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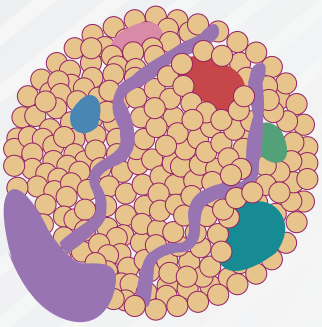
Role of Lipoprotein(a) in Atherosclerotic Cardiovascular Disease and Aortic Stenosis

Consensus Statement from the European Atherosclerosis Society Congress



Lipoprotein(a) (Lp[a]) is a liver-derived lipoprotein consisting of[1]

- A low-density lipoprotein-like moiety
- One plasminogen-like apolipoprotein(a) covalently bound to apolipoprotein B

According to estimates, approximately 20% of the global population has elevated levels of Lp(a)[1]

Lp(a) has been implicated in atherosclerotic development, including[1]

- Foam cell formation
- Smooth muscle cell (SMC) proliferation
- Plaque inflammation and instability

Emerging information highlights an association between Lp(a) and atherosclerotic cardiovascular disease (ASCVD)[1]

Factors influencing Lp(a) levels[2]

- Genetic variants
- Ethnicity
- Lifestyle
- Renal and hepatic function
- Sex
- Inflammation
- Hormones affecting lipoprotein metabolism, including growth and sex hormones

Lp(a) levels are predominantly, i.e., in more than 90% of cases, determined by genetic factors[2]

Lp(a) levels are[2]

- Lowest in Chinese individuals, followed by White, South Asian, and Black individuals
- Usually higher in women than in men
- Reduced by 10%–15% via low carbohydrate/high-fat diets

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Prevalence and clinical consequences of Lp(a) elevation

The top-third of the global population displays significantly high Lp(a) levels with a >20% increase in the risk of cardiovascular morbidity and mortality[2]

Findings from studies that examined the link between Lp(a) and major cardiovascular events (MACE)

1 Meta-analysis by O'Donoghue *et al.*[3]

Elevated Lp(a) >80th percentile is associated with an increased risk of MACE when low-density lipoprotein (LDL)-C levels are <130 mg/dL

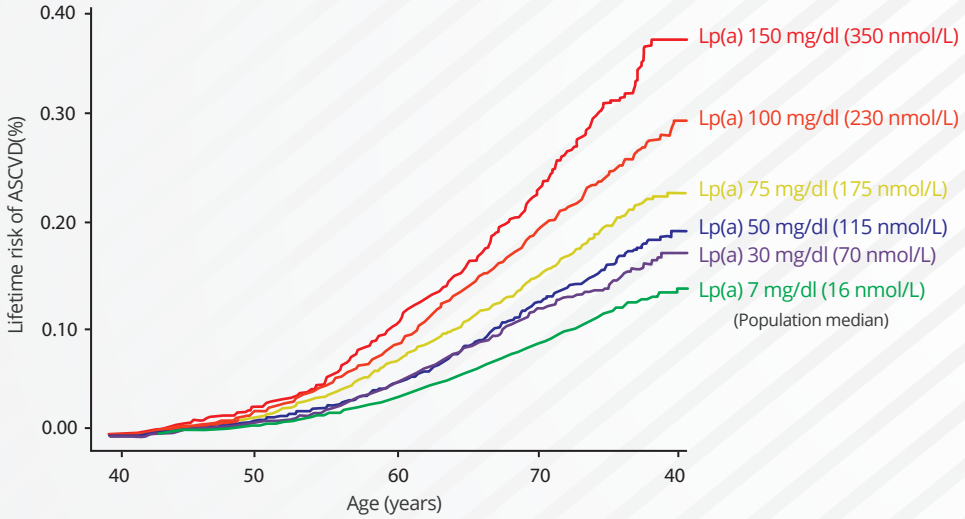
2 Copenhagen General Population study[4]

The risk of incident MACE is higher at Lp(a) ≥50 mg/dL than at Lp(a) <10 mg/dL even when LDL-C levels are <70 mg/dL

3 AIM-HIGH study[5]

Risk of MACE is ~90% higher at baseline Lp(a) >75th percentile despite lower LDL-C (~65 mg/dL) levels

Lifetime risk of cardiovascular events with increasing Lp(a) levels[2]



ASCVD, aortic valve stenosis (AVS), and cardiovascular mortality risk increases with increasing Lp(a) levels and is independent of sex and ethnicity[2]

Lp(a) levels >30 mg/dL are linked to a higher risk of arterial ischaemic stroke in paediatric patients[2]

Lp(a) levels are not associated with the risk of venous thromboembolism[2]

Very low Lp(a) concentrations may increase the risk of diabetes mellitus[2]

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Mechanisms underlying the pathogenicity of Lp(a)[2]

Lp(a) exerts pro-inflammatory and pro-atherosclerotic effects owing to the oxidized phospholipids (OxPLs) that it carries

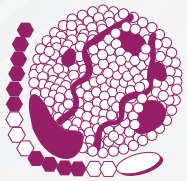
→

Lp(a) elevations result in the upregulation of inflammatory and calcification genes in vascular and valvular cells, promoting the incidence and progression of AVS

→

The role of Lp(a) in enhancing coagulation or impairing fibrinolysis remains unclear

Pro-inflammatory effects of Lp(a)



- ↑ Endothelial cell dysfunction
- ↑ OxPL delivery
- ↑ Monocyte chemoattraction
- ↑ Transendothelial monocyte migration
- ↑ Autotaxin delivery
- ↑ Macrophage IL-8 levels
- ↑ Macrophage apoptosis

Pro-atherosclerotic effects of Lp(a)

- ↑ Endothelial cell permeability
- ↑ SMC proliferation and migration
- ↑ Foam cell production
- ↑ Calcification

Thrombotic effects of Lp(a)

- ↑ Platelet responsiveness
- ↓ Plasminogen activity
- ↓ Clot permeability
- ↑ Endothelial cell PAI-1 expression

IL: Interleukin; PAI-1: Plasminogen activator inhibitor type 1

Cardiovascular disease is a leading global cause of mortality. High Lp(a) levels enhance the risk of MACE and highlight an urgent, unmet clinical need. Thus, patients with high Lp(a) levels should be provided with immediate, individualized, preventive treatment regimens, including management of LDL-C, glucose, blood pressure, and lifestyle modifications to lower their Lp(a) levels and their risk of MACE[2,6]

Recommendations for clinicians[2]

Testing for Lp(a) levels is recommended for

- All adults to examine their cardiovascular risk
- Young individuals with a history of ischaemic stroke or a family history of premature ASCVD
- Individuals with a family history of elevated Lp(a) or ASCVD

Management of individuals with elevated Lp(a) includes

- Early risk factor management if specific Lp(a) lowering therapies are not administered
- Comprehensive cardiovascular risk factor management
- Lipoprotein apheresis if the risk of progressive cardiovascular disease does not reduce

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Key points from the European Atherosclerosis Society (EAS) consensus statement[2]

EAS consensus statement

- All adults should undergo Lp(a) at least once
- There is a causal relationship between Lp(a) levels and cardiovascular outcomes in different ethnicities
- Very low Lp(a) levels are associated with a greater risk of diabetes mellitus
- Lp(a) levels are not linked to venous thrombotic events
- Results should be interpreted carefully considering the patient's absolute global cardiovascular risk following which lifestyle and risk factor management interventions should be implemented
- New phase II/III trials are testing Lp(a) lowering therapies

Future research challenges[2]

- Understanding the genetic regulation of Lp(a) and identification of causal variants and underlying mechanisms
- Examining the effects of Lp(a) in larger samples within different populations
- Elucidating the pathogenic mechanisms of Lp(a) moieties
- Clarifying the link between very low Lp(a) levels and diabetes mellitus
- Standardising Lp(a) measurements
- Identifying the degree of Lp(a) lowering at which clinical benefits can be seen
- Examining whether decreases in Lp(a) can reverse accelerated atherogenesis and AVS progression

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