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Association of Lipoprotein(a) Levels With Myocardial Infarction in Patients With Low-Attenuation Plaque

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ABSTRACT

BACKGROUND Lipoprotein(a) (Lp[a]) is associated with an increased risk of myocardial infarction (MI). However, the mechanism underlying this association has yet to be fully elucidated.

OBJECTIVES This multicenter study aimed to investigate whether association between Lp(a) and MI risk is reinforced by the presence of low-attenuation plaque (LAP) identified by coronary computed tomography angiography (CCTA).

METHODS In a derivation cohort, a total of 5,607 patients with stable chest pain suspected of coronary artery disease who underwent CCTA and Lp(a) measurement were prospectively enrolled. In validation cohort, 1,122 patients were retrospectively collected during the same period. High Lp(a) was defined as Lp(a) ≥50 mg/dL. The primary endpoint was a composite of time to fatal or nonfatal MI. Associations were estimated using multivariable Cox proportional hazard models.

RESULTS During a median follow-up of 8.2 years (Q1-Q3: 7.2-9.3 years), the elevated Lp(a) levels were associated with MI risk (adjusted HR [aHR]: 1.91; 95% CI: 1.46-2.49; $P < 0.001$). There was a significant interaction between Lp(a) and LAP ($P_{interaction} < 0.001$) in relation to MI risk. When stratified by the presence or absence of LAP, Lp(a) was associated with MI in patients with LAP (aHR: 3.03; 95% CI: 1.92-4.76; $P < 0.001$). Mediation analysis revealed that LAP mediated 73.3% ($P < 0.001$) for the relationship between Lp(a) and MI. The principal findings remained unchanged in the validation cohort.

CONCLUSIONS Elevated Lp(a) augmented the risk of MI during 8 years of follow-up, especially in patients with LAP identified by CCTA. The presence of LAP could reinforce the relationship between Lp(a) and future MI occurrence.
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Myocardial infarction (MI) remains the leading cause of morbidity and mortality worldwide despite targeting low-density lipoprotein cholesterol (LDL-C) by statin therapy.[1] Additional therapeutic targets may be needed to further improve cardiovascular health and outcome. Lipoprotein(a) (Lp[a]) is one such putative target.[2,3] Lp(a) is an LDL-like particle with an additional

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CACS = coronary artery calcium score

CAD = coronary artery disease

CCTA = coronary computed tomography angiography

C-index = Harrell concordance index

CT = computed tomography

CT-FFR = computed tomography derived fractional flow reserve

DM = diabetes mellitus

IDI = integrated discrimination index

LAP = low-attenuation plaque

LDL-C = Low-density lipoprotein cholesterol

Lp(a) = lipoprotein(a)

MI = myocardial infarction

NRI = net reclassification improvement

NRS = napkin-ring sign

PB = plaque burden

PCE = pooled cohort equation

PR = positive remodeling

PV = plaque volume

SC = spotty calcification

glycoprotein, that is, apolipoprotein(a) (apo [a]), which is covalently bound to its apolipoprotein B moiety.[4,5] Therefore, Lp(a) is an atherogenic, proinflammatory lipoprotein particle. Furthermore, Lp(a) has been proven to be a prothrombotic lipoprotein particle mainly from in vitro studies.[6] Epidemiological, genetic, and prospective cohort studies have provided robust evidence supporting that Lp(a) levels are associated with the risk of MI.[7-9] However, the mechanism underlying the association between elevated Lp(a) and MI risk remains unclear.

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Plaque rupture is the most common substrate of MI events.[10,11] Histologically, plaque characteristics prone to rupture include a large lipid-rich necrotic core with a thin-fibrotic cap,[12] which can be detected as low-attenuation plaque (LAP) on coronary computed tomography angiography (CCTA).[13] SCOT-HEART (Scottish Computed Tomography of the HEART Trial) demonstrated that LAP derived from CCTA was the strongest predictor of MI independent of clinical risk scores, severity of luminal stenosis, and calcium score.[14] Interestingly, the DIAMOND (Dual Antiplatelet Therapy to Inhibit Coronary Atherosclerosis and Myocardial Injury in Patients With Necrotic High-Risk Coronary Plaque Disease) study suggested that high concentrations of serum Lp(a) accelerate the progression of LAP volume in patients with advanced stable coronary artery disease (CAD).[15] Furthermore, plaque progression, especially the adverse plaque phenotype progression, increased the likelihood of plaque rupture and causes subsequent MI.[16] Nevertheless, it is unclear whether the association between Lp(a) and MI risk is amplified by the presence of LAP.

In an observational study[17] of patients with stable CAD, optical coherence tomography verified an association between high serum levels of Lp(a) and the prevalence of thin-cap fibroatheroma, which may lead to adverse cardiac events. Thus, we hypothesized that the association between Lp(a) and MI could be potentiated by the vulnerable plaque phenotype. This study aimed to investigate whether coronary atherogenesis and plaque characteristics related to/mediated the association between elevated Lp(a) and MI in a multicenter cohort of patients with stable chest pain undergoing CCTA.

METHODS

STUDY COHORT. Derivation cohort. From January 2010 to July 2022, consecutive patients >18 years of age with stable chest pain suspicious for CAD were prospectively enrolled from 3 tertiary medical centers. The inclusion criteria were as follows: 1) intermediate pretest probability of CAD according to the updated Diamond-Forrester score[18]; and 2) patients agree to undergo CCTA scan. The exclusion criteria were as follows: 1) history of acute coronary syndrome (ACS) or clinical instability; 2) history of coronary revascularization or MI; 3) contraindications to the usage of iodine contrast media; 4) compromised image quality of CCTA that was not feasible for an accurate analysis; 5) refusal to participate in our study; or 6) lost to follow-up.

Validation cohort. Between January 2010 and July 2022, consecutive patients with stable chest pain who underwent CCTA examination to investigate for suspected CAD at a different site from the derivation cohort were retrospectively included. The inclusion criterion was patients who had serum Lp(a) measurement and underwent CCTA examination within 1 week. The exclusion criteria were as follows: 1) history of ACS; 2) history of coronary revascularization or MI; 3) compromised image quality of CCTA; 4) missing data; or 5) lost to follow-up.

Institutional Review Board approval was obtained for the present study. Written informed consent was obtained in the derivation cohort study, but was waived in the external validation cohort because of the retrospective nature. The study was conducted following the principles of the Declaration of Helsinki.

ACQUISITION PROTOCOL AND IMAGE ANALYSIS OF CCTA. The dual-source computed tomography (CT) (Definition, Siemens Healthineers; SOMATOM Force, Siemens Healthineers) and 320-row CT scanner (Aquilion One Vision, Canon Medical Systems Corporation; uCT960 , Shanghai United Imaging Healthcare) were used for data acquisition, according to the Society of Cardiovascular Computed Tomography guidelines.[19]

Coronary arteries with a diameter ≥2 mm were elevated according to an 18-segment model. Any segment with the presence of atherosclerosis, defined as any tissue ≥1 mm^2 within or adjacent to the lumen that could be discriminated from surrounding pericardial, epicardial fat, or lumen and identified in >2 planes, was included for analysis. Obstructive CAD was defined as luminal stenosis ≥50% and nonobstructive CAD was defined as luminal

stenosis <50%. Quantified plaque characterization was performed semiautomatically by using dedicated plaque analysis software (Coronary Plaque Analysis, version 5.0.3; cFFR, version 3.5.1, Siemens Healthineers). The following parameters were measured: 1) coronary artery calcium score (CACS); 2) CAD categories, including normal, nonobstructive CAD, and obstructive CAD; 3) high-risk plaque (HRP) features, including LAP, positive remodeling (PR), spotty calcification (SC), and napkin-ring sign (NRS); 4) plaque burden (PB); CT derived fractional flow reserve (CT-FFR); and 5) total plaque volume (PV), noncalcified PV, calcified PV, and LAP volume. The details are provided in the Supplemental Appendix.

Two cardiovascular radiologists (M.S.Z. and M.M.Y., with 37 years and 9 years of experience in cardiac imaging, respectively) who were blinded to the Lp(a) level and clinical outcome independently analyzed the CCTA data.

LP(A) MEASUREMENT. Blood samples were collected at the time of recruitment, and plasma and serum were stored at −80° C in the derivation cohort. Lp(a) was then determined according to standardized operating procedures in the same core laboratory. Serum Lp(a) was measured by a latex-enhanced turbidimetric immunoassay (Denka Seiken) (details in the Supplemental Appendix). High Lp(a) was defined as Lp(a) ≥50 mg/dL.[20]

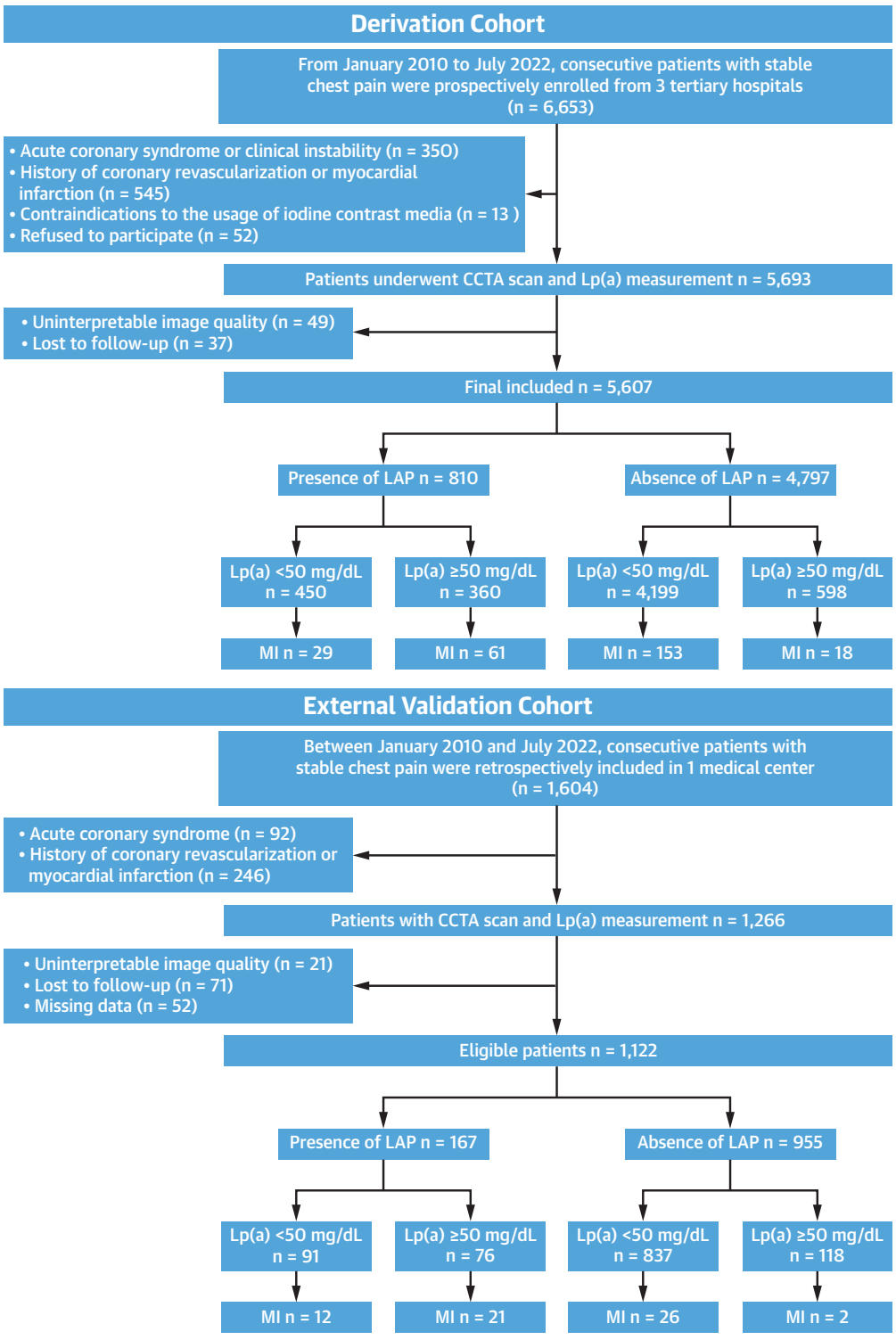
OUTCOMES. Follow-up information was obtained by clinical visits if possible, by detailed questionnaires sent by mail, or by phone contact if the questionnaires were not returned. The primary endpoint was a composite of time to fatal or nonfatal MI. Lost to follow-up means that we could not get the clinical information after the CCTA examination, including no answers to the telephone interview, no reply to email, no clinic visits recorded, or no medical record review. Patients lost to follow-up were not included for the main analysis. Each individual endpoint was reviewed and adjudicated by an independent clinical event committee.

STATISTICAL ANALYSIS. Statistical analysis was performed with MedCalc Statistical Software, version 15.2.2 (MedCalc Software bvba) and R software, version 4.3.2 (R Foundation). Details of the descriptive statistics, group comparison, and interobserver agreement are provided in the Supplemental Appendix. Multivariable logistic regression analysis was applied to determine the association between Lp(a) and LAP. The contribution of Lp(a) increment to LAP volume was assessed by multivariable linear regression analysis. Time-to-event rates were estimated with the use of Kaplan-Meier methods and compared by means of the log-rank test. The interaction between Lp(a) and LAP in relation to MI risk was investigated. Multivariable Cox regression analyses were applied to investigate the association between Lp(a) and MI stratified by the presence of LAP, as we hypothesized there were LAP-related disparities in the relationship between Lp(a) and incidence of MI. The proportional hazards assumption was assessed by the Schoenfeld residuals test. To further explore whether association between Lp(a) and MI is mediated by LAP, we used a counterfactual mediation method implemented in the regmedint R package[21,22] (details in the Supplemental Appendix). Confounder selection is illustrated in a directed acyclic graph (Supplemental Figure 1).

The 10-year atherosclerotic cardiovascular disease risk was calculated using the pooled cohort equation (PCE) based on established methods.[23] To investigate the incremental value of LAP and Lp(a) in prediction of MI, Cox proportional hazards models were built by adding Lp(a) and then LAP to PCE from the derivation cohort. Discrimination ability of the models was assessed by the Harrell concordance index (C-index) and compared with the likelihood ratio test. The net reclassification improvement (NRI) and integrated discrimination index (IDI) were used to assess the reclassification performance. A separate validation data set was used to evaluate the performance of the models. Statistical significance was defined as $P < 0.05$ derived from 2-tailed tests.

SENSITIVITY ANALYSES. To test the robustness and potential variations in different subgroups, we did the following sensitivity analyses: 1) multivariable Cox regression analyses were applied to investigate the association between Lp(a) and MI stratified by the presence of PR, SC, NRS, or PB ≥70%; 2) HRs with 95% CIs with the use of a multivariable Cox proportional hazards model that stratified by patient characteristics, LDL-C levels, and CACS, and relative hazards between subgroups were also examined for consistency with interaction test; 3) adjusted LDL-C and non–high-density lipoprotein cholesterol (non-HDL-C) corrected for Lp(a) by subtracting 0.15 × Lp(a) mass in multivariable Cox proportional hazards; 4) Kaplan-Meier survival analysis was repeated and the same Cox proportional hazards framework in patients with CT-FFR >0.8; 5) Nelson-Aalen curves were plotted and compared using Gray's test to account for competing risks due to other cause of mortality, and Fine and Gray competing risk model was used to obtain subdistribution HR; and 6) multiple imputation was conducted to account for missing outcome data for primary endpoint.

FIGURE 1 Study Flow Chart



In the derivation cohort, a total of 6,653 patients with stable chest pain were enrolled and 5,607 patients made up the final study sample. In the external validation cohort, a total of 1,604 patients were screened, and 1,122 patients were included for the final analysis. Reasons for exclusion are listed. CAD = coronary artery disease; CCTA = coronary CT angiography; LAP = low-attenuation plaque; Lp(a) = lipoprotein(a); MI = myocardial infarction.

TABLE 1 Baseline Clinical Characteristics in the Derivation Cohort

	Absence of LAP (n = 4,797)	Presence of LAP (n = 810)	*P* Value
Age, y	55 ± 12	54 ± 10	0.125
Male	2,923 (60.9)	490 (60.4)	0.842
BMI, kg/m^2	25.3 (24.0-27.1)	25.6 (24.1-27.3)	0.056
Risk factors			
Hypertension	2,135 (44.5)	347 (42.8)	0.397
Diabetes mellitus	1,752 (36.5)	381 (47.0)	<0.001
Dyslipidemia	1,956 (40.7)	368 (45.4)	0.014
Tobacco use			0.813
Never smoking	4,254 (88.7)	720 (88.9)	
Past smoking	368 (7.6)	58 (7.2)	
Current smoking	175 (3.6)	32 (3.9)	
Family history of CAD	516 (10.7)	103 (12.7)	0.112
Laboratory findings			
TC, mmol/L	4.02 (3.07-5.19)	4.11 (3.30-5.24)	0.615
HDL-C, mmol/L	1.34 (1.11-1.58)	1.35 (1.11-1.58)	0.878
LDL-C, mmol/L	2.93 (1.95-3.46)	3.06 (2.22-3.68)	<0.001
TG, mmol/L	1.21 (0.89-1.88)	1.20 (0.88-1.85)	0.127
Lp(a), mg/dL	7.3 (2.3-22.5)	36.5 (19.2-66.4)	<0.001
hs-CRP, mg/L	1.48 (1.00-2.50)	1.52 (1.07-2.98)	0.104
HbA1c, %	6.2 (5.5-7.0)	6.8 (6.0-7.3)	0.090
Medication in use			
Statin	3462 (72.1)	563 (69.5)	0.129
β-blocker	1983 (41.3)	324 (40.0)	0.498
ACEI/ARB	2246 (46.8)	382 (47.1)	0.887
Aspirin	351 (7.3)	62 (7.6)	0.789
PCE, %	5.3 ± 1.6	5.3 ± 2.3	0.282

Values are mean ± SD, n (%), or median (Q1-Q3).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LAP = low-attenuation plaque; LDL-C = low-density lipoprotein cholesterol; PCE = pooled cohort equation; TC = total cholesterol; TG = triglyceride; Lp(a) = lipoprotein(a).

TABLE 2 CCTA Findings Between Patients With and Without LAP in the Derivation Cohort

	Absence of LAP (n = 4,797)	Presence of LAP (n = 810)	*P* Value
Total CACS, median	80.1 (0-222.5)	82.3 (0-235.6)	0.454
CACS			0.655
0	1,203 (25.1)	219 (27.0)	
1-99	1,579 (32.9)	265 (32.7)	
100-399	1,118 (23.3)	183 (22.5)	
≥400	897 (18.6)	143 (17.6)	
CAD categories			0.341
Normal	1,104 (23.0)	176 (21.7)	
Nonobstructive	2,165 (45.1)	388 (47.9)	
Obstructive	1,528 (31.8)	246 (30.3)	
HRP features			
LAP	0 (0)	810 (100)	<0.001
PR	1,729 (36.0)	334 (41.2)	0.005
NRS	631 (13.1)	148 (18.2)	0.001
SC	489 (10.1)	80 (9.8)	0.831
Quantitative plaque volume, mm^3			
Total PV	181.4 (65.0-240.2)	169.9 (78.1-256.7)	0.888
Calcified PV	41.0 (0-103.5)	41.2 (0-100.6)	0.324
Noncalcified PV	79.7 (23.5-168.3)	78.4 (43.0-170.3)	0.920
LAP volume	0 (0-0)	15.5 (5.2-28.3)	<0.001
Plaque burden, %	52.9 ± 15.1	52.7 ± 11.6	0.680
CT-FFR	0.84 ± 0.10	0.80 ± 0.11	<0.001
CT-FFR >0.8	3,200 (66.7)	468 (57.7)	<0.001

Values are median (Q1-Q3), n (%), or mean ± SD.

CACS = coronary artery calcium score; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CT-FFR = computed tomography derived fractional flow reserve; HRP = high-risk plaque; LAP = low-attenuation plaque; NRS = napkin-ring sign; PR = positive remodeling; PV = plaque volume; SC = spotty calcification.

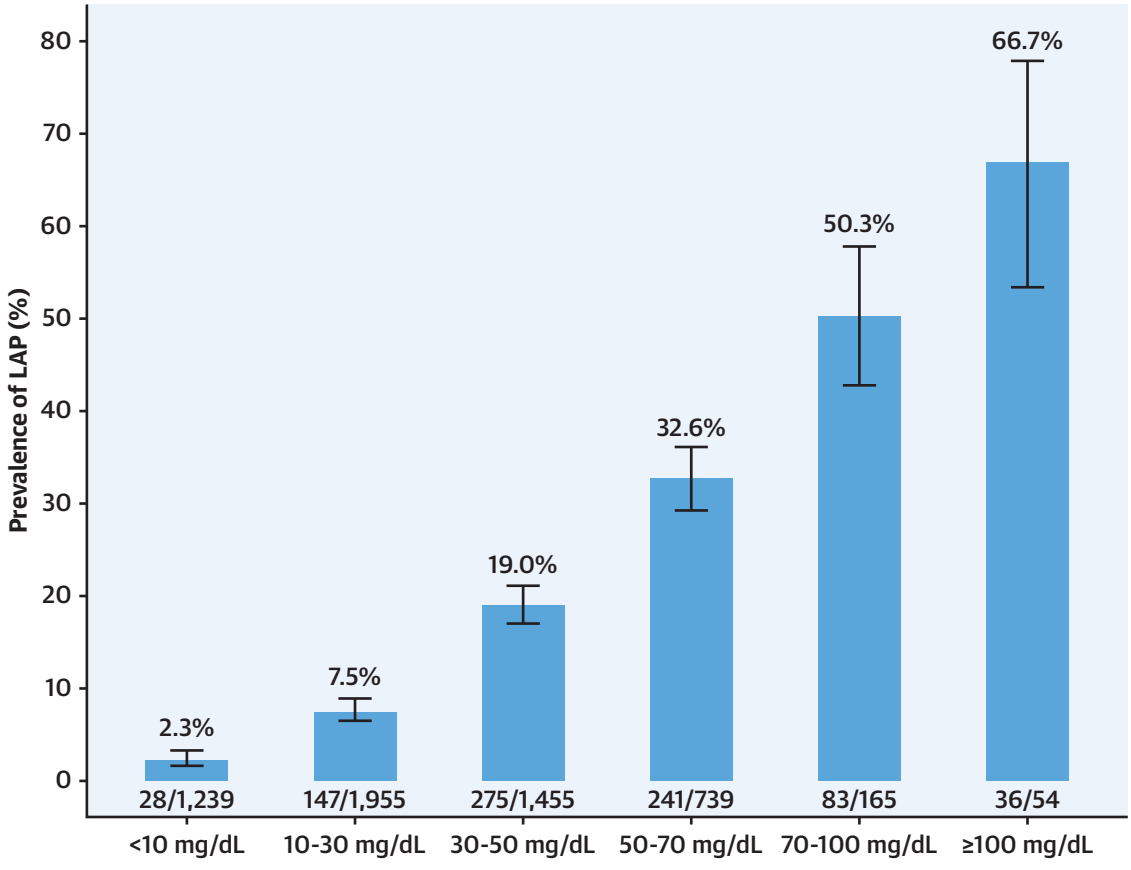
RESULTS

BASELINE CHARACTERISTICS. The flow chart of the 2 cohort studies is presented in **Figure 1**. According to the inclusion criteria, a total of 5,607 patients (mean age, 54 ± 11 years) who completed a median of 8.2 years (Q1-Q3: 7.2-9.3 years) of follow-up were included in the derivation study. Among those, 4,797 (85.6%) had an absence of LAP, and 810 (14.4%) had the presence of LAP. In addition, 1,122 patients (mean age, 56 ± 12 years) with a median of 8.0 years (Q1-Q3: 7.2-9.2 years) of follow-up were included in validation study.

Table 1 and Supplemental Table 1 summarize the clinical characteristics in the derivation study. In the derivation study, patients with LAP were more likely to have diabetes mellitus (DM) and dyslipidemia than those without LAP ($P < 0.05$ for both). Furthermore, in the LAP group, patients showed significantly higher levels of LDL-C and Lp(a) ($P < 0.001$ for both). There were no significant differences between the 2 groups with respect to age, sex, body mass index (BMI), hypertension, tobacco use, family history of CAD, total cholesterol, high-density lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein (hs-CRP), hemoglobin A1c, or medication prescription at baseline ($P > 0.05$ for all). The detailed patient characteristics of the validation cohort are summarized in Supplemental Table 2. The interobserver agreement for CCTA-derived parameters was excellent (Supplemental Table 3).

THE CCTA FINDINGS IN PATIENTS WITH AND WITHOUT LAP. In the derivation study, the patients with LAP had lower CT-FFR values and a lower incidence of CT-FFR >0.8 than those without LAP ($P < 0.001$ for both) (**Table 2**). Furthermore, the prevalence of PR and NRS was significantly higher in the LAP group (PR: 41.2% vs 36.0%, $P = 0.005$; NRS: 18.2% vs 13.1%, $P = 0.001$, respectively). There were no

FIGURE 2 Association of Lp(a) With LAP by CCTA



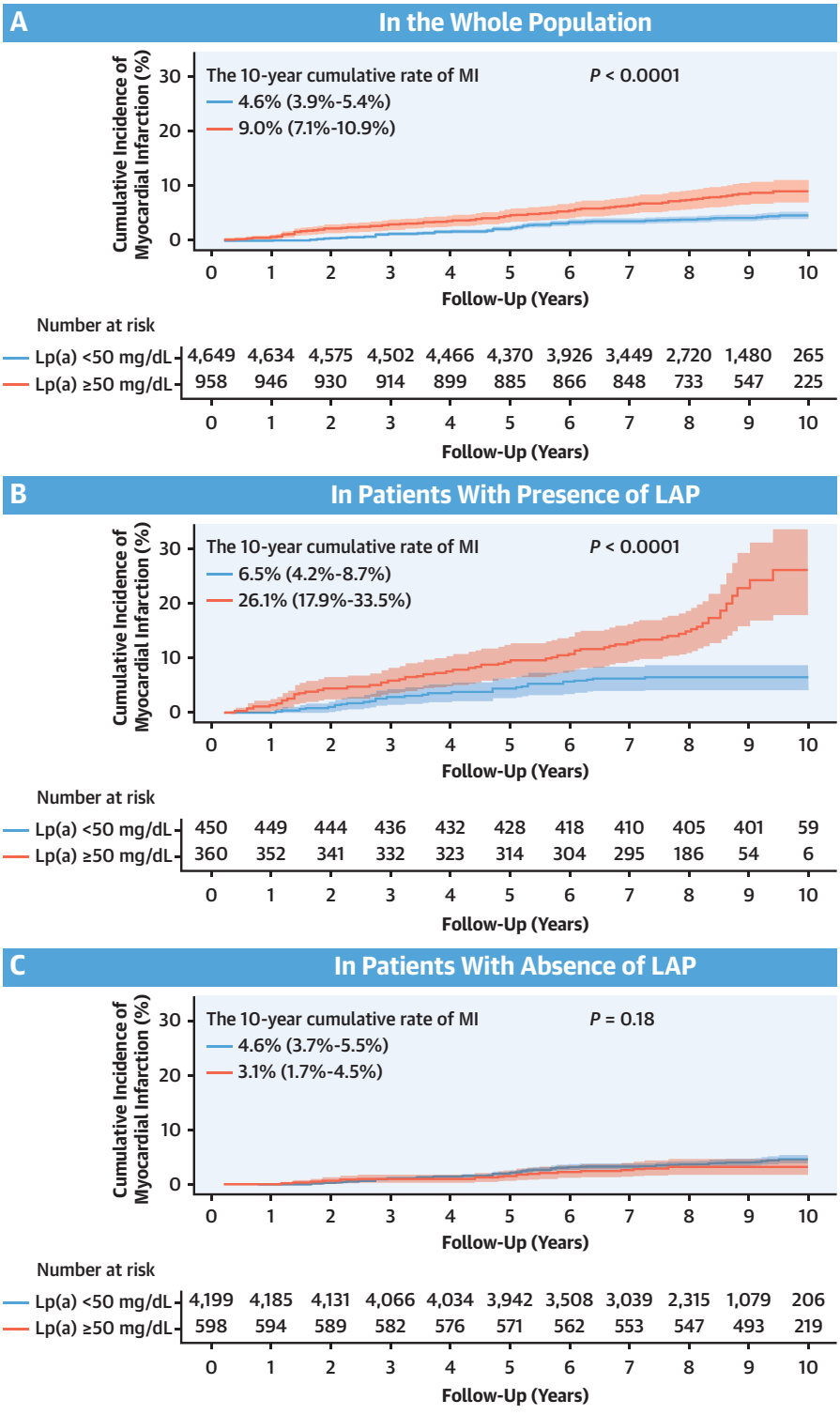
With the increased Lp(a) level, the incidence of LAP significantly increased ($P_{trend} < 0.001$). Abbreviations as in Figure 1.

differences in CACS, CAD categories, SC, total PV, calcified PV, noncalcified PV, and PB between those with and without LAP ($P > 0.05$ for all) (Table 2). The CCTA findings of the validation study are provided in Supplemental Table 4.

ASSOCIATION OF LP(A) WITH LAP. In the derivation patients, the distribution of Lp(a) levels are provided in Supplemental Figure 2. With increasing Lp(a), the incidence of LAP was significantly increased ($P_{trend} < 0.001$) (Figure 2). Multivariable logistic regression analysis revealed that elevated Lp(a) levels were independently associated with the presence of LAP on CCTA findings (adjusted OR: 5.31; 95% CI: 4.45-6.35; $P < 0.001$) after adjustment for age, sex, BMI, hypertension, dyslipidemia, DM, tobacco use, and hs-CRP (Supplemental Table 5). When Lp(a) was set as a continuous variable, each 50 md/dL increase in Lp(a) conferred 2.7-fold higher risk (adjusted OR: 2.73; 95% CI: 2.51-2.98; $P < 0.001$) for the presence of LAP. Furthermore, multivariable linear regression analysis indicated that increased Lp(a) levels were positively associated with LAP volume (standardized β: 0.35; 95% CI: 0.17-0.59; $P < 0.001$).

ASSOCIATION OF LP(A) WITH MI STRATIFIED BY THE PRESENCE OF LAP. In the derivation cohort, the patients with elevated Lp(a) had a higher 10-year cumulative MI rate than those without elevated Lp(a) in the overall population (9.0% vs 4.6%, log-rank $P < 0.001$) (Figure 3A). In the presence of LAP, the patients with elevated Lp(a) showed a higher 10-year cumulative MI rate than those without elevated Lp(a) (26.1% vs 6.5%, log-rank $P < 0.001$) (Figure 3B). However, in those without LAP, both groups showed similar low 10-year cumulative event rates (3.1% vs 4.6%, log-rank $P = 0.18$) (Figure 3C). In the overall population, the risk of MI was higher for patients with elevated Lp(a) than for those with nonelevated Lp(a) (adjusted HR: 1.91; 95% CI: 1.46-2.49;

FIGURE 3 Cumulative MI Rate Stratified by Lp(a) and LAP



(A) The patients with elevated Lp(a) level had a higher 10-year cumulative MI rate than those without elevated Lp(a) in the overall population (9.0% vs 4.6%, log-rank $P < 0.001$). (B) In the presence of LAP, patients with elevated Lp(a) still showed a higher 10-year cumulative MI rate than those without elevated Lp(a) (26.1% vs 6.5%; log-rank $P < 0.001$). (C) In those with absence of LAP, both the groups showed similar low 10-year cumulative event rate (3.1% vs 4.6%; log-rank $P = 0.18$). MI = myocardial infarction; other abbreviations as in Figure 1.

TABLE 3 Association of Elevated Lp(a) and MI Stratified by LAP in the Derivation Cohort

Risk Groups	Events Rate, % (n/N)	Age and Sex Adjusted		Multivariable Adjusted[a]		$P_{interaction}$
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	
In entire cohort						
Lp(a) <50 mg/dL	3.9 (182/4,649)	Reference	/	Reference	/	
Lp(a) ≥50 mg/dL	8.2 (79/958)	1.98 (1.52-2.59)	<0.001	1.91 (1.46-2.49)	<0.001	
Lp(a) per 50 md/dL	4.6 (261/5,607)	2.18 (1.96-2.30)	<0.001	2.05 (1.90-2.23)	<0.001	
Presence of LAP						<0.001
Lp(a) <50 mg/dL	6.4 (29/450)	Reference	/	Reference	/	
Lp(a) ≥50 mg/dL	16.9 (61/360)	3.15 (2.00-4.94)	<0.001	3.03 (1.92-4.76)	<0.001	
Lp(a) per 50 md/dL	11.1 (90/810)	2.25 (2.00-2.53)	<0.001	2.16 (1.89-2.46)	<0.001	
Absence of LAP						
Lp(a) <50 mg/dL	3.6 (153/4,199)	Reference	/	Reference	/	
Lp(a) ≥50 mg/dL	3.0 (18/598)	0.65 (0.40-1.07)	0.097	1.12 (0.74-1.70)	0.570	
Lp(a) per 50 md/dL	3.5 (171/4,797)	1.25 (0.92-1.70)	0.139	1.26 (0.93-1.71)	0.133	

[a]Further adjusted for body mass index, hypertension, diabetes mellitus, dyslipidemia, current or past tobacco use, high-sensitivity C-reactive protein, total coronary artery calcium score, coronary artery disease categories, plaque burden, positive remodeling, spotty calcification, napkin-ring sign, total PV, and CT-FFR.

Lp(a) = lipoprotein(a); MI = myocardial infarction; other abbreviations as in Table 1.

$P < 0.001$) (Table 3). There was a significant interaction between Lp(a) and LAP ($P_{interaction} < 0.001$). In those with LAP, elevated Lp(a) was significantly associated with the risk of MI in the fully adjusted model (adjusted HR: 3.03; 95% CI: 1.92-4.76; $P < 0.001$). However, in those without LAP, no association between Lp(a) and MI risk was observed (adjusted HR: 1.12; 95% CI: 0.74-1.70; $P = 0.57$). The same findings were observed in the validation cohort (Supplemental Table 6).

In multivariable Cox regression, the coexistence of the 2 risk factors showed an approximately 5-fold higher risk (adjusted HR: 4.58; 95% CI: 3.40-6.18; $P < 0.001$) of MI compared with the reference group (Lp[a] <50 mg/dL and absence of LAP) in the fully adjusted model (Table 4). Similar findings were observed in the validation cohort (Supplemental Table 7).

In the derivation cohort, the mediation analysis revealed that the presence of LAP had a significant indirect effect (β: 0.49; 95% CI: 0.29-0.69; $P < 0.001$) and mediated 73.3% (95% CI: 46.8%-99.7%; $P < 0.001$) for the relationship between Lp(a) and MI. In the validation cohort, LAP had a significant indirect effect (β: 0.86; 95% CI: 0.42-1.31; $P < 0.001$) and accounted for 64.1% (95% CI: 44.4%-83.8%; $P < 0.001$) of the effects for the association of Lp(a) with MI as well.

DIAGNOSTIC PERFORMANCE AND COMPARISONS OF MODELS. In the derivation set, the model with PCE plus Lp(a) (model B) improved the performance compared with the PCE model (model A) alone (C-index: 0.75; 95% CI: 0.72-0.79 vs 0.66; 95% CI: 0.62-0.70; $P < 0.001$; NRI: 0.37; 95% CI: 0.28-0.45; $P < 0.001$; IDI: 0.03; 95% CI: 0.02-0.05; $P < 0.001$). The addition of LAP (model C) further improved the performance of model B with a higher C-index value (0.82; 95% CI: 0.79-0.85; $P < 0.001$); NRI: 0.22; 95% CI: 0.04-0.38; $P = 0.02$; IDI: 0.20; 95% CI: 0.14-0.25; $P < 0.001$). Similar to the derivation set, the C-index value of model B was significantly higher than model A (0.71; 95% CI: 0.63-0.78 vs 0.62; 95% CI: 0.55-0.66; $P < 0.001$, with NRI: 0.31; 95% CI: 0.15-0.49, $P < 0.001$ and IDI: 0.03; 95% CI: 0.01-0.08; $P < 0.001$) in the validation cohort. Furthermore, model C was superior to model B with C-index of 0.83 (95% CI: 0.76-0.86; $P < 0.001$), NRI of 0.09 (95% CI:

TABLE 4 Joint Association of Elevated Lp(a) and LAP With MI in the Derivation Cohort

Risk Groups	Events Rate, % (n/N)	Age and Sex Adjusted		Multivariable Adjusted[a]	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Lp(a) <50 mg/dL and absence of LAP	3.6 (153/4,199)	Reference	/	Reference	/
Lp(a) ≥50 mg/dL and absence of LAP	3.0 (18/598)	0.70 (0.43-1.15)	0.169	0.69 (0.42-1.13)	0.143
Lp(a) <50 mg/dL and presence of LAP	6.4 (29/450)	1.52 (1.02-2.26)	0.040	1.50 (1.01-2.24)	0.045
Lp(a) ≥50 mg/dL and presence of LAP	16.9 (61/360)	4.90 (3.64-6.59)	<0.001	4.58 (3.40-6.18)	<0.001

[a]Further adjusted for body mass index, hypertension, diabetes mellitus, dyslipidemia, current or past tobacco use, high-sensitivity C-reactive protein, total coronary artery calcium score, coronary artery disease categories, plaque burden, positive remodeling, spotty calcification, napkin-ring sign, total PV, and CT-FFR.

Abbreviations as in Tables 1 and 2.

TABLE 5 Performance and Comparison of Predictive Models for MI

Models	C-Index (95%CI)	*P* Value	NRI (95% CI)	*P* Value	IDI (95% CI)	*P* Value
Train cohort						
Model A: PCE	0.66 (0.62-0.70)	<0.001	/	/	/	/
Model B: Model A+Lp(a)	0.75 (0.72-0.79)	<0.001	0.37 (0.28-0.45)	<0.001	0.03 (0.02-0.05)	<0.001
Model C: Model B+LAP	0.82 (0.79-0.85)	<0.001	0.22 (0.04-0.38)	0.020	0.20 (0.14-0.25)	<0.001
Test cohort						
Model A: PCE	0.62 (0.55-0.66)	<0.001	/	/	/	/
Model B: Model A+Lp(a)	0.71 (0.63-0.78)	<0.001	0.31 (0.15-0.49)	<0.001	0.03 (0.01-0.08)	<0.001
Model C: Model B+LAP	0.83 (0.76-0.86)	<0.001	0.09 (0.04-0.15)	<0.001	0.09 (0.002-0.18)	0.040

C-index = Concordance index; IDI = integrated discrimination index; NRI = net reclassification improvement; PCE = pooled cohort equation; other abbreviations as in Tables 1 and 2.

0.04-0.15; $P < 0.001$), and IDI of 0.09 (95% CI: 0.02-0.18; $P = 0.04$) (Table 5).

SENSITIVITY ANALYSIS. 1) The presence of PR, NRS, SC, or PB ≥70% did not modify the relationship between Lp(a) and MI ($P_{interaction} > 0.05$ for all) (Supplemental Tables 8 and 9). 2) The association between Lp(a) and MI in the presence or absence of LAP groups was not modified by age, sex, BMI, hypertension, DM, dyslipidemia, smoking status, family history of CAD, LDL-C level, and CACS ($P_{interaction} > 0.05$ for all) (Supplemental Table 10). 3) The association between elevated Lp(a) and MI remains unchanged after further adjustment for corrected LDL-C and non-HDL-C levels (Supplemental Table 11). 4) For patients with CT-FFR >0.8 from the 2 cohorts, the principal findings remained unchanged in Kaplan-Meier survival analysis and multivariable Cox proportional hazards regression models (Supplemental Tables 12 to 15, Supplemental Figures 3 and 4). 5) The cumulative incidence function of MI was significantly higher in patients with Lp(a) ≥50 mg/dL than in patients with Lp(a) <50 mg/dL after adjusting other causes of death as competing risks, with Gray's test $P < 0.001$ (Supplemental Figure 5). Elevated Lp(a) level remained associated with MI risk (adjusted subdistribution HR: 1.92; 95% CI: 1.48-2.50; $P < 0.001$) (Supplemental Table 16). 6) The results of multiple imputation to account for missing outcome data were similar to the main analysis (Supplemental Table 17). Detailed information for multiple imputation is presented in Supplemental Figures 6 to 9.

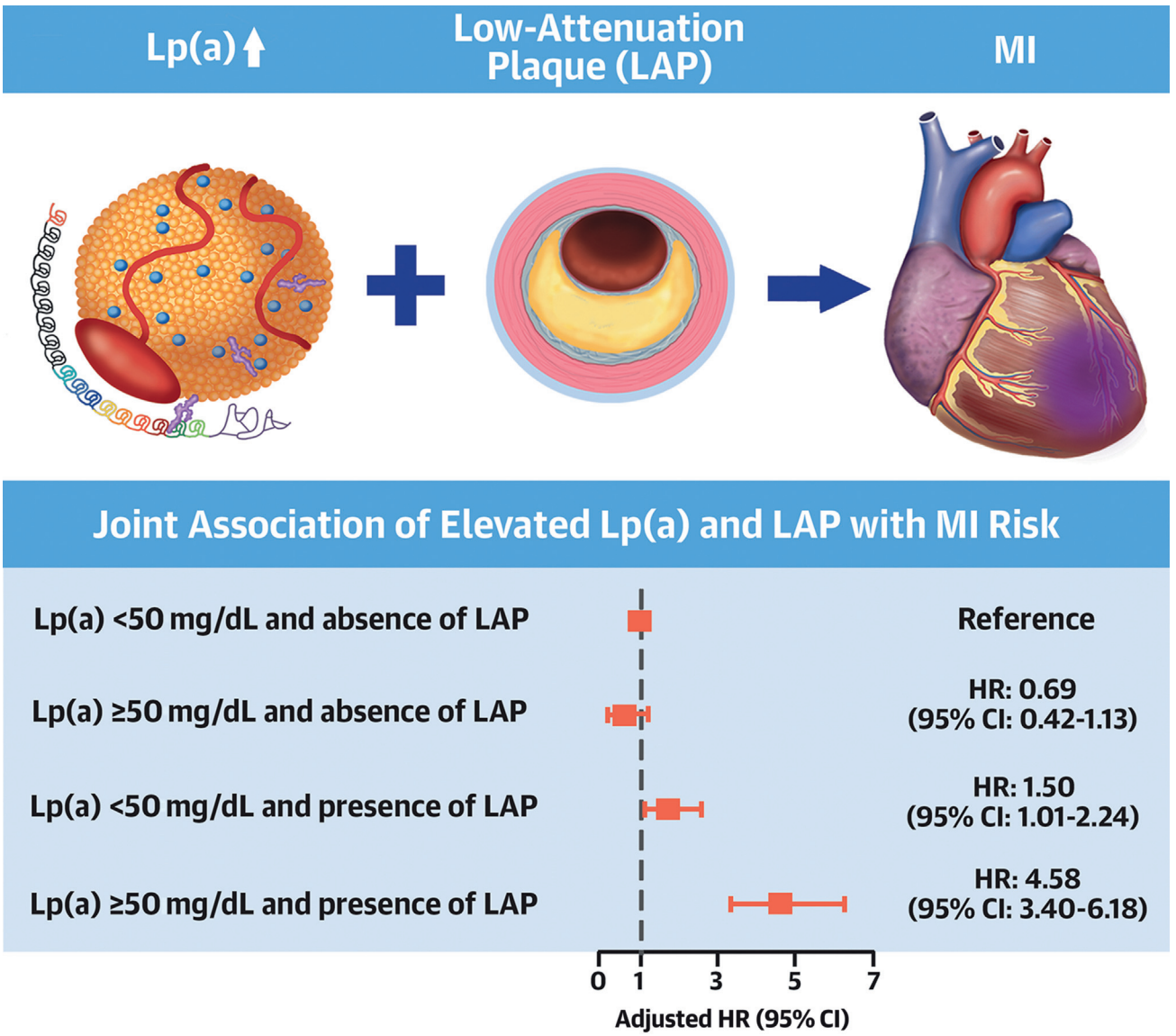
DISCUSSION

In this multicenter cohort of patients with stable chest pain undergoing CCTA, we found important insights into the association of Lp(a) and MI occurrence. In the overall population, high concentrations of serum Lp(a) were associated with MI during a median follow-up of 8.2 years (adjusted HR: 1.91; 95% CI: 1.46-2.49; $P < 0.001$). Elevation of Lp(a) was associated with MI especially in patients with evidence of LAP, but not in patients with absence of LAP. The concurrence of elevated Lp(a) and evidence of LAP was associated with a higher risk for MI when compared with either risk factor alone (Central Illustration). Furthermore, these results were consistent even in patients without flow-limiting lesions, defined as CT-FFR >0.8. This has important implications for risk assessment as well as the use of preventive therapies.

ASSOCIATION BETWEEN LP(A) AND THE PRESENCE OF LAP. A previous study demonstrated that Lp(a) is not as robustly associated with CAC as other lipid biomarkers.[24] It is possible that Lp(a) is more likely to be associated with noncalcified plaque or LAP, which could not be captured by CACS. Based on a study of patients with acute MI, intravascular ultrasound with radiofrequency showed a larger distribution of the necrotic core component at the culprit lesion in those with high serum levels of Lp(a).[25] Moreover, the CCTA examination revealed a higher prevalence of total plaques, noncalcified plaques, and LAP in the whole coronary arteries in the elevated Lp(a) group.[25] In support, we found that the Lp(a) level was not only strongly associated with the CCTA-verified presence of LAP but also correlated with the volume of LAP among patients with stable chest pain. However, it is unclear whether Lp(a) is associated with the new onset or progression of LAP in the current study because the initiation phase and propagation phase were 2 distinct stages in the pathophysiology of atherosclerosis.

THE PRESENCE OF LAP POTENTIATED THE RELATIONSHIP BETWEEN LP(A) AND MI. Several studies have suggested that Lp(a) is associated with MI not only in the general population[26] but also in patients with chronic kidney disease.[27] Our study was

CENTRAL ILLUSTRATION **Joint Association of Elevated Lipoprotein(a) and Low-Attenuation Plaque With Myocardial Infarction**



Yu M-M, et al. J Am Coll Cardiol. 2024;83(18):1743–1755.

Individuals with elevated Lp(a) and LAP showed the highest MI risk. Elevated Lp(a) level does not stratify MI risk among those without LAP. LAP = low-attenuation plaque; Lp(a) = lipoprotein(a); MI = myocardial infarction.

the first to find that elevated Lp(a) was associated with a substantially increased risk of MI especially in patients with the presence of LAP, although we found that elevated Lp(a) level significantly associated with baseline CCTA determined LAP. A high level of Lp(a) did not heighten the risk of MI in patients with absence of LAP. Furthermore, the results remained unchanged in patients with no flow-limiting lesions, as identified by CT-FFR. A previous study revealed that CCTA-derived HRP characteristics partially mediated the relationship between elevated Lp(a) levels and cardiovascular events in patients with confirmed CAD.[28] Our study further suggested the significance of LAP in patients suspected of CAD. Our study could have more profound guiding significance in the clinical setting of dealing with patients

suspected of CAD. Furthermore, LAP had an indirect effect on the relationship between Lp(a) and MI risk. The pathophysiologic mechanisms underlying these findings merit consideration.

We speculated that high levels of Lp(a) could play different roles in the initiation and development of necrotic plaque. Structurally, Lp(a) is an LDL-like particle to which apo(a) is covalently bound, the latter carrying proinflammatory oxidized phospholipids.[29,30] Accumulating Lp(a) particles, which are mostly driven by genetics,[31] might promote the presence of necrotic core plaque silently over decades. However, in the setting of necrotic core plaque, Lp(a) might rapidly stimulate inflammatory cell infiltration into the artery wall, contribute to increase of the necrotic core, and attenuate the fibrous cap.[32] Ultimately, it renders the plaque prone to rupture and causes MI. In other words, elevated Lp(a) level predominantly augmented the risk of vulnerable plaque rupture. Indeed, the concomitant of the 2 risk factors showed a higher cumulative MI rate than an isolated elevation of Lp(a) or evidence of LAP. Our findings highlight that the presence of a vulnerable plaque phenotype could reinforce the association between Lp(a) and MI risk.

CLINICAL IMPLICATIONS. The current guidelines[33] mainly focus on flow-limiting lesions and have not recommended management of HRP based on CCTA. We found that the coexistence of elevated Lp(a) and LAP predicts MI occurrence, even in patients with no flow-limiting lesions. This finding may partially help explain why the ischemia-guided revascularization approach can significantly reduce angina but fails to reduce future adverse events, as was shown by the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial.[34] A previous study demonstrated that total plaque burden is a better predictor of cardiovascular events than discrete stenoses.[35] The current study further found the plaque phenotype provides important information for clinical prognosis, and the identification of LAP by CT images is beneficial for decision making, especially in patients with increased concentrations of Lp(a). Patients with the concomitant presence of the 2 risk markers require Lp(a)-lowering therapy to restrict the progression of coronary atherosclerosis even in patients with no flow-limiting lesions.

STUDY LIMITATIONS. First, Lp(a) levels and distributions differ between different ethnic groups, and the C-index value of PCE in the current study was lower than other studies, which were predominantly derived from White and Black cohorts. Thus, the results from the present study may not be applied to other ethnic groups. Second, our study focused on a selected population with stable chest pain. Therefore, the results of the current study may not be applicable to all primary prevention settings. Third, the prevalence of elevated Lp(a) levels was 17% in our study, slightly lower than in Europe and North America. Previous studies have demonstrated that the prevalence of elevated Lp(a) levels varies around the world.[5] Fourth, the exact mechanism linking Lp(a) and MI occurrence remains unknown, and the contribution of Lp(a) to the initiation, progression, and rupture of vulnerable plaque is not completely understood. In addition, none of the patients measured the oxidized phospholipids, which might help to explain the development of LAP and the risk of adverse events from LAP. Therefore, future animal studies are warranted to investigate the exact mechanism linking Lp(a) and MI occurrence.

CONCLUSIONS

Lp(a) levels were strongly associated with MI risk especially in patients with LAP derived from CCTA. The presence of LAP could reinforce the relationship between Lp(a) and future MI occurrence, which has important implications for future risk assessment.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with stable chest pain, elevated serum Lp(a) is associated with an increased risk of MI, especially when LAP is identified by coronary CT angiography.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to investigate whether Lp(a) lowering therapy reduces LAP and prevents MI.

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KEY WORDS atherosclerotic plaque, computed tomography angiography, coronary artery disease, lipoprotein(a), myocardial infarction

APPENDIX For supplemental material, tables, and figures, please see the online version of this paper.