Role of Lp(a) as an ASCVD Risk Factor and its Heritability in Familial Hypercholesterolemia: Implications for Cascade Testing Programs

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Abstract

Background: Lipoprotein (a) [Lp(a)] is an LDL-like particle covalently bound to a glycoprotein, called apolipoprotein (a) [apo(a)], that is under unique genetic control and has potent athero-thrombotic and pro-inflammatory properties. Plasma concentrations of Lp(a) are positively skewed, highly heritable, inversely correlated with apo(a) isoform size, and vary markedly among ethnic groups. One in four people have plasma Lp(a) levels that are associated with increased risk of atherosclerotic cardiovascular disease (ASCVD). New evidence supports a causal role for Lp(a) in ASCVD and calcific aortic valve disease (CAVD); risk may be particularly higher in South Asians and Latin Americans. Individuals with elevated Lp(a) have a high life-time burden of ASCVD and this is important for coronary prevention, particularly in high risk conditions, such as familial hypercholesterolaemia (FH).

Investigation: An novel investigation was carried out to assess whether testing for Lp(a) was effective in detecting and risk stratifying individuals participating in FH cascade screening programs. Family members from index cases enrolled in the SAFEHEART and FHWA cohorts were tested for genetic FH and elevated Lp(a) based an established screening protocols. Elevated Lp(a) was defined as a plasma level ≥50 mg/dL. The prevalence and yield of new cases of high Lp(a) in relatives of FH probands both with and without high Lp(a) were estimated, and in the Spanish cohort the association was assessed between elevated Lp(a) and incident ASCVD events.

Findings: Systematic screening from index cases with both FH and elevated Lp(a) identified one new case of elevated Lp(a) for every 2.4 screened. Opportunistic screening from index cases with FH but without elevated Lp(a) identified one individual for 5.8 screened. Over 5-years follow-up, FH (HR=2.47; P=0.036)

and elevated Lp(a) (HR=3.17; P=0.024) alone were associated with a significantly increased risk of a new ASCVD event or death compared with individuals with neither disorder; the greatest risk was observed in relatives with both FH and elevated Lp(a) (HR=4.40; P<0.001), independent of conventional risk factors.

Conclusions and Future Perspective: Systematic testing for elevated Lp(a) during cascade screening for FH is highly effective in identifying new cases of high Lp(a). Opportunistic testing has a lower yield but may be a useful approach for detecting probands, with subsequent testing of relatives being more effective employing a systematic approach. The detection of new cases of elevated Lp(a) is important because these individuals are at increased risk of ASCVD, particularly with coexistent FH. Hence, cascade screening programs for FH should incorporate both systematic and opportunistic testing for elevated plasma Lp(a). Our findings also suggest that beyond FH there may be value in systematically screening for elevated Lp(a), but this requires further investigation. The practicabilities, organization and cost-effectiveness of screening strategies for high Lp(a) remain to be demonstrated. This is critical in an era of novel RNA-based therapies that can selectively and potently lower plasma Lp(a) concentrations and potentially mitigate risk of ASCVD and CAVD.

Keywords

Lipoprotein(a), Familial Hypercholesterolaemia, Screening, Inheritance, Risk of ASCVD