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Lipoprotein(a), the rediscovered risk factor, or how to get "back to the future"

Abbreviated title: Lipoprotein(a), the rediscovered risk factor

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KEYWORDS

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Abbreviations: apo(a), apolipoprotein(a); ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); MACE, major adverse cardiovascular events; NIHR, National Institute for Health Research; PCSK9, proprotein convertase subtilisin/kexin type 9.

Background

Elevated lipoprotein(a) – Lp(a) – is a known independent and genetically inherited risk factor for cardiovascular disease. Although its causal role in atherosclerosis and aortic valve calcification was established long ago, there is no international consensus regarding the measurement of Lp(a) and its threshold. To date, no pharmacological intervention targeting Lp(a) to prevent cardiovascular disease has been either approved or recommended. Recent clinical data have rekindled the cardiovascular community's interest in Lp(a), which may become a new player in the lipid-related risk reduction strategy in high-risk patients.

Lp(a): The long history of this neglected particle

Lp(a) was discovered more than 50 years ago, in 1963. The geneticist Kare Berg was seeking to define lipoprotein differences between individual human sera. Through an ingenious set of immunological investigations of human sera, he discovered a new antigen that was associated with low-density lipoprotein (LDL) particles [1, 2]. Berg soon showed that this new antigen was a genetic trait, and proposed that it should be called Lp(a): Lp referring to the lipoprotein, and (a) as this was the accepted terminology at that time for naming antigens in human immunogenetics. Therefore, the term Lp(a) initially referred to the antigenic structure of the new antigen rather than the lipoprotein as it is used today.

Lp(a) is composed of apolipoprotein(a) – apo(a) – covalently bound to the apolipoprotein B100 of an LDL-like particle (Fig. 1). Apo(a) is partly made of triple-looped structures called "kringles" because they are shaped like the Danish pretzel of the same name. Apo(a) contains various copies of kringle IV type 2 as well as a protease domain similar to that of plasminogen, which may partly explain its prothrombotic effect. Because of its variable structure (in terms of numbers of kringle IV), Lp(a) shows significant protein size heterogeneity within patients, and one individual usually carries two different isoforms, each inherited from one parent. Interindividual and intraindividual Lp(a) particle size heterogeneity renders measurement of its concentration complex [3, 4]. In addition, apo(a) polymorphism may affect its metabolism and its effect on Lp(a) concentration. After biosynthesis within the liver, small isoforms have a short maturation time, leading to quicker secretion of Lp(a); this explains the inverse correlation between plasma Lp(a) concentration and apo(a) isoform size.

There are no standardized assays to measure Lp(a) concentration, and cut-offs for risk remain a matter of debate, even among experts. Circulating concentrations of Lp(a) are genetically determined, and a desirable concentration is often proposed as < 50 mg/dL, which has led guidelines from the USA to consider a 50 mg/dL cut-off [5]. The recent European Society of Cardiology/European Atherosclerosis Society guidelines [6] propose a more extreme 180 mg/dL cut-off to identify patients with very high inherited Lp(a) concentration, who may have a lifetime risk of atherosclerotic cardiovascular disease (ASCVD), similar to the risk associated with heterozygous familial hypercholesterolaemia.

Lp(a) promotes atherosclerosis via its LDL moiety, which has a similar proportion of cholesterol content as traditional LDL particles. Furthermore, Lp(a) promotes inflammatory processes [7, 8] via accumulation of oxidized phospholipids [9], and induces prothrombotic cascade effects via the plasminogen-like apolipoprotein(a) moiety. A potential causal role for Lp(a) was first reported in 1974, with the observation that Lp(a) concentrations were higher in patients with coronary artery disease than in primary prevention individuals [10]. In addition, a significant correlation between elevated Lp(a) and calcific aortic valve disease was established [11]. It has been suggested that Lp(a) concentrations may help to identify patients with more progressive aortic valve disease, who may require early intervention [12]. Recent observational data from two Danish registries convincingly showed that high Lp(a) concentration was an independent predictor of total and cardiovascular mortality, but not of non-cardiovascular mortality. The authors concluded that a 50 mg/dL (105 nmol/L) increase in Lp(a) was significantly associated with a 1.16 hazard ratio for cardiovascular mortality. Interestingly, in this study, patients carrying the isoforms with a low number of repeats of kringle IV type 2 were at higher risk, supporting the previous physiopathological hypothesis [13].

Despite convincing data from epidemiological studies, Lp(a) failed to reach “mainstream” status within the medical community in France. Several factors may have contributed to this. Even today, Lp(a) is not widely known as a cardiovascular risk factor among cardiologists, endocrinologists and general practitioners. Few understand its deleterious role and biological properties, or know how it is regulated. Although international guidelines recommend one Lp(a) measurement during adulthood, this test is not currently reimbursed by French social security, which is a significant hurdle against its use for better individual cardiovascular risk assessment. Another hurdle against its widespread use is that Lp(a) measurements are not routinely available in all laboratories, and may need to be performed

in referral laboratories. One may acknowledge that the absence of validated and recommended pharmacological intervention targeting elevated Lp(a) to reduce clinical events may not encourage physicians to prescribe its routine measurement.

Lp(a): A spectacular come-back

Over the past few years, new clinical data have promoted a resurgence of interest in Lp(a) in patients at high cardiovascular risk.

First, several publications reported a strong relationship between high Lp(a) concentrations and the incidence of major adverse cardiovascular events (MACE), which was reinforced by a meta-analysis suggesting that Lp(a) has an independent deleterious role in patients, despite statin treatment [14-19]. Moreover, the thresholds at which risk increases markedly may occur in as many as 10% of the general population, meaning that the population attributable risk of elevated Lp(a) could be large. These compelling and consistent findings regarding the strong relationship between Lp(a) concentrations and cardiovascular events have generated renewed interest in Lp(a) among clinicians [20]. Several studies have reported the benefit of lipoprotein apheresis in high-risk patients with elevated Lp(a) [21]. At the same time, therapeutic innovation in lipid-lowering treatments has brought new insights, suggesting that a decrease in Lp(a) concentration by new drugs may produce significant risk reduction mediated through Lp(a) reduction, reinforcing the interest in Lp(a) and its reduction.

New approaches targeting atherogenic lipoproteins include inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) to decrease circulating LDL cholesterol. PCSK9 inhibitors have also been shown to significantly decrease Lp(a) concentrations [22]. New pharmacotherapeutic agents blocking Lp(a) synthesis with antisense oligonucleotide therapy are being developed, with ongoing phase III outcomes trials planned (ClinicalTrials.gov Identifier: NCT04023552) These new agents are promising, and may play a major role in decreasing the “lipid residual risk” in patients with ASCVD, provided that their clinical efficacy and safety are confirmed in large cardiovascular outcome trials.

PCSK9 inhibitors and Lp(a) modulation

PCSK9 is an enzyme encoded by the *PCSK9* gene in humans on chromosome 1. This protein plays a major regulatory role in cholesterol homeostasis, mainly by reducing the levels of LDL receptors on the plasma membrane [23]. Drugs that inhibit PCSK9 thus prevent degradation of LDL receptors,

which increases the survival time of hepatic LDL receptors and enhances LDL clearance from circulation. Evolocumab and alirocumab are two fully-human anti-PCSK9 antibodies, which induced a sustained prolonged decrease in LDL cholesterol of 50–70% and a reduction in MACE of 15% in two large phase III randomized cardiovascular outcome trials (FOURIER and ODYSSEY OUTCOMES), conducted in secondary prevention patients.

PCSK9 inhibitors have also been shown to reduce the concentration of other atherogenic particles, such as Lp(a) [23-25]. Absolute MACE risk reduction is more pronounced in patients at very high risk, such as those with peripheral artery disease, recent or multiple previous myocardial infarctions or residual severe multivessel coronary artery disease, or with elevated Lp(a) [24-26]. A recent publication from the FOURIER trial reported that evolocumab significantly reduced Lp(a) concentration, resulting in more cardiovascular benefits in patients with higher baseline Lp(a) concentrations. In these patients, a 24% relative risk reduction in the combined endpoint (myocardial infarction, stroke, cardiovascular death) was observed, whereas patients with a lower baseline Lp(a) concentration only had a 15% relative risk reduction in the evolocumab group [26]. Whether higher levels of Lp(a) modulation reflect a higher risk profile or whether specific Lp(a) modulation by PCSK9 inhibitors provides higher benefits remains to be investigated.

The magnitude of cardiovascular benefits directly linked to a decrease in Lp(a) remains a matter of debate. The ANITSCHKOW study [27], investigating the anti-PCSK9 antibody evolocumab, showed a modest 14% reduction in Lp(a) in a cohort with a baseline Lp(a) concentration of 75 mg/dL. No decrease in arterial wall inflammation measured by positron emission tomography/computed tomography was observed (results as reported on ClinicalTrials.gov) [27]. These findings highlight the need for more efficient and specific agents to decrease the adverse proinflammatory state associated with Lp(a) elevation. This controversy may be resolved by the ongoing dedicated cardiovascular outcome trials investigating Lp(a) specific inhibitors that reduce Lp(a) by a sufficient magnitude.

New lipid-lowering treatments specifically targeting Lp(a)

Research in the lipoprotein field has led to the recent development of an antisense oligonucleotide against apo(a), AKCEA-APO(a)-L_{Rx}, which selectively decreases Lp(a) concentrations by approximately 80% [28].

Results from a dose-finding phase 2b AKCEA-APO(a)-L_{Rx} study were published recently. Five

regimens according to dosage and interval of administration of AKCEA-APO(a)-L_{Rx} versus placebo (a saline solution administrated subcutaneously) were randomly administered to 286 patients (n = 47 in the placebo group) with ASCVD and Lp(a) concentrations of ≥ 60 mg/dL for a duration of 6–12 months. The percentage of Lp(a) decrease from inclusion to month 6 was the primary biological efficacy endpoint. At baseline, the mean Lp(a) concentration was 100.0 mg/dL in the AKCEA-APO(a)-L_{Rx} group and 103.3 mg/dL in the placebo group. A dose response with AKCEA-APO(a)-L_{Rx} was observed regarding decrease in Lp(a) concentration. The magnitude of decrease varied from 35% at a dose of 20 mg/month to 72% at a dose of 60 mg/month; it reached 80% in the arm receiving 20 mg/week. The mean decrease was 6% in the placebo group. Lp(a) concentrations < 50 mg/dL were achieved in more than 80% of patients [29]. No safety issue was reported, especially concerning liver and renal function, platelet count, “influenza-like” symptoms and MACE. As reported for PCSK9 inhibitors, the most frequent adverse event was a local reaction at the injection site, with no clinical impact on adherence.

These promising findings have led to an ongoing phase III outcomes trial investigating cardiovascular benefits in high-risk patients with elevated Lp(a) concentrations. This study, named “Assessing the Impact of Lipoprotein (a) Lowering With TQJ230 on Major Cardiovascular Events in Patients With CVD (Lp(a) HORIZON)” (ClinicalTrials.gov Identifier: NCT04023552), will randomize 7680 patients in secondary prevention to AKCEA-APO(a)-L_{Rx} (TQJ230) or placebo. Key inclusion criteria combine the need for secondary prevention with an Lp(a) concentration ≥ 70 mg/dL at randomization, optimal LDL cholesterol-lowering treatment and optimal medical treatment for other cardiovascular risk factors. The spectrum of patients is large, including those who have had a myocardial infarction or ischaemic stroke 3 months to 10 years before, and patients with asymptomatic peripheral artery disease. The primary endpoint is a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and urgent coronary revascularization requiring hospitalization in patients with Lp(a) ≥ 70 mg/dL at baseline; the same primary endpoint will be reported in the subgroup of patients with Lp(a) ≥ 90 mg/dL at baseline. Other “usual” efficacy and safety endpoints have also been prespecified in this large randomized controlled trial to validate this new lipid-lowering therapy. In this therapeutic class, a phase 1 study with a single dose of another oligonucleotide antisense named AMG 890 has been initiated, mainly to evaluate the safety of this new entity (ClinicalTrials.gov Identifier: NCT03626662).

Conclusions

Healthy lifestyle remains the cornerstone for cardiovascular prevention. Statins are still the first-line lipid-lowering therapy in the pharmacological approach to cardiovascular risk reduction in high-risk patients. Nevertheless, residual risk in established or high-risk patients with ASCVD remains a challenging issue, which has been attributed, in part, to insufficient lowering of LDL cholesterol and other lipid abnormalities, such as high Lp(a) or triglyceride concentrations. Therefore, new lipid-targeting treatments are needed for further risk reduction, especially for high lipid-mediated residual risk. In this rapidly changing field, Lp(a) should be a systematic component in the evaluation of residual lipid risk, as it might explain part of the risk that may not be well controlled by usual lipid-lowering therapy. One may argue that recent data advocate the use of PCSK9 inhibitors in high-risk patients with elevated Lp(a). In addition, the development of new agents specifically targeting Lp(a) are on the way, and may soon bring new therapeutic responses to further decrease cardiovascular risk.

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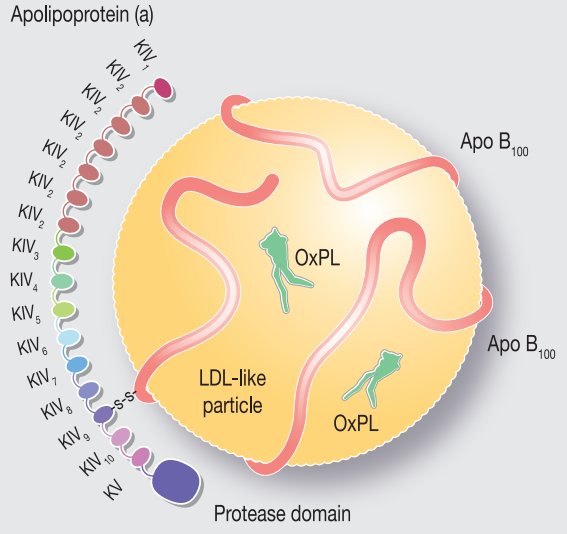
Figure legend

Figure 1. Lipoprotein(a) structure. Apo: apolipoprotein; EC: endothelial cell; IL: interleukin; KIV: kringle IV; KV: kringle V; LDL: low-density lipoprotein; OxPL: oxidized phospholipids; PAI: plasminogen activator inhibitor; SMC: smooth muscle cell; TFPI: tissue factor pathway inhibitor.



Proatherogenic

- ↑ Foam cell formation
- ↑ Necrotic core formation
- ↑ Calcification
- ↑ SMC proliferation
- ↑ EC adhesion molecule expression

Prothrombotic

- ↓ Plasminogen activation
- ↓ Clot permeability
- ↑ TFPI activity
- ↑ EC PAI-1 expression
- ↑ Platelet responsiveness

Pro-inflammatory

- ↑ Macrophage IL-8 formation
- ↑ Oxidized phospholipids
- ↑ Monocyte chemoattractant activity
- ↑ Monocytes cytokine release