Decoding lipoprotein (a): lessons of the past and prospects for the future

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Lipoprotein (a) (Lp(a)) is low-density lipoprotein-like particle contains an additional apolipoprotein(a) component, a highly polymorphic glycoprotein structurally homologous to plasminogen. Apo(a) exhibits significant sequence homology with plasminogen, particularly in its kringle IV, kringle V, and protease-like regions. Consequently, Lp(a) particles exhibit considerable heterogeneity in size and density, as copy-number variations in the kringle IV2 region of the LPA gene result in apo(a) proteins with varying numbers of kringle units, while maintaining an identical primary sequence. It is genetically inherited, with marked interindividual and ethnic variability and minimally influenced by lifestyle or environmental factors. It promotes atherosclerosis, triggers vascular inflammation, and increases the risk of thrombosis. Lp(a) is a key risk factor for atherosclerotic cardiovascular disease, aortic valve disease, but not for venous thrombosis. Lp(a) facilitates retention of apolipoprotein B particles, delivers pro-inflammatory oxidized phosholipids, drives endothelial cells, smooth muscle cells, and monocyte activation, contributes to microcalcifications, and is causally linked to MACE in both, primary and secondary prevention. About 20% of the general population has a high Lp(a) concentration, and for these individuals, it represents a very significant risk factor. Most relevant societies, including the ACC, AHA, ESC/EAS, Canadian Cardiovascular Society, Endocrine Society, etc. recommend that Lp(a) should be measured at least once in lifetime, preferably in nmol/L, for comprehensive cardiovascular risk assessment. For individuals with high Lp(a) concentrations, it is recommended to incorporate it into the overall risk assessment and accordingly manage other risk factors. With the emergence of new Lp(a)-lowering therapies (antisense oligonucleotides, small interfering ribonucleic acid agents) that significantly reduce circulating Lp(a) levels, and renewed optimism for targeted intervention and improved cardiovascular outcomes.