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Atherosclerosis newsletter

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For many years, lipoprotein(a) (Lp(a)) has been known as an independent risk factor for atherosclerotic cardiovascular diseases (ASCVD). Its concentration in plasma is strongly determined by variations in the *LPA* gene, which encodes apolipoprotein(a) (apo(a)), i.e. the specific protein component of Lp(a). Results of Mendelian Randomization studies point to the causality of Lp(a) in the pathogenesis of ASCVD. Unfortunately, currently available drugs allow no or only moderate lowering of Lp(a) plasma levels and it is not well known whether these effects contribute to cardiovascular risk reduction exerted by some drugs. Moreover, the genetically determined size polymorphism of apo(a) makes it difficult to standardize Lp(a) for the measurement by traceable clinical routine methods. As a result, risk threshold varies considerably depending on the methods used. The September and October issues of *Atherosclerosis* contain several articles and editorials on Lp(a).

Volume 288, Issue September 2019

Volume 289, Issue October 2019

Serum lipoprotein (a) is associated with increased risk of stroke in Chinese adults: A prospective study

Stroke is the third most common cause of death in most Western countries and the leading cause of death in China in recent years. Previous studies have demonstrated that Lp(a) is associated with an increased risk of stroke in Western countries. However, less evidence has been obtained so far for the Chinese population. Zhang et al. aimed to investigate the association between serum Lp(a) levels and the risk of stroke among middle-aged and elderly Chinese.

A community-based prospective cohort study of 8500 participants aged 40 years or older was conducted in Jiading district, Shanghai, China, in 2010. Incident strokes were documented at follow-up visit during the period 2014–2015.

During a mean follow-up of 5.1 years, 444 incident cases of stroke occurred. The incidence of stroke was higher in participants with elevated serum Lp(a). Participants with higher serum Lp(a) levels had lower event-free survival rate.

In the population, serum Lp(a) levels are associated with increased risk of incident stroke.

Statin treatment increases lipoprotein(a) levels in subjects with low molecular weight apolipoprotein(a) phenotype

Lp(a) is a low density lipoprotein (LDL)-like lipoprotein to which apo(a) is linked through a disulfide bridge. In humans, more than 30 genetically determined apo(a) size isoforms (phenotypes) exist; their sizes are inversely correlated with circulating Lp(a) concentrations accounting for approximately 50% of the inter-individual concentration differences, yet numerous additional polymorphisms and mutations with varying functionality have been described. An elevated plasma Lp(a) level is an established independent risk factor for cardiovascular disease (CVD). High levels of Lp(a) may contribute to the considerable residual cardiovascular risk in statin-treated dyslipidemic patients, including those with familial hypercholesterolemia (FH) with LDL-cholesterol below target levels. Whether statins modify Lp(a) levels is not clear, as inconsistent data have been reported. Yahya et al. aimed at evaluating the effect of statin treatment initiation on Lp(a) levels in patients with dyslipidemia, and the interactions with apo(a) phenotype, *LPA* single nucleotide polymorphisms (SNPs) and change in LDL cholesterol.

The study population consisted of patients with dyslipidemia, predominantly familial hypercholesterolemia, who first initiated statin treatment (initiation group) or were already on stable statin treatment (control group) for at least 4 months. Plasma Lp(a) levels were determined with a particle-enhanced immunoturbidimetric assay before and at least 2 months after start of statin treatment in individuals of the initiation group, and at two time points with an interval of at least 2 months in the control group. High and low molecular weight (HMW and LMW, respectively) apo(a) phenotypes were determined by immunoblotting, and the common *LPA* SNPs rs10455872, rs3798220 and rs41272110 by Taqman assay.

Plasma Lp(a) levels increased significantly neither in the initiation group nor in the control group. In patients with the LMW apo(a) phenotype, Lp(a) levels increased significantly in the initiation group, but neither in the control group nor in patients characterized by the HMW apo(a) phenotype. The increase in Lp(a) levels upon statin treatment was not associated with common *LPA* SNPs or change in LDL cholesterol.

Statins affect Lp(a) levels differently in patients with dyslipidemia depending on the apo(a) phenotype. Statins increase Lp(a) levels exclusively in patients with the LMW apo(a) phenotype.

The effect of statins on Lp(a) levels, focusing on its major genetic regulator—the apo(a) size polymorphism- are further discussed in the accompanying editorial by Enkhmaa and Berglund.

Lipoprotein(a) reductions from PCSK9 inhibition and major adverse cardiovascular events: Pooled analysis of alirocumab phase 3 trials

Lp(a) is an LDL-like particle with glycoprotein apolipoprotein (a) [apo(a)] bound covalently to apolipoprotein B-100 (apoB-100). It mediates atherogenicity by its LDL moiety, which has a similar proportion of cholesterol content to traditional LDL particles. Lp(a) also induces pro-inflammatory responses by accumulation of oxidized phospholipids and potentially exerts pro-thrombotic effects by the plasminogen-like apo(a) moiety. Elevated Lp(a) levels are considered a causal factor for cardiovascular disease. In phase 3 ODYSSEY trials, alirocumab has been shown to reduce low-density lipoprotein cholesterol (LDL-C) and Lp(a) levels, with concomitant reductions in the risk of major adverse cardiovascular events (MACE). In this study, Ray et al. assessed whether lower on-study and greater percentage reductions in Lp(a) are associated with a lower risk of MACE.

They conducted a *post-hoc* analysis of data pooled from 10 phase 3 ODYSSEY trials comparing alirocumab with control (placebo or ezetimibe) in patients with cardiovascular disease and/or risk factors, and hypercholesterolemia despite statin/other lipid-lowering therapies.

Median baseline Lp(a) levels were 23.5 mg/dL. Median Lp(a) changes from baseline with alirocumab were −25.6% *vs*. −2.5% with placebo in placebo-controlled trials, and −21.4% *vs.* 0.0% with ezetimibe in ezetimibe-controlled trials. During follow-up, 104 patients experienced MACE. A 12% relative risk reduction in MACE per 25% reduction in Lp(a) was no longer significant after adjustment for LDL-C changes. In subgroup analysis, the association between Lp(a) reduction and MACE remained significant in a fully adjusted model among participants with baseline Lp(a) ≥50 mg/dL.

The results show that, in this population, Lp(a) reduction was not significantly associated with MACE independently of LDL-C reductions. Reducing the risk of MACE by targeting Lp(a) may require greater reductions in Lp(a), with more potent therapies and/or higher initial Lp(a) levels.

In his editorial, Kronenberg further discusses the causal association between high Lp(a) concentrations and CVD.

Comparison of lipoprotein(a) serum concentrations measured by six commercially available immunoassays

Lp(a) is an established causal risk factor for CVD, independently of LDL and other risk factors. The recognition of Lp(a) as an atherogenic molecule has raised the demand for reliable quantification methods in the clinical laboratory. Scharnagl et al. aimed to compare commercial immunochemical assays currently available.

They measured Lp(a) serum concentrations using six different assays, providing Lp(a) in mg/dl (Denka Seiken, Abbott Quantia, Beckman, Diasys 21FS, and Siemens N Latex) or in nmol/l (Roche TinaQuant, Diasys 21 FS) in 144 serum samples covering the clinically relevant range of Lp(a) concentrations. All assays relied on five-point calibrations using calibrators provided by the manufacturers. Apo(a) phenotyping was performed by sodium dodecyl sulfate-agarose gel electrophoresis (SDS-agarose) followed by immunoblotting.

Most bivariate correlation coefficients were greater than 0.90. Compared to an established International federation of clinical chemistry and laboratory medicine (IFCC)-proposed reference material, the results of the different assays diverged from the target values (43.3 mg/dl or 96.6 nmol/l) by −8% (Siemens N Latex) and +22% (Abbott Quantia). Stratification of the samples into five groups with increasing Lp(a) concentrations and difference plots showed that the differences among assays were concentration-dependent. Some assays overestimated Lp(a) at high concentrations compared to the Denka Seiken assay.

Current commercial immunological assays for measuring Lp(a) concentrations are differently calibrated. Their biases differ significantly across the clinically relevant concentration range in a non-linear manner. This is not conclusively explained by apo(a) phenotypes. Further international efforts to harmonize assays for Lp(a) are needed.

Methodological issues related to adequate manufacturer standardization of clinical assays for Lp(a) measurement, irrespective of whether mass or molar concentration assays are used, is also the focus of the accompanying editorial by Kronenberg and Tsimikas.