disease[5–7,10]

- Many case-control studies and prospective cohort studies found elevated Lp(a) plasma levels associated with increased risk of CHD, ischaemic stroke, and peripheral artery disease, independently of, but interacting with other risk factors.[1–3,5–7,10,15] Several studies and a meta-analysis thereof also found a significant association of Lp(a) levels with risk of venous thromboembolism.[16] In this case, Lp(a) appears to aggravate the risk of thrombophilic risk factors.[17,18]
- Gerd Utermann was the first who found on the protein level that the size of apo(a) isoforms and hence number of kringle IV repeats determines both the plasma concentration of Lp(a) and the cardiovascular risk exerted by elevated Lp(a) levels.[7] Nowadays this strategy is termed Mendelian randomization and applied to polymorphisms on the DNA level and much larger populations. It confirmed the genetic causality of elevated Lp(a) levels for various atherosclerotic vascular diseases as well as for aortic valve calcification.[5–7,10] The genetic association of LPA with venous thromboembolism is controversial.[10,19,20]
- Transgenic mice which overexpress human apo(a) and human apoB were found to form Lp(a) particles and to develop atherosclerosis.[21]
- *In vitro* Lp(a) exerts several atherogenic, thrombogenic, and pro-inflammatory properties which make the causality of Lp(a) in the pathogenesis of atherothrombotic but also venous thrombotic diseases biologically plausible (*Figure 1*).[6,22]

As of now, therapeutic options to lower Lp(a) levels have been very limited, but new drug developments look very promising:

- Interventions by lifestyle or diet have minimal or no effects on Lp(a) levels.
- Sex hormones as well as thyroid hormones were found to lower Lp(a) levels. In fact, Lp(a) levels increase after menopause and castration and decrease with replacement therapy of oestrogens or testosterone. However, the approximate 20% lowering effects are rather moderate and were not translated into clinical benefit for preventing cardiovascular events. Thyromimetics, which also lower Lp(a) by 20% are still under investigation.[23]
- Statins do not have any significant effect on Lp(a) levels, either because Lp(a) is catabolized by other than the LDL receptor pathway or because Lp(a) transports PCSK9 which counteracts the statin effect.[23,24] Of note, very elevated Lp(a) is a reason for reduced LDL-C lowering on statin treatment because the cholesterol of Lp(a) contributes to the measured or calculated LDL-C but is not targeted by statins.[4] For example, an Lp(a) level of 600 mg/L can be estimated to contribute 20 mg/dL or 0.5 mmol/L of 'statin-resistant LDL-C'.
- Nicotinic acid lowers Lp(a) levels by about 25%, probably by interfering with its production. However, despite its positive effects on Lp(a) as well as the conventional lipoprotein traits LDL-C, HDL-C, and triglycerides, nicotinic acid was not found to reduce cardiovascular risk more than statin treatment, so it is not recommended for preventive treatment.[5,6,23]
- Fibrates have no effect on Lp(a).[23]
- Drugs that interfere with the production of apoB containing lipoproteins, namely inhibitors of microsomal transfer protein and apoB-antisense lower Lp(a) levels by 25%. These drugs are however only certified for the treatment of homozygous familial hypercholesterolemia.[5,6,23]
- Inhibitors of PCSK9 were found to lower Lp(a) levels by 25%.[5,6,23] It is not known whether this effect contributes to the lowering of cardiovascular risk by PCSK9 inhibitors. This may depend on the mechanism by which PCSK9 lowers Lp(a) levels. Alirocumab was reported to increase the catabolism of Lp(a).[25] Whether this is helpful will depend on the catabolic site and mechanism.[13] It has been suggested that Lp(a) removal is enhanced by binding of the PCSK9 antibodies to the PCSK9 transported by Lp(a) and by subsequent removal of the immunocomplexes into macrophages.[26] Such a pathway may bear some risks.
- Interestingly, CETP inhibitors were also found to reduce Lp(a) levels by up to 50%, again through a yet unknown mechanism. The ongoing anacetrapib trial will tell whether this translates into clinical benefit.[23]
- As of now LDL-apheresis and Lp(a) apheresis are the only available treatments by which Lp(a) can be effectively and safely removed. These interventions lower Lp(a) levels by up to 60% and 80%, respectively.[25,26] A recently published registry study following 170 CHD patients with Lp(a) levels found a significantly reduced event rate during 5 years after the start of Lp(a) apheresis as compared to the two years before the start of Lp(a) apheresis.[29]
- Most recently antisense technology has been used to develop a specific therapy to lower Lp(a) plasma levels.[6,23,30] The most recent generation of antisense oligonucleotides directed against apo(a) mRNA lowers Lp(a) levels dose dependently, by 30 to

**Table 1 Summary of recommendations from the European Atherosclerosis Society (EAS) and European Society of Cardiology (ESC) regarding the screening for lipoprotein(a)**

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| 2010 EAS consensus panel.[2] | Lp(a) should be measured once in all subjects at intermediate or high risk of CVD who present with:<br>• Premature CVD.<br>• Familial hypercholesterolemia.<br>• A familial history pf premature CVD and/or elevated Lp(a).<br>• Recurrent CVD despite statin treatment.<br>• ≥3% 10-year risk of fatal CVD according to the European guidelines and<br>• ≥10% 10-year risk of fatal and/or non-fatal CHD according to AHA guidelines. |
| 2016 ESC guidelines for the management of dyslipidaemias.[4] | Lp(a) should be recommended in selected cases at high risk, in patients with family history of premature CVD, and for reclassification in subjects with borderline risk.<br>Lp(a) screening should be considered in individuals with:<br>• Premature CVD (<55 years in men and <65 years women).<br>• Familial hypercholesterolemia.<br>• A family history of premature CVD and/or elevated Lp(a).<br>• Recurrent CVD despite optimal statin treatment.<br>• ≥5% 10-year risk of fatal CVD according to SCORE.<br>Treatment with a PCSK9 antibody may be considered in FH patients with CVD or with other factors putting them at very high risk for CHD, such as other CV risk factors, family history, and high Lp(a). |

AHA, American Heart Association; CV, cardiovascular; CVD, cardiovascular disease; Lp(a), lipoprotein(a); PCSK9, proprotein convertase kexin 9; FH, familial hypercholesterolemia. Reproduced from reference 5.

more than 80% in a single-dose approach and by 60% to more than 90% in a multidose approach.[30] Except local injection reactions, no treatment-related adverse effect was reported to have happened among 62 patients within the approximate 100 days of follow-up of a phase 2 study.[30]

In conclusion, it is very likely that Lp(a) is a causal risk factor and hence therapeutic target for primary and secondary prevention of several cardiovascular diseases, namely atherosclerotic vascular diseases, aortic calcification, and perhaps also venous thromboembolic diseases. Because as yet no effective Lp(a) lowering treatment is available, Lp(a) plasma levels are rather rarely determined in daily practice. However, already now, knowing a patient's Lp(a) level has achieved some clinical utility:

- High Lp(a) levels aggravate the risk mediated by conventional risk factors[1–3,10,13] and therefore can help to make treatment decisions towards earlier or more intensive hypolipidemic drug treatment.[1,5,6,23]
- Very elevated Lp(a) levels can be the reason for reduced LDL-C lowering upon statin treatment because the cholesterol of Lp(a) contributes to the measured or calculated LDL-C but is not targeted by statins.[4]
- Lp(a) should be considered as an etiological factor of atherosclerotic cardiovascular disease[5,6,10] but also venous thromboembolic events,[17–19] especially in patients where the early onset, progression of disease, or recurrence of events are not well explained by the classic risk factors.
- Eventually, in patients with progressing or refractory cardiovascular disease despite optimal or maximally possible control of conventional risk factors, high plasma levels of Lp(a) may serve as the indication to initiate Lp(a)- or LDL-apheresis[27,28] and perhaps in the future anti-apo(a) antisense oligonucleotides.[6,30]

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## References

References are available as supplementary material at *European Heart Journal* online.