REVIEW ARTICLE

CONTENTS

The role of lipoprotein (a) in the development of cerebral atherosclerosis

Khrystyna Kukharchuk[1], Maria Cherska[1], Tamara Kazykina[2] , Vitalina Pidlepenska[2]
[1]SI "V.P. KOMISARENKO INSTITUTE OF ENDOCRINOLOGY AND METABOLISM OF THE NAMS OF UKRAINE", KYIV, UKRAINE
[2]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

Aim: To review information sources on this issue in order to provide up-to-date knowledge on the pathogenesis of this condition

Materials and Methods: The PubMed, Embase, and the Cochrane Library databases were searched for studies from inception to April 16, 2022, without language restrictions. Databases were searched for studies from inception 2010 to December, 2024, without language restrictions. Key words for search: Lipoprotein(a), Lp[a], dyslipidemia, classical vascular risk factors, cardiovascular disease, cardiovascular risk, cardiovascular risk factor, cerebral atherosclerosis. More than 37 sources was analyzed.

Conclusions: Cardiovascular diseases remain the leading cause of disability and mortality globally. While dyslipidemia is a well-established risk factor for coronary atherosclerosis and myocardial infarction, its role in the development of intracranial atherosclerosis is less well characterized. Current evidence suggests that plasma measurement of lipoprotein(a) [Lp(a)] using validated assays is sufficient for cardiovascular risk stratification, obviating the need for genetic testing of Lp(a). Advanced diagnostic methods have demonstrated that elevated Lp(a) levels are associated with increased vascular wall inflammation, reinforcing its causal role in atherogenesis. Intracranial atherosclerosis, a major cause of ischemic stroke, is linked to a heightened risk of recurrent cerebrovascular events and the progression of vascular cognitive impairment. Although Lp(a) is a recognized risk factor for stroke, its predictive value appears to be lower than that for coronary heart disease or composite cardiovascular outcomes. Therefore, the clinical implications of elevated Lp(a) levels in relation to carotid and intracranial atherosclerosis merit further investigation, particularly in the context of stroke prevention and vascular dementia.

KEY WORDS: cerebral atherosclerosis, Lipoprotein (a), cardiovascular risk

Wiad Lek. 2025;78(10):2216-2223. doi: 10.36740/WLek/210019 DOI

INTRODUCTION

Cardiovascular diseases (CVD) are the primary causes of disability and mortality globally. Over the past 70 years, significant advancements in medicine have allowed the identification of both established and new risk factors for these diseases, which, in turn, have facilitated the development and implementation of numerous pharmacological approaches for primary and secondary prevention [1].

AIM

The aim is to review information resources on this problem for the provision of modern knowledge in the pathogenesis of this pathology.

MATERIALS AND METHODS

The PubMed, Embase, and the Cochrane Library databases were searched for studies from inception to April 16, 2022, without language restrictions. Databases were searched for studies from inception 2010 to December, 2024, without language restrictions.

Key words for search: Lipoprotein(a), Lp[a], dyslipidemia, classical vascular risk factors, cardiovascular disease, cardiovascular risk, cardiovascular risk factor, cerebral atherosclerosis. More than 37 sources was analyzed.

INCLUSION CRITERIA

According to the PICOS (population, intervention, comparison, outcome, and study design), the criteria for considering studies for this review were as follows: types of participants: adult (age > 18 years) general population.

Types of studies: random controlled trails (RCTs), post hoc analyses of RCTs, or observational cohort studies.

EXCLUSION CRITERIA

Cross-sectional studies due to the high risk for bias, studies focusing on children and adolescents; studies not reporting multivariable adjusted outcomes. In addition, articles without sufficient data (reviews, editorials, preclinical studies) and studies not relevant for the purpose of the current meta-analysis were excluded. If the same population was used in multiple studies, we selected the article with the most information or the largest sample size.

REVIEW AND DISCUSSION

THE ROLE OF LIPOPROTEIN (A) AS A CVD RISK FACTOR

Despite substantial progress in CVD treatment, the residual risk of these diseases remains high, even among patients receiving adequate therapy. This is likely due to the still-high prevalence of classical risk factors, such as elevated cholesterol levels, smoking, hypertension, obesity, diabetes, and low physical activity. However, residual risk, which cannot be fully explained by these factors, points to the existence of additional contributors to disease development. Elevated concentrations of lipoprotein (a) [Lp(a)] are present in 10–20% of the population and have long been associated with an increased risk of ischemic heart disease (IHD) and other ischemic cardiovascular conditions. However, Lp(a) is currently not targeted for treatment in CVD prevention.

European and American guidelines, including the 2016 European Guidelines on Dyslipidemias and the 2018 American Heart Association/American College of Cardiology Guidelines, recommend measuring Lp(a) levels to assess risk in high-risk groups [2,3]. These recommendations align with the positions of the European Atherosclerosis Society and the National Lipid Association in the USA, which also advocate screening for elevated Lp(a) levels in individuals at moderate and high CVD risk. Early studies on the composition of Lp(a) suggested that this lipoprotein might contribute to the development of atherosclerosis through its lipid component. Modern techniques, such as fluorodeoxyglucose-positron emission tomography, confirm the presence of increased inflammation in the arterial walls of patients with elevated Lp(a) levels, further supporting its role in atherosclerosis progression [4-7]. A recent study based on data from the UK Biobank, encompassing over 460,000 individuals, became the largest investigation into the risk of atherosclerotic cardiovascular diseases (ASCVD) associated with Lp(a) levels [8]. The findings of this study validated the recommendations of the American College of Cardiology/American Heart Association for using Lp(a) as a marker of elevated risk. This marker may guide the initiation of statin therapy in individuals with a moderate (5%-7.4%) or intermediate (7.5%-19.9%) 10-year predicted risk of ASCVD.

The evidence linking Lp(a) levels to ASCVD is robust, as confirmed by a large population study that demonstrated a consistent risk of ASCVD with progressive increases in Lp(a) levels [9]. Regarding whether the size of apolipoprotein A (apo(A)) might be associated with ASCVD, there is significant interest. However, it is currently believed that measuring the molar concentration of Lp(a) is sufficient for risk assessment, as additional measurement of apo(A) size does not provide significant added value for clinical risk evaluation.

In 2009, two large genetic epidemiological studies were published, confirming Lp(a) as a causal risk factor for ischemic heart disease (IHD) [10]. The first study, conducted using the Mendelian randomization method and including over 40,000 individuals, demonstrated an increased risk of myocardial infarction (MI) associated with high Lp(a) levels and a reduced number of repeats in the LPA gene encoding kringle IV type 2 (KIV2), which is also linked to elevated Lp(a) concentrations. Instrumental analysis revealed that doubling Lp(a) concentration increases MI risk by approximately 20%. The second case-control study included 3,100 IHD cases genotyped for 49,000 gene variants across 2,100 candidate genes, identifying two single nucleotide polymorphisms (SNPs) in LPA (rs10455872 and rs3798220) with the strongest association to IHD risk among all tested SNPs. Together, these studies provided strong genetic evidence of a causal link between Lp(a) and IHD, consistent with earlier research examining Lp(a) phenotypes and their association with IHD risk. Additionally, further studies on the general population cohort in Copenhagen found that high Lp(a) levels and corresponding risk-related genotypes are associated with increased cardiovascular and overall mortality and more frequent recurrences of cardiovascular events, further confirming the genetic link between Lp(a) and CVD. The PROCARDIS study, which included approximately 4,000 patients and a control group of similar size, demonstrated that carriers of certain genetic variants had 39% lower median Lp(a) levels and a 21% reduced risk of IHD, indicating potential therapeutic benefits of lowering Lp(a) levels. Similarly, a large genetic study involving over 100,000 individuals, conducted by Emdin et al., reported a 29% reduction in IHD risk and decreased risks of peripheral arterial disease, heart failure, and stroke with a one standard deviation (SD) reduction in Lp(a) levels. Finally, recent Mendelian randomization studies using genetic data provided compelling evidence of a causal link between reducing Lp(a) levels and lowering the risk of cardiovascular diseases, highlighting the potential of such therapeutic approaches for future risk reduction [11-14].

For predicting CVD risk, measuring Lp(a) plasma levels using validated methods is sufficient, without requiring LPA

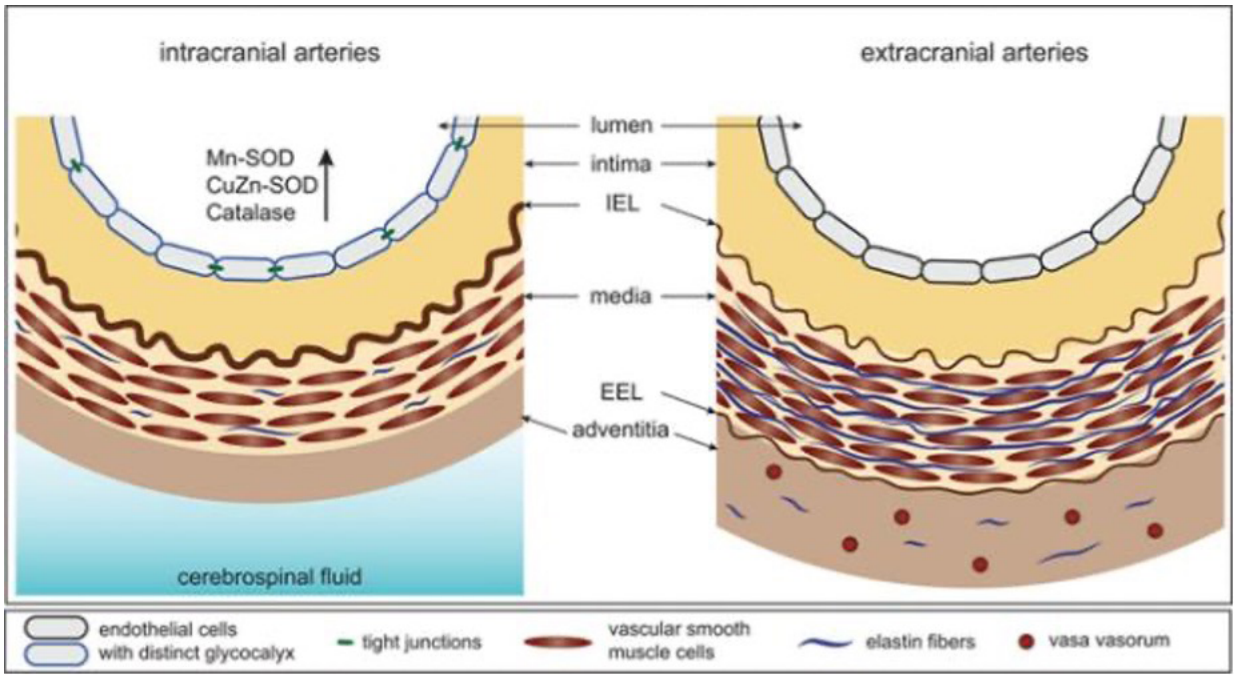

Fig. 1. Key Structural Characteristics of Intracranial and Extracranial Arteries Intracranial arteries are muscular-type arteries that generally have thinner medial and adventitial layers, fewer elastic medial fibers, and a thicker and denser internal elastic lamina (IEL). They lack an external elastic lamina (EEL) and vasa vasorum and are surrounded by cerebrospinal fluid rich in nutrients. Animal studies suggest the presence of tight junctions and a specific glycocalyx. Additionally, intracranial arteries are reported to exhibit enhanced antioxidant responses. CuZn-SOD refers to copper-zinc superoxide dismutase, while Mn-SOD refers to manganese superoxide dismutase.
Source: compiled by the authors based on [16]

genotyping. This is supported by the findings of the Bruneck study, where incorporating Lp(a) concentration data significantly improved risk prediction based on the Framingham and Reynolds risk scores, while adding information about apo(A) isoform size did not provide additional benefits [15].

THE ROLE OF LIPOPROTEIN (A) IN CEREBRAL ATHEROSCLEROSIS

Intracranial atherosclerosis, a leading cause of ischemic stroke, is associated with an increased risk of recurrent strokes and the development of dementia. Recent European studies have identified a much higher prevalence of intracranial atherosclerotic lesions than previously assumed, highlighting the potentially significant role of intracranial atherosclerotic disease as one of the most common causes of ischemic stroke worldwide. Even minor stenosis of intracranial vessels (<50%) can have clinical significance. The role of non-stenotic plaques in ischemic stroke development underscores the need for a deeper understanding of the mechanisms and pathogenesis of intracranial atherosclerosis (Fig. 1) [16].

Hoff (1972) noted that there are no significant differences in the chemical and enzymatic characteristics of plaques between intracranial and extracranial arteries [17]. Dyslipidemia is a well-established risk factor for coronary atherosclerosis and myocardial infarction; however, its role in intracranial atherosclerosis remains insufficiently studied. High levels of low-density lipoprotein cholesterol (LDL-C) are primarily associated with extracranial lesions, whereas a high apo(B) to apo(A) ratio and low apo(A) levels—the main protein of high-density lipoproteins (HDL-C)—correlate with intracranial lesions. Extracranial atherosclerosis may also act as a risk factor for developing intracranial lesions.

Key differences between intracranial and extracranial atherosclerosis include a later onset of disease and a more stable plaque phenotype in intracranial arteries. These differences may be attributed to the anatomical features of intracranial vessels, which may also relate to their role in regulating cerebrovascular resistance.

The progression of atherosclerosis involves stages of fatty streak formation and fibrous plaque development [18]. It has been hypothesized that plaque morphology may be more important for clinical outcomes than the degree of stenosis. The rupture of an unstable plaque, characterized by a large lipid core and a thin fibrous cap with signs of inflammation, can lead to thrombus formation and ischemic stroke in patients with intracranial atherosclerosis.

Studies have shown that elevated serum levels of Lp(a) are associated with a higher risk of cardiovascular diseases (CVD) and cerebrovascular disorders [19]. High Lp(a) levels are an independent risk factor not only for CVD but also for atherosclerotic obliterative diseases.

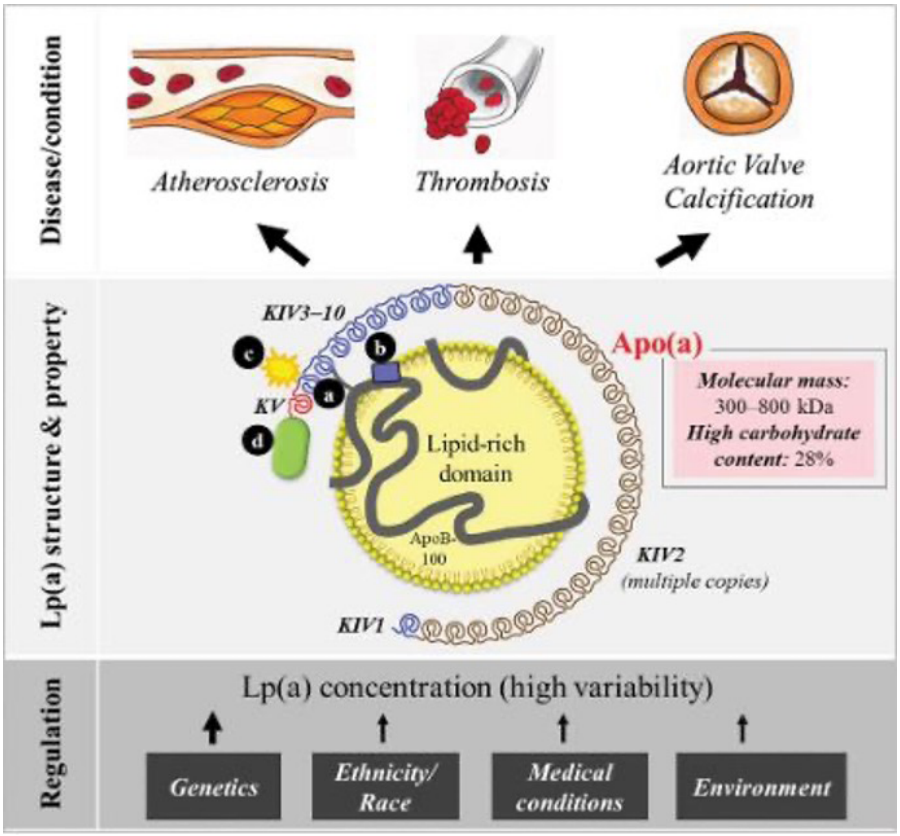

Fig. 2. Lipoprotein (a): Structure, Genetic Regulation, and Correction Options
Source: compiled by the authors based on [27]

However, the findings on its impact on cerebrovascular diseases remain inconclusive, and study data are still contradictory [19]. Moreover, elevated Lp(a) levels are often detected in clinical practice among patients with acute and recurrent strokes during lipid profile analysis.

Liqun et al. (2010) found that Lp(a) levels correlate with the severity of carotid atherosclerosis. Yubao and colleagues (2015) demonstrated that blood lipid levels vary in patients with different types of atherosclerotic plaques in intracranial arteries. However, further investigation is required to determine how specific lipid parameters affect the development of atherosclerotic plaques. In a study by Haitao (2015), the development of carotid atherosclerosis in patients with cerebral infarction was shown to correlate with levels of triglycerides (TG) and LDL-C. These markers were higher in patients with carotid plaques compared to those without such plaques [19 - 21].

LARGE-SCALE POPULATION STUDIES AND LP(A) IN ISCHEMIC STROKE RISK

A large-scale population study demonstrated that high Lp(a) levels are correlated with an increased risk of ischemic stroke. A recent retrospective case-control analysis confirmed that elevated Lp(a) levels positively correlate with ischemic stroke risk. This study also showed that high Lp(a) levels are an independent risk factor for carotid atherosclerotic stenosis. Furthermore, the risk of acute ischemic stroke is heightened in patients with such stenosis if their Lp(a) levels are elevated [22].

Lp(a) levels are relatively stable and are not influenced by factors such as sex, age, diet, smoking, lipid-altering medications, or environmental conditions. Carotid atherosclerosis correlates with Lp(a) and cholesterol levels in patients with acute ischemic stroke. Both Lp(a) and cholesterol serve as independent risk factors for this type of atherosclerosis, underscoring the necessity of developing therapies aimed at reducing Lp(a) levels [22].

The Larsson (2020) study utilized the UK Biobank cohort for Mendelian randomization to evaluate the causal effect of circulating Lp(a) levels on atherosclerotic and cerebrovascular diseases. The study included 367,586 individuals of European ancestry. The results confirmed a moderate association between genetically predicted Lp(a) levels and ischemic stroke risk [23]. A key advantage of this study was its evaluation and comparison of associations between genetically determined Lp(a) levels and atherosclerotic, cerebrovascular, thrombotic, and valvular diseases within a single European population cohort.

UNCERTAINTY IN LP(A) AND STROKE RELATIONSHIPS

Despite consistent evidence linking Lp(a) to ischemic heart disease (IHD), the impact of Lp(a) on ischemic stroke prevalence has been less conclusive in previous

observational studies. Most research focused on the general risk of ischemic stroke, leaving the relationship between Lp(a) levels and stroke subtypes poorly explored [24]. The association of Lp(a) with cerebrovascular diseases and stroke remains less clearly defined. However, recent data from pooled Danish cohorts confirmed that Lp(a) is a risk factor for stroke, albeit less prominently than for coronary artery disease or cardiovascular disease (CVD) [25].

Additionally, a large genetic analysis (N>100,000) identified four single nucleotide polymorphisms (SNPs) in the LPA gene associated with lower Lp(a) levels. These SNPs correlated with a 13% reduced risk of stroke when Lp(a) levels were reduced by one standard deviation (SD) [26].

WHAT IS LIPOPROTEIN (A)?

Lipoprotein (a) [Lp(a)] is a modified form of low-density lipoprotein (LDL) that acts as a genetically determined risk factor for atherosclerosis, IHD, stroke, thrombosis, and aortic stenosis. It comprises an LDL particle linked to apolipoprotein (a) [apo(a)] through a disulfide bond, forming a structure that is primarily synthesized in the liver [39]. Lipoprotein (a) [Lp(a)] is a modified form of low-density lipoprotein (LDL) and a genetically determined risk factor for the development of atherosclerosis, ischemic heart disease (IHD), stroke, thrombosis, and aortic stenosis [27] (Fig. 2). Structurally, Lp(a) is a variant of LDL, where apolipoprotein (a) [apo(a)] binds to apolipoprotein B100, forming a bond stabilized by disulfide bridges. These molecules create structures assembled in the membranes of hepatocytes [28].

Apo(a) is synthesized in the liver, where it binds to apolipoprotein B100 of LDL to form Lp(a). The assembly of Lp(a) is a two-step process: the first step is non-covalent and likely occurs intracellularly, while the second step, involving covalent bond formation, happens extracellularly [29]. Apo(a) has a unique structure, including looped domains stabilized by internal disulfide bonds known as "kringles." These domains are also present in other coagulation factors, such as plasminogen [30]. The relationship between plasma Lp(a) levels and apo(a) variants is inverse. Variations in the number of kringle repeats in the apo(a) structure can explain the variability of Lp(a) levels in populations. Individuals with fewer kringle repeats have smaller Lp(a) particles but higher serum concentrations, while larger apo(a) isoforms lead to protein accumulation in cell structures.

Approximately 20% of individuals have high Lp(a) levels exceeding 42 mg/dL, a characteristic noted in Danish cohorts. Additionally, Lp(a) levels may vary depending on racial or ethnic backgrounds, with higher concentrations typically observed in individuals of African descent compared to those of European or Asian origin [31]. The concentration of Lp(a) is predominantly genetically regulated and linked to the LPA gene locus on chromosome 6, which encodes apo(a). Since Lp(a) levels are genetically determined, there are currently no recommendations for genetic testing of the LPA gene. Measuring Lp(a) levels in blood is considered sufficient for evaluating the impact of genetic variants [32].

MANAGEMENT OF ELEVATED LIPOPROTEIN(A) LEVELS: CURRENT STRATEGIES AND FUTURE DIRECTIONS

For patients with elevated lipoprotein(a) [Lp(a)] levels, current guidelines suggest reducing concentrations to below 50 mg/dL, although specific therapeutic targets remain under debate. Nicotinic acid (niacin) has demonstrated the ability to reduce Lp(a) levels by approximately 20–30%; however, despite its favorable effects on other lipid parameters, clinical trials have not shown a significant reduction in cardiovascular event rates associated with its use [33]. Statins, while foundational in the treatment of hypercholesterolemia, exhibit inconsistent effects on Lp(a). Some studies suggest that statins may increase Lp(a) levels, although their benefits in reducing low-density lipoprotein cholesterol (LDL-C) and atherosclerotic cardiovascular risk remain undisputed. In patients with elevated Lp(a), statins remain a cornerstone of lipid-lowering therapy primarily for their LDL-C–lowering effect and associated reduction in ischemic heart disease (IHD) risk. PCSK9 inhibitors have shown promise, reducing Lp(a) levels by an average of 26% and improving cardiovascular outcomes in high-risk populations. Nevertheless, it remains unclear whether Lp(a) persists as an independent risk factor once LDL-C is effectively controlled with PCSK9-targeted therapy [34]. Lipid apheresis is reserved for patients with severely elevated Lp(a) refractory to pharmacotherapy. While apheresis can acutely reduce Lp(a) concentrations, levels often rebound post-procedure, and its utility is limited by cost and accessibility. Emerging therapies, particularly antisense oligonucleotides (e.g., AKCEA-Apo(a)-LRx) and small interfering RNA (siRNA) agents (e.g., pelacarsen), are currently in clinical development. These agents directly target apo(a) mRNA, leading to substantial reductions in Lp(a) levels in early-phase trials [35]. Their long-term efficacy and safety, particularly with respect to cardiovascular outcomes, require validation in large-scale randomized controlled studies. Hormonal therapies have also been explored. While estrogen may lower Lp(a) levels, it has not been associated with improved cardiovascular outcomes and is not recommended due to its complex risk-benefit profile. Conversely, testosterone replacement therapy (TRT) has shown

modest Lp(a)-lowering effects, but its clinical relevance in cardiovascular prevention remains uncertain and warrants further investigation [36]. L-carnitine supplementation has been linked to reductions in Lp(a) levels; however, it may paradoxically raise trimethylamine N-oxide (TMAO), a metabolite implicated in atherosclerosis development, raising concerns about its overall cardiometabolic safety. Several ongoing clinical trials are evaluating next-generation therapies aimed at inhibiting apo(a) synthesis, with the goal of substantially lowering Lp(a) levels and thereby attenuating cardiovascular risk [37]. The clinical impact of these agents must be established in terms of both biomarker reduction and hard outcomes such as myocardial infarction, stroke, and cardiovascular mortality.

CONCLUSIONS

Today, cardiovascular diseases remain the main cause of disability and mortality worldwide. Despite receiving correct therapy, a number of patients have a residual risk that cannot be explained by classical risk factors. Dyslipidemia is one of the risk factors for the development of atherosclerosis, in particular coronary atherosclerosis and myocardial infarction. It has been proven that by measuring the level of Lp(a) in plasma, the risk of cardiovascular diseases can be predicted. It has been established that Lp(a) can contribute to the development of atherosclerosis through its lipid component, but its specific role in the development of atherosclerosis of the carotid arteries in patients with intracranial atherosclerosis is not well understood. A number of studies in recent years have revealed a higher prevalence of intracranial atherosclerotic lesions than previously thought and, as a consequence, a significant role of intracranial atherosclerotic disease as one of the most common causes of ischemic stroke worldwide. Therefore, the clinical implications of elevated Lp(a) levels in relation to carotid atherosclerosis and intracranial sclerosis deserve further investigation, especially in the context of stroke and vascular dementia prevention.

REFERENCES

1. Xu J, Murphy SL, Kockanek KD, Arias E. Mortality in the United States, 2018. NCHS Data Brief. 2020;(355):1-8.
2. Reyes-Soffer G, Chair HN, Berglund L et al. Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association. Arteriosclerosis, Thrombosis, and Vascular Biology. 2022;42(1):e48-e60. doi:10.1161/ATV.0000000000000147. DOI
3. Townsend N, Wilson L, Bhatnagar P et al. Cardiovascular disease in Europe: epidemiological update 2016 [published correction appears in Eur Heart J. 2019;40(2):189. doi: 10.1093/eurheartj/ehy342]. DOI
4. Dhindsa DS, Sandesara PB, Shapiro MD, Wong ND. The Evolving Understanding and Approach to Residual Cardiovascular Risk Management. Front Cardiovasc Med. 2020;7:88. doi:10.3389/fcvm.2020.00088. DOI
5. Kamstrup PR. Lipoprotein(a) and Cardiovascular Disease. Clinical Chemistry. 2021;67(1):154–166. doi:10.1093/clinchem/hvaa247. DOI
6. Kamstrup PR. Lipoprotein(a) and ischemic heart disease--a causal association? A review. Atherosclerosis. 2010;211(1):15-23. doi:10.1016/j.atherosclerosis.2009.12.036. DOI
7. Wilson DP, Jacobson TA, Jones PH et al. Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association [published correction appears in J Clin Lipidol. 2022;16(5):e77-e95. doi: 10.1016/j.jacl.2022.08.007. DOI
8. Patel AP, Wang M, Pirruccello JP et al. Lp(a) (Lipoprotein[a]) Concentrations and Incident Atherosclerotic Cardiovascular Disease: New Insights From a Large National Biobank. Arterioscler Thromb Vasc Biol. 2021;41(1):465-474. doi:10.1161/ATVBAHA.120.315291. DOI
9. Chao TH, Lin TH, Cheng CI et al. 2024 Guidelines of the Taiwan Society of Cardiology on the Primary Prevention of Atherosclerotic Cardiovascular Disease --- Part I. Acta Cardiol Sin. 2024;40(5):479-543. doi:10.6515/ACS.202409_40(5).20240724A. DOI
10. Langsted A, Kamstrup PR, Nordestgaard BG. High lipoprotein(a) and high risk of mortality. Eur Heart J. 2019;40(33):2760-2770. doi:10.1093/eurheartj/ehy902. DOI
11. Madsen CM, Kamstrup PR, Langsted A et al. Lipoprotein(a)-Lowering by 50 mg/dL (105 nmol/L) May Be Needed to Reduce Cardiovascular Disease 20% in Secondary Prevention: A Population-Based Study. Arterioscler Thromb Vasc Biol. 2020;40(1):255-266. doi:10.1161/ATVBAHA.119.312951. DOI
12. Burgess S, Ference BA, Staley JR et al. Association of LPA Variants With Risk of Coronary Disease and the Implications for Lipoprotein(a)-Lowering Therapies: A Mendelian Randomization Analysis. JAMA Cardiol. 2018;3(7):619-627. doi:10.1001/jamacardio.2018.1470. DOI
13. Lamina C, Kronenberg F. Lp(a)-GWAS-Consortium. Estimation of the Required Lipoprotein(a)-Lowering Therapeutic Effect Size for Reduction in Coronary Heart Disease Outcomes: A Mendelian Randomization Analysis. JAMA Cardiol. 2019;4(6):575-579. doi:10.1001/jamacardio.2019.1041. DOI
14. Li YH, Chen JW, Lin TH et al. A performance guide for major risk factors control in patients with atherosclerotic cardiovascular disease in Taiwan. J Formos Med Assoc. 2020;119(3):674-684. doi:10.1016/j.jfma.2019.04.007. DOI

15. Willeit P, Kiechl S, Kronenberg F et al. Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck Study [published correction appears in J Am Coll Cardiol. 2016 Feb 16;67(6):737.
16. Ritz K, Denswil NP, Stam OC et al. Cause and mechanisms of intracranial atherosclerosis. Circulation. 2014;130(16):1407-1414. doi:10.1161/CIRCULATIONAHA.114.011147. DOI
17. Hoff HF. A histoenzymatic study of human intracranial atherosclerosis. Am J Pathol. 1972;67(3):583-600.
18. Kim JS, Kang DW, Kwon SU. Intracranial atherosclerosis: incidence, diagnosis and treatment. J Clin Neurol. 2005;1(1):1-7. doi:10.3988/jcn.2005.1.1.1. DOI
19. Zhao Y, Wang Z, Ji R et al. Relationship between carotid atherosclerosis and lipoprotein (a) in patients with acute ischemic stroke. Front. Neurol. 2024;15:1383771. doi: 10.3389/fneur.2024.1383771. DOI
20. Zhu L, Zheng J, Gao B et al. The correlation between lipoprotein(a) elevations and the risk of recurrent cardiovascular events in CAD patients with different LDL-C levels. BMC Cardiovasc Disord. 2022;22(1):171. doi:10.1186/s12872-022-02618-5. DOI
21. Di Fusco SA, Arca M, Scicchitano P et al. Lipoprotein(a): a risk factor for atherosclerosis and an emerging therapeutic target. Heart. 2022;109(1):18-25. doi:10.1136/heartjnl-2021-320708. DOI
22. Langsted A, Nordestgaard BG, Kamstrup PR. Elevated Lipoprotein(a) and Risk of Ischemic Stroke [published correction appears in J Am Coll Cardiol. 2020;75(18):2385. doi: 10.1016/j.jacc.2020.03.063. DOI
23. Larsson SC, Gill D, Mason AM et al. Lipoprotein(a) in Alzheimer, Atherosclerotic, Cerebrovascular, Thrombotic, and Valvular Disease: Mendelian Randomization Investigation. Circulation. 2020;141(22):1826-1828. doi:10.1161/CIRCULATIONAHA.120.045826. DOI
24. Pan Y, Li H, Wang Y et al. Causal Effect of Lp(a) [Lipoprotein(a)] Level on Ischemic Stroke and Alzheimer Disease: A Mendelian Randomization Study. Stroke. 2019;50(12):e439. doi: 10.1161/STR.0000000000000214. DOI
25. Gudbjartsson DF, Thorgeirsson G, Sulem P et al. Lipoprotein(a) Concentration and Risks of Cardiovascular Disease and Diabetes. J Am Coll Cardiol. 2019;74(24):2982-2994. doi:10.1016/j.jacc.2019.10.019. DOI
26. Arora P, Kalra R, Callas PW et al. Lipoprotein(a) and Risk of Ischemic Stroke in the REGARDS Study. Arterioscler Thromb Vasc Biol. 2019;39(4):810-818. doi:10.1161/ATVBAHA.118.311857. DOI
27. Reyes-Soffer G et al. "Lipoprotein (a): a genetically determined, causal, and prevalent risk factor for atherosclerotic cardiovascular disease: a scientific statement from the American Heart Association. Arterioscler Thromb and Vasc Biol. 2022;42(1):e48-e60. doi/full/10.1161/ATV.0000000000000147.
28. Langsted A, Nordestgaard BG, Kamstrup PR. Elevated lipoprotein(a) and risk of ischemic stroke. J Am Coll Cardiol. 2019;74:54–66. doi: 10.1016/j.jacc.2019.03.524. DOI
29. Farzam K, Zubair M, Senthilkumaran S. Lipoprotein A. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2024.
30. Scipione CA, Koschinsky ML, Boffa MB. Lipoprotein(a) in clinical practice: New perspectives from basic and translational science. Crit Rev Clin Lab Sci. 2018;55(1):33-54. doi:10.1080/10408363.2017.1415866. DOI
31. Shiyovich A, Berman AN, Besser SA et al. Lipoprotein(a) as a cardiovascular risk factor among patients with and without diabetes Mellitus: the Mass General Brigham Lp(a) Registry. Cardiovasc Diabetol. 2024;23(1):257. doi:10.1186/s12933-024-02348-2. DOI
32. Cegla J, France M, Marcovina SM, Neely RDG. Lp(a): When and how to measure it. Ann Clin Biochem. 2021;58(1):16-21. doi:10.1177/0004563220968473. DOI
33. Boffa MB, Koschinsky ML. Lipoprotein (a): truly a direct prothrombotic factor in cardiovascular disease? J. Lipid Res. 2016;57:745–757.
34. Volgman AS, Koschinsky ML, Mehta A, Rosenson RS. Genetics and Pathophysiological Mechanisms of Lipoprotein(a)-Associated Cardiovascular Risk. J Am Heart Assoc. 2024;13(12):e033654. doi:10.1161/JAHA.123.033654. DOI
35. Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. J Lipid Res. 2016;57(11):1953-1975. doi: 10.1194/jlr.R071233. DOI
36. Patel AP, Wang M, Pirruccello JP et al. Lp(a) (Lipoprotein[a]) Concentrations and Incident Atherosclerotic Cardiovascular Disease: New Insights From a Large National Biobank. Arterioscler Thromb Vasc Biol. 2021;41(1):465-474. doi:10.1161/ATVBAHA.120.315291. DOI
37. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I et al. Lipoprotein(a) Reduction in Persons with Cardiovascular Disease. N Engl J Med. 2020;382(3):244-255. doi:10.1056/NEJMoa190523. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Maria Cherska
V.P. Komisarenko Institute of Endocrinology and
Metabolism of the National Academy of
Medical Sciences of Ukraine

69 Vyshhorodska St, 04114 Kyiv, Ukraine
e-mail: emariya83@gmail.com

ORCID AND CONTRIBUTIONSHIP

Khrystyna Kukharchuk: 0000-0002-2495-2693 B D
Maria Cherska: 0000-0002-3689-2683 A E F
Tamara Kazykina: 0000-0002-1454-4717 B
Vitalina Pidlepenska: 0009-0004-9417-5297 B

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 09.01.2025
ACCEPTED: 28.08.2025

CREATIVE COMMONS 4.0