

Lipoprotein(a) in Endocrine Diseases: Clinical Significance, Cardiometabolic Risk and Therapeutic Perspectives

Fatbardh Ramadani*

Department of Internal Medicine and Endocrinology, Kosovo

***Corresponding Author:** Fatbardh Ramadani, Department of Internal Medicine and Endocrinology, Kosovo.

Received: September 28, 2026; **Published:** October 12, 2026

Abstract

Background: Lipoprotein(a) [Lp(a)] is an atherogenic lipoprotein composed of an LDL-like particle and apolipoprotein(a) [apo(a)]. Plasma Lp(a) concentration is determined predominantly by genetic factors, particularly variation in the LPA gene, and remains relatively stable throughout life. Epidemiological, genetic and clinical evidence has identified Lp(a) as an independent risk factor for atherosclerotic cardiovascular disease (ASCVD) and aortic valve stenosis [1,2].

Aim: This review examines the role of Lp(a) in endocrinology, focusing on diabetes mellitus, obesity, thyroid disorders, polycystic ovary syndrome (PCOS), menopause and other endocrine disorders. It also discusses Lp(a) measurement, clinical interpretation, and current and emerging therapeutic strategies.

Materials and Methods: Publications indexed in PubMed and contemporary literature were reviewed, including ESC/EAS and National Lipid Association guidelines, systematic reviews, meta-analyses and clinical studies of emerging Lp(a)-targeted therapies. Particular attention was given to publications from 2020 to 2026.

Results: Elevated Lp(a) levels are consistently associated with coronary artery disease, myocardial infarction, ischemic stroke, peripheral arterial disease and aortic stenosis [1,2]. In endocrine practice, Lp(a) is particularly relevant in patients with diabetes, thyroid disorders or PCOS, and during the menopausal transition. Contemporary guidance recommends measuring Lp(a) at least once in adulthood [1,3]. Emerging antisense oligonucleotide and small interfering RNA (siRNA) therapies have produced substantial reductions in Lp(a), although their effects on cardiovascular events have yet to be established conclusively [4-7].

Conclusion: Lp(a) is an important contributor to cardiometabolic risk and connects lipidology, endocrinology and preventive cardiology. Incorporating Lp(a) measurement into risk assessment may improve the identification of patients with residual cardiovascular risk. Specific Lp(a)-lowering therapies may substantially change the management of these patients in the future.

Keywords: *Lipoprotein(a); Lp(a); Apolipoprotein(a); Endocrinology; Diabetes Mellitus; Hypothyroidism; PCOS; Obesity; Menopause; Atherosclerosis*

Introduction

Cardiovascular diseases remain among the leading causes of morbidity and mortality. Diabetes mellitus, arterial hypertension, obesity, dyslipidemia and hormonal disorders are established factors that contribute to the development of atherosclerosis.

However, optimal control of traditional risk factors does not eliminate cardiovascular risk entirely. This remaining risk is known as residual cardiovascular risk and has prompted interest in additional risk factors, among which Lp(a) has a distinctive role [1,2].

Lp(a) is an LDL-like lipoprotein containing apolipoprotein B-100 linked to apo(a). Unlike most metabolic parameters, its concentration is predominantly genetically determined [2].

Current evidence supports a causal role for Lp(a) in ASCVD and an association with aortic valve stenosis [1,2].

Endocrine disorders are also frequently accompanied by changes in lipid metabolism. A broad 2024 review of lipoproteins in endocrine diseases identified important lipoprotein alterations in thyroid disorders, PCOS, menopause, and disorders of the pituitary, adrenal glands, parathyroid glands and gonads [8].

Structure and biology of Lp(a)

Lp(a) consists of apolipoprotein B-100, an LDL-like lipid component and apolipoprotein(a). Apo(a) is covalently linked to apoB-100 by a disulfide bond.

The LPA gene, located on chromosome 6q26-27, determines apo(a) production. An important feature is variation in the number of kringle IV type 2 (KIV-2) repeats. Apo(a) isoform size is inversely associated with plasma Lp(a) concentration [2]. Consequently, individuals with similar LDL-C profiles may have markedly different Lp(a) concentrations.

Genetic role

Lp(a) is one of the most strongly genetically determined biomarkers of lipid metabolism. Genetic factors have a much greater influence on Lp(a) than lifestyle factors. Diet has a relatively small effect; physical activity does not substantially lower Lp(a); weight loss is not considered a specific treatment for elevated Lp(a); and levels may remain relatively constant throughout life. These characteristics make Lp(a) particularly useful for assessing lifetime cardiovascular risk [2,3].

Pathophysiological mechanisms

Atherogenesis: The LDL-like component of Lp(a) promotes the transport and deposition of lipids in the arterial wall.

Inflammation: Lp(a) carries oxidized phospholipids, which may contribute to inflammation in the vascular wall.

Thrombotic processes: Because apo(a) is structurally similar to plasminogen, an effect on the fibrinolytic system has been proposed.

Valvular calcification: Lp(a) is associated with inflammatory and calcific processes in the aortic valve and has been identified as a risk factor for aortic stenosis [1,2].

Lp(a) and cardiovascular disease

The relationship between Lp(a) and ASCVD is documented by epidemiological, genetic and clinical studies [1,2]. Elevated Lp(a) is associated with coronary artery disease, myocardial infarction, ischemic stroke, peripheral arterial disease and aortic stenosis.

The 2025 ESC/EAS focused update identifies Lp(a) above 50 mg/dL, approximately 105 nmol/L, as a cardiovascular risk-enhancing factor, with risk increasing further at higher levels [1]. Risk should not, however, be viewed as simply “normal” or “high” on either side of a single threshold. The NLA describes the relationship between Lp(a) and cardiovascular risk as a continuum [3].

Measurement of Lp(a)

The 2024 NLA update recommends measuring Lp(a) at least once in every adult [3]. Measurement should be considered particularly in people with premature ASCVD, a family history of premature ASCVD, familial hypercholesterolemia, intermediate cardiovascular risk, ASCVD without a clear explanation, or a family history of elevated Lp(a).

Lp(a) and diabetes mellitus

Diabetes mellitus is a major endocrine disease associated with high cardiovascular risk. The relationship between diabetes and Lp(a) is complex. Some epidemiological studies have reported an inverse association between Lp(a) concentration and the onset of type 2 diabetes. Nevertheless, the relationship between Lp(a), established diabetes and cardiovascular risk remains clinically important.

In patients with diabetes, Lp(a) should be interpreted alongside LDL-C, ApoB, triglycerides, HbA1c, blood pressure, kidney function, smoking status and obesity. In this setting, Lp(a) may help identify risk that persists despite control of traditional risk factors.

Lp(a) and obesity

Obesity is associated with insulin resistance, hypertriglyceridemia, reduced HDL-C, chronic inflammation, hypertension and type 2 diabetes. Lp(a), however, behaves differently from most of these biomarkers. Because its concentration is predominantly genetically determined, weight loss is not expected to produce large reductions in Lp(a). Thus, a patient with obesity who loses 10-15% of body weight may achieve substantial improvement in metabolic risk while still having elevated Lp(a).

Lp(a) and thyroid disease

Thyroid disease is an important cause of secondary dyslipidemia [8]. Hypothyroidism is particularly associated with increased LDL-C, increased total cholesterol, changes in ApoB and altered lipoprotein metabolism. Its relationship with Lp(a) is more complex.

Recent literature suggests that hypothyroidism may be associated with changes in Lp(a), but findings on the effect of levothyroxine treatment on Lp(a) levels are not fully consistent [8,9]. A patient with elevated TSH, elevated LDL-C and elevated Lp(a) should therefore be assessed for multiple potential sources of lipid-related risk, rather than managed on the basis of Lp(a) alone.

Lp(a) and PCOS

PCOS is a complex endocrine and metabolic disorder involving hyperandrogenism, ovulatory dysfunction, insulin resistance, obesity and lipid abnormalities. Recent reviews show that PCOS is associated with important alterations in lipoprotein metabolism [8]. However, evidence specifically concerning Lp(a) in PCOS is more limited than evidence concerning LDL-C, triglycerides and HDL-C. An observed association does not necessarily establish a causal role.

Lp(a) and menopause

Menopause is an important period of change in cardiometabolic risk. The menopausal transition may involve increased visceral fat, changes in insulin resistance, increased LDL-C, changes in triglycerides and changes in Lp(a). The literature on lipoproteins during menopause has expanded substantially in recent years [8]. Menopause should therefore be considered an important time to reassess cardiovascular risk, particularly in women with a family history of ASCVD or other risk factors.

Lp(a) in other endocrine disorders

Alterations in lipoprotein metabolism have also been reported in acromegaly, growth hormone deficiency, Cushing syndrome, hypopituitarism, hyperparathyroidism, hypogonadism and other gonadal and adrenal disorders. The literature specifically addressing Lp(a) in these conditions is considerably more limited. A 2024 review summarizes lipoprotein changes across a broad range of endocrine diseases [8].

Current therapeutic strategy

At present, the management of elevated Lp(a) should focus primarily on reducing overall cardiovascular risk, because a widely approved treatment specifically targeting Lp(a) is not yet available. This includes lowering LDL-C, managing diabetes, controlling hypertension, smoking cessation, weight management, physical activity and treatment of other risk factors. The NLA recommends more intensive management of modifiable risk factors in patients with elevated Lp(a) [3].

Statins

Statins remain a cornerstone of treatment for atherosclerotic risk when indicated. Although some small studies have suggested a slight increase in Lp(a) during statin treatment, individual-participant data from randomized trials have not shown a consistent, clinically important effect on Lp(a) [1]. Elevated Lp(a) is therefore not a reason to discontinue a statin when statin therapy is clinically indicated.

PCSK9 inhibitors

PCSK9 inhibitors have a strong LDL-C-lowering effect and can also reduce Lp(a). Their effect on Lp(a), however, is more modest than their effect on LDL-C. In clinical practice, their value for patients with elevated Lp(a) stems primarily from substantial LDL-C reduction, with an additional effect on Lp(a).

Lipoprotein apheresis

Lipoprotein apheresis can produce substantial reductions in Lp(a) and LDL-C. The 2024 NLA update describes an approved indication in the United States for patients meeting specific criteria involving familial hypercholesterolemia, coronary or peripheral arterial disease, and elevated Lp(a) [3]. Its use is nevertheless limited by cost, the need for repeated procedures and limited availability of specialized centers.

Specific Lp(a)-Lowering therapies

This is a particularly promising area of therapeutic development. Antisense oligonucleotides target apo(a) messenger RNA and reduce its production in the liver. Small interfering RNA (siRNA) agents also target hepatic apo(a) production, using an RNA interference mechanism. Early studies have demonstrated substantial Lp(a) reductions with these approaches [4-7].

A network meta-analysis published in 2026, including 51 studies and 17,810 participants, reported substantial reductions in Lp(a) with emerging targeted therapies, including olpasiran, pelacarsen, muvalaplin, zerlasiran and lepodisiran [7].

Pelacarsen

Pelacarsen is an antisense oligonucleotide that targets apo(a) production. Early-phase studies have shown substantial reductions in Lp(a), making it a leading candidate for specific Lp(a)-lowering treatment [5]. The central question, however, extends beyond how much pelacarsen lowers Lp(a): does it reduce myocardial infarction, stroke and cardiovascular mortality? Answering this requires results from clinical outcome trials.

Olpasiran

Olpasiran is an siRNA therapy that targets apo(a) production. Clinical studies have demonstrated substantial reductions in Lp(a). Cardiovascular outcome trials aim to determine whether these reductions translate into clinical benefit [5,7].

Lepodisiran

Lepodisiran is another siRNA therapy. A potentially important feature of this therapeutic class is the possibility of administration at long intervals, which may support long-term adherence.

Zerlasiran

Zerlasiran is another siRNA therapy targeting apo(a) production. Early studies have shown substantial reductions in Lp(a), but its long-term clinical significance will be determined by outcome trials [6,7].

Muvalaplin

Muvalaplin represents a different approach. It is an oral small molecule that inhibits the formation of Lp(a). Its theoretical advantage is oral administration, in contrast to injectable RNA-based therapies [6]. Recent reviews identify muvalaplin as a leading candidate among emerging Lp(a)-lowering treatments.

Does lowering Lp(a) necessarily lower risk?

This remains the central scientific question. Elevated Lp(a) is associated with higher ASCVD risk; emerging therapies can substantially lower Lp(a); but whether lowering Lp(a) reduces clinical events remains to be established conclusively. The third step has not yet been definitively demonstrated. The ESC/EAS also notes that it remains uncertain whether lowering Lp(a) reduces ASCVD or aortic stenosis, and how large a reduction would be required to produce clinical benefit [1].

Discussion

Lp(a) is a distinctive risk factor because it is genetically determined, atherogenic and relatively unaffected by lifestyle factors. These characteristics make it particularly relevant in endocrinology. For example, a patient with diabetes and well-controlled LDL-C may still have considerable cardiovascular risk associated with elevated Lp(a). Similarly, a patient with hypothyroidism should be evaluated for additional causes of dyslipidemia and cardiovascular risk. Evidence concerning Lp(a) in PCOS and menopause is still developing and requires careful interpretation. Lp(a) should be considered alongside LDL-C, ApoB and a comprehensive assessment of cardiovascular risk.

Conclusion

Lp(a) is a predominantly genetically determined atherogenic lipoprotein and an important independent risk factor for ASCVD and aortic stenosis [1,2]. In endocrinology, it is particularly relevant to patients with diabetes mellitus, obesity, thyroid disease or PCOS, as well as women undergoing the menopausal transition.

Measuring Lp(a) at least once in adulthood is recommended by the NLA and supported by contemporary European guideline approaches [1,3]. Until a specific treatment becomes widely approved, management should focus on lowering LDL-C and intensively controlling other cardiovascular risk factors.

The development of antisense oligonucleotide and siRNA therapies—including pelacarsen, olpasiran, lepodisiran and zerlasiran—and oral agents such as muvalaplin may substantially change Lp(a) management [4-7]. Before these therapies become standard clinical practice, however, trials must demonstrate that lowering Lp(a) reduces cardiovascular events.

Bibliography

1. Mach F, *et al.* "2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias". *European Heart Journal* 46.42 (2025): 4359-4378.
2. Tsimikas S, *et al.* "Lipoprotein(a): a clinical update". *Circulation* 149 (2024): 132-148.

3. Koschinsky ML., *et al.* "A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice". *Journal of Clinical Lipidology* 18.3 (2024): e308-e319.
4. Nicholls SJ., *et al.* "Olpasiran for the treatment of elevated lipoprotein(a)". *New England Journal of Medicine* 387 (2022): 1855-1864.
5. Tsimikas S., *et al.* "Lipoprotein(a) reduction in persons with cardiovascular disease". *New England Journal of Medicine* 382.3 (2020): 244-255.
6. Bittner VA., *et al.* "Lipoprotein(a)-lowering therapies in development: current evidence and future perspectives". *Current Atherosclerosis Reports* (2025).
7. "Comparative effects of emerging Lp(a)-lowering agents and PCSK9-directed therapies on lipoprotein(a): a network meta-analysis of randomised clinical trials". *European Heart Journal* (2026).
8. Olejarz M., *et al.* "Lipoprotein alterations in endocrine disorders—a review of the recent developments in the field". *Frontiers in Endocrinology (Lausanne)* 15 (2024): 1354098.
9. "Exploring the effect of thyroid hormone on serum lipoprotein(a) levels in patients with thyroid hormone dysfunction: a systematic review". *Endocrine Regulations* (2024).
10. Nordestgaard BG., *et al.* "Lipoprotein(a) and cardiovascular disease". *Lancet* (2024).
11. Nambi V., *et al.* "Lipoprotein(a) and cardiovascular risk: clinical implications of an inherited risk factor". *Circulation* (2024).
12. Tsimikas S., *et al.* "Emerging therapies for lowering lipoprotein(a)". *European Heart Journal* (2024).
13. Koren MJ., *et al.* "Preclinical and clinical development of therapies targeting lipoprotein(a)". *Journal of Clinical Lipidology* (2025).
14. "Lp(a)-lowering agents in development: A new era in tackling the burden of cardiovascular risk?" *Current Atherosclerosis Reports* (2025).
15. "Efficacy and safety of lipoprotein(a)-targeted therapeutics: a systematic review and network meta-analysis" (2026).

Volume 15 Issue 11 November 2026

©All rights reserved by Fatbardh Ramadani.