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**LIPOPROTEIN A - THE GENETIC LINK TO HEART DISEASE**

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Lipoprotein(a) (Lp(a)) is a genetically determined lipoprotein implicated as a potent, independent risk factor for cardiovascular disease (CVD), including atherosclerosis, myocardial infarction, stroke, and aortic valve stenosis. Structurally akin to low-density lipoprotein (LDL), Lp(a) is distinguished by apolipoprotein(a) (apo(a)), covalently linked to apolipoprotein B-100. Encoded by the *LPA* gene, Lp(a) levels–elevated in 20-30% of individuals (>50 mg/dL or >125 nmol/L)–are 90% heritable, driven by variable kringle IV type 2 repeats, and resistant to lifestyle modification. This thesis examines Lp(a)'s biochemical basis, pathophysiological impact, and the persistent challenge of reducing its associated CVD risk.

Lp(a) is synthesized in the liver, with smaller apo(a) isoforms linked to higher plasma concentrations and greater risk. Its pathogenicity stems from a triad of effects: atherogenesis via cholesterol deposition in arterial walls, inflammation from oxidized phospholipids, and prothrombotic activity due to apo(a)'s homology with plasminogen, which impairs fibrinolysis. Studies like the Framingham Heart Study and a 2018 Lipoprotein(a) Foundation meta-analysis confirm a 50-70% increased risk of myocardial infarction with elevated Lp(a), independent of LDL cholesterol. The Copenhagen General Population Study further ties Lp(a) to aortic stenosis, highlighting its broad vascular impact.

Clinically, Lp(a) testing is recommended for patients with premature CVD, familial hypercholesterolemia, or unexplained events despite normal lipids. Yet, therapeutic options remain limited. Statins, effective for LDL, negligibly affect Lp(a) and may slightly elevate it. Niacin and PCSK9 inhibitors (e.g., evolocumab) reduce Lp(a) modestly (20-30%), but side effects and cost hinder their use. Lipoprotein apheresis offers dramatic reductions (60-70%) but is invasive and niche. Promisingly, antisense oligonucleotides like pelacarsen, targeting *LPA* mRNA, achieve up to 80% reductions in phase II trials, though outcome data are pending. For now, managing Lp(a) relies on controlling modifiable risk factors.

Lp(a)'s genetic fixity and therapeutic resistance underscore an unmet need in CVD prevention, with emerging therapies offering cautious optimism.