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LP(a) as an Undecleared Risk Factor in CVD

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Introduction

Despite of the advances in lipid management, outstanding risk in many patients points to a need to investigate other contributors as possible therapeutic targets.

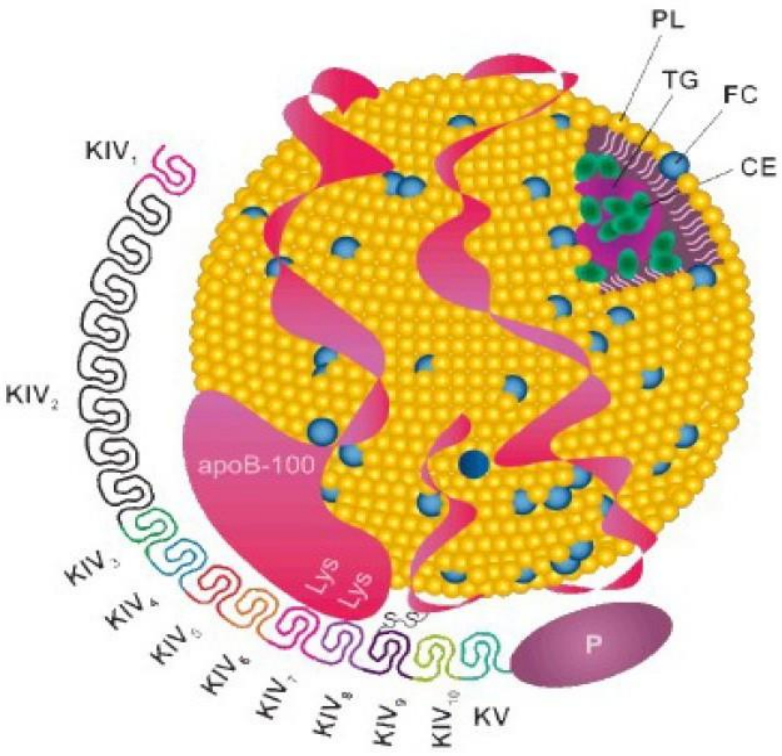
Lipoprotein(a) represents a thrilling new biomarker in the field of lipidology and preventive cardiology as a ASCVD risk assessment because it is estimated to be elevated in almost 20% of the world's population. Thus, it is time to consider using it in the medical practice.

What is LP(a)

It is a large lipoprotein made by the liver, is LDL-like particle with Apolipoprotien (a) convalently bound to Apolipoprotien (B), it is very sticky, and the structure of it is highly heterogeneous secondary to many different Apo (a) isoforms within the population.

LP(a) levels are explaned by genetics.

- Number of repeats in KIV-2 (kringle IV type 2) inversely correlated to plasma levels.
- SNPs (single nucleotide polymorphism) in LP (a) are associated with plasma level.



What is the link between LP(a) and CVD?

Actually, proposed pathophysiologic mechanisms supporting a causal link between elevated circulating concentrations of LP(a) and ASCVD and aortic stenosis, because the the cholestrol content of LDL portion of LP (a) may promote cholestrol deposition in the arterial intima and at aortic valve leaflets, leading to symptomatic atherosclerosis resulting in MI and ischemic stroke, and valvular aortic stenosis as well, apo(a) has homology with plasminogen and may inhibit fibrinolysiss, thus increase the thrombosis, through inhibition of fibrinolysis at sites of plaque rupture, apo(a) has the potential to cause MI and ischemic stroke, thrombosis at sites of turbulent flow may promote atherosclerosis and valvular aortic stenosis. finally, Apo(a) possesses unique properties including enthothelial dysfunction and pro-inflammatory responses, and pro-osteogenic effects promoting calcification.

Laboratory Measurement of LP(a)

Measurement of LP (a) is currently not standardized or harmonized. Available assays report lpa in either mg/dl or nmol/L and may exhibit isoform -dependent bias. Evedince is incomlete regarding the utility of using different risk cut points of LP(a) based of age, gender, ethnicity, or the presence of comorbid conditions. Risk increase starting at> 30 mg/dl and become clinically significant >50 mg/dl some individuals with exteme levels >180 mg/dl may have a prognosis similar to HTZ FH.

LP(a) testing in clinical practice

A decision to measure LPA should be after a thoughtful benefit-risk discussion between the patient and physician as well the presence of comorbid conditions, race and /or concern of future risk.

Based on the guidelines and current evidence LP(a)testing is reasonable to refine risk assessment for ASCVD in adults with (as primary prevention) as follow :

- First degree relative with premature ASCVD (<55 y im=n men ,<65 y in women) particularly in the absence of traditional risk factors .
- A personal history of premature ASCV.
- Primary severe hypercholestrolemia (LDL-C >190 mg/dl) or suspected FH.
- To aid in the clinician-patient discussion about whether to prescribe a statine in those aged 40-75 y with borderline (5-7,4) 10-y ASCVD risk.
- Risk-enhancing factors of family member with severe hypercholestrolemia.

- To identify a possible cause for a less than anticipated LDL-C lowering to evidence-based LDL-C lowering therapy as well identify those to evidence-based LDL lowering therapy.
- Cascade screening of family members with sever hypercholestrolemia

On the other hand population where LPA testing may be reasonable as secondary prevention as follow

- Personal history of premature ASCVD
- Recurrent or progressive ASCVD, despite optimal lipid-lowering therapy
- Ischemic stroke who are aged 55y
- FH patients with ASCVD
- How do you treat elevated LP(a)

People with high LP(a) levels should take steps to lower their LDL-C if it is high. Managing conditions such as diabetes and high blood pressure is also important for people with LP(a).

Although in general beneficial, lifestyle changes including low fat and physical exercise, not smoking, healthy weight have no significant effect on LPA levels hormone replacement therapy in women lowers LPA levels and in the studies for primary and secondary prevention, HRT was observed to modify CVD risk across LP(a) quintiles but HRT related adverse event outweighed any benefit on CVD therefore, HRT can be recommended as the sole purpose of lowering LPA. Statin therapy has demonstrated a clinical benefit in patient with elevated LP(a) and history of CV events concluded that those with LPA levels >50 mg/dL on statin therapy are at a significantly higher risk of CVD as compared to those with levels <30 mg/dL. Independent of other conventional CVD risk factors.

There is uncertainty about the clinical value for of PCSK9 inhibitor-associated LP(a) reduction. An analysis of the FOURIER trial demonstrated that evolucamab reduced LP(a) by 27% and that the reduction in MACE was 23%. Patient with higher baseline LP (a) had greater absolute reductions and tended to derived greater benefit from PCSK9 inhibition, Similarly In ODYSSEY OUTCOMES. There was also a greater absolute benefit on MACE with alirocumab in patient with higher baseline level of LP(a) , While these results are encouaging the impact of PCSK9 inhibitors on LP(a) is fairly modest, and additional analysis is needed before PCSK9 inhibitors can be recommended as LP(a)- targeted therapy.

Finally, Lipoprotein apheresis is the only therapy approved by the FDA for treating high LP(a) levels and it is only approved for people with FH who have LDL>100 mg/dl and LDL >60 MG/DL, AND CORONARY OR OTHER ARTERY DISEASE AS well as used for those with elevated LP (a) and recurrent ASCVD events. Apheresis is a treatment like dialysis in which a machine removes LP (a) and LDL -C from the blood.

Conclusion

Lipiprotien(a) represents and exciting new biomarker in the field of lipidology and preventive cardiology. Elevated LPA is causally implicated in ASCVD, and testing in specific patients may help to tailor the appropriate intensity of preventive measures. However, because of the lack of standardization and heterogeneity of the available data, optimal cut-offs remain a source of intense debate. The current focus of clinical care is on traditional risk factor control in patients with high LPA as targeted treatment options are limited. Actively being investigated, and if successful, they could become an important component of primary and secondary prevention. Finally treatment of patient with elevated LP(a) including agents that reduced it by (approximately 20-30 %) such as PCSK9 inhibitors, high dose of niacin, estrogen, aspirin 80-160 mg. Or LP(a) apheresis that reduce it by (aproximately 50-80%) with refer the patient to lipid specialist for assessment.

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