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Lp(a) and Cardiovascular Disease: Role of PCSK9 Inhibition and Other New Therapies

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Lipoprotein(a) {Lp(a)} is a lipoprotein that consists of a protein, apoprotein (a), covalently linked to the apo B moiety of LDL. Its function is unknown, but Lp(a) has some structural homology with plasminogen, giving it a potential role in thrombosis and atherosclerosis. Measurement of Lp(a) is difficult, and early methodological problems and lack of standardization led to its role as a CV risk factor being questioned. However, more recent large scale studies and meta-analyses have suggested that there is a continuous relationship between Lp(a) and CV risk, and that this relationship is independent of other risk factors. Myocardial infarction is elevated by roughly 2- to 2.5-fold in individuals with Lp(a) levels above the 90th percentile.

Because the circulating level of Lp(a) is predominantly (>90%) determined by the apo(a) gene, it has been possible to confirm these findings in Mendelian randomization studies, the findings of which have reinvigorated Lp(a) as an important CV risk factor. It is estimated that 20% of the population have Lp(a) levels above 50 mg/dL, and this level has been set as desirable in recent guidelines.
Levels of Lp(a) are not significantly altered by statins but are reduced by 30-40% by niacin. However, there have been no studies examining the effects of niacin in individuals with Lp(a) > 80th percentile.

The PCSK9 inhibitors evolocumab and alirocumab reduce Lp(a) concentrations by up to 30%, and thus may have potential in patients with high levels. However, a recent genetic analysis in over 30,000 subjects found that a lifetime 10-mg/dL lower, genetically predicted Lp(a) concentration was associated with a 5.8% lower CHD risk. The estimate for a short term clinical trial, assuming there is the same relationship between Lp(a) exposure and risk as is seen with LDL exposure, is only a 2.7% risk reduction for each 10mg/dL Lp(a) decrease. This suggests that very large Lp(a) reductions will be required to produce a significant result in the relatively short timeframe of a clinical trial. Analyses of the influence of Lp(a) on risk reduction with the PCSK9 inhibitors are just becoming available, and may show if the genetic predictions are accurate.

Much greater reductions in Lp(a) have been seen with a novel apo (a) m-RNA antisense molecule, which produced up to a 90% reduction in circulating levels, and if this is used in people with high Lp(a) levels, genetic studies would predict that reductions of this magnitude will result in significant CV risk reduction.

▶ References

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