



Lipoprotein(a): Facts and mysteries

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Received: August 20, 2025 **Accepted:** September 28, 2025 **Published:** October 01, 2025

Cite this article: Kostner G. Lipoprotein(a): Facts and mysteries. *Adv Lipoprotein(a) Res.* 2026;1:202502. <https://doi.org/10.70401/alr.2025.0001>

Justification to launch a journal devoted specifically to Lp(a)

Lp(a) has been known for over 60 years, yet it is astonishing how many open questions exist regarding its metabolism and physiological significance. Originally described as a sinking pre- β lipoprotein and a genetic variant of beta-lipoprotein (LDL) by Berglund, it gradually became apparent that it is a one-of-a-kind compound. In its early days, Lp(a) was analyzed by specific antibodies that were available only in a few specialized laboratories. This minimized the attention to Lp(a) despite reports stating that “Lp(a) positive individuals” are more prone to cardiovascular disease (CVD). Later, it was found that Lp(a) is a regular plasma compound with highly variable concentrations that are genetically determined. With the availability of new high-throughput laboratory methods, the interest in Lp(a) research started to grow. In the years leading to 2000, there was an ongoing debate about whether Lp(a) was correlated with CVD risk and, if so, whether this correlation was causal. We postulated a causality of high Lp(a) in myocardial infarction (MI) and CVD patients based on a pilot study in which we measured Lp(a) levels in young volunteers. The volunteers were asked whether their parents or relatives suffered from MI or stroke. The results were convincing as the offspring of parents with premature CVD or stroke had significantly higher plasma Lp(a) values as compared to those without such family history. We defined a cut-off concentration for Lp(a) of 30 mg/dl (approximately 75 nmols/L) in this study, a value that is currently propagated in consensus documents of numerous atherosclerosis societies.

The discussions about causality as a risk factor became obsolete after the publication of the Copenhagen City Heart studies from the Danish laboratory of Kamstrup *et al.*, which demonstrated by Mendelian Randomization beyond any doubt the causal relationship between high Lp(a) levels and CVD, MI, and stroke.

These later findings prompted the pharmaceutical industry to develop specific drugs to significantly lower Lp(a). Currently, 5-6 medications are in various stages of clinical trials and their outcomes may ultimately determine the future of Lp(a) research and the justification for launching a journal on this topic.

The number of online open access journals in recent years in the field of medical and biological sciences is growing rapidly, raising the obvious question on the justification of launching another journal like ALR that is devoted solely to Lp(a) research. However, there is a compelling argument in favor of it—manuscripts submitted to *Advances of Lipoprotein(a) Research* (ALR) will be free of charge for both authors and readers in the first 5 years. Thus, ALR is not established for making profit like many other medical journals whose titles are depicted from a pile of timely keywords. This will certainly warrant the trustworthiness of the journal as it focuses on the quality and reliability of data and not on the number of articles published.

ALR welcomes manuscripts dealing with Lp(a) in the field of lipid metabolism, genetics, epidemiology, pathophysiology, and drug treatment. In the era of Artificial Intelligence (AI) tools such as ChatGPT and Gemini, it is easier to draft a review, a case report or a scientific letter. The focus of ALR, however, will be directed to original manuscripts with new solid data, without the use of AI. Our Editorial Board, consisting of highly renowned scientists from almost all continents will ensure that this endeavor succeeds. For newcomers to the field, a recently published book on Lp(a) is recommended for basic knowledge. Numerous recognized scientists in the field illustrate an in-depth overview of the current state of knowledge in this book. Despite the knowledge accumulated over the years, there are still fields that remain unexplored. ALR aims to be a forum not only to advance the research in Lp(a) but also to foster collaboration among interested scientists.

Open fields in Lp(a) research

In the last 5 to 10 years, Lp(a) research was dominated by genetic epidemiology, its role in vascular diseases and the development of new medications. Today, the causality of Lp(a) as a risk factor for CVD, stroke and premature MI has been widely accepted. On the



other hand, the complexity of the genetic apo(a) polymorphism has only been explored recently and this has opened up a variety of topics that need to be re-examined.

Points that need to be addressed:

1. Genetic polymorphism related to CHD and MI risk.

Gerd Utermann's laboratory was the first to report the size polymorphism of apo(a) based on the number of repetitive kringle-IV (K-IV)^[5]. The number of K-IV repeats correlates inversely with the plasma Lp(a) concentration, yet this accounts for only about 50% of plasma apo(a) levels. Recently, it was found that several polymorphisms (SNP's) exist in the coding and non-coding region of K-IV that profoundly impact Lp(a) levels^[6]. These SNP's need to be further investigated in relation to the atherogenicity of Lp(a).

2. Harmonization of methods for measurement of Lp(a) in clinical laboratories.

The current high-throughput methods for clinical laboratories are based on immunoturbidimetry and immunonephelometry using polyclonal antibodies. These antibodies react with repetitive K-IV's and it is possible that large apo(a) isoforms with more K-IV's give falsely higher readings than smaller isoforms. This is currently corrected in commercial assays through algorithms that result in approximations. Comparing the Lp(a) values measured in a larger population obtained with different commercial tests available in Europe with a reference method based on LC-MS, a relatively large number of runaway values was observed, the significance of which was hard to explain. One possible reason might be due to the recently described SNP's^[6] but other factors cannot be excluded. The IFCC working group on apolipoproteins is addressing the issue by developing a generally available reference standard, and a gold standard method for Lp(a) quantitation (<http://www.ifcc.org/ifcc-scientific-division/sd-working-groups/wg-apo-ms/>). It would be desirable for this group together with other research laboratories to provide a reliable standard that can be verifiably implemented by the diagnostic industry for their assays in near future. A mere statement that a method has been standardized against any IFCC or WHO reference material will no longer be sufficient.

3. Has apo(a)/Lp(a) any physiological significance?

The answer to this question is of relevance as the medications currently in clinical trials can lower Lp(a) by 80 % or more. There is also a treatment strategy based on CRISPR-CAS9 that may completely abolish apo(a) production, with almost no possibility to reverse this process. Before the CRISPR-CAS9 methodology is approved for human use, it must be clarified that apo(a) has no important physiological function. Current studies are in favor of 'no physiological function' as few individuals with the so-called NULL-allele with no detectable amounts of plasma apo(a) appear to be healthy^[7,8].

4. How and where is Lp(a) catabolized?

In vitro studies have shown that all cell surface receptors relevant for lipid metabolism may bind and in turn internalize Lp(a). These include the LDL-receptor, the apoE receptor, LRP1, SRB-1, CD36, SRA the asialo-glycoprotein receptor the plasminogen receptor and more. However, it is unclear, which of these receptors might be relevant *in vivo*. So far, the new Lp(a) lowering drugs in clinical trials interfere only with apo(a) biosynthesis or Lp(a) assembly, however, if the relevant catabolic pathway is uncovered, it may certainly widen the spectrum of new drugs for treatment of high Lp(a).

Also, it is not fully understood which organ in humans catabolizes Lp(a). Studies in rats, mice, rabbits and hedgehogs have shown that approximately 50% of intravenously administered Lp(a) is taken up by the liver, comparable to LDL. However, the fate of the remaining fraction remains elusive. A part of Lp(a) might be cleared by the kidney or secreted in the urine, but these possibilities require further clarification. The answer to all these questions may be the basis for further drug development strategies.

5. Apo(a) biosynthesis and Lp(a) assembly.

We studied the expression of apo(a) in transgenic mice containing the full human apo(a) gene, including the promoter region. It was found that a HNF4 response element drives the expression of apo(a) and, that the binding of HNF4 to this element is inhibited by FXR agonists. FXR almost silenced the apo(a) gene completely, yet despite this we observed about 70 other response elements for nuclear receptors and transcription factors in the promoter region of apo(a)^[8]. Further studies should address whether these response elements are operative under physiological or pathological conditions.

After biosynthesis, apo(a) binds to LDL and forms the bona-fide Lp(a) fraction in plasma. Currently, there is a discussion about whether this assembly occurs in the liver cells or elsewhere. Some studies are in favor of an intracellular hypothesis while others of an extracellular hypothesis. The solution of this question will be relevant for drug treatment, since the new compound Muvalapin is said to interfere with the Lp(a) assembly and reduce plasma Lp(a) by up to 70%^[9]. Contrarily, tranexamic acid, a compound that also inhibits Lp(a) assembly *in vitro*, has no effect *in vivo*. This apparent discrepancy might reflect on where Lp(a) is assembled.

6. Apo(a) distribution in fasting and post-prandial plasma.

The structure of Lp(a) is typically shown as an LDL particle with one apo(a) glycoprotein bound by a di-sulfide group to apoB. We have

observed that the ratio of apo(a): apoB is not always 1:1 and that not all apo(a) is bound to LDL. In fact, some apo(a) is found in VLDL/IDL, HDL, and even in the bottom fraction at density 1.21. The amount of apo(a) in density fractions other than LDL is much greater in post-prandial plasma and in plasma of patients with hypertriglyceridemia. There are limited studies published that address the relevance of this heterogeneity in apo(a) distribution for Lp(a) metabolism and atherogenicity.

7. Population Screening for elevated Lp(a) and recommendations for treatment.

Most consensus papers from relevant societies recommend that Lp(a) should be measured in healthy individuals only once after puberty. If the values are below threshold (30 or 50 mg/dl corresponding to some 75 or 125 nmols/L), the individual does not require attention. The rationale of this strategy is that Lp(a) plasma levels remain stable over life. It is noteworthy that i) the threshold (cut-off) concentration of Lp(a) is still under dispute, and ii) plasma Lp(a) levels in fact are not really stable. In healthy individuals Lp(a) levels increase significantly with age and this is pertinent for individuals at borderline concentrations. Pre-menopausal women have higher plasma Lp(a) compared with males; sex hormones including estrogens, progesterone, and testosterone, influence plasma Lp(a) levels. In addition, patients with kidney disease have elevated Lp(a) levels while patients with liver disease may have reduced plasma Lp(a). After successful treatment of patients with kidney or liver disease, Lp(a) levels return to pre-treatment values^[10]. These factors need to be considered for lifelong measurement of plasma Lp(a) levels.

8. How far should the reduction of Lp(a) go in patients at CVD risk?

It is well known that mean and median plasma Lp(a) concentrations differ among ethnic groups. Few studies also showed that the cut-off values for CHD and MI in these groups vary widely. This should be verified by additional studies, and recommendations need to be adapted accordingly.

There is also no consensus on how much Lp(a) should be reduced in different patient groups. Should we aim for plasma levels in CHD patients or post MI patients to be below the threshold of 30 or 50 mg/dl or near zero? Answers to these questions could be provided upon completion of the current clinical trials^[11].

9. Other open questions.

Additional studies are required to understand the relevance of Lp(a) in health and disease. To name a few: (i) Why do some patients treated with statins for high LDL-C show a reduction of Lp(a) whereas others may show an increase? (ii) What is the mechanism behind PCSK9 inhibitors in reducing Lp(a) and does it interfere with Lp(a) biosynthesis or catabolism? (iii) Why do patients with T2DM have lower plasma Lp(a) levels compared to healthy individuals with the same isoform? (iv) What is the relevance of oxidatively modified phospholipid binding to Lp(a), and is this binding influenced by Lp(a) lowering drugs?

I call upon the scientific community to address the questions mentioned above. *Advances in Lipoprotein Research (ALR)* will certainly provide a forum for scientists to promote and share their work in these research areas.

Declarations

Authors contribution

The author contributed solely to the article.

Conflicts of interest

Gerhard Kostner is the Editor-in-Chief of *Advances in Lipoprotein(a) Research*. No other conflicts of interest to declare.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

None.

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