# Lipoprotein (a) Biology and the Role in Cardiovascular Medicine

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*Lipoprotein (a) -Lp(a) - is an apoB-based plasma lipoprotein associated with major cardiovascular disease (CVD). Hepatocytes produce it with no clear physiological role. The liver also catabolizes it by means of the LDL receptor. Close structural resemblance with plasminogen may induce an unconfirmed increased risk for thrombosis, while growth factor-like activity may have pro-inflammatory effects. It promotes atherosclerosis and stimulates macrophages to transform to foam cells under the intima. There is a strong inherited -genetic influence on serum Lp(a) levels. Kringle IV type 2 single nucleotide polymorphisms and copy number variations are the major determinants of Lp(a) concentration and volume. Small molecular volume determined by apo(a) isoforms are the most pathogenic for CVD. Serum Lp(a) levels are remarkably constant with age. Multiple epidemiologic trials demonstrated a strong association between Lp(a) levels and cardiovascular disease, mainly coronary disease and ischemic stroke. No specific treatment to lower Lp(a) and consecutive reduction in CV risk is currently available. PCSK9 inhibitors and plasmapheresis have the most profound effect on Lp(a) serum concentration.*

*Keywords: lipoproteins, cardiovascular disease, outcome*

Cardiovascular disease (CVD) and mainly atherothrombosis is a major contributor to worldwide morbidity and mortality, despite continuous improvement in prognosis with prevention and modern therapy [1]. Serum lipid disorders are among the many risk factors responsible for CVD epidemics and play a central pathogenic role [2,3]. In the last six decades, different fractions of serum lipids were chemically identified and described thoroughly. Multiple long-term epidemiological studies established their pathophysiological influence on CVD progression [4]. It is widely accepted that of all lipid fractions low-density lipoprotein particles (LDL) has the most relevant disease-inducing potential, by its long-term pro-inflammatory and pro-thrombotic actions, therefore it aggravates the inflammatory status in some patients with associated pathologies [5-7]. Recently new players that contribute to CVD pathogenesis were identified and their relationship with morbi-mortality was revealed. Among these, there is a major research interest in high-density lipoprotein (HDL) manipulation [8], selective blocking of proprotein convertase subtilisin/kexin type 9 enzyme [9] and reduction of lipoprotein(a) – Lp(a) – in plasma [10].

Lp(a) is a plasma lipoprotein closely related in structure and function to human low-density lipoprotein particles (LDL). Other apolipoprotein B (apoB) containing lipid fractions except Lp(a), are strongly correlated with atherosclerotic CVD, such as very-low density (VLDL) and intermediate density (IDL) lipoproteins [11]. Lp(a) currently came into focus with the identification of its role as potential factor to worsen atherosclerosis, induce atherothrombosis and malignancies [12-14].

In the current review, we provide updated evidence relating to the structure, function and pathophysiologic role of Lp(a) in cardiovascular disease.

*The structure of Lp(a)*

Lp(a) is a complex phospholipid macromolecule based on the structure of LDL, that contains apolipoprotein B-100 (apoB-100) and cholesterol esters and triacylglycerol as the main lipid constituents in the core, all packed by an external layer of phospholipids [14]. Hepatocytes synthesize Lp(a) just as the LDL molecule and excrete it in plasma. Lp(a) contains two supplemental molecules of a large glycoprotein called apo(a), characterized by triple loop amino-acid chains named kringles [15,16]. Internal glycosylated disulfide bonds stabilize the long chains of the triple-looped kringles. There are five cysteine-rich kringle molecules [17]. The fourth kringle (KIV) demonstrates the highest genetically determined polymorphism and is responsible for the major size variation of apo(a); ten different types (T1-T10) were identified [18]. The smaller size of apo(a) is associated with significantly higher Lp(a) concentration in plasma [19] and higher risk of CVD [20]. Similar kringle-like structures stabilized by chemical bonds found in Lp(a) are found in some coagulation factors implicated both in coagulation and fibrinolysis (plasminogen molecule, its tissue activator and prothrombin), mainly on the fourth kringle of the Lp(a) [21]. This fourth kringle has similar structure to the fibrinogen-binding subunit of the serine protease plasminogen and may impair plasmin generation and subsequent spontaneous fibrinolysis.

Another covalent disulfide bridge holds ApoB-100 and the two apo (a) in the Lp (a) macromolecule together. All apoB-100 containing serum lipoproteins have a diameter of less than 70 nm and can easily get in and out of the subintimal space where they initiate the atherosclerotic process.

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Lp(a) migrates in the pre-beta lipoprotein domain by serum electrophoresis [22]. Depending on electrophoretic migration of Lp(a) with respect to apoB there are 6 alleles: Lp(a)S1, Lp(a)S2, Lp(a)S3, Lp(a)S4 (S stands for *slow mobility*), Lp(a)F (*fast mobility*) and Lp(a)B (similar to apoB). An individual has no more than two apo(a) alleles that determine Lp(a) serum concentration.

*Genetic factors determining Lp(a) serum levels*

The complex link between genetic trait and serum levels of Lp(a) translate into large inter-individual variations. This mainly depends on the genes codifying apo(a) on chromosome 6 [23]. The wide variation of Lp(a) serum concentration is much more striking when compared to other serum lipoproteins. Lp(a) plasma levels variate between less than 0.1 mg/dL to more than 200 mg/dL and are remarkably stable in time [24]. This is due to constant apo(a) production determined by apo(a) gene, while apoB-100 is depending on both genetic and environmental factors. Black people have higher serum Lp(a) serum levels with respect to Caucasians, Asians or Hispanics with no established clinical relevance [25].

Two alleles of the LPA gene code apo(a), found on chromosome 6q26. LPA genes have different variants including single nucleotide polymorphisms (SNP) and different KIV repeats [18], generating more than 40 isoforms of apo(a) [26,27]. Although Lp(a) serum levels are controlled by LPA-coded synthesis, there is some modulation from the APOE gene and PCSK9 R46L loss of function gene mutation [28]. The Lp(a) quantitative trait has very strong heritability and this has been demonstrated in all studied populations [29].

Other gene loci correlated with Lp(a) quantity in serum are located on chromosomes 1q23, 11p14-15 and 13q23-31 [29], but they have variable phenotypic influence.

There is a strong correlation between genetic KIV-2 copy number variation (CNV) of the LPA gene and Lp(a) concentration. This translates into increased risk for CAD. Short KIV-2 CNVs determine higher Lp(a) serum levels: hepatocytes process faster shorter apo(a) isoforms coded by small KIV-2. They are packed more efficiently with apoB than larger apo(a) molecules. In addition, a certain penta-nucleotide polymorphism repeat of the promoter sequence (above the transcription site) of the LPA gene may determine Lp(a) serum levels [30].

Two SNPs in the LPA domain correlate with Lp(a) levels: rs1853012 and rs 1800769 [31] with different expression in different geographic locations.

Mainly the KIV-2 CNV that code for apo (a) isoform size determines total serum concentration of serum Lp (a). Except KIV-2 CNV, other gene mutations of the LPA domain may determine final Lp(a) levels.

Apo(a) coding gene is closely situated to the plasminogen-coding gene on the same chromosome 6 [32].

*Serum levels of Lp(a) and methods of measurement*

There are several kits available to measure Lp(a) plasma concentration based on ELISA techniques. They are based on measurement of apo(a) concentration by means of specific anti-apo(a) antibodies. However, ELISA-based methods cannot differentiate between apo(a) polymorphism and provide either overestimated or underestimated Lp(a) concentrations. US National Heart, Lung, and Blood Institute recommends to use isoform size-independent tests that assess Lp(a) particle numbers in nmol/l rather than total mass expressed in mg/dL [33]. The standard and precise method to assess Lp(a) relies on immuno-turbidimetry or nephelometry that is independent of apo(a) isoforms or kringle types [34].

The Framingham Heart Study showed that the 90$^{th}$ percentile for Lp(a) is 39 mg/dL; it is slightly higher in women [35]. However, ESC/EAS guidelines establish that CV risk is significant when Lp(a) is higher than 80$^{th}$ percentile of 50 mg/dL in European population [36]. The global prevalence of Lp(a) higher than 50 mg/dL occurs in about 1.43 billion people [26]. The Canadian Guidelines recommend a cutoff value for increased Lp(a) of > 30 mg/dL [37].

*Lp(a) physiological role*

The full functions and pathophysiological correlates of Lp(a) are not fully clarified [29]. Genetically determined very low levels of Lp(a) are not associated with any disease or clinical dysfunction. Up-to-date information converges toward a deleterious role of this lipoprotein in humans (atherothrombosis, aortic valve disease or malignancies) [12,38,39]. Lp(a) has a role in tissue recovery after trauma (and in association with periosteum conservation during surgery and specific antimicrobial coating it have been shown to be effective in wound healing) and stimulates macrophage activation mediated by apo(a) [40,41]. Lp(a) easily accumulates under the endothelial layer where it binds to migrated macrophages and sub-intimal matrix glycoproteins [42]. In the subendothelial space, apo(a) impairs migration of smooth muscle cells via CD51/CD61 and RhoA/Rho-kinase pathways [41]. Some experimental trials identified anti-angiogenic and anti-neoplastic of metabolized apo(a) fragments with no clear significance for humans [44].

Structural similarity between Lp(a) and plasminogen may impair fibrinolysis promoted by the latter due to competitive fixation to different cellular substrates [45]. There is no clear established link between Lp(a) and increased risk for thrombosis venous, pulmonary or arterial. In addition, Lp(a) activates macrophages mediated by the dedicated VLDL membrane receptor and induces LDL loading and foam-cell formation [46]. Lp(a) attachment to fibrin strands allows cholesterol delivery to sites of endothelial injury. Apo(a) may also function as a growth factor-like structure as far as some serine proteases contain kringle molecules. Interleukin-6 molecule (Il-6) has similar chemokine-like chemical structure with Lp(a). Tocilizumab, a specific anti-Il-6 monoclonal antibody, may also lower Lp(a) by blocking Il-6 effect on LPA gene [47].

*Lp(a) metabolism*

Lp(a) is part of non-HDL cholesterol levels (calculated as the difference between total cholesterol and HDL) that reflects apoB plasma levels and is a useful marker for atherosclerotic CVD risk along with others coronary risk factors [3,48].

Lp(a) assemb6ly with formation of the covalent bond between apo(a) and apoB mainly takes place on hepatocyte membrane [49]. The cytoplasm of the hepatocytes contains no apo(a)-apoB conglomerates. There is a close relationship between the hepatocyte production of apo(a) and apoB-100, with slower catabolism of Lp(a) in some trials, it being impaired in liver chronic pathologies or malignancies [50-52]. Other apo(a) RNA containing tissues are the brain, the lungs, the adrenal glands and the gonads [53,54]. However, apo(a) embedded in Lp(a) has hepatic origin only.

Lp(a) degradation pathways are not elucidated. Hepatocytes may also function as the main Lp(a) catabolic site via clearance through the LDL receptor, although other

hepatocyte receptors may be involved in its removal from plasma [55]. CD36 receptors that are multiligand scavenger receptors, scavenger receptor class B type 1 (SR-BI) and the plasminogen receptors influence hepatic Lp(a) metabolism. Very high expression of LDL receptors on hepatocyte membrane and very low serum levels of LDL, as it occurs with PCSK9 inhibition would favor Lp(a) degradation via LDL receptor. Despite common LDL-receptor mediated degradation, Lp(a) catabolism is 30% lower than that of LDL cholesterol. The catabolic rate does not depend on the molecular mass of different apo(a) isoforms.

Lp(a) is excreted in urine and there is a significant renal arteriovenous gradient of Lp(a) that shows kidneys have a significant role in the catabolism of this substrate [56]. Patients with kidney failure have increased serum levels of Lp(a) and it may be a risk factor for the vascular access in hemodialyzed [57] and also aggravate the cardio-vascular risk needing specific management [58,59], demonstrating that Lp(a) is metabolized via normal renal function.

*Clinical consequences of increased serum levels of Lp(a)*

Lp(a) induces atherosclerosis through some different mechanisms. The first is the increased foam cell production mediated by specific macrophage receptors, similar to ox-LDL effect [49]. Atherosclerotic lesions responsible for atherothrombotic events frequently contain Lp(a) [60,61]. Lp(a) also mediates ox-LDL production that amplifies vascular inflammation [62]. Second, apo(a) has also a potent pro-inflammatory effect on the endothelium and in the subendothelial space [63]. Lp(a) induces phenotypic expression of intercellular adhesion mollecule-1 (ICAM-1) facilitating the endothelial capture of circulating monocytes [64]. Third, structural similarity to plasminogen molecule of kringle IV of apo(a) may promote tissue-factor dependent thrombosis and impair endogenous fibrinolysis, but this is not demonstrated even for the two single nucleotide polymorphisms of apo(a) that are most atherogenic (rs10455872 and rs3798220) [65].

Many epidemiological trials demonstrated increased cardio-vascular risk when Lp(a) serum levels are higher than the 95$^{th}$ percentile (Table 1) [66]. The strongest clinical correlation of Lp(a) is with coronary artery disease (CAD) of all other forms of CVD (67,68). In the largest meta-analysis up-to-date on 36 prospective trials comprising 126.634 patients every 1 SD increase of Lp(a) determined a risk increase for CAD of 13% after adjustment for age, sex, other lipid and conventional risk factors [22]. A report from the Framingham Offspring study demonstrated a 2.4 times increase in CAD risk at a mean follow-up of 12.3 years [67]. Lp(a) correlates with the angiographic complexity of CAD [69] and cardiac mortality [70] in acute coronary syndromes. In women Lp(a) increases CV risk mainly in those with high levels of total cholesterol in a recently published study of three women cohorts enrolled in Women's Health Study [71].

Data from the JUPITER Trial also demonstrated that every 1 SD increase of Lp(a) determines a 27% increase in CAD risk in patients treated with rosuvastatin [72]. This sustain the concept of residual lipid risk depending on Lp(a) and other apoB-100 containing lipo-proteins in patients optimally treated with statins for LDL reduction. It is suggested adding Lp(a) > 47 mg/dL and/or high-risk genotypes of LPA (such as rs3798220, and rs10455872 SNP or LPA KIV-2) to CV risk prediction would marginally but significantly improve risk classification at 20-year follow up [73].

In a meta-analysis comprising 90.904 patients with 5029 ischemic strokes found a 29% increase of stroke risk mainly in young patients (OR 1.41; 95% CI, 1.26-1.57; RR 1.29; 95% CI, 1.06-1.58) [74]. Another meta-analysis with ischemic stroke as main outcome indicated a relative risk of 2.14 (95% CI, 1.85-2.97) with small apo(a) isoforms [75]. In a cohort of 10.127 subjects without stroke at baseline Lp(a) ≥ 50 mg/dL was associated with a 42% relative increase in stroke risk when compared with those with Lp(a) <10 mg/dL in participants without atrial fibrillation (HR, 1.42; 95% CI, 1.07–1.90) (76). Lp(a) was not associated with incident atrial fibrillation.

The relationship with stroke is more prominent in men than in women [77].

There is very little information regarding the impact of lowering Lp(a) serum levels on hard clinical end-points,

**Table 1**

A SUMMARY OF SOME OF THE PROSPECTIVE STUDIES DEMONSTRATING THE ASSOCIATION OF LP(A) AND THE RISK FOR ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

| Study | Follow-up (years) | Patient number | Lp(a) cutoff level | Cardiovascular disease | RR (95% CI); p |
|---|---|---|---|---|---|
| Ohira et al. [77] | 13.5 | 14.221 (3467 blacks, 10.574 whites) | > 300 microg/mL | Ischemic stroke | 2.42 (1.30-4.53) |
| Bennet A et al. [88] | 19 | 6.387 Icelanders | > 43.8 mg/dL | CAD | 1.6 (1.37-1.84) |
| Kwon et al. [89] | 3.1 | 6.252 Koreans | > 20.1 mg/dL | Cardiac death, non-fatal MI | 1.773 (1.194-2.634); 0.005 |
| Gurdasani et al. [90] | 16 | 18.720 Europeans | > 26.6 mg/dL | PAD, CAD, ischemic stroke | PAD: 1.37 (1.25-1.50) CAD: 1.13 (1.04-1.22) |
| Virani et al. [91] | 20 | 3.467 blacks 9851 whites | > 24 mg/dL | CVD, CAD, ischemic stroke | CVD: 1.35 (1.06-1.74) CAD: 1.27 (0.94-1.71) Stroke: 1.60 (1.10-2.34) |
| Kamstrup et al. [73] | 17 | 8720 Danish | > 47 mg/dL | MI, CAD | MI: 2.0 (1.5-2.7) CAD: 1.7 (1.3-2.3) |
| Aronis et al. [76] | 15.8 | 10.127 | > 50 mg/dL | Ischemic stroke | 1.42 (1.07-1.90) |
| Cook et al. [71] | 9.9 | 24.558 women | > 50 mg/dL | CVD | 1.735 (1.373-2.251) |

despite that Lp(a) increases the risk for CVD. In a mendelian randomization analysis, lowering Lp(a) with 101.5 mg/dL has the same impact on CAD risk as a reduction of 38.67 mg/dL in LDL cholesterol [25]. Monoclonal antibodies such as the PCSK9 inhibitors [78,79], tibolone, a synthetic steroid [80], and the seldom used nicotinic acid reduce Lp(a) serum concentration by about 30% [81]. In patients treated with evolocumab Lp(a) lowers with 27% accompanying the 59% reduction in LDL levels as shown in the FOURIER trial. The mechanisms implicated in Lp(a) reduction with evolocumab are both a reduction in hepatic production and accelerated metabolism [82]. Different emergent therapeutic methods, such as gene-silencing techniques (antisense nucleotide inhibitors and small RNAi) are currently under investigation to reduce Lp(a) and other remnant apoB-containing particles [83-85]. Another way to reduce Lp(a) levels with 75% is plasmapheresis in small trials with no outcome hard-endpoints [86]. Despite available data demonstrate a definite link between Lp(a) and CVD while no specific therapy to reduce serum Lp(a) is available, there is no proof that selectively reducing the Lp(a) would reduce CV risk. As far as the consequences of Lp(a) reduction are unknown, guidelines consider intensification of LDL reduction therapy in patients with high serum Lp(a) and high CV risk [35].

Lp(a) is not recommended for routine screening to assess CV risk in all individuals. Currently Lp(a) should be considered for assessment of CV risk in high-risk patients with early CV events in parents, familial hypercholesterolemia or for reclassification of patients with moderate CV risk (class IIa recommendation, level of evidence C) [35]. Lp(a) should also be checked in patients with premature CVD or recurrent atherosclerotic CV events despite optimal LDL levels [35]. European guidelines recommend as additional plasma analyses Lp(a)/apoA1 or apoB/apoA1 ratio to characterize CVD risk.

## Conclusion

Lp(a) is an apoB-100 containing lipoprotein that increases CV risk, mainly for CAD but also for ischemic stroke. Its serum levels are constant and genetically determined by specific genes coding for apo(a), with no effect of environmental factors. It is responsible for residual risk and recurrent events even when other lipid fractions such as LDL are optimally controlled by current evidence-based therapy, such as statins.

No trials are available to prove that lowering Lp(a) may improve CVD outcome, because of the lack of specific agents to target it selectively. PCSK9 monoclonal antibodies used to lower LDL in atherosclerotic CVD may also moderately lower Lp(a) with unclear prognostic effect that confounds with the pronounced lowering of LDL. Future agents are under development such as second-generation antisense nucleotide inhibitors and small interfering RNA and trials are under way.

Drugs with demonstrated effects on CV outcome, such as statins, ezetimibe and PCSK9 inhibitors are indicated in high-risk patients with atherosclerotic CVD to lower their serum apoB-100 lipoproteins, until these dedicated trials will be performed.

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