

Role of lipoprotein(a) in plaque progression

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KEYWORDS

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Identified by Berg in 1963, lipoprotein(a) represents a key contemporary residual risk pathway in atherosclerotic cardiovascular disease (ASCVD) secondary prevention. Indeed, epidemiological and genetic studies have undoubtedly demonstrated that lipoprotein(a) is one of the strongest causal risk factors of ASCVD. Although a risk threshold has been set between 30 and 50 mg/dL, depending on the ethnicity, a linear risk gradient across the distribution has been demonstrated. In the context of the atherosclerotic process, hyperlipoproteinaemia(a) contributes to the atherosclerotic plaque formation by deposition of cholesterol in the same manner as low-density lipoprotein (LDL) cholesterol, due to the LDL particle component of lipoprotein(a). Lipoprotein(a) accumulates in human coronary and carotid atherosclerotic lesions. High concentrations of lipoprotein(a) are associated with accelerated progression of the necrotic core, but not with coronary calcium score (CAC), although in the latter case, the evaluation of lipoprotein(a) can overcome the potential limitation of CAC to capture the totality of ASCVD risk in asymptomatic individuals. Finally, in the absence of a pharmacological approach to lower lipoprotein(a) to the extent required to achieve a cardiovascular benefit, implementation strategies that increase awareness among the population, patients, and healthcare providers on the importance of lipoprotein(a) in the development of ASCVD are eagerly needed.

History

The identification of lipoprotein(a) occurred at a time of growth in the knowledge of circulating lipoproteins when numerous allotypes were identified. To distinguish between different genetic types of human β -lipoproteins and to prove heredity of this type of system, Berg *et al.* used rabbits hyperimmunized with β -lipoproteins isolated from 20 healthy donors. An unknown inheritable factor of human serum β -lipoproteins, the lipoprotein(a) antigen, was then identified. Thus, individuals possessing this factor were called lipoprotein(a)⁺ and those negative, lipoprotein(a)⁻. When separated by ultracentrifugation, these atypical pre- β -lipoproteins, not floating at the density 1.006 g/mL, were called 'sinking pre- β lipoproteins' or pre- β 1-lipoproteins. In 1974, Berg *et al.* noted that these pre- β 1-lipoproteins were closely

related to the phenotype lipoprotein(a)⁺, and this association occurred more frequently in patients with coronary heart disease (CHD).¹

Lipoprotein(a) structure and levels

Lipoprotein(a) resembles low-density lipoprotein (LDL) in its lipid composition and the presence of apo B100 but is distinguished by the unique glycoprotein apo(a), which is covalently attached to apo B100. Overall, lipoprotein(a) levels are under strict genetic control by the *LPA* gene locus, characterized by a variable number of Kringle (K)IV₂ repeats, which are transcribed and translated into apo(a) isoforms of different sizes. Apo(a) is a glycoprotein characterized by repeats of an unusual 'kringle' structure (remindful of a Scandinavian pastry). Lipoprotein(a) is thus the product of disulphide bond formation between the Cys⁴³²⁶ in apolipoprotein (apo)B and the only unpaired cysteine (Cys¹⁵⁶⁸) in

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KIV₉ of plasminogen-like glycoprotein apo(a) in a 1:1 molar ratio.

Concerning circulating levels, association studies using the size polymorphism of apo(a) or the number of KIV₂ repeats in the gene demonstrated an inverse correlation between isoform size/KIV₂ repeat number and lipoprotein(a) levels. It is estimated that isoform size can explain 40-70% of the variance in plasma concentrations, while variants in *LPA* gene determine 30-40%.² Unfortunately, this represents a biochemical drawback in the quantification of lipoprotein(a) in clinical practice, namely, none of the available commercial assays for lipoprotein(a) quantification is 100% inherently isoform insensitive. Thus, despite attempts in harmonizing commercial assays, a single conversion factor between mg/dL of lipoprotein mass and nmol/L of apo(a) is not feasible and should be avoided in clinical practice. Measurement of molar concentration (Lp(a)-P in nmol/L) most accurately assesses the true atherogenic risk of lipoprotein(a).

Lipoprotein(a) today

Nowadays, the existing link between coronary artery disease (CAD) risk and elevated levels of lipoprotein(a) is a well-known fact (Figure 1). The early report by Kamstrup showed a stepwise increase in the risk of myocardial infarction (MI) with extremely high levels of lipoprotein(a) predicting a three- to four-fold rise in the risk of MI, with no evidence of a threshold effect.⁴ Relative to that it has been estimated that lipoprotein(a) levels in the atherothrombotic range are generally accepted as >30-50 mg/dL, that are present between 20 and 30% of the

global population.⁵ However, considering that most patients with elevated lipoprotein(a) levels are Blacks, followed by South Asians, Caucasians, Hispanics and East Asians, it proves difficult to establish a certain atherosclerotic cardiovascular disease (ASCVD) threshold. It has been suggested that a cut-off of 30 mg/dL is not appropriate in Whites and Hispanics (for whom 50 mg/dL should be considered), but remains suitable in black individuals. Differences in risk threshold exist also in the case of primary care populations and secondary prevention, namely, the risk increases for lipoprotein(a) between 25 and 30 mg/dL in primary prevention, whereas in secondary prevention the recurrence of events seems to set at values >50 mg/dL.⁵ However, the relationship between lipoprotein(a) and ASCVD appeared linear across the distribution with a hazard ratio (HR) of 1.11 [95% confidence interval (CI) 1.10-1.12] per 50 nmol/L increment. Besides these peculiarities, the routine assessment of lipoprotein(a) levels is important since it helps to reclassify patients in both primary prevention and secondary prevention. Data extrapolated from a cross-sectional case-control study in a tertiary hospital in The Netherlands showed that individuals with lipoprotein(a) levels >387.7 nmol/L had an odds ratio of 2.64 for ASCVD (95% CI 1.45-4.89) and 3.39 for MI (95% CI 1.56-7.94), exposing these individuals to an ASCVD risk similar to that of heterozygous familial hypercholesterolaemia.⁶ The usefulness of adding lipoprotein(a) in CVD risk discrimination has been demonstrated in numerous studies, e.g. extreme lipoprotein(a) levels can improve MI and CHD risk prediction in a general population. However, owing to the impact of genetics on lipoprotein(a) levels, a one-time measurement may be helpful in refining cardiovascular (CV) risk prediction. Repeated monitoring

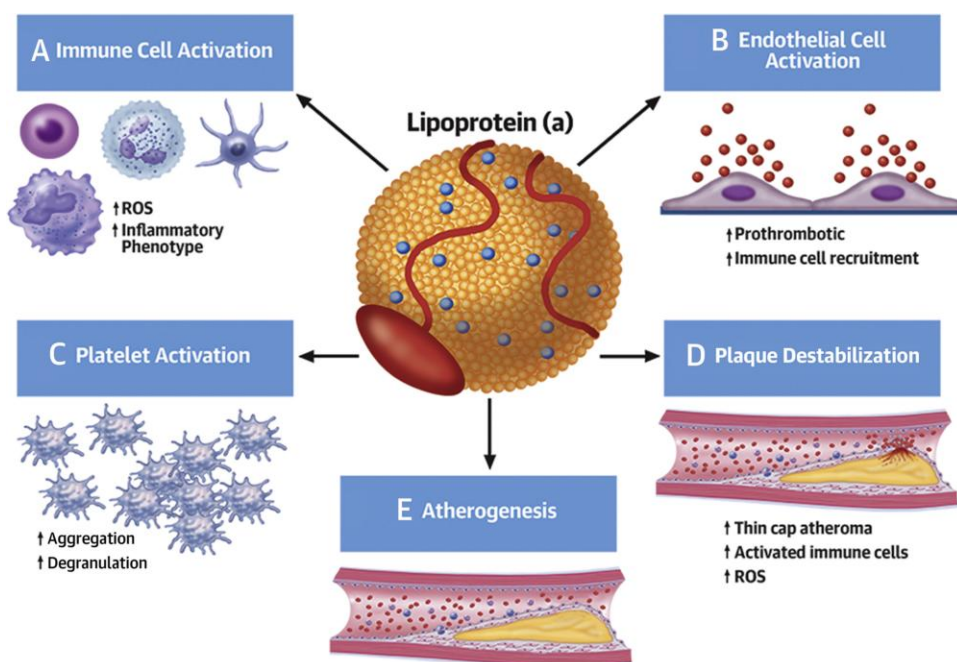


Figure 1 Role of lipoprotein(a) in atherosclerotic cardiovascular disease with permission of Elsevier.³

seems unlikely to be clinically relevant in understanding an individual patient's residual risk of an incident CV event in the context of primary prevention.⁷

Lipoprotein(a) in atherosclerotic cardiovascular disease

In the context of atheromata, high lipoprotein(a) contributes to the atherosclerotic plaque formation by deposition of cholesterol due to the LDL particle component of lipoprotein(a), in the same manner as LDL cholesterol (LDL-C). It is estimated that the cholesterol transported by lipoprotein(a) consists roughly of 30% of its total mass expressed in mg/dL. The impact of lipoprotein(a) on plaque development is supported by studies demonstrating the accumulation of lipoprotein(a) in human coronary and carotid atherosclerotic lesions. Lipoprotein(a) colocalizes with the presence of macrophages in specimens obtained by coronary atherectomy, along with foamy macrophages and necrotic cores, representing plaque vulnerability in coronary arteries from victims of sudden cardiac death. The prothrombotic and proinflammatory effects of lipoprotein(a) were suggested to promote plaque destabilization, leading to plaque rupture and atherothrombotic events. Atherosclerotic plaque progression monitoring with coronary-computed tomography angiography (CCTA), a non-invasive imaging technique, allows the quantification of calcified and noncalcified plaque or the detection of coronary stenosis. The liaison between lipoprotein(a) and progression of coronary plaque volumes and composition was the aim of the study by Kaiser *et al.* demonstrating that high concentrations of lipoprotein(a) were associated with accelerated progression of necrotic core in patients with advanced multivessel CAD, despite preventative therapies. Patients with concentrations >70 mg/dL had an accelerated progression of low-attenuation coronary plaque volume after 12 months with an absolute 10.5% increase for each 50 mg/dL rise in lipoprotein(a) (95% CI 0.7-20.3%). CCTA-derived low-attenuation plaque presents the intravascular ultrasound-verified necrotic core and is considered one of two important constituents of high-risk plaques.⁸ Conversely, lipoprotein(a) does not associate with coronary calcium score (CAC) one of the most thoroughly studied and widely available tests in CV medicine. CAC scoring is a useful way of improving CV risk assessment in asymptomatic people and serves as a guide for initiating or deferring preventive therapies. Raised lipoprotein(a) and CAC score were independently associated with ASCVD risk, respectively, HR=1.29 (95% CI 1.04-1.61) for lipoprotein(a) >130 nmol/L, HR=1.68 (95% CI 1.30-2.16) for CAC 1-99 and HR=2.66 (95% CI 2.07-3.43) for CAC ≥100.⁹ The present results highlight that when a patient without clinical CVD is identified with either CAC ≥100 or lipoprotein(a) >50 mg/dL, the next step in the risk evaluation should be to measure either lipoprotein(a) or CAC to identify patients at highest risk. Another important aspect to consider is that CAC can be thought of as analogous to C-reactive protein (CRP). Lipoprotein(a)-associated ASCVD risk is observed only

with concomitant elevation of hsCRP. During a mean follow up of 13.6 years, a significant correlation was observed between lipoprotein(a) and hsCRP, while lipoprotein(a) associated with ASCVD risk only in individuals with concomitant elevation of hsCRP (>2 mg/L), namely, an HR of 1.36 (95% CI 1.02-1.81) with lipoprotein(a) of 50-99.9 mg/dL and an HR of 2.09 (95% CI 1.40-3.13) with lipoprotein(a) ≥100 mg/dL.¹⁰

In patients with ST-segment elevation MI (STEMI), complete revascularization by percutaneous coronary intervention (PCI) reduces the risk of CV death or MI. High lipoprotein(a) levels are associated with a poor prognosis after PCI in stable CAD patients. This suggests that lipoprotein(a) measurements may be useful for patient risk stratification before selective PCI. Indeed, it should be recalled that recurrent MI after PCI remains a relatively common complication in contemporary practice and confers a significantly increased risk of death, stroke, and bleeding. In a registry study comprising 12 064 with a median follow up of 7.4 years, the group with high levels of lipoprotein(a) had an HR for primary endpoint and repeated revascularization, respectively, of 1.17 (95% CI 1.05-1.30) and 1.13 (95% CI 1.02-1.25).¹¹ These findings were in line with those of a prospective cohort study in which a 6% rise in the risk of revascularization was found every 10 mg/dL increment in lipoprotein(a) levels.¹²

Another aspect worth considering is diabetes, a condition which increases mortality risk, and nearly doubles in combination with manifestations of CVD, e.g. MI or stroke, translating into an estimated reduction in life expectancy of 12 years. Near-infrared spectroscopy (NIRS) was used for analysis of the composition of the atherosclerotic plaque in coronary arteries in 312 patients with CAD with or without a diagnosis of diabetes. Circulating levels of lipoprotein(a) were independently associated with NIRS in patients with diabetes but not in patients without diabetes. Of note, even in patients with diabetes achieving LDL-C <70 mg/dL, lipoprotein(a) remained associated with NIRS.¹³

An increased risk of heart failure, stroke, and death can be the consequence of atrial fibrillation which represents the most common cardiac arrhythmia. An association between lipoprotein(a) levels at enrolment and incident atrial fibrillation (AF) risk during a median 11 years of follow up was found in 20 432 participants of the UK Biobank. Both epidemiological and genetic approaches showed that each 50 nmol/L rise in lipoprotein(a) at enrolment was associated with a 3%/4% increased risk of developing atrial fibrillation. When a mediation analysis was performed, 37.8% of the effect of lipoprotein(a) on incidence of atrial fibrillation risk was independent of prevalent CAD and atherosclerotic stenosis at enrolment.¹⁴

Atherosclerosis is firmly established as the culprit for causing not only CHD, but also stroke. Indeed, studying atherosclerosis in the carotid artery bifurcation has proved instrumental, given the paramount role of atherosclerosis in the carotid artery bifurcation in the development of ischaemic stroke. Relative to the contribution of lipoproteins, besides LDL-C, a role is

played by lipoprotein(a). Among 49 699 individuals from the Copenhagen General Population Study and 10 813 individuals from the Copenhagen City Heart Study, the HR for ischaemic stroke was 1.60 (95% CI 1.24-2.05) for individuals with lipoprotein(a) levels >93 mg/dL. For every 50 mg/dL rise in lipoprotein(a), the HR for ischaemic stroke was 1.20 (95% CI 1.13-1.28).¹⁵

Conclusion

The awareness of the association between ASCVD risk and hyperlipoproteinaemia(a) has emerged in the recent decades from both epidemiological and genetic studies and has highlighted the need to improve treatments for patients with ASCVD, as therapeutic approaches capable of lowering lipoprotein(a) to the extent required to achieve a CV benefit are lacking. Indeed, lipoprotein(a) has been acknowledged as one of the main drivers of residual risk. While the use of PCSK9 inhibitors has led to a mean modest reduction in lipoprotein(a) levels by roughly 25%, statins increase lipoprotein(a). Thus, lipoprotein apheresis is the most effective strategy today in the case of hyperlipoproteinaemia(a). This drawback leaves open the key question of how much should the reduction of lipoprotein(a) be in order to reach a CV benefit. The final answer will be given by the results of lipoprotein(a) Horizon trial with pelacarsen, an antisense oligonucleotide targeting *APO(a)* directly in the liver. The study will test the effect of the ASO TQJ230 against apo(a) in patients with previous MI, stroke, or symptomatic peripheral artery disease, with an optimized LDL-C-lowering therapy and lipoprotein(a) ≥ 70 mg/dL. Two other RNA-based approaches have been tested, namely, olpasiran and SLN360.¹⁶ In the meantime, since all the major guidelines have endorsed the evaluation of lipoprotein(a) at least once during a lifetime, the idea behind is to not wait until the first event happens. In conclusion, considering data implementation strategies that increase awareness among the population, patients, and healthcare providers on the importance of lipoprotein(a) in the development of ASCVD are eagerly awaited, especially in relation to a positive family history of premature CAD.

Conflict of interest: None declared.

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