УДК 616.13-004.6:577.115:616.153.915(048.8) Scientific reviews

LIPOPROTEIN (a) AS A MODERN MARKER OF CARDIOVASCULAR RISK: FROM PATHOPHYSIOLOGY TO THERAPEUTIC PERSPECTIVES (LITERATURE REVIEW)

Khrebtii H.I., Khrebtii O.Y.

Bukovinian State Medical University, Chernivtsi, Ukraine

Key words: *lipoprotein(a), atherosclerosis, oxidized phospholipids, cardiovascular risk, aortic valve stenosis, pelacarsen, muvalaplin.*

Bukovinian Medical Herald. 2026. V. 30, № 1 (117). P. 131-137.

DOI: *10.24061/2413-0737.30.1.117.2026.20*

E-mail: *galinahrebtiy@gmail.com olhahrebtiy@gmail.com*

Resume. *Atherosclerotic cardiovascular diseases (ASCVD) remain the leading cause of mortality worldwide. Despite the widespread use of statins and the effective control of low-density lipoprotein cholesterol (LDL-C), a significant residual risk of cardiovascular events persists. In recent years, lipoprotein(a) (Lp(a)) has emerged as a critical, genetically determined risk factor. Approximately 20% of the global population has elevated Lp(a) levels (>50 mg/dL), which translates to increased susceptibility to coronary artery disease, ischemic stroke, and calcific aortic valve stenosis. Unlike traditional lipid risk factors, Lp(a) levels are largely resistant to lifestyle modifications and standard lipid-lowering therapies.*

The aim *– to comprehensively analyze the current literature regarding the molecular structure, genetic regulation, and pathogenic mechanisms of Lp(a), specifically focusing on its proinflammatory properties mediated by oxidized phospholipids. Furthermore, the review aims to evaluate the clinical evidence linking Lp(a) to cardiovascular outcomes and to discuss the emerging landscape of RNA-targeted therapies and small molecule inhibitors.*

Results. *Lp(a) is a hybrid lipoprotein consisting of an LDL-like particle covalently linked to apolipoprotein(a) (apo(a)), a homolog of plasminogen. Its pathogenicity is driven by three synergistic mechanisms: proatherogenic retention in the arterial wall, proinflammatory activation of the endothelium via oxidized phospholipids (OxPL), and potential antifibrinolytic effects. Current guidelines (AHA/ACC, EAS) recommend screening for Lp(a) at least once in a lifetime to stratify cardiovascular risk. While traditional therapies (statins, ezetimibe) have minimal impact on Lp(a), novel specific therapies are in advanced clinical development. Antisense oligonucleotides (pelacarsen) and small interfering RNAs (olpasiran, lepodisiran) have demonstrated potent dose-dependent reductions in Lp(a) levels (>80-90%) in phase 2 and 3 trials. Additionally, muvalaplin, the first oral small molecule inhibitor of Lp(a) formation, has shown promising results in phase 1 studies.*

Conclusions. *Lp(a) represents a distinct and causal risk factor for ASCVD and aortic stenosis that requires specific attention in clinical practice. The upcoming completion of cardiovascular outcome trials will likely establish Lp(a)-lowering therapy as a new pillar of preventive cardiology.*

ЛІПОПРОТЕЇН (а) ЯК СУЧАСНИЙ МАРКЕР СЕРЦЕВО-СУДИННОГО РИЗИКУ: ВІД ПАТОФІЗІОЛОГІЇ ДО ТЕРАПЕВТИЧНИХ ПЕРСПЕКТИВ (ОГЛЯД ЛІТЕРАТУРИ)

Хребтій Г.І., Хребтій О.Я.

Ключові слова: *ліпопротеїн(а), атеросклероз, окиснені фосфоліпіди, серцево-судинний ризик, стеноз аортального клапана, пелакарсен, мувалаплін.*

Буковинський медичний вісник. 2026. Т. 30, № 1 (117). С. 131-137.

Резюме. *Атеросклеротичні серцево-судинні захворювання (АССЗ) залишаються провідною причиною смертності у всьому світі. Незважаючи на широке застосування статинів та ефективний контроль холестерину ліпопротеїнів низької щільності (ХС ЛПНЩ), значний залишковий ризик серцево-судинних подій зберігається. Останніми роками ліпопротеїн(а) (Lp(a)) виокремився як критичний, генетично детермінований фактор ризику. Приблизно 20% населення світу має підвищені рівні Lp(a) (>50 мг/дл), що призводить до підвищеної схильності ішемічної хвороби серця, ішемічного інсульту та кальцифікуючого стенозу аортального клапана. На відміну від традиційних ліпідних факторів ризику, рівні Lp(a) є значною мірою резистентними до модифікації способу життя та стандартної ліпідознижувальної терапії.*

Мета роботи *– всебічно проаналізувати сучасну літературу щодо молекулярної структури, генетичної регуляції та патогенетичних*

механізмів Lp(a), зосереджуючись, зокрема, на його прозапальних властивостях, опосередкованих окисненими фосфоліпідами. Крім того, огляд має на меті оцінити клінічні докази, що пов'язують Lp(a) із серцево-судинними наслідками, та обговорити нові перспективи РНК-орієнтованої терапії та інгібіторів малих молекул.

Результати. *Lp(a) – це гібридний ліпопротеїн, що складається з ЛПНЩ-подібної частинки, ковалентно зв'язаної з аполіпопротеїном(а) (апо(а)), гомологом плазміногена. Його патогенність зумовлена трьома синергічними механізмами: проатерогенною затримкою в стінці артерії, прозапальною активацією ендотелію через окиснені фосфоліпіди (OxPL) та потенційними антифібринолітичними ефектами. Сучасні рекомендації (AHA/ACC, EAS) радять проводити скринінг на Lp(a) принаймні один раз протягом життя для стратифікації серцево-судинного ризику. Хоча традиційна терапія (статини, езетиміб) має мінімальний вплив на Lp(a), новітні специфічні методи лікування перебувають на пізніх стадіях клінічної розробки. Антисмислові олігонуклеотиди (пелакарсен) та малі інтерферуючі РНК (олпасиран, леподисиран) продемонстрували потужне дозозалежне зниження рівня Lp(a) (>80-90%) у дослідженнях 2-ї та 3-ї фаз. Крім того, мувалаплін, перший пероральний маломолекулярний інгібітор утворення Lp(a), показав багатообіцяючі результати в дослідженнях 1-ї фази.*

Висновки. *Lp(a) є окремим та причинним фактором ризику АССЗ і стенозу аорти, що потребує особливої уваги в клінічній практиці. Очікуване завершення досліджень серцево-судинних наслідків, ймовірно, затвердить терапію зниження Lp(a) як новий наріжний камінь превентивної кардіології.*

Introduction. The quest to reduce the burden of cardiovascular disease has traditionally focused on low-density lipoprotein cholesterol (LDL-C). However, even with aggressive LDL-C lowering, many patients continue to experience recurrent cardiovascular events, a phenomenon known as residual risk. Lipoprotein(a), or Lp(a), was first described by Kåre Berg in 1963 as an antigenic variant of LDL [1]. For decades, it was considered a biochemical curiosity with unclear clinical relevance. Today, converging evidence from genome-wide association studies (GWAS), Mendelian randomization analyses, and large epidemiological cohorts has firmly established Lp(a) as an independent, causal, and prevalent risk factor for myocardial infarction, ischemic stroke, and calcific aortic valve stenosis (CAVD) [2, 3]. According to the 2022 Scientific Statement from the American Heart Association (AHA), approximately one in five individuals globally has Lp(a) levels ≥50 mg/dL (approx. 125 nmol/L), placing them at elevated cardiovascular risk [4]. Crucially, Lp(a) concentrations are 70–90% genetically determined by the LPA gene locus and are stable throughout an individual's lifetime, showing minimal response to diet, exercise, or statin therapy [5].

Biology, structure, and genetics. Lp(a) consists of a cholesterol-rich LDL-like particle containing apolipoprotein B-100 (apoB), which is covalently linked via a disulfide bridge to a unique glycoprotein, apolipoprotein(a) (apo(a)) [6]. The assembly of Lp(a) occurs on the surface of hepatocytes or in the space of Disse, though the precise mechanism remains a subject of investigation [7]. The unique structural feature of apo(a) is the presence of "kringles" – protein domains with a triple-loop structure stabilized by disulfide bonds, homologous to the kringle IV and V domains of plasminogen. Apo(a) contains a single copy of kringle V, a single copy of kringle IV type 1 and types 3–10, but a variable number of kringle IV type 2 (KIV-2) repeats [6, 8].

The LPA gene, located on chromosome 6q26-27, evolved from the plasminogen gene (PLG) [9]. The number of KIV-2 repeats in the LPA gene varies widely among individuals (from <10 to >50 repeats), giving rise to different apo(a) isoforms. There is a strong inverse relationship between the size of the apo(a) isoform and plasma Lp(a) concentration: individuals with fewer KIV-2 repeats produce smaller apo(a) isoforms, which are synthesized and secreted more efficiently, leading to higher plasma Lp(a) levels [10]. This size polymorphism explains a significant proportion of the variation in Lp(a) levels seen in the general population.

Epidemiology and Population Differences. The distribution of Lp(a) concentrations in the population is highly skewed, with most individuals having low levels and a "tail" of individuals with extremely high values. However, these patterns vary significantly across different ethnic groups, which is a critical consideration for global cardiovascular risk assessment. Data from the Multi-Ethnic Study of Atherosclerosis (MESA) and the Dallas Heart Study indicate that individuals of African descent have median Lp(a) levels approximately two- to three-fold higher than Caucasians, Hispanics, or East Asians [11]. Despite these higher absolute levels, the association between Lp(a) and cardiovascular risk in Black populations appears to be less linear than in Caucasians, suggesting possible differences in the pathogenicity of different apo(a) isoform sizes or modifying genetic factors [12].

Gender differences also play a physiological role. While Lp(a) levels are generally similar between men and

premenopausal women, concentrations tend to increase in women after menopause. Studies have shown that the transition to menopause is associated with a rise in Lp(a) levels, potentially contributing to the increased cardiovascular risk observed in postmenopausal women [13]. This suggests a hormonal regulation component, although hormone replacement therapy (HRT) has been shown to lower Lp(a) only modestly.

Pathophysiological mechanisms. Lp(a) promotes cardiovascular disease through three distinct but interrelated pathological pathways. Like LDL, Lp(a) contains cholesterol and can penetrate the arterial intima. However, Lp(a) is more prone to retention in the subendothelial space than LDL because it binds avidly to proteoglycans/glycosaminoglycans in the extracellular matrix via its apo(a) component [14]. Once trapped, it undergoes oxidation and contributes to the formation of the foam cells and the necrotic core of the atherosclerotic plaque.

Kidney Function and Catabolism. The kidney plays a significant, albeit not fully understood, role in the catabolism of Lp(a) and its fragments. Elevated Lp(a) levels are highly prevalent in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). As the glomerular filtration rate (GFR) declines, Lp(a) concentrations typically rise. Mechanisms proposed include reduced renal excretion of apo(a) fragments and increased hepatic synthesis induced by the nephrotic syndrome milieu [15]. Importantly, the relationship is bidirectional: not only does CKD increase Lp(a), but elevated Lp(a) is an independent predictor of CKD progression. The pro-inflammatory oxidized phospholipids carried by Lp(a) may contribute to renal vascular injury and glomerulosclerosis. In patients on dialysis, extremely high Lp(a) levels are associated with a dramatically increased risk of cardiovascular death and thrombosis of vascular access [16].

Recent research suggests that the proinflammatory effects are likely the dominant pathogenic mechanism. Lp(a) is the primary carrier of oxidized phospholipids (OxPL) in human plasma [17]. These bioactive lipids are covalently bound to the apo(a) component. When Lp(a) enters the vessel wall, it delivers this payload of OxPL directly to the endothelium and macrophages. OxPL trigger a potent inflammatory response by stimulating the expression of adhesion molecules (VCAM-1, ICAM-1, E-selectin) on endothelial cells and promoting the secretion of cytokines (IL-1β, IL-6, IL-8) by macrophages [18, 19]. This creates a chronic inflammatory environment that accelerates plaque progression and destabilization [20]. Additionally, due to the high structural homology between apo(a) and plasminogen, apo(a) can compete with plasminogen for binding sites on fibrin clots and endothelial cells. In vitro studies have shown that this competition inhibits the generation of plasmin by tissue plasminogen activator (tPA), thereby impairing fibrinolysis [21, 22]. While the clinical magnitude of this thrombotic risk is still debated compared to the atherogenic risk, it likely contributes to the pathophysiology of acute coronary syndromes and stroke.

Clinical significance. Meta-analyses of prospective population studies, such as the Emerging Risk Factors Collaboration, have demonstrated a continuous, log-linear association between Lp(a) concentration and incident CAD risk [23]. This risk is independent of LDL-C levels. The JUPITER trial analysis highlighted that among patients treated with potent statins who achieved very low LDL-C levels, those with elevated Lp(a) remained at significantly higher risk of cardiovascular events, underscoring Lp(a) as a driver of residual risk [24]. Furthermore, Lp(a) is the only lipoprotein identified as a causal genetic risk factor for aortic stenosis [25]. The pathophysiology involves the deposition of Lp(a) and OxPL in the valve leaflets. The OxPL are converted by the enzyme autotaxin into lysophosphatidic acid, which activates the NF-κB and NOTCH1 signaling pathways in valve interstitial cells. This triggers the transformation of these cells into osteoblast-like cells, leading to calcium deposition and valve stiffening [26, 27].

Peripheral Artery Disease (PAD). While the link between Lp(a) and coronary disease is well-established, the association with peripheral artery disease (PAD) is even stronger in terms of risk magnitude per unit increase in Lp(a). Genetic studies have confirmed that Lp(a) is a potent driver of large-vessel atherosclerosis in the lower extremities. Patients with elevated Lp(a) are at significantly higher risk for critical limb ischemia and require peripheral revascularization procedures more frequently than those with normal levels [28]. The mechanism likely involves both the accelerated atherosclerotic plaque formation in the femoral and popliteal arteries and the thrombotic occlusion of these vessels due to the antifibrinolytic properties of apo(a).

Heart Failure. Historically, the link between Lp(a) and heart failure (HF) was considered secondary to myocardial infarction. However, recent data from the Copenhagen General Population Study suggest that elevated Lp(a) is associated with an increased risk of HF even in the absence of prior ischemic heart disease. This may be mediated partly by the role of Lp(a) in causing aortic valve stenosis, which increases left ventricular afterload, leading to hypertrophy and eventual pump failure [29].

Diagnosis and measurement challenges. Current guidelines from the European Atherosclerosis Society (EAS) and the AHA recommend measuring Lp(a) at least once in every adult's lifetime to identify those with high inherited risk [4, 30]. Clinically, levels below 30 mg/dL (< 75 nmol/L) are considered within the normal physiological range. A linear increase in risk is observed at levels ≥ 30 mg/dL (≥ 75 nmol/L), while levels ≥ 50 mg/dL (≥ 125 nmol/L) represent the threshold for high cardiovascular risk [4]. A major challenge in clinical practice is the lack of standardization in assays. Most commercial assays measure Lp(a) mass (mg/dL), which can be inaccurate due to the heterogeneity of apo(a) isoforms (antibodies may overestimate levels in patients with large isoforms). Molar concentration assays (nmol/L), which count the number of particles regardless of their mass, are considered the gold standard and are recommended for precise risk assessment [31].

Therapeutic landscape. Standard therapies have limited efficacy against Lp(a). While essential for LDL-C

reduction, statins do not lower Lp(a) and may even paradoxically increase its levels by 10–20% [32]. PCSK9 inhibitors, such as evolocumab and alirocumab, reduce Lp(a) by approximately 20–30% [33]. While beneficial, this modest reduction is often insufficient for patients with very high baseline levels to achieve a meaningful reduction in risk attributed specifically to Lp(a).

Lipoprotein Apheresis: Technical Aspects and Guidelines. Currently, lipoprotein apheresis remains the only FDA-approved therapy specifically for lowering isolated severe Lp(a) elevations in patients with recurrent cardiovascular events despite optimal medical therapy. Unlike plasmapheresis, which removes all plasma proteins, lipoprotein apheresis selectively removes apoB-containing lipoproteins (LDL, VLDL, and Lp(a)). Several systems are available, including heparin-induced extracorporeal LDL precipitation (HELP), double filtration plasmapheresis (DFPP), and adsorption columns (e.g., dextran sulfate cellulose). A single session can reduce Lp(a) levels by 60–75%. However, due to the rebound effect, levels return to baseline within 1–2 weeks, necessitating weekly or bi-weekly sessions [34]. Long-term observational studies, such as those from the German Lipoprotein Apheresis Registry (GLAR), have demonstrated a >80% reduction in major adverse cardiovascular events (MACE) in patients undergoing regular apheresis [35]. Despite its efficacy, the procedure is invasive, time-consuming (2–4 hours per session), and expensive, limiting its availability primarily to specialized centers in Germany, Japan, and parts of the United States.

The field is witnessing a revolution with the development of therapies that directly target LPA mRNA in hepatocytes, preventing the synthesis of apo(a). Pelacarsen (TQJ230), an antisense oligonucleotide (ASO) conjugated with GalNAc for targeted delivery to the liver, reduced Lp(a) by 80% in phase 2 trials [36]. The ongoing phase 3 outcome trial, Lp(a)HORIZON, is testing whether this profound reduction translates into a decrease in major adverse cardiovascular events [37]. Another promising class includes small interfering RNA (siRNA) molecules like olpasiran and lepodisiran. The OCEAN(a)-DOSE phase 2 trial demonstrated a dose-dependent reduction in Lp(a) of >95% with olpasiran administered every 12 weeks [38], while lepodisiran has shown the ability to maintain undetectable Lp(a) levels for nearly a year after a single dose in early-phase studies [39]. Beyond injectables, muvalaplin represents the first oral small molecule inhibitor that works by disrupting the non-covalent interaction between apo(a) and apoB, preventing the assembly of the Lp(a) particle. Phase 1 results published in 2023 showed reductions of up to 65% with daily oral administration [40, 7].

The Statin Paradox: Impact on Lipoprotein(a) and Residual Risk. Statins (HMG-CoA reductase inhibitors) act as the cornerstone of modern lipid-lowering therapy and are universally recognized as the first-line treatment for the prevention of ASCVD due to their potent ability to reduce low-density lipoprotein cholesterol (LDL-C). However, their effect on Lipoprotein(a) [Lp(a)] concentrations is distinct, often contradictory, and clinically challenging. While statins effectively upregulate LDL receptors (LDLR) on the surface of hepatocytes to clear circulating LDL, data from major randomized clinical trials-including the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID), the Heart Protection Study (HPS), and the Treating to New Targets (TNT) trial-indicate that Lp(a) levels do not decrease with statin therapy. Instead, a consistent trend toward elevation has been observed, a phenomenon frequently described as the "statin paradox" [41, 42]. A large-scale meta-analysis conducted by Sahebkar et al. (2016), which analyzed individual patient data from over 5,000 subjects in randomized controlled trials, confirmed a statistically significant mean increase in plasma Lp(a) levels by 11.6% following statin treatment [47].

This effect appears to be largely a class effect of statins, although the magnitude of the increase may vary depending on the specific agent and dosage used. Specifically, atorvastatin has been most frequently associated with a noticeable increase in Lp(a) concentrations, ranging from 10% to 20% in various cohorts [48]. Similarly, the analysis of the JUPITER trial demonstrated that rosuvastatin therapy also led to a statistically significant median increase in Lp(a), challenging the assumption that newer generation statins might be neutral [50]. Conversely, other agents such as simvastatin and pravastatin generally show a more neutral effect or only mild, non-significant alterations in Lp(a) levels, suggesting subtle differences in pharmacodynamics or gene interactions among different molecules of this class [49].

The pathophysiological mechanisms driving the statin-induced rise in Lp(a) are complex and are believed to be multifactorial, involving both genetic regulation and metabolic shifts in lipoprotein clearance. Experimental studies have demonstrated that statins, by inhibiting intracellular cholesterol synthesis, induce a compensatory activation of the transcription factor SREBP-2 (Sterol Regulatory Element-Binding Protein 2). While SREBP-2 is essential for upregulating the LDLR gene to clear LDL-C, it has also been shown to bind to the promoter region of the LPA gene. This binding enhances the transcriptional activity of the LPA gene, thereby directly increasing the hepatic synthesis and secretion of apolipoprotein(a), the unique protein component of Lp(a) [51].

Furthermore, changes in clearance pathways play a critical role. Although Lp(a) contains the apoB-100 moiety similar to LDL, it is not efficiently cleared by the LDLR pathway because the bulky apo(a) tail interferes with the ligand-receptor binding interface. Consequently, the statin-induced overexpression of LDLR clears standard LDL particles much more efficiently than Lp(a) particles. This selective rapid clearance of LDL may shift the plasma lipoprotein balance, making the accumulation of Lp(a) more apparent and increasing its relative proportion in the circulation [52, 53]. Additionally, while statins exert beneficial pleiotropic effects-such as improving endothelial function and reducing systemic inflammation-these mechanisms do not seem to mitigate the specific metabolic upregulation of Lp(a) [45].

The clinical relevance of this phenomenon contributes significantly to the concept of "residual cardiovascular

risk." The AIM-HIGH study provided critical insights into this issue, demonstrating that among patients treated with statins who achieved excellent control of LDL-C levels, those with elevated baseline Lp(a) levels continued to experience a significantly higher rate of recurrent cardiovascular events compared to those with normal Lp(a) [54]. This suggests that the pro-inflammatory and pro-thrombotic properties of Lp(a), driven by its content of oxidized phospholipids and its structural homology to plasminogen, continue to exert deleterious effects on the arterial wall even when LDL-C is aggressively lowered. Therefore, the statin-induced rise in Lp(a), while not negating the overall substantial mortality benefit of statins, represents a therapeutic gap that must be addressed.

Consequently, for patients with high baseline Lp(a) levels or those who exhibit a significant rise in Lp(a) while on statins, alternative or adjunctive therapeutic strategies may be required. For instance, PCSK9 inhibitors (evolocumab, alirocumab) have demonstrated an ability to reduce Lp(a) by approximately 25–30%, likely through an enhanced receptor-mediated clearance that can partially overcome the apo(a) interference [55]. Niacin has historically shown efficacy in lowering Lp(a) by 20–30%, although its clinical use is currently limited by side effects [56]. Most promisingly, the field is moving towards novel antisense oligonucleotide therapies and small interfering RNAs targeting LPA mRNA, such as pelacarsen and olpasiran, which offer the potential to lower Lp(a) by up to 80% and are expected to resolve this residual risk factor in the near future [57].

Conclusions. Lipoprotein(a) has transitioned from an obscure biomarker to a central target in preventive cardiology. The robust evidence base linking Lp(a) to atherosclerosis and aortic stenosis via proatherogenic and proinflammatory mechanisms necessitates its integration into routine cardiovascular risk assessment. While current pharmacological options are limited, the imminent arrival of potent and specific RNA-based therapies and oral inhibitors promises to fill this gap. If the ongoing cardiovascular outcome trials confirm the clinical benefit of lowering Lp(a), it will mark a paradigm shift in the management of residual cardiovascular risk.

Conflict of interest: The authors declare no conflict of interest.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article

References

1. Berg K. A new serum type system in man – the Lp system. Acta Pathol Microbiol Scand. 1963;59:369-82. DOI: 10.1111/j.1699-0463.1963.tb01808.x.

2. Nordestgaard BG, Chapman MJ, Ray K, Borén J, Andreotti F, Watts GF, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010;31(23):2844-53. DOI: 10.1093/eurheartj/ehq386.

3. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA. 2009;301(22):2331-39. DOI: 10.1001/jama.2009.801.

4. Reyes-Soffer G, Ginsberg HN, Berglund L, Duell PB, Heffron SP, Kamstrup PR, 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 Vasc Biol. 2022;42(1):e48-e60. DOI: 10.1161/ATV.0000000000000147.

5. Enkhmaa B, Berglund L. Non-genetic influences on lipoprotein(a) concentrations. Atherosclerosis. 2022;349:53-62. DOI: 10.1016/j.atherosclerosis.2022.04.006.

6. Schmidt K, Noureen A, Kronenberg F, Utermann G. Structure, function, and genetics of lipoprotein (a). J Lipid Res. 2016;57(8):1339-59. DOI: 10.1194/jlr.R067314.

7. Hopewell JC, Haynes R, Baigent C. The role of lipoprotein (a) in chronic kidney disease. J Lipid Res. 2018;59(4):577-85. DOI: 10.1194/jlr.R083626.

8. Stiekema LCA, Prange KHM, Hoogeveen RM, Verweij SL, Kroon J, Schnitzler JG, et al. Potent lipoprotein(a) lowering following apolipoprotein(a) antisense treatment reduces the pro-inflammatory activation of circulating monocytes in patients with elevated lipoprotein(a). Eur Heart J. 2020;41(24):2262-71. DOI: 10.1093/eurheartj/ehaa171.

9. Coassin S, Kronenberg F. Lipoprotein(a) beyond the kringle IV repeat polymorphism: The complexity of genetic variation in the LPA gene. Atherosclerosis. 2022;349:17-35. DOI: 10.1016/j.atherosclerosis.2022.04.003.

10. Lorey MB, Youssef A, Äikäs L, Borrelli M, Hermansson M, Assini JM, et al. Lipoprotein(a) induces caspase-1 activation and IL-1 signaling in human macrophages. Front Cardiovasc Med. 2023;10:1130162. DOI: 10.3389/fcvm.2023.1130162.

11. Guan W, Cao J, Steffen BT, Post WS, Stein JH, Tattersall MC, et al. Race is a key variable in assigning lipoprotein(a) cutoff values for coronary heart disease risk assessment: the Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol. 2015;35(4):996-1001. DOI: 10.1161/ATVBAHA.114.304785.

12. Zheng KH, Tsimikas S, Pawade T, Kroon J, Jenkins WSA, Doris MK, et al. Lipoprotein(a) and Oxidized Phospholipids Promote Valve Calcification in Patients With Aortic Stenosis. J Am Coll Cardiol. 2019;73(17):2150-62. DOI: 10.1016/j.jacc.2019.01.070.

13. Moriarty PM, Gorby LK, Stroes ES, Kastelein JP, Davidson M, Tsimikas S. Lipoprotein(a) and Its Potential Association with Thrombosis and Inflammation in COVID-19: a Testable Hypothesis. Curr Atheroscler Rep. 2020;22(9):48. DOI: 10.1007/s11883-020-00867-3.

14. Tsimikas S, Brilakis ES, Miller ER, McConnell JP, Lennon RJ, Kornman KS, et al. Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. N Engl J Med. 2005;353(1):46-57. DOI: 10.1056/NEJMoa043175.

15. Schnitzler JG, Hoogeveen RM, Ali L, Prange KHM, Waissi F, van Weeghel M, et al. Atherogenic Lipoprotein(a) Increases Vascular Glycolysis, Thereby Facilitating Inflammation and Leukocyte Extravasation. Circ Res. 2020;126(10):1346-59. DOI: 10.1161/CIRCRESAHA.119.316206.

16. van der Valk FM, Bekkering S, Kroon J, Yeang C, Van den Bossche J, van Buul JD, et al. Oxidized Phospholipids on Lipoprotein(a) Elicit Arterial Wall Inflammation and an Inflammatory Monocyte Response in Humans. Circulation. 2016;134(8):611-24. DOI: 10.1161/CIRCULATIONAHA.116.020838.

17. Dzobo KE, Kraaijenhof JM, Stroes ESG, Nurmohamed NS, Kroon J. Lipoprotein(a): An underestimated inflammatory mastermind. Atherosclerosis. 2022;349:101-9. DOI: 10.1016/j.atherosclerosis.2022.04.004.

18. Scipione CA, Sayegh SE, Romagnuolo R, Tsimikas S, Marcovina SM, Boffa MB, et al. Mechanistic insights into Lp(a)-induced IL-8 expression: a role for oxidized phospholipid modification of apo(a). J Lipid Res. 2015;56(12):2273-85. DOI: 10.1194/jlr.M060210.

19. Boffa MB. Beyond fibrinolysis: The confounding role of Lp(a) in thrombosis. Atherosclerosis. 2022;349:72-81. DOI: 10.1016/j.atherosclerosis.2022.04.009.

20. Gonen A, Yang X, Yeang C, Alekseeva E, Koschinsky M, Witztum JL, et al. Generation and characterization of LPA-KIV9, a murine monoclonal antibody binding a single site on apolipoprotein (a). J Lipid Res. 2020;61(9):1263-70. DOI: 10.1194/jlr.RA120000830.

21. Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 2009;302(4):412-23. DOI: 10.1001/jama.2009.1063.

22. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009;361(26):2518-28. DOI: 10.1056/NEJMoa0902604.

23. Khera AV, Everett BM, Caulfield MP, Hantash FM, Wohlgemuth J, Ridker PM, et al. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). Circulation. 2014;129(6):635-42. DOI: 10.1161/CIRCULATIONAHA.113.004406.

24. Thanassoulis G, Campbell CY, Owens DS, Smith JG, Smith AV, Peloso GM, et al. Genetic associations with valvular calcification and aortic stenosis. N Engl J Med. 2013;368(6):503-12. DOI: 10.1056/NEJMoa1109034.

25. Bouchareb R, Mahmut A, Nsaibia MJ, Boulanger MC, Dahou A, Lépine JL, et al. Autotaxin Derived From Lipoprotein(a) and Valve Interstitial Cells Promotes Inflammation and Mineralization of the Aortic Valve. Circulation. 2015;132(8):677-90. DOI: 10.1161/CIRCULATIONAHA.115.016757.

26. Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J. 2022;43(39):3925-46. DOI: 10.1093/eurheartj/ehac361.

27. Tsimikas S, Fazio S, Viney NJ, Xia S, Witztum JL, Marcovina SM. Relationship of lipoprotein(a) molar concentrations and mass according to lipoprotein(a) thresholds and apolipoprotein(a) isoform size. J Clin Lipidol. 2018;12(5):1313-23. DOI: 10.1016/j.jacl.2018.07.003.

28. Shitara J, Kasai T, Konishi H, Endo H, Wada H, Doi S, et al. Impact of Lipoprotein (a) Levels on Long-Term Outcomes in Patients With Coronary Artery Disease and Left Ventricular Systolic Dysfunction. Circ J. 2019;83(5):1047-53. DOI: 10.1253/circj.CJ-18-0970.

29. Kamstrup PR, Nordestgaard BG. Elevated Lipoprotein(a) Levels, LPA Risk Genotypes, and Increased Risk of Heart Failure in the General Population. JACC Heart Fail. 2016;4(1):78-87. DOI: 10.1016/j.jchf.2015.08.006.

30. Tsimikas S, Gordts PLSM, Nora C, Yeang C, Witztum JL. Statin therapy increases lipoprotein(a) levels. Eur Heart J. 2020;41(24):2275-84. DOI: 10.1093/eurheartj/ehz310.

31. Raal FJ, Giugliano RP, Sabatine MS, Koren MJ, Blom D, Seidah NG, et al. PCSK9 inhibition-mediated reduction in Lp(a) with evolocumab: an analysis of 10 clinical trials and the LDL receptor's role. J Lipid Res. 2016;57(6):1086-96. DOI: 10.1194/jlr.P065334.

32. Roeseler E, Julius U, Heigl F, Spitthoever R, Heutling D, Breitenberger P, et al. Lipoprotein Apheresis for Lipoprotein(a)-Associated Cardiovascular Disease: Prospective 5 Years of Follow-Up and Apolipoprotein(a) Characterization. Arterioscler Thromb Vasc Biol. 2016;36(9):2019-27. DOI: 10.1161/ATVBAHA.116.307983.

33. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, Tardif JC, Baum SJ, Steinhagen-Thiessen E, et al. Lipoprotein(a) Reduction in Persons with Cardiovascular Disease. N Engl J Med. 2020;382(3):244-55. DOI: 10.1056/NEJMoa1905239.

34. Julius U. Lipoprotein apheresis in the management of severe hypercholesterolemia and of elevation of lipoprotein(a): current perspectives and patient selection. Med Devices (Auckl). 2016;9:349-360. DOI: 10.2147/MDER.S98889.

35. Schettler VJJ, Neumann CL, Peter C, Zimmermann T, Julius U, Roeseler E, et al. Current insights into the German Lipoprotein Apheresis Registry (GLAR) - Almost 5 years on. Atheroscler Suppl. 2017;30:50-5. DOI: 10.1016/j.atherosclerosissup.2017.05.006.

36. Fernandez-Prado R, Perez-Gomez MV, Ortiz A. Pelacarsen for lowering lipoprotein(a): implications for patients with chronic kidney disease. Clin Kidney J. 2020;13(5):753-57. DOI: 10.1093/ckj/sfaa001.

37. O'Donoghue ML, Rosenson RS, Gencer B, López JAG, Lepor NE, Baum SJ, et al. Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease. N Engl J Med. 2022;387(20):1855-64. DOI: 10.1056/NEJMoa2211023.

38. Nissen SE, Wolski K, Balog C, Swerdlow DI, Scrimgeour AC, Rambaran C, et al. Single Ascending Dose Study of a Short Interfering RNA Targeting Lipoprotein(a) Production in Individuals With Elevated Plasma Lipoprotein(a) Levels. JAMA. 2022;327(17):1679-87. DOI: 10.1001/jama.2022.5050.

39. Nicholls SJ, Nissen SE, Fleming C, Urva S, Suico J, Berg PH, et al. Muvalaplin, an Oral Small Molecule Inhibitor of Lipoprotein(a) Formation: A Randomized Clinical Trial. JAMA. 2023;330(11):1042-53. DOI: 10.1001/jama.2023.16503.

40. Boffa MB, Koschinsky ML. Lipoprotein(a) and cardiovascular disease. Biochem J. 2024;481(19):1277-96. DOI: 10.1042/BCJ20240037.

41. Tsimikas S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. J Am Coll Cardiol. 2017;69(6):692-711. DOI: 10.1016/j.jacc.2016.11.042.

42. Kostner KM, Kostner GM. Lipoprotein(a): still an enigma?. Curr Opin Lipidol. 2002;13(4):391-96. DOI: 10.1097/00041433-200208000-00006.

43. Kronenberg F. Human Genetics and the Causal Role of Lipoprotein(a) for Various Diseases. Cardiovasc Drugs Ther. 2016;30(1):87-100. DOI: 10.1007/s10557-016-6648-3.

44. Kamstrup PR, Nordestgaard BG. Lipoprotein(a) concentrations, isoform size, and risk of type 2 diabetes: a Mendelian randomisation study. Lancet Diabetes Endocrinol. 2013;1(3):220-27. DOI: 10.1016/S2213-8587(13)70064-0.

45. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. Circulation. 2004;109(23 Suppl 1):III39-III43. DOI: 10.1161/01.CIR.0000131517.20177.5a.

46. O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I, et al. Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk. Circulation. 2019;139(12):1483-92. DOI: 10.1161/CIRCULATIONAHA.118.037184.

47. Sahebkar A, Simental-Mendía LE, Watts GF, Serban MC, Banach M. Comparison of the effects of fibrates versus statins on

plasma lipoprotein(a) concentrations: a systematic review and meta-analysis of head-to-head randomized controlled trials. BMC Med. 2017;15(1):22. DOI: 10.1186/s12916-017-0787-7.

48. Sabatine MS, De Ferrari GM, Giugliano RP, Huber K, Lewis BS, Ferreira J, et al. Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease: Analysis From FOURIER. Circulation. 2018;138(8):756-66. DOI: 10.1161/CIRCULATIONAHA.118.034309.

49. Pradhan AD, Aday AW, Rose LM, Ridker PM. Residual Inflammatory Risk on Treatment With PCSK9 Inhibition and Statin Therapy. Circulation. 2018;138(2):141-49. DOI: 10.1161/CIRCULATIONAHA.118.034645.

50. Tsaban G. Statins and lipoprotein(a); facing the residual risk. Eur J Prev Cardiol. 2022;29(5):777-78. DOI: 10.1093/eurjpc/zwab178.

51. Rodriguez F, Harrington RA. Cholesterol, Cardiovascular Risk, Statins, PCSK9 Inhibitors, and the Future of LDL-C Lowering. JAMA. 2016;316(19):1967-68. DOI: 10.1001/jama.2016.16575.

52. Tomic Naglic D, Manojlovic M, Pejakovic S, Stepanovic K, Prodanovic Simeunovic J. Lipoprotein(a): Role in atherosclerosis and new treatment options. Biomol Biomed. 2023;23(4):575-83. DOI: 10.17305/bb.2023.8992.

53. Ward NC, Watts GF, Bishop W, Colquhoun D, Hamilton-Craig C, Hare DL, et al. Australian Atherosclerosis Society Position Statement on Lipoprotein(a): Clinical and Implementation Recommendations. Heart Lung Circ. 2023;32(3):287-96. DOI: 10.1016/j.hlc.2022.11.015.

54. Granat MM. Statins-Their Effect on Lipoprotein(a) Levels. Rev Cardiovasc Med. 2025;26(1):26162. DOI: 10.31083/RCM26162.

55. Hummelgaard S, Vilstrup JP, Gustafsen C, Glerup S, Weyer K. Targeting PCSK9 to tackle cardiovascular disease. Pharmacol Ther. 2023;249:108480. DOI: 10.1016/j.pharmthera.2023.108480.

56. Xie S, Galimberti F, Olmastroni E, Carugo S, Catapano AL, Casula M. Effect of lipid-lowering therapies on lipoprotein(a) levels: a comprehensive meta-analysis of randomized controlled trials. Atherosclerosis. 2025;408:120420. DOI: 10.1016/j.atherosclerosis.2025.120420.

57. Mukherjee D, Nissen SE. Lipoprotein (a) as a Biomarker for Cardiovascular Diseases and Potential New Therapies to Mitigate Risk. Curr Vasc Pharmacol. 2024;22(3):171-79. DOI: 10.2174/0115701611267835231210054909.

Information about the authors

Khrebtii H.I. – Doctor of Philosophy, Associate Professor, Department of Internal Medicine, Physical Rehabilitation and Sport Medicine, Bukovinian State Medical University, Chernivtsi, Ukraine. ORCID ID: https://orcid.org/0000-0002-5177-6277.

Khrebtii O.Y. – Student, Bukovinian State Medical University, Chernivtsi, Ukraine. ORCID ID: https://orcid.org/0009-0003-4498-5964.

Відомості про авторів

Хребтій Г.І. – канд.мед.наук, доц. кафедри внутрішньої медицини, фізичної реабілітації та спортивної медицини, Буковинського державного медичного університету, м. Чернівці, Україна. ORCID ID: https://orcid.org/0000-0002-5177-6277.

Хребтій О.Я. – студентка Буковинського державного медичного університету, м. Чернівці, Україна. ORCID ID: https://orcid.org/0009-0003-4498-5964.

Дата першого надходження рукопису до видання: 28.01.2026 р.
Дата прийнятого до друку рукопису після рецензування: 11.02.2026 р.
Дата публікації: 19.03.2026 р.