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Review Article

Is Lipoprotein(a) a Modifiable Risk Factor?

J Bolodeoku* and T Gbaa

JB Consulting MDP Limited, Building 3, Level 1, Regus, 111 Concorde Road, Maidenhead, Berkshire SL6 4BY

***Corresponding author:** John Bolodeoku, JB Consulting MDP Limited, Building 3, Level 1, Regus, 111 Concorde Road, Maidenhead, Berkshire SL6 4BY, UK, john.1.bolodeoku@kcl.ac.uk

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Abstract

Lipoprotein(a) [Lp(a)] has emerged as an important cardiovascular risk factor, with elevated levels associated with increased risk of coronary artery disease, stroke, and aortic stenosis. While traditionally considered a non-modifiable risk factor due to its strong genetic determination, recent advances in pharmacological interventions have challenged this paradigm. This review examines current evidence regarding the modifiability of Lp(a) levels and discusses emerging therapeutic strategies that may transform Lp(a) from a genetic burden into a treatable cardiovascular risk factor.

Introduction

Lipoprotein(a) consists of a Low-Density Lipoprotein (LDL)-like particle covalently bound to apolipoprotein(a) [apo(a)], a unique glycoprotein with structural homology to plasminogen [1]. First described by *Berg* in 1963, Lp(a) has gained significant attention as an independent cardiovascular risk factor, with plasma concentrations varying dramatically between individuals and populations [2]. The Lp(a) particle combines the atherogenic properties of LDL with potential antifibrinolytic effects arising from its plasminogen-like structure, creating a dual mechanism of cardiovascular harm [3].

Genetic Determinants and Population Variability

Genetic Architecture

Lp(a) levels are primarily determined by the LPA gene, which encodes apo(a). The gene exhibits remarkable structural variability, particularly in the kringle IV type-2 (KIV-2) copy number repeats, which inversely correlate with plasma Lp(a) concentrations [4]. Genetic factors account for approximately 90% of the inter-individual variation in Lp(a) levels, making it one of the most heritable lipoproteins [5].

Population Differences

Significant ethnic disparities exist in Lp(a) distribution, with individuals of African descent having median levels 2-3 times higher than those of European ancestry [6]. These differences reflect distinct evolutionary pressures and genetic variants that have accumulated across populations over millennia [7].

Cardiovascular Risk Association

Coronary Artery Disease

Multiple large-scale studies have established Lp(a) as an independent risk factor for coronary artery disease. The Copenhagen City Heart Study demonstrated that individuals with Lp(a) levels >50 mg/dL had a 2-fold increased risk of myocardial infarction compared to those with levels <10 mg/dL [8]. Meta-

analyses have consistently shown that each 50 mg/dL increase in Lp(a) is associated with approximately 20% increased coronary risk [9].

Stroke and Peripheral Arterial Disease

Elevated Lp(a) levels are also associated with increased risk of ischemic stroke and peripheral arterial disease. The EPIC-Norfolk study found that individuals in the top quartile of Lp(a) distribution had 40% higher stroke risk compared to the bottom quartile [10].

Aortic Stenosis

Emerging evidence suggests that Lp(a) plays a role in the development and progression of calcific aortic stenosis. Mendelian randomisation studies have provided causal evidence linking elevated Lp(a) with aortic valve disease [11].

Traditional Approaches: Limited Modifiability

Lifestyle Interventions

Unlike other lipoproteins, Lp(a) levels show minimal response to traditional lifestyle modifications. Dietary changes, exercise, and weight loss typically result in less than 10% change in Lp(a) concentrations [12]. This resistance to lifestyle intervention reflects the genetic dominance in Lp(a) regulation.

Conventional Lipid-Lowering Therapy

Most conventional lipid-lowering drugs (statins, ezetimibe, fibrates, bile acid sequestrants, bempedoic acid) do not meaningfully lower Lp(a); some may slightly increase it.

a. Statins: Generally, increase Lp(a) levels by 10-20%, potentially through upregulation of LPA gene expression [13]

b. Ezetimibe: Minimal effect on Lp(a) levels [14]

c. Fibrates: Modest reductions of 10-15% in some studies [15]

d. Niacin: Reduces Lp(a) by approximately 20–40% [1,2]. However, large outcome trials failed to show incremental cardiovascular benefit when added to contemporary background therapy, and its use is limited by flushing, hepatotoxicity, and glucose intolerance. As a result, niacin is not recommended solely for Lp(a) lowering in current practice [16,17].

Hormone Replacement Therapy

Postmenopausal hormone replacement therapy can reduce Lp(a) levels by 20-50%, but the associated cardiovascular risks limit its utility as a specific Lp(a)-lowering intervention [18].

PCSK9 Inhibitors

PCSK9 inhibitors provide modest but consistent Lp(a) reductions of 20-30% on average, in addition to their 50–60% LDL-C reduction. Outcome trials (FOURIER, ODYSSEY OUTCOMES) suggest that part of the residual risk reduction may be mediated through Lp(a) lowering, particularly in patients with high baseline Lp(a). While not primarily Lp(a)-targeting agents, they offer an additional benefit for patients with elevated levels [21]. The mechanism appears independent of LDLR-mediated pathways and may involve effects on apo(a) production or clearance [22]. Inclisiran, a PCSK9-targeting siRNA, appears to have a similar magnitude of Lp(a) reduction. PCSK9 inhibitors are currently the most clinically relevant Lp(a)-lowering lipid drugs in routine use [16,19-21].

Emerging Therapeutic Strategies

The development of antisense oligonucleotides (ASOs) targeting LPA mRNA represents a breakthrough in Lp(a) modification. Pelacarsen (formerly IONIS-APO(a)-LRx) has demonstrated dose-dependent reductions in Lp(a) levels of up to 80% in phase II trials [22]. The ongoing HORIZON trial will determine whether Lp(a) reduction with pelacarsen translates to cardiovascular benefit [23]. Small interfering RNA (siRNA) therapies offer another promising approach. Olpasiran, a siRNA targeting LPA mRNA, achieved Lp(a) reductions of up to 95% in phase II studies with quarterly dosing [24]. A phase 1 trial of 48 individuals with elevated lipoprotein(a) demonstrated that lepodisiran was well tolerated and achieved dose-dependent, long-lasting reductions in serum lipoprotein(a) levels [25].

Muvalaplin: An oral small molecule that disrupts apo(a)-apoB binding, preventing Lp(a) formation [26]

Lipoprotein Apheresis

For patients with extremely elevated Lp(a) levels (typically >60 mg/dL) and progressive cardiovascular disease, lipoprotein apheresis can acutely reduce Lp(a) by 60-80% [27]. However, the procedure is invasive and expensive, and levels return to baseline within days to weeks [28].

Gene Therapy

Approaches targeting hepatic LPA expression show promise in preclinical studies [29].

Clinical Implications and Guidelines

Risk Assessment

Current guidelines increasingly recognize Lp(a) measurement for cardiovascular risk stratification, particularly in intermediate-risk patients or those with premature cardiovascular disease [30]. The 2019 ESC/EAS guidelines recommend measuring Lp(a) at least once in every adult's lifetime [31]. Lp(a) estimation in high-risk patients undergoing treatment in a lipid clinic in the UK revealed 54% of the patients had Lp(a) had </= 32 nmol/L, while 46% had levels >/= 32 nmol/L and when stratified using the HEART UK cut off, 54%, 12%, 18%, 15%, and 1% were stratified into normal, minor risk,, moderate risk, high risk and very high risk, respectively (see Figure 1) [32].

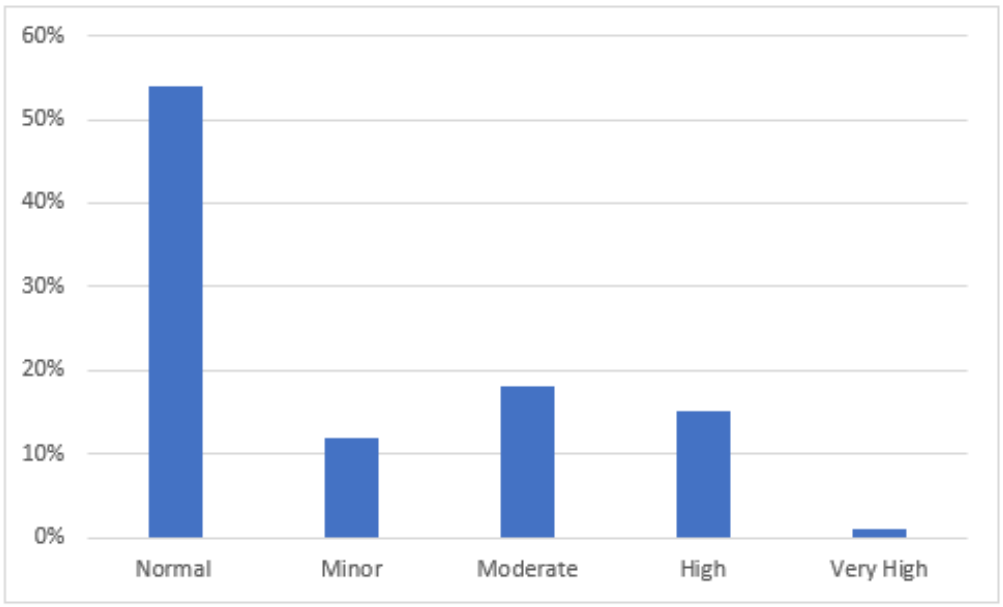

Figure 1: Proportion of Cases Classified as Normal, Minor, Moderate, High, and Very High using the HEART UK cut-off.

Treatment Thresholds

While optimal target levels remain debated, many experts consider Lp(a) >50 mg/dL (125 nmol/L) indicative of increased cardiovascular risk, warranting enhanced risk factor modification [33]. Some suggest lower thresholds of >30 mg/dL in high-risk populations [34].

Risk Communication

The genetic nature of elevated Lp(a) has implications for family screening and risk communication. Cascade testing of family members may identify additional individuals with elevated levels who could benefit from enhanced cardiovascular prevention [35].

Future Perspectives

Precision Medicine

The strong genetic component of Lp(a) makes it an ideal target for precision medicine approaches. Genetic risk scores incorporating LPA variants could identify individuals most likely to benefit from specific Lp(a)-lowering therapies.

Combination Therapy

Future strategies may involve combining different Lp(a)-lowering mechanisms to achieve optimal reduction while minimizing side effects. The synergy between different therapeutic approaches remains an active area of investigation.

Prevention vs. Treatment

The preventive potential of Lp(a)-lowering therapy in asymptomatic individuals with elevated levels represents an important frontier. Early intervention during the subclinical phase of atherosclerosis may yield the greatest benefit.

Conclusion

Lipoprotein(a) is transitioning from a non-modifiable genetic risk factor to a potentially treatable therapeutic target. While traditional approaches have shown limited efficacy, novel RNA-based therapies and other innovative strategies demonstrate unprecedented efficacy in reducing Lp(a). The ongoing cardiovascular outcome trials will determine whether these dramatic biochemical changes translate into meaningful clinical benefit. If successful, these therapies could transform the management of cardiovascular risk for millions of individuals worldwide with elevated Lp(a) levels.

The answer to whether Lp(a) is a modifiable risk factor appears to be evolving from “no” to “yes, but with the right tools.” As these therapeutic advances move from clinical trials to clinical practice, Lp(a) may finally shed its designation as an “untreatable” risk factor and join the ranks of modifiable cardiovascular risk factors.

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