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Original Article

High Baseline Lipoprotein(a) Level as a Risk Factor for Coronary Artery Calcification Progression: Sub-analysis of a Prospective Multicenter Trial

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Lipoprotein(a), or Lp(a), is a low-density lipoprotein-like particle largely independent of known risk factors for, and predictive of, cardiovascular disease (CVD). We investigated the association between baseline Lp(a) levels and the progression of coronary artery calcification (CAC) in patients with hypercholesterolemia undergoing statin therapy. This study was a sub-analysis of a multicenter prospective study that evaluated the annual progression of CAC under intensive and standard pitavastatin treatment with or without eicosapentaenoic acid in patients with an Agatston score of 1 to 999, and hypercholesterolemia treated with statins. We classified the patients into 3 groups according to CAC progression. A total of 147 patients (mean age, 67 years; men, 54%) were analyzed. The proportion of patients with Lp(a) >30 mg/dL significantly increased as CAC progressed (non-progression; 5.4%, 0<CAC progression ≦100; 7.7%, and CAC progression >100; 23.6%). Logistic regression analysis showed that Lp(a) >30 mg/dL was an independent predictor of the annual change in Agatston score >100 (OR: 5.51; 95% CI: 1.28-23.68; $p=0.02$), even after adjusting for age, sex, hypertension, diabetes mellitus, current smoking, body mass index, and lipid-lowering medications. Baseline Lp(a) >30 mg/dL was a predictor of CAC progression in this population of patients with hypercholesterolemia undergoing statin therapy.

Key words: lipoprotein(a), coronary artery calcification, statins, hypercholesterolemia

Lipoprotein(a), or Lp(a), is a low-density lipoprotein (LDL)-like particle. Apolipoprotein B is covalently linked to apolipoprotein(a) by a single disulfide bond [1]. Circulating concentrations of Lp(a) vary widely across individuals and ethnic subgroups, mediated in large part by genetic variations at the *LPA* gene locus [2]. A meta-analysis of 126,634 participants in 36 prospective studies found that Lp(a) was an independent risk factor for coronary heart disease and stroke [3]. Mendelian randomization studies have linked

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genetic variations at the *LPA* locus to both circulating Lp(a) concentrations and the risk for cardiovascular disease (CVD), supporting a causal role of Lp(a) in CVD pathogenesis [4,5]. Generic methods to modulate circulating Lp(a) concentrations in daily practice remain to be determined, and the further accumulation of evidence based on the monitoring of patients with high Lp(a) levels (even when undergoing treatment with lipid-lowering drugs such as statins) is crucial [2,6].

Among the methods available for the assessment of CVD risk, coronary artery calcification (CAC), which is determined by computed tomography (CT), is an excellent marker for the clinical measurement of the burden of CVD risk [7]. Detrano *et al.* reported that the adjusted risk for a coronary event increased by a factor of 9.67 among participants with CAC scores > 300 compared to participants with no coronary calcification [8]. After serial assessments, the progression of CAC scores has been proposed as a useful predictor of cardiac outcome [9-11].

We recently reported the results of a prospective multicenter study (Effect of pitavastatin and EPA on coronary artery calcification detected by computed tomography: PEACH study) that examined the effects of intensive and standard pitavastatin treatment with or without eicosapentaenoic acid (EPA) on the annual progression of CAC [12]. In that study, we found that the overall CAC progression rate over 1 year was 40% and that the CAC progression in each patient group was not affected by the allocated treatments. A determination of the factors involved in CAC progression is of interest.

Cross-sectional studies have reported an association between Lp(a) and CAC [13,14]. Data from a large Asian cohort of 14,583 participants suggested a robust association between higher Lp(a) level and CAC in both men and women, regardless of LDL cholesterol level and other CVD risk factors [14]. However, that study was limited by the nature of cross-sectional studies with regard to causality. Longitudinal studies (including short-term studies) are required to confirm the progression of CAC using baseline Lp(a) levels. In the present study, we analyzed the association between baseline Lp(a) levels and the annual progression of CAC in patients with hypercholesterolemia who were undergoing statin therapy.

Methods

Ethical considerations. The principal study was a prospective, open-label, multicenter trial conducted between May 2010 and August 2011. That study was approved by the Ethics Committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (Certificate No. 1652) and other hospitals involved. All participants provided written informed consent before enrolling. The study was conducted in accord with the principles contained within the Declaration of Helsinki. The study is registered at the UMIN Clinical Trials Registry (UMIN000003171; Effect of pitavastatin and EPA on coronary artery calcification detected by computed tomography: PEACH study).

Study design. The current study was a pre-specified sub-analysis of the PEACH study [12]. Eligible patients were adults (> 20 years old) with an Agatston score of 1 to 999, with hypercholesterolemia (LDL cholesterol ≥ 140 mg/dL at screening or taking a statin), and no history of CVD. The exclusion criteria were a history of coronary revascularization, including percutaneous coronary intervention and coronary artery bypass surgery; Agatston score of 0 or > 1,000; familial hypercholesterolemia; use of cyclosporine; and use of lipid-lowering agents excluding statins. Patients were enrolled after an evaluation for eligibility at each institution, including baseline multi-detector row computed tomography (MDCT) image acquisition. The participants were randomly allocated into 3 groups: the pitavastatin 2 mg/day, pitavastatin 4 mg/day, or pitavastatin 2 mg/day combined with EPA 1,800 mg/day groups. After taking pitavastatin 2 mg/day for 2 months to check for tolerance, the allocated treatment was started.

Baseline blood test data were obtained just before the allocated treatment was started. MDCT and blood tests were performed again at the 1-year follow-up. Figure 1 is a flow diagram of the study design. In the principal study, we enrolled 217 patients at 27 centers in Japan. Among them, 157 patients were included in the primary analysis. Ten patients were excluded because their stored blood samples were not available for the measurement of Lp(a). A final total of 147 patients were included in this *post-hoc* analysis. The primary outcome of the sub-study was the association between the patients' baseline Lp(a) level and their annual CAC pro-

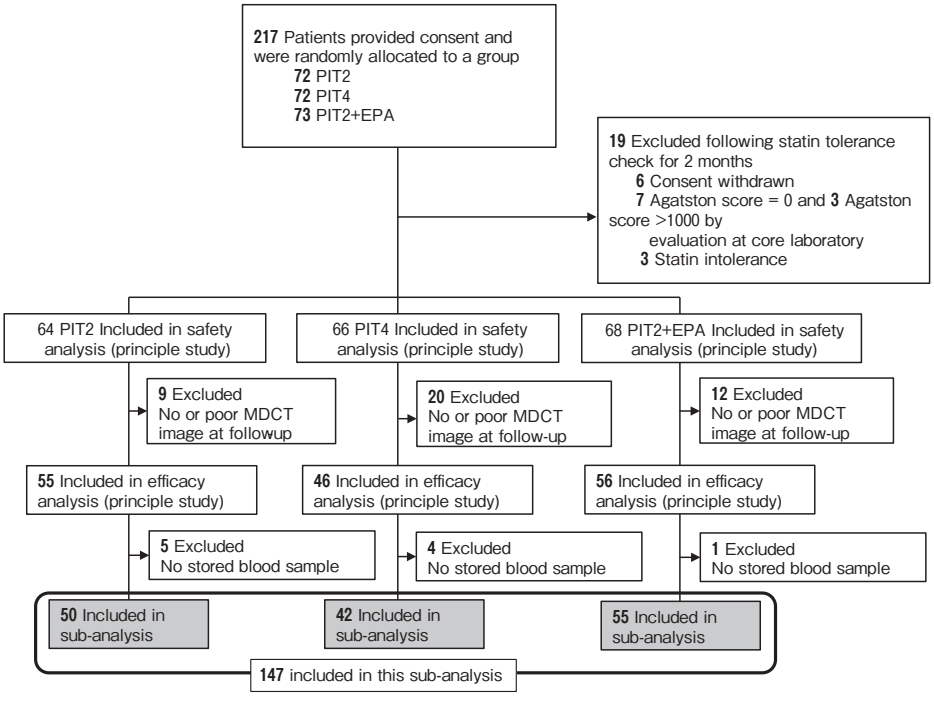

Fig. 1 Flow diagram of patient enrollment. PIT2, pitavastatin 2 mg/day; PIT4, pitavastatin 4 mg/day; EPA, eicosapentaenoic acid 1,800 mg/day; MDCT, multidetector row computed tomography.

gression (Agatston score).

MDCT imaging and CAC analysis. MDCT imaging was performed as described [15]. All recruiting sites had previous cardiac CT experience and were equipped with 64-slice or higher advanced CT technology. ECG triggering was performed at 80% of the RR interval. MDCT images were documented in a digital imaging and communications in medicine (DICOM) format, which was sent to the core laboratory at L&L Co. (Osaka, Japan) for blinded analysis. The local sites generated the total Agatston score, which was used as the inclusion criterion of this study. A calcium threshold ≥130 Hounsfield units was used. As described by Agatston, the calcium score was determined by multiplying the area of each calcified lesion by a weighing factor corresponding to the peak pixel intensity for each lesion [16].

The image analysis was performed by a trained radiologist and trained cardiologist (Y.K.) who were blind to the patients' data. Disagreements in data analysis between the 2 observers were resolved by consensus. We divided the participants into three groups according to the severity of CAC progression over 1 year: no progression, 0<CAC progression≤100, and CAC progression >100. CAC progression was defined as any CAC increase over the year.

Risk factors and laboratory analyses. Data on demographics, smoking status, and medication were collected for each participant. Current smoking was defined as a history of cigarette smoking during the past year. Diabetes was confirmed according to the criteria of the American Diabetes Association [17] or based on a history of diabetes mellitus treatment. Hypertension was defined as having a seated blood pressure of ≥140/90 mmHg or undergoing treatment with antihypertensive medication. Body mass index (BMI) was calculated as body weight (kg) divided by squared height (m).

All laboratory values were determined at an independent central study laboratory (SRL, Tokyo, Japan). Standard enzymatic methods were used to measure total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, and triglycerides. High-sensitivity C-reactive protein levels were determined using an assay (Roche-Hitachi; Hitachi, Tokyo, Japan). Residual serum was separated and stored at −80°C, and the serum concentration of Lp(a) was measured using an enzyme-linked immunosorbent assay (Shino-Test, Tokyo, Japan) [18].

Statistical analysis. Continuous variables are mean (standard deviation) or median (25th percentile, 75th percentile), as appropriate. Categorical variables

are frequency and proportion (%). The Kruskal-Wallis test was used to compare continuous variables among the groups. The chi-square test was used to compare categorical variables. Pearson's correlation coefficients were used to assess relationships between Lp(a) and other parameters. Data that were not normally distributed, as determined by the Kolmogorov-Smirnov test, were logarithmically transformed before linear regression analysis. Logistic analysis was performed to determine the odds ratio (OR) with 95% confidence intervals (95%CI) for the progression of CAC associated with baseline Lp(a) level (>30 mg/dL and ≤ 30 mg/dL). The following variables were entered into the logistic model: age, sex, hypertension, diabetes mellitus, current smoking, BMI, and lipid-lowering medications (pitavastatin 2 mg/day, pitavastatin 4 mg/day, or pitavastatin 2 mg/day combined with EPA 1,800 mg/day). A p-value <0.05 was considered significant. Statistical analyses were performed using SPSS 27.0 for Windows (IBM, Armonk, NY, USA).

Results

Baseline characteristics. Table 1 summarizes the baseline characteristics of participants. The mean age was 67 years, and 54% were men. The proportions of patients with hypertension and diabetes mellitus were 81% and 27%, respectively. The median baseline Lp(a) level was 10.2 mg/dL, and 9.5% of participants (n = 14) had an Lp(a) level > 30 mg/dL.

Association between metabolic parameters and baseline Lp(a) levels. A bivariate correlation analysis with baseline Lp(a) and other metabolic parameters showed that age was positively correlated with the baseline Lp(a) level, and the triglycerides level was negatively correlated with the baseline Lp(a) level (Table 2). There was no correlation between the baseline Lp(a) level and CAC scores.

Comparison of variables according to CAC progression. At the 1-year follow-up, 110 patients (75%) showed CAC progression. When we compared baseline parameters among the groups with no CAC progression, $0 <$ CAC progression ≤ 100, and CAC progression > 100, it was revealed that the proportion of patients with diabetes mellitus was significantly increased and the LDL cholesterol levels were significantly decreased as the severity of CAC progression increased (Table 3). The Lp(a) levels in patients with no progression, $0 <$ CAC progression ≤ 100, and CAC progression > 100 were 11.6 (6.8, 17.2), 8.6 (5.0, 20.3), and 13.1 (4.1, 40.4), respectively, and did not differ significantly among the groups ($p = 0.23$; Kruskal-Wallis test) (Fig. 2A). The proportion of patients with Lp(a) >30 mg/dL in patients with CAC progression was significantly greater than those of the other groups (no progression; 5.4%, $0 <$ CAC progression ≤ 100; 7.7%, and CAC progression > 100; 26.3%, $p = 0.03$) (Fig. 2B).

Association between baseline Lp(a) and CAC progression. The logistic analysis showed that the odds

Table 1 Patient characteristics

	n = 147
Age (years)	67 (10)
Sex: men, n (%)	80 (54)
BMI (kg/m^2)	25.0 (4.0)
Hypertension, n (%)	118 (81)
Diabetes mellitus, n (%)	39 (27)
Current smoking, n (%)	22 (15)
Lp(a) (mg/dL)	10.2 (5.0, 21.3)
Hemoglobin A1c (%)	5.7 (0.7)
Triglycerides (mg/dL)	117 (89, 165)
LDL cholesterol (mg/dL)	93.6 (24.3)
HDL cholesterol (mg/dL)	55.5 (13.7)
Serum creatinine (mg/dL)	0.77 (0.68, 0.90)
hsCRP (mg/L)	0.054 (0.031, 0.106)
Agatston score	96 (25, 244)

Data are mean (std. dev.), number (%), or median (25th, 75th percentiles), as appropriate. Lp(a), lipoprotein a; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

Table 2 Correlation between baseline Lp(a)* and other parameters

	r	p-value
Age	0.281	0.001
BMI	−0.106	0.208
Fasting blood glucose	−0.178	0.033
Hemoglobin A1c	−0.06	0.530
Total cholesterol	−0.021	0.804
Triglycerides*	−0.218	0.008
HDL cholesterol	0.06	0.492
LDL cholesterol	−0.009	0.915
Serum creatinine	−0.089	0.287
hsCRP*	0.015	0.853
Agatston score*	0.124	0.136

*Lp(a), triglycerides, hsCRP, and Agatston score were log-transformed.

Table 3 Comparison of variables among patients with CAC progression over a 1-year period

	No progression (n = 37)	0 < CAC progression ≤ 100 (n = 91)	CAC progression > 100 (n = 19)	*p*-value
Age (years)	66.3 (9.4)	67.1 (10.2)	68.7 (7.1)	0.68
Sex: men, n (%)	20 (54)	45 (49)	15 (79)	0.06
BMI (kg/m^2)	25.9 (4.7)	24.9 (3.7)	23.9 (3.4)	0.26
Diabetes mellitus, n (%)	8 (22)	21 (23)	10 (53)	0.02
Hypertension, n (%)	30 (81)	74 (81)	14 (74)	0.74
Current smoking, n (%)	8 (22)	12 (13)	2 (11)	0.41
Systolic BP (mmHg)	134.7 (21.5)	131.0 (16.5)	131.8 (19.8)	0.68
Diastolic BP (mmHg)	76.4 (12.9)	74.4 (10.8)	73.5 (10.8)	0.74
Hemoglobin A1c (%)	5.7 (0.6)	5.7 (0.7)	6.0 (1.0)	0.26
Total cholesterol (mg/dL)	182.8 (30.9)	175.9 (30.9)	166.5 (31.6)	0.23
LDL cholesterol (mg/dL)	101.4 (24.5)	93.1 (22.7)	80.7 (26.8)	0.01
Triglycerides (mg/dL)	123 (92, 128)	108 (84, 165)	141 (89, 155)	0.63
HDL cholesterol (mg/dL)	53.5 (12.4)	56.4 (14.6)	54.8 (11.5)	0.70
Serum creatinine (mg/dL)	0.78 (0.69, 0.86)	0.78 (0.63, 0.90)	0.76 (0.71, 0.98)	0.68
hsCRP (mg/dL)	0.054 (0.034, 0.123)	0.051 (0.025, 0.105)	0.070 (0.038, 0.115)	0.58

Data are mean (std. dev.), number (%), or median (25th, 75th percentiles), as appropriate.

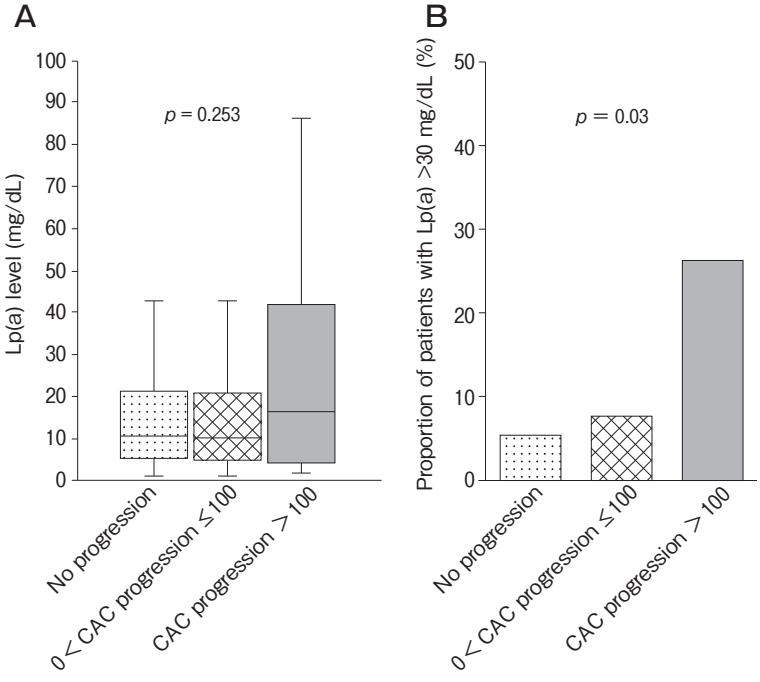

Fig. 2 Comparison of lipoprotein (Lp(a)) levels (**A**) and the proportion of patients with high Lp(a) (**B**) among the groups classified by coronary artery calcification (CAC) progression severity over 1 year.

Table 4 Odds ratios (95% confidence intervals) for coronary artery calcification progression > 100 according to baseline Lp(a) levels

	Model 1	Model 2	Model 3	Model 4
Lp(a) ≤ 30 mg/dL	Reference	Reference	Reference	Reference
Lp(a) > 30 mg/dL	4.72 (1.39–16.08), $p = 0.01$	6.84 (1.90–32.16), $p < 0.01$	5.59 (1.31–23.81), $p = 0.01$	5.51 (1.28–23.68), $p = 0.02$

Model 1, no adjustment: Model 2, adjusted for age and sex: Model 3, Model 2+hypertension, diabetes mellitus, current smoking, and BMI: Model 4, Model 3+lipid-lowering medications.

ratio of natural log-transformed Lp(a) for the annual progression of CAC > 100 was not significant (OR: 1.49, 95%CI: 0.88-2.53, $p = 0.13$). When the risk for annual CAC progression > 100 according to baseline Lp(a) level higher or lower than 30 mg/dL was calculated (Table 4), the patients with an Lp(a) level > 30 mg/dL showed a significantly increased risk for CAC progression compared to the patients with an Lp(a) level ≤ 30 mg/dL in the crude model (OR: 4.72, 95%CI: 1.39-16.08; Model 1) and after adjusting for all confounding variables (OR: 5.51, 95%CI: 1.28-23.68; Model 4).

Discussion

This study is the first to report an association between the baseline Lp(a) level and CAC progression over a 1-year follow-up in patients with hypercholesterolemia and undergoing statin therapy. Patients with CAC progression > 100 over the 1-year follow-up showed a greater proportion of high baseline Lp(a) compared to those who had no progression or CAC progression < 100 with LDL cholesterol lower than 100 mg/dL with statin therapy. The logistic analysis revealed that a baseline Lp(a) level > 30 mg/dL presented a 6.84-fold increased risk for CAC progression > 100 compared to the Lp(a) levels ≤ 30 mg/dL.

Our present findings are considered complementary to a recent sub-analysis of the JUPITER (Justification for the use of statin in prevention: An intervention trial evaluating rosuvastatin) trial, which reported that higher Lp(a) concentrations were associated with an increased risk for CVD events under statin therapy [19]. That sub-analysis reported that rosuvastatin reduced the incidence of CVD with no interaction which baseline Lp(a) levels. In the present study, the LDL cholesterol levels in the patients with CAC progression > 100 were lower than those in the patients with CAC progression ≤ 100. Taken together, our findings suggest that the Lp(a) level may be a significant risk factor for CVD events in people with a low LDL cholesterol level undergoing statin therapy. This suggestion also has important clinical implications with regard to assessments (for instance, using CAC) used to identify patients with a high Lp(a) level. This is because generic methods for modulating circulating Lp(a) concentrations in daily practice remain to be determined, and careful monitoring of patients with a high Lp(a) level is needed.

In terms of a clinical cutoff point for Lp(a), the 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia consider Lp(a) > 30 mg/dL to be a risk factor, and those guidelines suggest measuring Lp(a) to inform decision-making, particularly in patients at intermediate risk and those with a family history of premature CAD, and in younger patients [20]. A large meta-analysis showed an inflection for risk of myocardial infarction at Lp(a) > 30 mg/dL [3]. Data from the Multi-Ethnic Study of Atherosclerosis (MESA) reported that cutoff values of Lp(a) for identifying the risk of CVD events differ among races, from 30 mg/dL to 50 mg/dL [21]. Tsimikas reported that Lp(a) levels are skewed leftward, and most individuals (approx. 70%) have values in the normal range of < 30 mg/dL [22].

In the present study, the median Lp(a) value was 10.2 mg/dL, and the proportion of patients with Lp(a) > 30 mg/dL and > 40 mg/dL were 9.5% and 3.4%, respectively. Considering these results, we used Lp(a) > 30 mg/dL as the cutoff value for the high Lp(a) level, and we observed that high Lp(a) was a significant risk factor for CAC progression. However, the appropriate cutoff value for Asian populations should be determined by further studies.

The mechanisms underlying the association between elevated Lp(a) and the development of CAC remain unclear. Elevated Lp(a) may lead to atherosclerosis when particles become trapped within the arterial intima, and may also serve as a carrier of oxidized phospholipids by apolipoprotein B 100, which may propagate atherosclerosis via inflammatory pathways [23]. In addition, it was reported that Lp(a) and oxidized phospholipids mediate macrophage apoptosis in endoplasmic reticulum-stressed macrophages by signaling through the CD36/Toll-like receptor 2 pathway [24]. We thus speculate that Lp(a) may contribute to CAC through the development of atherosclerosis via multiple pathways.

In this study, the patients with baseline Lp(a) > 30 mg/dL showed a significantly increased risk for CAC progression with low LDL cholesterol and undergoing statin therapy. CAC incidence and progression is considered an excellent surrogate marker for the prediction of CVD risk [7]. A cross-sectional study of an Asian population reported that Lp(a) levels were positively associated with CAC score [14]. However, that was a cross-sectional study and it therefore could not

show a causal relationship between Lp(a) and CAC progression. Recent data from a health checkup program suggest that people with a baseline Lp(a) level ≥ 50 mg/dL have a 1.33-fold increased risk for CAC progression compared to those with an Lp(a) level < 50 mg/dL [25]. The present study is the first longitudinal study to evaluate the association between baseline Lp(a) and CAC progression in patients with hypercholesterolemia undergoing statin therapy.

This study has several limitations. First, as the study was of people with hypercholesterolemia undergoing statin therapy, the results cannot be applied to the general population. Second, although the Agatston score as a marker for quantifying CAC is an excellent surrogate marker for the prediction of CVD, we analyzed only CAC progression as the endpoint, not actual CVD events. We thus cannot conclude that there is an association between high Lp(a) and CVD events. Third, the duration of follow-up was 1 year, and a longer follow-up period might reveal a difference in the impact of Lp(a) on the progression of CAC. In addition, data on coronary CT angiography were not available in this study. Fourth, changes in plaque volumes and morphology could not be evaluated. Finally, the relationship between the change in Lp(a) and the change in CAC remains unclear. Prospective studies for evaluating the effect of lowering Lp(a) on the progression of CAC are warranted to address this issue.

In, conclusion, high Lp(a) played a role in CAC progression in this population of patients with hypercholesterolemia undergoing statin therapy. Our findings suggest that measuring Lp(a) levels will help in the risk assessment for CVD events as well as treatment options.

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