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LIPOPROTEIN (a) IN STROKE: FROM PATHOPHYSIOLOGY TO EMERGING THERAPEUTIC POSSIBILITIES

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ABSTRACT

Background: Lipoprotein(a) [Lp(a)] is a genetically determined lipoprotein increasingly recognized as an independent cardiovascular risk factor. Its role in ischemic stroke has gained attention, although its clinical relevance remains incompletely defined.
Objective: To summarize current evidence on the role of Lp(a) in stroke pathophysiology, its diagnostic value, and therapeutic possibilities.
Materials and Methods: A systematic review of literature published between 2016 and 2026 was conducted using PubMed, Web of Science, and Google Scholar. Meta-analyses, cohort studies, clinical trials, and guideline-based publications addressing Lp(a) and stroke were included.
Results: Elevated Lp(a) levels are associated with an increased risk of ischemic stroke, supported by observational studies and meta-analyses. This relationship is largely driven by proatherogenic, proinflammatory, prothrombotic, and antifibrinolytic mechanisms. Lp(a) levels are strongly genetically determined, primarily by LPA gene variants. Evidence does not support a significant association between Lp(a) and hemorrhagic stroke. Therapeutic options remain limited, as standard lipid-lowering therapies have minimal impact on Lp(a). PCSK9 inhibitors provide modest reductions, while novel RNA-based therapies show substantial Lp(a) lowering, though their clinical benefit in stroke prevention is yet to be confirmed.
Conclusions: Lp(a) is an important but underutilized marker of ischemic stroke risk. Further studies are needed to establish the clinical effectiveness of targeted therapies and to refine its role in routine risk assessment.

KEYWORDS

Lipoprotein (a), Stroke, Stroke Prevention, LPA gene, RNA-based therapy, ASO

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Introduction

Stroke is defined as the sudden onset of focal or global neurological deficits caused exclusively by vascular factors, lasting longer than 24 hours unless death occurs earlier or symptoms resolve following thrombolytic treatment [1,2]. It is the second leading cause of death among non-communicable diseases and the third most common cause of death and disability worldwide. According to the World Health Organization (WHO), nearly 12 million strokes occur annually, resulting in approximately 7 million deaths. Despite significant advances in stroke diagnostics, acute-phase treatment, and modification of risk factors such as hypertension, smoking, hypercholesterolemia, excessive salt intake, hyperglycemia, renal failure, and alcohol consumption, the incidence and mortality rates remain largely unchanged. Moreover, neurological deficits may persist for months or even lifelong [3]. Furthermore, the Lancet Neurology Commission predicts an increase in stroke-related mortality from 6.6 million in 2020 to 9.7 million by 2050 [4]. Therefore, identifying additional potential risk factors and developing effective methods to reduce them is essential for stroke prevention and limiting its consequences.

In recent years, growing evidence has suggested an increased cardiovascular risk-particularly coronary artery disease and aortic stenosis-in individuals with elevated levels of lipoprotein(a) [Lp(a)]. This molecule consists of a low-density lipoprotein (LDL) particle linked to apolipoprotein(a) [apo(a)]. It is involved in multiple mechanisms, including atherosclerosis, inflammation, and coagulation processes. Lp(a) levels are largely genetically determined, with minimal influence from diet and environmental factors [5,6].

Due to its pathophysiological role, the association between Lp(a) and other vascular diseases has been extensively studied. Increasing evidence suggests that Lp(a) can be considered an independent risk factor for stroke [7,8].

The aim of this article is to summarize current evidence regarding the role of lipoprotein(a) in stroke pathogenesis, discuss indications for measuring Lp(a) levels, and review available therapeutic options in clinical practice.

Materials and Methods

This study was conducted as a systematic search of current scientific data regarding the role of lipoprotein(a) in the pathogenesis, diagnosis, and therapeutic management of stroke. The literature search was performed using the following electronic databases: PubMed, Google Scholar, and Web of Science. The following keywords were used: "lipoprotein(a)", "stroke", "Lp(a)", "apheresis", "cerebrovascular disease", "atherosclerosis", "thrombosis", "stroke risk", "PCSK9 inhibitors", and "RNA therapy". The analysis included meta-analyses, systematic reviews, cohort studies, clinical trials, and guideline-based publications published in English or Polish between 2016 and 2026. Particular emphasis was placed on studies evaluating the association between Lp(a) levels and stroke, determinants of elevated Lp(a), underlying pathophysiological mechanisms, and therapeutic strategies aimed at reducing Lp(a) levels and their effectiveness in stroke prevention. Case reports, experimental studies based solely on animal models, and publications without full-text access were excluded. In cases of overlapping data, studies with the highest methodological quality or largest sample size were selected.

Results

Characteristics of Lipoprotein(a)

Lipoprotein(a) is a spherical macromolecular complex structurally similar to low-density lipoprotein (LDL). Like LDL, it contains apolipoprotein B-100 (apoB-100), has a comparable size, and an identical lipid composition. However, it is distinguished by the presence of apolipoprotein(a) [apo(a)], which is covalently attached to apoB-100 via a disulfide bond [6,9,10]. Apo(a) consists of multiple repeating protein loops known as kringle domains, which surround the lipid core of the particle. Two types of kringle domains are present: KIV and KV [7,9–11]. KV occurs as a single copy, whereas KIV exists in 10 different subtypes and is repeated between 12 and 52 times, resulting in 34 isoforms of apo(a). This makes apo(a) one of the most polymorphic lipoproteins [11,12].

Apo(a) exhibits significant structural homology with plasminogen. Although plasminogen contains a greater variety of kringle domains (KI–KV), approximately 94% of the amino acid sequence of apo(a) is homologous to that of plasminogen. Apo(a) also contains lysine-binding sites, which interfere with receptors necessary for plasminogen activation [10,11].

The physiological role of Lp(a) remains unclear. However, numerous pathophysiological processes associated with Lp(a) have been described, including proatherogenic, proinflammatory, prothrombotic, and antifibrinolytic effects [5,7,10].

The exact site of Lp(a) synthesis has not been fully elucidated. Some studies suggest that it is produced primarily in hepatocytes, while others indicate that its formation may occur on the hepatocyte surface or extracellularly [10,11].

Lp(a) Concentration

Lp(a) levels are predominantly genetically determined and show significant interindividual and interpopulation variability. They remain relatively constant throughout life, with minimal influence from environmental factors such as diet and physical activity [9]. Plasma concentrations range widely, from 1 mg/dL to over 1000 mg/dL [11,13].

Lp(a) is one of the most strongly genetically regulated lipoproteins. It is estimated that 70–90% of its plasma concentration is determined by a single gene, LPA, located on chromosome 6 (6q2.6–2.7), which encodes apo(a) [5,6,12,14]. This gene is located within the same cluster as the plasminogen (PLG) gene and shares approximately 70% homology with it [10,11].

The LPA gene is highly polymorphic due to variability in the number of kringle IV type 2 (KIV-2) repeats, resulting in multiple Lp(a) isoforms with different molecular weights. A strong inverse relationship has been demonstrated between isoform size and plasma concentration. Up to 70% of variability in Lp(a) levels is attributed to KIV-2 copy number, with an additional 22% explained by other factors [6,9]. Smaller isoforms, characterized by fewer KIV-2 repeats, are associated with higher plasma concentrations due to more efficient hepatic synthesis, whereas larger isoforms correspond to lower Lp(a) levels [6,13].

Due to strong genetic determination, significant differences in Lp(a) levels have been observed across ethnic groups. Data from the UK Biobank indicate mean Lp(a) levels of approximately 16, 19, 31, and 75 nmol/L among Chinese, White, South Asian, and Black individuals, respectively [7,15].

Among non-genetic factors, kidney disease, thyroid disorders, liver disease, inflammation, and statin therapy have been shown to influence Lp(a) levels. Reduced levels are observed in liver dysfunction, hyperthyroidism, and sepsis, whereas hypothyroidism, renal failure, statin use, and menopause are associated with increased concentrations [15]. The effects of diet, diabetes, and aging remain inconsistent across studies [9,10].

According to the 2025 ESC/EAS dyslipidemia guideline update, Lp(a) levels above 50 mg/dL (125 nmol/L) are associated with increased cardiovascular risk [16].

Pathophysiological Mechanisms

Lipoprotein(a) is involved in multiple complex and interrelated mechanisms. In the context of stroke, its proatherogenic, proinflammatory, prothrombotic, and antifibrinolytic effects are of greatest importance [13].

Lp(a) contributes to atherogenesis through several pathways. Owing to its lysine-binding sites, Lp(a) attaches to components of the extracellular matrix (ECM) within the arterial wall. Compared to LDL particles, Lp(a) shows greater accumulation in the vascular wall. It promotes the expression of vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and intercellular adhesion molecule-1 (ICAM-1), thereby enhancing monocyte adhesion to the endothelium and initiating atherosclerotic plaque formation [5,13,14].

Its proatherogenic effect is further amplified by inflammation mediated by oxidized phospholipids (OxPLs) carried by Lp(a). Elevated Lp(a) levels are associated with increased OxPL deposition in the arterial wall, promoting inflammation and vascular calcification. Chronic vascular inflammation contributes to plaque instability [5,7,14].

Due to structural similarity between apo(a) and plasminogen, Lp(a) competes for binding sites on fibrin, leading to inhibition of plasminogen activation into plasmin and, consequently, impaired fibrinolysis. Smaller apo(a) isoforms exhibit higher affinity to binding sites on fibrin [13,14]. Additionally, Lp(a) interferes with the binding of tissue plasminogen activator (t-PA) to platelet surfaces and increases the production of plasminogen activator inhibitor-1 (PAI-1) [14].

Another consequence of reduced plasmin formation is decreased activation of transforming growth factor-β (TGF-β), which promotes proliferation of vascular smooth muscle cells [7,14].

These mechanisms also occur in cerebral vessels and may directly contribute to ischemic cerebrovascular events [7].

Clinical Data

Lp(a) and Ischemic Stroke. Following the recognition of elevated Lp(a) as a predictor of cardiovascular disease, increasing attention has been given to its association with stroke risk. Numerous observational studies and meta-analyses have demonstrated a correlation between elevated plasma Lp(a) levels and the incidence of ischemic stroke [7].

A meta-analysis of 41 studies by Kumar et al. (2021) showed a statistically significant association between elevated Lp(a) and ischemic stroke risk (SMD 0.76; 95% CI 0.53–0.99). This relationship was observed in both Asian (SMD 0.81; 95% CI 0.56–1.05) and Caucasian populations (SMD 0.72; 95% CI 0.36–1.08) [17]. Similarly, analysis of the REGARDS study (Arora et al., 2019) demonstrated that ischemic stroke occurred more frequently in individuals within the highest Lp(a) quartile compared to the lowest, with a hazard ratio (HR) of 1.45 (95% CI 0.96–2.19). The association appeared stronger in Black individuals (HR 1.96; 95% CI 1.10–3.46) than in White individuals (HR 1.14; 95% CI 0.64–2.04), although this difference was not statistically significant. No significant differences were observed between sexes [8]. Kao et al. (2025) reported that Lp(a) levels >125 nmol/L were associated with increased ischemic stroke risk (HR 1.12; 95% CI 1.02–1.22; $p = 0.019$), although this association was observed only in men. The relationship was independent of age and race [18].

In the Copenhagen General Population Study and the Copenhagen City Heart Study, Langsted et al. (2019) demonstrated that individuals with Lp(a) levels above 93 mg/dL had a 60% higher risk of ischemic stroke compared to those with levels below 10 mg/dL. Additionally, genetic variants such as rs10455872 and a higher number of kringle IV type 2 repeats were associated with increased stroke risk, supporting a causal genetic link [19]. Elevated Lp(a) also amplifies stroke risk in the presence of other risk factors such as advanced age, hypertension, and smoking [19].

Overall, Lp(a) may serve as a predictor of ischemic stroke; however, the evidence is less robust than for coronary artery disease, highlighting the need for further research. The relationship may vary depending on stroke subtype, population characteristics, and coexisting risk factors.

Lp(a) and Hemorrhagic Stroke. In contrast to ischemic stroke, the association between Lp(a) and hemorrhagic stroke remains unclear.

Analysis of UK Biobank data (Kao et al., 2025) showed no significant association between Lp(a) levels >125 nmol/L and the risk of hemorrhagic stroke (HR 0.95; 95% CI 0.79–1.13), subarachnoid hemorrhage (HR 0.96; 95% CI 0.73–1.26), or intracerebral hemorrhage (HR 0.92; 95% CI 0.73–1.16) [18]. Similarly, Daghlas et al. (2026) found no association between genetically predicted Lp(a) levels and all-cause ICH and deep ICH [20].

Some smaller studies have reported conflicting findings. For example, Fu et al. (2020) observed a 1.64-fold increased risk of hemorrhagic stroke in men with elevated Lp(a) levels in a Chinese population. However, this study included only 196 cases [21]. Conversely, a study in peritoneal dialysis patients suggested a potential protective effect of higher Lp(a) levels [22].

Overall, based on larger and more robust datasets, Lp(a) does not appear to be a risk factor for hemorrhagic stroke and may have a neutral or even protective role. However, further high-quality studies are needed.

Lp(a) and Stroke Recurrence. Cohort studies indicate that elevated Lp(a) levels may also increase the risk of recurrent ischemic stroke, not only primary events. This is particularly important given the limited options for reducing Lp(a) levels compared to other modifiable risk factors. Due to its proatherogenic properties, Lp(a) appears to be especially relevant in large-artery stroke subtypes [7,23].

Lange et al. (2017) demonstrated that Lp(a) levels above 30 mg/dL were associated with a 2.6-fold increased risk of recurrent cerebrovascular events in patients after a first ischemic stroke [24].

However, the number of studies addressing stroke recurrence remains limited, and further research is needed.

Measurement of Lp(a)

Currently, there are no specific guidelines regarding Lp(a) measurement in the context of stroke risk assessment. However, the European Atherosclerosis Society and the National Lipid Association recommend measuring Lp(a) at least once in every adult to identify individuals at increased risk of atherosclerotic cardiovascular disease. This is particularly relevant in patients with premature cardiovascular events, including stroke, and in cases of ischemic stroke of unknown etiology [16,25]. In pediatric populations, routine screening is not recommended due to insufficient clinical evidence. Measurement may be considered in children and adolescents with a history of ischemic or hemorrhagic stroke. In this group, the absence of typical environmental risk factors suggests a potentially greater role of Lp(a) in stroke pathogenesis [23].

Therapeutic Interventions

Despite strong epidemiological and genetic evidence linking elevated Lp(a) levels with ischemic stroke risk, therapeutic options for reducing Lp(a) remain limited. Currently, no medications are specifically approved for lowering Lp(a). However, increasing evidence has emerged regarding the effects of existing lipid-lowering therapies, as well as novel agents directly targeting Lp(a). Importantly, the extent to which Lp(a) reduction translates into clinical benefit is still under investigation [7, 10, 16].

At present, in patients with elevated Lp(a), the cornerstone of management is aggressive control of modifiable cardiovascular risk factors, including LDL cholesterol, controlling blood pressure, optimizing glycemic control, smoking cessation, and weight reduction [23].

PCSK9 Inhibitors. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, such as evolocumab, alirocumab, and inclisiran, have been shown to reduce Lp(a) levels by approximately 20–30% [7,26]. This effect is likely related to enhanced hepatic clearance of Lp(a) particles via upregulation of LDL receptors [27,28]. In the ODYSSEY OUTCOMES trial, treatment with alirocumab was associated with a reduced risk of stroke, independent of baseline LDL levels [29]. Similarly, the FOURIER trial demonstrated that adding evolocumab to statin therapy reduced the incidence of all types of stroke [30]. However, it remains unclear whether these clinical benefits are directly attributable to Lp(a) reduction or primarily driven by LDL lowering.

Statins. Statins remain the cornerstone of lipid-lowering therapy and are widely used in the primary and secondary prevention of ischemic stroke. However, in contrast to their well-established LDL-lowering effect, statins have minimal impact on Lp(a) levels and may even lead to a modest increase of up to 10% [7,10,14,31]. The mechanism underlying this increase is not fully understood. Importantly, there is no evidence to suggest

that statin-induced increases in Lp(a) translate into a higher risk of stroke. Given their proven benefit in reducing cardiovascular and cerebrovascular events, current ESC/EAS guidelines recommend continued statin therapy regardless of Lp(a) levels [7, 16, 31]. Additionally, recommendations proposed by Galimberti et al. (2022) suggest estimating the degree of LDL reduction required to offset the excess cardiovascular risk associated with elevated Lp(a), taking into account patient age and baseline Lp(a) concentration [32].

ASO. In recent years, significant progress has been made in the development of therapies directly targeting Lp(a) synthesis. Antisense oligonucleotides (ASO) represent one such approach. These synthetic single-stranded nucleotides degrade LPA mRNA via RNase H, thereby reducing hepatic production of apo(a). Pelacarsen is the most extensively studied ASO. It has demonstrated dose-dependent reductions in Lp(a) levels ranging from approximately 30% to 90% in early-phase clinical trials [7,31,33]. The drug is administered via subcutaneous injection and is generally well tolerated, with mild injection-site reactions being the most commonly reported adverse events. Pelacarsen is a second-generation ASO conjugated with N-acetylgalactosamine (GalNAc), which enhances hepatocyte uptake, improves efficacy, and allows for less frequent dosing (monthly administration) [7,31]. The ongoing phase 3 randomized controlled trial Lp(a)HORIZON is expected to determine whether these reductions translate into reduced cardiovascular morbidity and mortality[33].

siRNA-Based Therapies. Another promising therapeutic strategy involves small interfering RNA (siRNA). These double-stranded RNA molecules selectively inhibit LPA gene expression, leading to reduced apo(a) synthesis in hepatocytes and consequently lower plasma Lp(a) levels [7, 26, 31]. Among the most advanced agents in this class is olpasiran, which has demonstrated substantial efficacy in lowering Lp(a) concentrations in clinical studies. Depending on the dosing regimen, reductions of approximately 70% to over 100% have been reported [31, 34]. Notably, the therapeutic effect appears to be sustained over time, with significant reductions persisting for several months after administration. For example, in some dosing groups, a reduction of around 40% was maintained for more than 12 months following a single dose [26]. Treatment with siRNA-based therapies has been generally well tolerated, with no major safety concerns identified to date. The most commonly reported adverse events are mild and limited to injection-site reactions [34]. Similar efficacy and safety profiles have also been observed for other agents in this class, such as zerlasiran and lepodisiran [26]. Given their potent and sustained effects, as well as infrequent dosing schedules (every months), siRNA-based therapies may offer high patient adherence and represent a promising future strategy for stroke prevention. Currently, large-scale outcome trials, such as OCEAN(a)-OUTCOMES, are underway to determine whether these therapies reduce major adverse cardiovascular events [7,31]. Their specific impact on stroke prevention remains to be established.

Discussion

In recent years, lipoprotein(a) has gained increasing recognition as a significant cardiovascular risk factor. Emerging evidence suggests that elevated Lp(a) levels can be considered an independent risk factor for ischemic stroke. This association has been consistently demonstrated in observational studies and meta-analyses across different populations and in the presence of other risk factors. Although, the strength of the relationship appears to be less pronounced than in the case of coronary artery disease. Importantly, genetic data provide strong support for a causal link between Lp(a) and cerebrovascular events. Variants within the LPA gene, including polymorphisms such as rs10455872, as well as a lower number of kringle IV type 2 repeats, are associated with higher plasma Lp(a) concentrations and increased stroke risk. These findings suggest that Lp(a) is not merely a marker of vascular risk but may play a direct role in disease pathogenesis. Clinical studies indicate that elevated Lp(a) levels are associated not only with the occurrence of primary ischemic stroke but also with an increased risk of recurrent cerebrovascular events. However, the number of studies addressing stroke recurrence is relatively small, and further research is needed to confirm these observations. In contrast, no consistent association has been demonstrated between Lp(a) and hemorrhagic stroke.

The mechanisms underlying this relationship are complex and multifactorial. Lp(a) has been shown to promote atherosclerosis, destabilize atherosclerotic plaques, enhance vascular inflammation, and interfere with fibrinolysis, thereby creating a prothrombotic environment.

From a clinical perspective, measurement of Lp(a) appears justified, particularly in individuals with premature or unexplained cardiovascular events, including ischemic stroke. Current guidelines recommend at least one lifetime measurement in adults. However, thresholds specifically defining increased stroke risk

remain insufficiently established. This limits the integration of Lp(a) into routine cerebrovascular risk stratification.

Therapeutic options targeting Lp(a) are currently limited. Conventional lipid-lowering therapies, including statins, have minimal or no effect on Lp(a) levels and may even lead to a modest increase. Nevertheless, their overall benefit in reducing cardiovascular and cerebrovascular risk supports their continued use. PCSK9 inhibitors have been shown to reduce Lp(a) levels by approximately 20–30% and are associated with a reduction in stroke incidence, although it remains uncertain whether this effect is directly mediated by Lp(a) lowering.

In recent years, significant progress has been made in the development of therapies specifically targeting Lp(a). Antisense oligonucleotides and siRNA-based therapies have demonstrated substantial and sustained reductions in Lp(a) levels in clinical trials. These approaches represent a major advancement in the field. However, it remains unclear whether such reductions translate into meaningful clinical benefits, particularly in terms of stroke prevention. Ongoing large-scale randomized trials are expected to provide further insight into this issue.

Taken together, Lp(a) appears to be an important but still underutilized factor in cerebrovascular risk assessment. Further large-scale, prospective studies are required to clarify its role in stroke pathogenesis, establish clinically relevant thresholds, and determine the effectiveness of targeted therapeutic interventions.

Conclusions

Lipoprotein(a) represents an important factor in the assessment of ischemic stroke risk. Elevated Lp(a) levels are associated with increased risk, while current therapeutic options for reducing its concentration remain limited. Conventional lipid-lowering therapies have little or no effect on Lp(a). Emerging RNA-based and antisense therapies show promising results in significantly lowering Lp(a) levels; however, their clinical effectiveness in stroke prevention has yet to be established. At present, elevated Lp(a) should prompt intensified management of other modifiable stroke risk factors. Further research is needed to refine recommendations regarding Lp(a) measurement and to determine the role of targeted therapies in stroke prevention.

Authors' contribution:

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