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Original Article

The Comparison of the Associations of Lipoprotein(a) and the Atherogenic Index of Plasma With Coronary Artery Calcification in Patients Without High LDL-C: A Comparative Analysis

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Conflict of Interest
The authors have no conflicts of interest to declare.

ABSTRACT

Objective: Lipoprotein(a) (Lp[a]) and the atherogenic index of plasma (AIP) have been reported as predictive markers of coronary artery calcium (CAC). However, previous studies demonstrated that the cardiovascular risk associations with Lp(a) are attenuated in patients with low-density lipoprotein cholesterol (LDL-C) levels ≤135 mg/dL. However, few articles have identified the risk factors of CAC in patients without high LDL-C. Therefore, we performed this study to investigate the association of Lp(a) and AIP with CAC in patients with LDL-C levels ≤135 mg/dL.
Methods: This study included 625 lipid-lowering agent naive patients with LDL-C levels ≤135 mg/dL who underwent coronary computed tomographic angiography. We performed multivariate logistic regression analysis to evaluate the risk factors for a coronary artery calcium score (CACS) >0, CACS ≥400, and CAC ≥90th percentile.
Results: The mean age of the patients was 55.0±7.9 years and their mean LDL-C level was 94.7 ±23.3 mg/dL. Multivariate regression analysis showed that age, male sex, diabetes, hypertension, Lp(a), and AIP were independent predictors of CAS>0. Age, male sex, and diabetes were independent predictors of CACS≥400. Diabetes, hypertension, and AIP were independent predictors of CAC ≥90th percentile (all p<0.05). Unlike Lp(a), higher AIP tertiles were associated with significantly higher CAC percentiles and greater proportions of patients with CACS ≥400 and CAC ≥90th percentile.
Conclusion: In patients without high LDL-C, AIP could be a more reliable predictor of CAC than Lp(a).

Keywords: Vascular calcification; Lipoprotein (a); Low density lipoprotein cholesterol

INTRODUCTION

High low-density lipoprotein cholesterol (LDL-C) levels are a major risk factor for coronary artery disease (CAD). However, CAD also occurs in patients without high LDL-C. Sachdeva et al. reported that approximately 75% of patients admitted to a hospital with a CAD event demonstrated a relatively normal LDL-C level of less than 130 mg/dL, and 23% had an LDL-C

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Conceptualization: Hong SP, Kim CY, Jung HW; Data curation: Hong SP, Kim CY, Jung HW; Formal analysis: Hong SP, Kim CY, Jung HW; Funding acquisition: Hong SP, Jung HW; Investigation: Hong SP, Kim CY, Jung HW; Methodology: Hong SP, Kim CY, Jung HW; Project administration: Hong SP, Kim CY, Jung HW; Resources: Hong SP, Kim CY, Jung HW; Software: Hong SP, Kim CY, Jung HW; Supervision: Hong SP, Kim CY, Jung HW; Validation: Hong SP, Jung HW; Visualization: Hong SP, Jung HW; Writing - original draft: Hong SP, Jung HW; Writing - review & editing: Hong SP, Jung HW.

level of less than 70 mg/dL.[1] To prevent CAD in patients without high LDL-C, it is necessary to identify CAD-causing lipoproteins other than LDL-C.

Coronary artery calcium (CAC) has been reported as a marker of coronary artery atherosclerosis and a predictor of future atherosclerotic cardiovascular disease (ASCVD).[2,3] Many studies have reported that small dense LDL-C (sdLDL) is the most powerful atherosclerotic lipoprotein parameter for predicting CAD, even more powerful than LDL-C.[4,5] Previous articles have shown that the atherogenic index of plasma (AIP), defined as the logarithm of the ratio of plasma concentration of triglycerides (TGs) to high-density lipoprotein cholesterol (HDL-C) had a significant correlation with LDL particle size. Therefore, AIP has been described as a surrogate marker for sdLDL.[6] Lipoprotein(a) (Lp[a]) is a low-density lipoprotein-like particle and apolipoprotein(a) is attached to apolipoprotein B via a disulfide bridge. Among several atherogenic lipoproteins, Lp(a) and AIP have demonstrated strong associations with CAC.[7-12] In the ARIC study, an abundance of sdLDL predicted CAD events, even in the group with LDL-C levels <100 mg/dL.[13] In addition, the JUPITER study confirmed the CAD risk associated with sdLDL, even in patients treated with rosuvastatin and with an average LDL-C levels of 54 mg/dL.[14] However previous studies demonstrated that the ASCVD risk associations with Lp(a) were attenuated in patients with LDL-C levels below 135 mg/dL.[15,16] To date, few articles have compared the associations of Lp(a) and AIP with CAC in patients without high LDL-C. Therefore, we performed this study to compare the associations of Lp(a) and AIP with CAC in patients with LDL-C levels ≤135 mg/dL.

MATERIALS AND METHODS

1. Study population and data collection

The study population was selected from the coronary computed tomographic angiography (CCTA) registry of our center. Between January 2013 and September 2020, 3,696 Korean patients who visited our hospital for chest discomfort underwent CCTA and lipid profile evaluation (total cholesterol [TC], LDL-C, HDL-C, TG, apolipoprotein [apo] A1, apo B, and Lp[a]). Total lipids and lipid subclass levels were measured with the patients in a fasting state (>8 hours after the last meal). Among the 3,696 patients, 1,207 patients had LDL-C levels ≤135 mg/dL. Of the 1,207 patients, 312 patients who underwent percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), 235 patients who were maintained on lipid-lowering drugs (including statins), 30 patients with end-stage renal disease, and 5 patients with motion artifacts on CCTA were excluded. Finally, 625 patients were included in the analysis. The CCTA analysis was performed on 625 patients. The inclusion and exclusion criteria are shown in a flow diagram (**Fig. 1**). Among 625 patients, revascularization was performed after CCTA in patients with typical angina pectoris who met the following criteria: 1) Left main disease with stenosis >50%, 2) Proximal left anterior descending artery stenosis >50%, 3) 2- or 3-vessel disease with stenosis >50% with impaired left ventricular function (ejection fraction ≤35%), 4) Large area of ischemia detected by functional testing (>10%) or abnormal invasive fractional flow reserve, 5) A single remaining patent coronary artery with stenosis >50%, 6) Hemodynamically significant coronary stenosis in the presence of limiting angina or angina equivalent, with insufficient response to optimized medical therapy. The choice between CABG and PCI was made after an assessment of surgical risk and CAD complexity.[17] The coronary revascularization rate was investigated. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The Institutional Review Board of Daegu Catholic University Medical Center approved the study and waived

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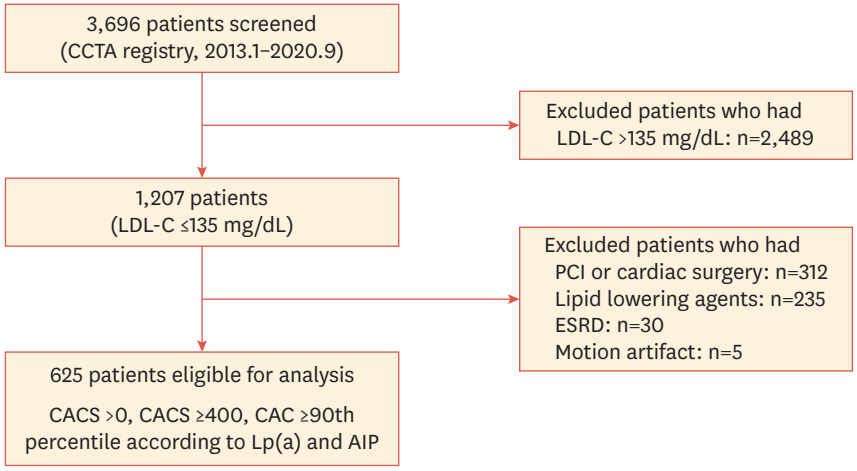

Fig. 1. Enrollment flow chart for analysis.
AIP, atherogenic index of plasma; CAC, coronary artery calcium; CACS, coronary artery calcium score; CCTA, coronary computed tomographic angiography; ESRD, end-stage renal disease; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCI, percutaneous coronary intervention.

the requirement for patients to provide informed consent because of the study's retrospective nature (CR-22-031-L).

2. Acquisition and analysis of CCTA images

Computed tomography (CT) scans were performed with a 256-slice CT device (Definition Flash; Siemens Healthineers AG, Erlangen, Germany) or a 512-slice CT (Revolution CT; GE Healthcare, Chicago, IL, USA). All patients with an initial heart rate ≥60 beats/min were given an oral beta-blocker (propranolol 20 mg) to achieve a target heart rate of 50 to 60 beats/min. Sublingual nitroglycerin was administered immediately before scanning. An iodine contrast agent (60–70 mL) was administered into the antecubital vein within 10 seconds followed by 25 mL of saline solution injected at 5.0 mL/second. The CT-reconstructed imaging data were transferred to a GE Centricity system (GE Healthcare Bio-Sciences Corp., Piscataway, NJ, USA) for postprocessing and subsequent image analysis. A radiologist read each scan independently at a central reading center. Plaque incidence and severity were investigated. Plaques were defined as structures ≥1 mm^2 within and/or adjacent to the vessel lumen and were clearly distinguishable from the lumen and the surrounding pericardial tissue.[18] Stenosis of 50% or more in 1 vessel was defined as 1 vessel disease, and stenosis of 50% or more in 2 or more vessels was defined as multivessel disease. The coronary artery calcium score (CACS) was calculated with the Agatston method using a commercially available reconstruction program for 3-dimensional reconstruction and measurement (Aquarius iNtuition TM Ver.4.4.12; TeraRecon, Foster City, CA, USA).[19,20] CACS >0 was defined as detectable coronary artery calcium.[10] The CAC percentiles reported followed the results of Hoff et al.[21]

3. Statistical analysis

Data were expressed as number (%) and mean ± standard deviation. Categorical data were compared using the χ^2 test or the Fisher exact test. Continuous variables were compared using the Student's *t*-test and Kruskal–Wallis H test when they were normally and non-normally distributed, respectively. We divided patients into 3 groups according to CACS (CACS =0, 0< CACS <400, and CACS ≥400) and CAC percentile (CACS =0, CACS >0 and CAC <90th percentile, and CAC ≥90th percentile) to compare clinical characteristics and lipid data in each group (**Table 1**). Hypertension (HTN) was defined as a systolic blood pressure

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Table 1. Characteristics of individuals according to CACS and CAC percentiles

Variables	Total patients (n=625)	CACS =0 (n=313)	0< CACS <400 (n=229)	CACS ≥400 (n=83)	*p*-value	CACS =0 (n=313)	CACS >0 and CAC <90th percentile (n=235)	CAC ≥90th percentile (n=77)	*p*-value
Age (yr)	55.0±7.9	52.3±8.6	57.1±6.0	59.4±5.4	<0.001	52.3±8.6	58.2±5.4	56.3±7.2	<0.001
Male	390 (62.4)	148 (47.3)	177 (77.3)	65 (78.3)	<0.001	148 (47.3)	196 (83.4)	46 (59.7)	<0.001
Diabetes	143 (22.9)	42 (13.4)	61 (26.6)	40 (48.2)	<0.001	42 (13.4)	64 (27.2)	37 (48.1)	<0.001
HTN	242 (38.7)	94 (30.0)	102 (44.5)	46 (55.4)	<0.001	94 (30.0)	106 (45.1)	42 (54.5)	<0.001
Smoking	205 (32.8)	90 (28.8)	89 (38.9)	26 (31.3)	0.044	90 (28.8)	90 (38.8)	25 (32.5)	0.062
SBP (mmHg)	126.1±17.5	126.3±17.3	125.2±18.0	128.3±16.8	0.362	126.3±17.3	125.2±17.5	128.6±18.4	0.326
DBP (mmHg)	75.7±11.9	75.6±12.1	75.5±11.8	76.4±11.4	0.827	75.6±12.1	75.5±11.9	76.4±11.1	0.845
BMI (kg/m^2)	24.4±3.60	24.7±3.94	24.1±3.28	24.0±2.91	0.060	24.7±3.94	24.1±3.22	24.0±3.08	0.061
eGFR (mL/min/1.73 m^2)	93.7±18.1	97.4±16.7	91.2±17.5	86.6±21.3	<0.001	97.4±16.7	90.7±16.3	87.8±24.3	<0.001
FBG (mg/dL)	114.0±44.2	108.3±41.4	114.2±37.2	134.9±62.7	<0.001	108.3±41.4	116.3±39.0	130.0±62.5	<0.001
TC (mg/dL)	154.5±27.8	156.5±27.5	153.9±28.5	148.6±26.2	0.065	156.5±27.5	153.3±28.0	149.8±27.8	0.126
TG (mg/dL)	121.6±90.4	116.9±88.1	124.4±96.8	131.8±79.9	0.344	116.9±88.1	118.3±82.2	151.1±115.8	0.009
HDL-C (mg/dL)	46.6±15.1	48.7±16.1	45.2±13.1	42.8±15.2	0.001	48.7±16.1	45.5±13.2	41.7±15.0	<0.001
LDL-C (mg/dL)	94.7±23.3	95.4±22.8	94.9±24.6	91.3±21.2	0.348	95.4±22.8	94.9±24.2	90.9±22.3	0.303
Apo B (mg/dL)	85.9±18.6	85.0±18.1	87.2±19.5	85.3±18.2	0.374	85.0±18.1	86.8±19.8	86.5±17.3	0.506
Apo A1 (mg/dL)	128.2±30.1	131.8±29.1	125.9±28.9	121.6±34.9	0.008	131.8±29.1	125.7±29.1	121.6±34.8	0.008
Lp(a) (mg/dL)	20.3±24.0	16.2±17.2	24.9±29.0	23.4±28.1	<0.001	16.2±17.2	25.3±29.2	22.0±27.5	<0.001
TG/HDL-C	3.15±3.42	3.02±3.81	3.19±3.12	3.53±2.58	0.474	3.02±3.81	3.00±2.67	4.15±3.68	0.023
AIP	0.36±0.32	0.33±0.34	0.38±0.31	0.44±0.30	0.007	0.33±0.34	0.36±0.30	0.50±0.31	<0.001

Data are given as mean ± standard deviation, or as number (%).
CACS, coronary artery calcium score; CAC, coronary artery calcium; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Apo B, apolipoprotein B; Apo A1, apolipoprotein A1; Lp(a), lipoprotein(a); AIP, atherogenic index of plasma.

≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or current antihypertensive treatment. Diabetes mellitus (DM) was defined as follows: a fasting plasma glucose concentration ≥126 mg/dL, a 2-hour plasma glucose concentration ≥200 mg/dL on a standard 75-g oral glucose tolerance test, hemoglobin a1c ≥6.5%, or current treatment of diabetes.[22] We investigated the smoking history of patients and classified both current and past smokers as having a smoking history. The estimated glomerular filtration rate (eGFR) was investigated as an indicator of renal function. Univariate analysis using logistic regression was performed to identify potential independent predictors of CACS >0, CACS ≥400 and CAC ≥90th percentile. Variables with a *p*-value <0.05 in the univariate analysis were included in the multivariate analysis to identify independent predictors of CACS >0, CACS ≥400 and CAC ≥90th percentile. The *p*-value <0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The mean age and LDL-C level of the 625 patients were 55.0±7.9 years and 94.7±23.3 mg/dL, respectively. Of the total patients, 62.4% were male and 22.9% had diabetes. After CCTA, 79 cases of revascularization were performed, of which 77 were PCI and 2 were CABG. The mean CACS and CAC percentile of all patients were 194.3±573.0 and 32.5%±38.1%, respectively. CACS >0 was present in 49.9% of the total patients, CACS ≥400 in 13.3% of all patients and CAC ≥90th percentile in 12.3% of the patients.

1. Characteristics of individuals according to CACS and CAC percentiles

The characteristics of individuals according to CACS and CAC percentiles are presented in **Table 1**. In a comparison among CACS =0, 0< CACS <400, and CACS ≥400, the CACS ≥400

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group showed significantly higher age, fasting blood glucose (FBG), and AIP than the other 2 groups. The CACS ≥400 group showed significantly lower eGFR, HDL-C, and apo A1 than the other 2 groups. The proportions of men, patients with DM, and patients with HTN were significantly higher in the CACS ≥400 group than in the other 2 groups. The lowest AIP was found in the CACS =0: it was higher in the 0< CACS <400 group and highest in the CACS ≥400 group. However, there was no significant difference in Lp(a) between the 0< CACS <400 and CACS ≥400 groups. In a comparison among CACS =0, CAC <90th percentile (CACS >0), and CAC ≥90th percentile, the CAC ≥90th percentile group showed significantly higher FBG, TG, TG/HDL-C ratio and AIP than the other 2 groups. Furthermore, the CAC ≥90th percentile group showed significantly lower eGFR, HDL-C, and apo A1 than the other 2 groups. The proportions of patients with DM, and HTN were significantly higher in the CAC ≥90th percentile group than in the other 2 groups. The lowest AIP was observed in the CACS =0 group, while higher levels were observed in the CAC <90th percentile (CACS >0) group, and the highest values were found in the CAC ≥90th percentile group. However, there was no significant difference in Lp(a) between the CAC <90th percentile (CACS >0), and CAC ≥90th percentile groups.

2. Independent predictors of CACS >0, CACS ≥400, and CAC ≥90th percentile

According to the multivariate regression analysis, age (odds ratio [OR], 1.108; 95% confidence interval [CI], 1.069–1.148; p<0.001), male (OR, 4.687; 95% CI, 2.755–7.973; p<0.001), DM (OR, 2.481; 95% CI, 1.436–4.285; p=0.001), HTN (OR, 1.883; 95% CI, 1.198–2.960; p=0.006), Lp(a) (OR, 1.020; 95% CI, 1.010–1.029; p<0.001) and AIP (OR, 2.064; 95% CI, 1.041–4.094; p=0.038) were independently associated with CACS >0 (**Table 2**). Age (OR, 1.113; 95% CI, 1.057–1.171; p<0.001), male (OR, 2.115; 95% CI, 1.003–4.460; p=0.049), and DM (OR, 2.779; 95% CI, 1.522–5.076; p=0.001) were independent predictors for CACS ≥400 (**Table 3**). DM (OR, 2.872; 95% CI, 1.607–5.134; p<0.001), HTN (OR, 1.765; 95% CI, 1.024–3.043; p=0.041) and AIP (OR, 3.233; 95% CI, 1.415–7.389; p=0.005) were independent predictors for CAC ≥90th percentile (**Table 4**).

Table 2. Independent predictors for CACS >0

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.106	1.079–1.134	<0.001	1.108	1.069–1.148	<0.001
Male	3.854	2.726–5.450	<0.001	4.687	2.755–7.973	<0.001
Diabetes	3.089	2.065–4.618	<0.001	2.481	1.436–4.285	0.001
HTN	2.102	1.514–2.920	<0.001	1.883	1.198–2.960	0.006
Smoking history	1.446	1.034–2.024	0.031	0.920	0.527–1.605	0.768
BMI	0.948	0.906–0.991	0.019	0.953	0.896–1.013	0.119
SBP	0.999	0.990–1.008	0.848			
DBP	1.001	0.988–1.014	0.911			
eGFR	0.975	0.965–0.985	<0.001	0.994	0.982–1.006	0.290
LDL-C	0.997	0.991–1.004	0.423			
Apo B	1.005	0.997–1.014	0.245			
Apo A1	0.992	0.987–0.997	0.004	0.996	0.989–1.003	0.235
Lp(a)	1.016	1.008–1.023	<0.001	1.020	1.010–1.029	<0.001
AIP	2.007	1.225–3.288	0.006	2.064	1.041–4.094	0.038

CACS, coronary artery calcium score; OR, odds ratio; CI, confidence interval; HTN, hypertension; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; Apo B, apolipoprotein B; Apo A1, apolipoprotein A1; Lp(a), lipoprotein(a); AIP, atherogenic index of plasma.

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Table 3. Independent predictors for CACS ≥400

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	1.126	1.077–1.177	<0.001	1.113	1.057–1.171	<0.001
Male	2.411	1.392–4.177	0.002	2.115	1.003–4.460	0.049
Diabetes	3.965	2.451–6.414	<0.001	2.779	1.522–5.076	0.001
HTN	2.195	1.376–3.501	0.001	1.581	0.911–2.743	0.104
Smoking history	0.925	0.563–1.521	0.759			
BMI	0.961	0.899–1.028	0.244			
SBP	1.008	0.995–1.021	0.221			
DBP	1.006	0.987–1.026	0.548			
eGFR	0.978	0.967–0.990	<0.001	0.997	0.983–1.011	0.633
LDL-C	0.993	0.983–1.003	0.153			
Apo B	0.988	0.986–1.011	0.787			
Apo A1	0.991	0.983–0.999	0.031	0.996	0.986–1.005	0.392
Lp(a)	1.006	0.997–1.014	0.211			
AIP	2.391	1.194–4.789	0.014	1.503	0.601–3.761	0.384

CACS, coronary artery calcium score; OR, odds ratio; CI, confidence interval; HTN, hypertension; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; Apo B, apolipoprotein B; Apo A1, apolipoprotein A1; Lp(a), lipoprotein(a); AIP, atherogenic index of plasma.

Table 4. Independent predictors for CAC percentile ≥90th percentile

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Diabetes	3.857	2.352–6.326	<0.001	2.872	1.607–5.134	<0.001
HTN	2.088	1.291–3.378	0.003	1.765	1.024–3.043	0.041
Smoking history	0.983	0.591–1.636	0.947			
BMI	0.965	0.900–1.034	0.313			
SBP	1.009	0.996–1.023	0.192			
DBP	1.006	0.986–1.026	0.569			
eGFR	0.982	0.970–0.994	0.003	0.991	0.978–1.003	0.155
LDL-C	0.992	0.982–1.002	0.127			
Apo B	1.002	0.989–1.015	0.746			
Apo A1	0.991	0.983–1.000	0.039	0.997	0.988–1.007	0.589
Lp(a)	1.003	0.994–1.013	0.536			
AIP	4.320	2.103–8.871	<0.001	3.233	1.415–7.389	0.005

CACS, coronary artery calcium score; OR, odds ratio; CI, confidence interval; HTN, hypertension; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; Apo B, apolipoprotein B; Apo A1, apolipoprotein A1; Lp(a), lipoprotein(a); AIP, atherogenic index of plasma.

3. Characteristics of CCTA according to tertiles of the AIP and Lp(a)

The characteristics of CCTA stratified by tertiles of based on the AIP and Lp(a) are shown in **Table 5**. The cut-off points of AIP between tertiles were 0.209 (between the first and second tertiles) and 0.485 (between the second and third tertiles). The cut-off points of Lp(a) between tertiles were 6.6 (between the first and second tertiles) and 18.9 (between the second and third tertiles). In a comparison of CACS and CAC percentiles according to the tertiles of AIP, the CACS and CAC percentiles increased as the tertiles of AIP increased. However, no positive correlation was observed between the CACS or CAC percentiles and the tertiles of Lp(a) (**Fig. 2**). When comparing the tertiles of AIP, significant increase in CAC percentile, and the proportion of patients with CACS ≥400, CAC ≥90th percentile, plaque, multivessel disease, revascularization were observed in ascending order from tertiles 1 to tertiles 2, and 3. In a comparison of the tertiles of Lp(a), no significant relationships were found with the CAC percentile or the proportions of patients with CACS ≥400, CAC ≥90th percentile, plaque, multivessel disease, and revascularization (**Table 5**).

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Table 5. Characteristics of coronary computed tomographic angiography stratified by tertiles of the Lp(a) and AIP

Variables	Total patients (n=625)	Tertile 1 of the AIP <0.209 (n=208)	Tertile 2 of the AIP 0.209–0.485 (n=209)	Tertile 3 of the AIP >0.485 (n=208)	*p*-value	Total patients (n=625)	Tertile 1 of the Lp(a) <6.6 (n=207)	Tertile 2 of the Lp(a) 6.6–18.9 (n=206)	Tertile 3 of the Lp(a) >18.9 (n=210)	*p*-value
CACS	194.3±573.0	134.7±415.7	189.4±586.7	258.9±680.7	0.086	194.3±573.0	188.3±540.4	169.7±473.9	218.9±682.5	0.677
CACS >0	312 (49.9)	90 (43.3)	113 (54.1)	109 (52.4)	0.060	312 (49.9)	99 (47.8)	91 (44.2)	120 (57.1)	0.024
CACS ≥400	83 (13.3)	21 (10.1)	22 (10.5)	40 (19.2)	0.008	83 (13.3)	28 (13.5)	26 (12.6)	28 (13.3)	0.960
CAC percentile	32.5±38.1	27.4±36.0	33.0±36.6	37.0±41.0	0.037	32.5±38.1	32.9±38.5	29.9±38.3	34.0±37.3	0.528
≥90th percentile	77 (12.3)	15 (7.2)	21 (10.0)	41 (19.7)	<0.001	77 (12.3)	28 (13.5)	26 (12.6)	22 (10.5)	0.620
CAC volume (mm^3)	155.1±452.0	110.4±334.5	147.8±459.6	207.0±535.6	0.089	155.1±452.0	151.2±421.3	136.6±378.4	172.6±539.0	0.716
CAC mass (mg)	39.1±123.8	29.0±101.0	34.8±117.6	53.4±147.6	0.110	39.1±123.8	38.1±114.7	36.2±112.1	41.6±142.2	0.901
Presence of plaque	393 (62.9)	114 (54.8)	136 (65.1)	143 (68.8)	0.010	393 (62.9)	131 (63.3)	122 (59.2)	138 (65.7)	0.385
Multivessel disease	59 (9.4)	9 (4.3)	22 (10.5)	28 (13.5)	0.005	59 (9.4)	13 (6.3)	19 (9.2)	26 (12.4)	0.100
Revascularization	79 (12.7)	15 (7.2)	25 (12.0)	39 (18.8)	0.002	79 (12.7)	21 (10.1)	27 (13.1)	31 (14.8)	0.357

Data are given as mean±standard deviations, or as number (%).
Lp(a), lipoprotein(a); AIP, atherogenic index of plasma; CACS, coronary artery calcium score; CAC, coronary artery calcium.

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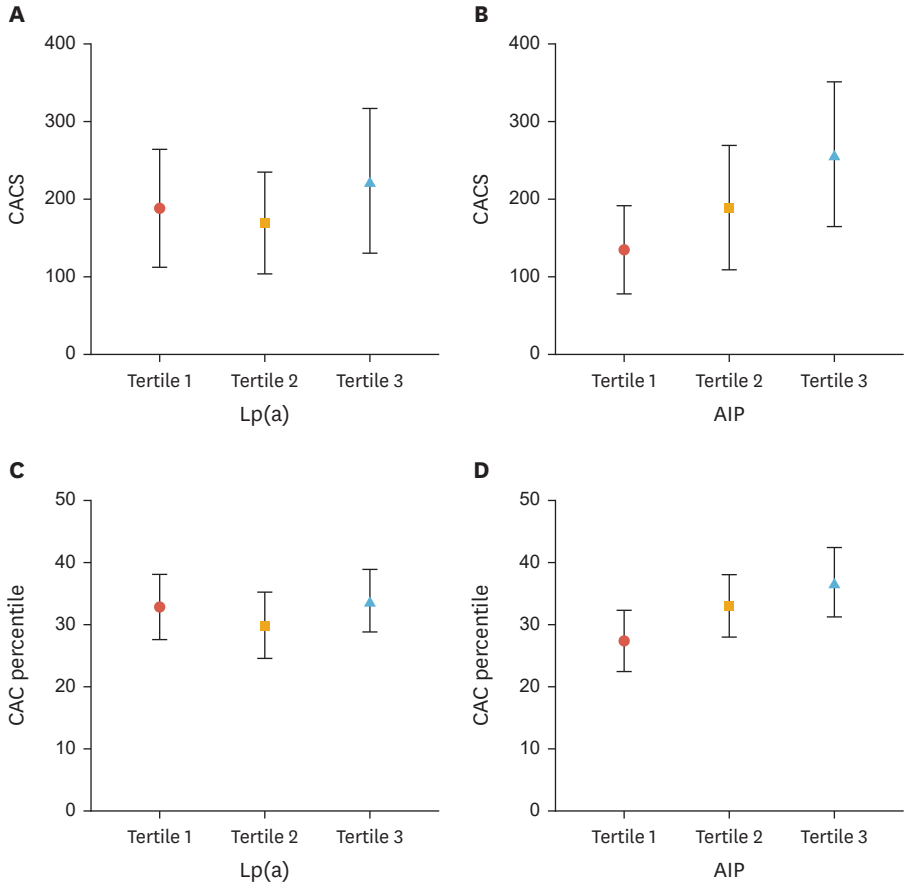

Fig. 2. Comparison of mean CACS between the tertiles of the Lp(a) (A). Comparison of mean CACS between the tertiles of the AIP (B). Comparison of mean CAC percentile between the tertiles of the Lp(a) (C). Comparison of mean CAC percentile between the tertiles of the AIP (D). The column bar graph demonstrated the mean CACS or mean CAC percentile with a 95% confidence interval.
CACS, coronary artery calcium score; Lp(a), lipoprotein(a); AIP, atherogenic index of plasma; CAC, coronary artery calcium.

DISCUSSION

The primary findings of our study were as follows: In Korean patients with LDL-C levels below 135 mg/dL, 1) both Lp(a) and AIP were independent predictors of CACS >0, 2) AIP was an independent predictor of CAC ≥90th percentile and 3) in contrast to Lp(a), higher AIP tertiles were significantly associated with a higher CAC percentile and greater proportions of patients with CACS ≥400 and CAC ≥90th percentile.

The current methods for assessing the severity of CAC include absolute CACS and age-, sex-specific CAC percentiles. Both CACS and CAC percentiles have been identified as strong predictors of cardiovascular events.[23,24] The absence of CAC (CACS =0) has been associated with a very low risk of future cardiovascular events[25,26], while CACS ≥400 and CAC ≥90th percentile have been identified as the highest cardiovascular risk groups.[23,27,28] We investigated the predictors of CACS >0, CACS ≥400, and CAC ≥90th percentile to identify risk factors for CAC. Previous studies have demonstrated strong associations of Lp(a) and AIP with CAC.[7,12] However, several studies have shown a weakened association between Lp(a) and ASCVD risk in patients without high LDL-C.[15,16,29,30] Therefore, whether a consistent

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association exists between Lp(a) and CAC is questionable in patients without high LDL-C. In the present study, Lp(a) did not predict CACS ≥400 and CAC ≥90th percentile whereas, AIP independently predicted both CAC >0 and CAC ≥90th percentile. In addition, in contrast to Lp(a), higher AIP tertiles showed the significant associations with higher CAC percentiles and greater proportions of patients with CACS ≥400 and CAC ≥90th percentile (**Table 5**). The fact that atherosclerosis is a time-dependent pathological change may explain why, according to the multivariate analysis, AIP predicted CAC ≥ 90th percentile, but not CACS ≥400. That is, it is difficult to predict the current CACS based on the current AIP. However, AIP can better predict CAC ranking in specific groups defined according to age and sex. Considering the above results, AIP could be a more reliable marker than Lp(a) for predicting CAC in patients without high LDL-C.

Our findings support the view that the correlation between Lp(a) and CAD risk is attenuated in patients with low LDL-C levels. The biological evidence underlying to this association is not yet fully understood. However, Zhu et al.[30] presented the following suggestions. Patients with very low LDL-C levels tend to have high levels of activity of LDL receptors and a strong metabolic capacity for Lp(a). Even high Lp(a) levels can be metabolized in a timely manner, and its biological effects are attenuated. Conversely, patients with high LDL-C levels have low levels or activity of LDL receptors and Lp(a) is not efficiently metabolized, resulting in amplified biological effects.[30] Several papers have demonstrated a strong association between sdLDL and arterial calcification.[31,32] Previous articles have shown that AIP had a significant correlation with LDL particle size and that it could be a marker of sdLDL.[6] High AIP has been associated with a high incidence of ASCVD, as well as high CACS.[33-35] In this study, higher AIP tertiles were significantly associated with higher proportions of patients with plaque, multivessel disease, and revascularization. However, tertiles of Lp(a) showed no significant relationships with the proportions of patients with plaque, multivessel disease, and revascularization The present study demonstrated that AIP plays an important role in both coronary calcification and atherosclerosis in patients without high LDL-C. Efforts to reduce AIP in patients without high LDL-C may further reduce ASCVD risk. Obesity and smoking are well known to be associated with high AIP.[36-39] We expect that future studies will demonstrate that regulating these 2 factors prevents the generation of CAC or inhibits its progression.

This study has limitations. First, this was a single-center study. Second, the study population was composed of Koreans. Studies with large numbers of patients or participants of different races are needed to confirm and generalize our findings. Third, because our study targeted patients who underwent CCTA for chest discomfort, the plaque incidence, and CACS were high. Therefore, in order to apply the results of this study to the general population, a large-scale study including asymptomatic patients should be conducted. However, unlike previous papers that compared the relationship between Lp(a) or AIP with CAC separately, this study is the first to compared the associations of Lp(a) and AIP with CAC. Moreover, our study was the first to demonstrate that AIP could be a more reliable marker than Lp(a) for CAC prediction in patients without high LDL-C. Although LDL-C is the main target for preventing coronary atherosclerosis, ASCVD still occurs in patients without high LDL-C.[1] Thus, our study suggests that different atherogenic lipoprotein parameters according to the patient's LDL-C level should be used to predict residual ASCVD risk.

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