Inconsistent Association Between Lipoprotein(a) and Coronary Artery Calcium

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Lipoprotein(a) [Lp(a)] is a low-density lipoprotein (LDL)-like particle connected via a disulfide bond to apolipoprotein(a) [apo(a)]. Due to its structure and ability to carry oxidized phospholipids, Lp(a) confers a unique atherosclerotic cardiovascular disease (ASCVD) risk profile involving atherogenesis, anti-fibrinolysis, and inflammation[1]. While subclinical atherosclerotic burden may be one mediator for the heightened risk attributable to Lp(a), there has been an inconsistent association between Lp(a) and coronary artery calcium (CAC) in observational cohort studies[2–4]. Beyond understanding the mechanisms underlying Lp(a) and subclinical atherosclerosis, assessment of their potential independent pathways may be important to guide personalized risk assessment and treatment among individuals without clinical ASCVD.

In this issue of the *European Journal of Preventive Cardiology*, Sung et al. evaluated the association between baseline Lp(a) and incident CAC and CAC progression among nearly 42,000 statin naïve young adults in the Kangbuk Samsung Health Study of South Korea[5]. Lp(a) was evaluated across quintiles (Q1: 2-3 mg/dL, Q2: 3-5 mg/dL, Q3: 6-10 mg/dL, Q4: 10-21

mg/dL, Q5: 22-337 mg/dL), clinical thresholds (<30, 30-49, 50-99, ≥100 mg/dL), and continuously. Over a median 4-years of follow-up, there was a similar crude rate of incident CAC across baseline Lp(a) quintiles and clinical thresholds of Lp(a), which was between 2 to 3 events per 1,000 person-years. In multivariable modeling, Lp(a) was not significantly associated with incident CAC or CAC progression across Lp(a) quintiles or clinically relevant thresholds. Sensitivity analyses including those on statin therapy yielded similar results.

The study by Sung et al. further underlines the complex relationship of Lp(a) with CAC and broader subclinical atherosclerosis burden. Strengths of the analysis include measurement of Lp(a) and CAC among nearly 42,000 participants and robust statistical analyses, including assessment of Lp(a) across several different modeling strategies. Furthermore, CAC progression was evaluated in multiple ways among the approximate 9,600 individuals with baseline prevalent CAC, which provides excellent statistical power. While the focus on younger adults helps contribute data for this demographic group, this may limit broader generalizability to middle-aged and older adults with a higher burden of risk factors that may interact with Lp(a) to increase risk for CAC development. Less than 15% of participants in the current study had hypertension, whereas the prevalence of hypertension is considerably higher in the US and European countries and prior work suggests that hypertension modifies the association between Lp(a) and ASCVD[6]. Additional limitations of the analysis to consider include a single-center design in South Korea and a study sample consisting of 85% men, which may limit generalizability to other race/ethnicities and women, respectively.

Prior meta-analyses including a mix of cross-sectional and prospective studies suggest that there is a positive association between Lp(a) and CAC in primary prevention; however, there has been considerable heterogeneity across all studies with I^2 values ranging from 76% to 91%[2–

[4]. Such heterogeneity may be attributable to several factors, including the Lp(a) threshold and assay used, race/ethnicity studied, lipid-lowering therapy, as well as differences in study follow-up time. While Lp(a)-mediated ASCVD risk is generally similar across race/ethnicity, population mean Lp(a) levels differ (Black ~ 75 nmol/L, South Asian ~ 30 nmol/L, White ~ 25 nmol/L, Latino ~ 15 nmol/L)[7]. Such heterogeneity may be further complicated by assay differences (mass-based, mg/dL versus particle-based, nmol/L) as well as lipid-lowering therapies that may affect Lp(a) values, most commonly statins (10-20% potential increase in Lp(a) values). Lastly, there has been a mix of studies that include cross-sectional and prospective assessment of CAC which may complicate interpretation of Lp(a) as a potential contributor to the development of calcified plaque. Prior studies that have only included those with baseline CAC=0 may be affected by healthy participant bias.

Beyond heterogeneity in Lp(a) measurement and statistical methods, there are important pathophysiological considerations when evaluating the association between Lp(a) and CAC. Prior work from the Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated that Lp(a) and CAC were independent and additive for ASCVD risk[8]. In general, Lp(a) has been more strongly associated with non-calcified plaque and high-risk plaque features (positive remodeling, spotty calcification, low-attenuation, napkin ring) as opposed to calcified plaque alone. Among approximately 1,800 asymptomatic adults in the Miami Heart Study, individuals with Lp(a) $\geq$125 nmol/L were four times more likely to have presence of high-risk plaque compared to those with Lp(a) <125 nmol/L, independent of traditional risk factors. Among those without CAC, those with high Lp(a) were significantly more likely to have any plaque (24.2 vs 14.2%)[9]. In another study from MESA, Lp(a) was less strongly associated with CAC when compared with other lipid biomarkers[10]. Additionally, these findings may be partly explained by the association

between Lp(a) and ASCVD risk through multiple mechanisms in addition to traditional atherosclerosis, including potential pro-thrombotic and pro-platelet effects as well as vascular inflammation contributed to by oxidized phospholipids. Oxidized phospholipids carried by the apo(a) moiety may be particularly important contributors to the development of non-calcified, high-risk plaque and acute CHD events[7].

Given their potentially independent contributing pathways for ASCVD risk, Lp(a) and CAC may provide complimentary information for risk assessment and defining eligibility for preventive therapies among individuals without clinical ASCVD. Thus, there is a continuum of risk that may be captured with the concurrent measurement of Lp(a) and CAC, which may help guide personalization in statin and non-statin lipid-lowering therapy, LDL-cholesterol goals, as well as aspirin in those without clinical ASCVD[11]. While the majority of participants in ongoing Phase 3 outcome trials evaluating Lp(a)-lowering therapies have a history of clinical ASCVD, prior work suggests that individuals with advanced subclinical atherosclerosis (e.g. CAC $\geq$300) have similar risk[12]. Thus, if such Lp(a)-lowering trials are indeed positive and show significant ASCVD risk reduction benefit, measurement of CAC may help identify the highest risk individuals to facilitate earlier risk reduction with Lp(a)-lowering therapies prior to an index event.

In summary, the association between Lp(a) and CAC remains complex and further work will be required to define their degree of association across standardized lab assays, uniform follow-up time, and demographically diverse samples. The totality of evidence suggests an inconsistent association between Lp(a) and CAC (**Table**), suggesting unique risk pathways, which may be able to be harnessed in routine ASCVD risk assessment to guide personalization

in preventive lifestyle and pharmacotherapies across the spectrum of subclinical atherosclerosis burden.

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Table. Contributions to Inconsistent Association between Lipoprotein(a) and Coronary Artery Calcium	
Source	**Future Directions**
Lp(a) Thresholds	• Emphasize reporting of continuous Lp(a) and standardized Lp(a) thresholds • Genetic and epidemiological data suggest that ASCVD risk begins as low as ≥30 mg/dL or ≥75 nmol/L
Race/Ethnicity	• While Lp(a)-mediated risk is generally similar across race/ethnicity, population mean Lp(a) levels differ: o Black ~75 nmol/L, South Asian ~30 nmol/L, White ~25 nmol/L, Latino ~20 nmol/L, East Asian ~15 nmol/L • Prioritize ancestral diversity and sufficiently power analyses to identify potential race/ethnicity differences
Assay Differences	• Mass-based (mg/dL) versus particle-based (nmol/L) • Transition to universal, standardized particle-based assay for enhanced precision
Temporal Variability	• Mix of cross-sectional and prospective studies, prospective studies with different length of follow-up • Emphasize prospective follow-up
Baseline ASCVD Risk	• Lp(a) may interact with several adjacent risk factors to increase risk of subclinical atherosclerosis • Consider assessment across specific risk factors (e.g. diabetes, obesity, inflammation) and similar covariable adjustment across studies
CAC Incidence versus Progression	• Healthy participant bias for studies including only those with CAC=0 at baseline • Risk factors for CAC initiation versus progression may differ • Uniform modeling strategies for assessing CAC progression
Plaque Type	• Lp(a) is more strongly associated with non-calcified plaque and high-risk plaque features as opposed to calcified plaque

	• Consideration of prothrombotic and proinflammatory effects of oxidized phospholipids carried by apo(a) moiety of Lp(a)

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