Impact of Serum Lipoprotein (A) Level on Coronary Artery Calcification: An Intravascular Ultrasound Study

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Research Article

Keywords: Coronary heart disease, Lipoprotein (a), Coronary artery calcification, Intravascular ultrasound

Posted Date: May 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-500843/v1

Abstract

Background

Plasma lipoprotein(a) [Lp(a)] participates in the development of coronary heart disease (CAD). However, the relationship between Lp(a) level and the characteristic of coronary artery calcification has not been investigated.

Methods

A total of 123 patients with CAD who underwent percutaneous coronary intervention(PCI) were analyzed.Calcification burden of coronary culprit plaque was measured by the angle and thickness with intravascular ultrasound imaging(IVUS). Patients were divided into 2 groups: low Lp(a) group, < 150mg/L; high Lp(a) group, ≥ 150mg/L.

Results

Mean patient age was 62.6 ± 10.1years, and 75.6% were men. Among 139 lesions, compared with the high Lp(a) group, the low Lp(a) group had significantly greater median maximum calcification angle (166.4°[102.1, 260.5] vs 118.4° [83.4,169.7], P = 0.007) and thick calcification(40.7% vs 21.2%, P = 0.013).Plaques with a maximum calcification angle of ≥ 180° were more frequently observed in the low Lp(a) group (42.6% vs 18.8%, P = 0.002).The calcification lesions of maximum arc ≥ 180° +thick calcification were larger in the low Lp(a) group (35.2% vs 11.8%, P = 0.001). Multivariate logistic regression analysis showed that low Lp(a) level was a independent predictor of a greater calcification burden: calcification arc ≥ 180°(OR 4.43, 95%CI1.93-10.13;P < 0.001),and thick calcification + maximum calcification arch ≥ 180°(OR 5.92, 95% CI 2.36–14.82; P < 0.001).

Conclusion

In patients with CAD, Low Lp(a) level was associated with high burden of coronary artery calcification. Our findings might provide a new perspective of Lp(a) level on plaque-stabilizing effects in coronary atherosclerotic plaque.

1. Introduction

Lipoprotein (a) (Lp(a)) is a cholesterol-rich lipoprotein with molecular structure simialr to low-density lipoproteins (LDL) and represents an atherothrombogenic lipoprotein[1].Atherosclerosis occurs in the presence of risk factors, especially dyslipidemia[2]. Lp(a) are associated with coronary heart disease (CAD)[3] and coronary atheroma progression[4].

Coronary artery calcification(CAC) is a well-known marker of aadvanced atherosclerotic plaque[2]. Recently study demonstrate that higher Lp(a) levels are associated with annual increases of CAC volume[5].In clinical practice,the intravascular ultrasound(IVUS) has a higher sensitivity of calcification detection compared to coronary angiography[6]. Measuring plaque calcification with the high imaging resolution of coronary IVUS is well described and validated[7].

However, there is no study about the relationship between the calcification lesions characteristics of intravascular imaging and Lp(a) level. In this study, we sought to evaluate the association between Lp(a) and calcification plaque including quantitative and qualitative analyses by IVUS in patients with CAD who underwent percutaneous coronary intervention(PCI).

2. Methods

2.1 Study population

Patients were enrolled in the the Third Xiangya Hospital, Central South University between January 2019 and December 2020.This was a retrospective, single-center observational study. 155 consecutive coronary artery disease (CAD) patients accepted PCI were enrolled.The inclusion criteria were:(1)Patients who underwent PCI. (2)Patients who were evaluated using IVUS.The exclusion criteria were: (1)Chronic kidney disease (CKD), which was defined as an estimated glomerular filtration rate(eGFR) of < 30mL/min/1.73 m^2;(2)Adequate IVUS images were not obtained;(3)In-stent restenosis (ISR) , stent thrombosis or the same culprit vessel was treated, previously. Patients were divided into 2 groups: low Lp(a) group, <150mg/L; high Lp(a) group, ≥ 150mg/L[8]. Finally, 139 lesions in 123 patients were included in (***Fig.1***).

This study was approved by the medical ethic committee of our institute, and written informed consent was obtained from each patient.

2.2 Measurement of Lp(a) levels

At baseline,blood samples were obtained by certified technicians from each participant in the early morning after overnight fasting. Lp(a) level was measured inserum by Biochemical Diagnostics Laboratory (third Xiangya Hospital,Changsha,China) using a latex-enhanced turbidimetric immunoassay (Hitachi 7600, Tokyo, Japan), with a total imprecision <5%.

2.3 Procedures

After injection of 100 U/kg of unfractionated heparin, PCI was performed with a 6Fr or 7Fr guide catheter. Balloon dilation and the stenting procedure were performed at the operator's discretion.The image acquisition was performed with IVUS system(Volcano corporation, Rancho Cordova, USA) and the 20 MHz IVUS catheter was advanced>5 mm beyond the lesion, and an imaging was performed to a point>5 mm proximal to the lesion.

IVUS images of the culprit lesion were obtained before PCI. All IVUS images were analyzed by analysts who were blinded to patient and procedural information.

2.4 Data analysis

2.4.1 Angiographic image acquisition and analysis

Quantitative coronary angiography (QCA) analysis was performed Pre- and post-PCI using an off-line quantitative coronary angiographic system(Medis Medical Imaging Systems,Leiden, Netherlands).Using the guiding catheter for magnification calibration, the reference diameter, minimal lumen diameter, and lesion length, and the percent diameter stenosis were measured.

2.4.2 IVUS image analysis

After intracoronary administration of 0.1–0.2mg nitroglycerin, IVUS imaging of the target lesion segment was performed before PCI. Segments were selected for analysis by using proximal and distal side branches as reference points.Conventional IVUS measurements included the cross-sectional area (CSA) of the external elastic membrane (EEM), lumen, and plaque plus media (EEM CSA minus lumen CSA) at each segment.The plaque burden was calculated as the plaque plus media CSA divided by the lesion EEM CSA multiplied by 100.The qualitative IVUS variables included calcifcation was defined as brighter echoes than adventitia with acoustic shadowing.Attenuated plaque(AP)was defined as hypoechoic plaque with deep ultrasonic attenuation despite the absence of bright calcification[9].The maximum angle of the calcifcation was measured(***Fig.2A***).Thin calcifcation was defined as smooth surface with a reverberation pattern, and irregular surface without reverberation was the thick calcifications[6](***Fig.2 B,C***).

2.5 Statistical analysis

Quantitative data are presented as mean±standard deviation (SD) or median[interquartile range (IQR)] and compared with (Student's t-test). Categorical variables were expressed as frequencies and compared with chi-square or Fisher exact test.Unconditional logistic regression was performed for estimates of odds ratios (ORs) and 95% confidence intervals (CIs). Logistic regression analysis was perfprmed to compare the odds ratios (ORs) of the calcified plaque (maximum calcified angle ≥180°) and the feature of calcified plaque（maximum calcified angle ≥180°）thick calcification）between 2 groups (low Lp(a) group<150mg/L and high Lp(a) group, ≥150mg/L).For all analyses, P<0.05 was considered statistically significant.All statistical analyses were conducted using SPSS (version 19; IBM-SPSS, Chicago, IL).

3. Results

3.1 Patients and angiographic features

The baseline patient characteristics are listed in Table 1. The median Lp(a) were 209.0 [95.0, 361.0]. The low Lp(a) group consisted of 49 patients(54 lesions), and the high Lp(a) group 74 patients(85

lesions).The mean age of the patients was 62.6 ± 10.1years,75.6% were men and 32.5% had diabetic mellitus. The high Lp(a) group had higher levels of low-density lipoprotein cholesterol (1.95 ± 0.80 vs 1.65 ± 0.58 mmol/L; P = 0.024).There were no significant differences in age, diabetes, blood fasting sugar,creatinine, eGFR, drugs or clinical manifestation.

Angiographic data were shown in Table 2.The percent diameter stenosis, lesion length, and distribution of plaques in the 3 coronary arteries were not different between the two groups.

Table 1
Baseline patient characteristics

	LP(𝛂) < 150mg/L (n = 49)	LP(𝛂) ≥ 150mg/L (n = 74)	P
Age (years)	61.4 ± 11.0	62.7 ± 9.7	0.49
Male gender,(%)	81.6	71.6	0.21
Hypertension,(%)	59.2	58.1	0.91
Diabetes,(%)	28.6	35.1	0.45
Smoking,(%)	59.2	51.4	0.39
Blood fasting sugar (mmol/L)	5.7 ± 1.4	5.7 ± 2.1	0.85
LP(𝛂) (mg/L)	79.0 [59.5, 110.0]	314.0 [250.0, 500.0]	**< 0.0001**
LDL(mmol/L)	1.65 ± 0.58	1.95 ± 0.80	**0.024**
TG(mmol/L)	2.2 ± 2.5	1.5 ± 1.2	0.09
Cholesterol(mmol/L)	3.7 ± 1.0	3.9 ± 1.1	0.41
Creatinine, mg/dL	82.5 ± 18.9	82.4 ± 22.1	0.99
eGFR,mL/min/1.73 m^2	78.4 ± 22.4	79.4 ± 23.5	0.81
Previous PCI,(%)	49.0	44.6	0.63
Previous MI,(%)	34.7	27.0	0.36
ACS,(%)	61.2	73.0	0.17
Drugs			
Clopidogrel,(%)	40.8	32.4	0.34
Ticlopidine,(%)	12.2	18.9	0.33
ACE-I/ARBs,(%)	46.9	60.8	0.13
Beta-blockers,(%)	53.1	52.7	0.97
Statins,(%)	59.2	54.1	0.76

Data are presented as mean ± standard deviation, number (%), or median (25th–75th percentile), as appropriate.

LDL,low-density lipoprotein;TG,total triglycerides;eGFR,estimated glomerular filtration rate;PCI,percutaneous coronary intervention; MI,myocardial infarction; ACS, acute coronary syndrome;ACE-I/ARBs,angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

Table 2
Quantitative coronary angiography and IVUS findings of the lesions

	LP(□) < 150mg/L (n = 54)	LP(□) ≥ 150mg/L (n = 85)	P
CAG findings			
Target vessel			
LAD,(%)	61.1	68.2	0.39
LCX,(%)	18.5	17.6	0.90
RCA,(%)	18.5	14.1	0.49
Others (%)	2.0	0.0	0.39
Multivessel disease	92.6	91.8	0.86
Percent diameter stenosis,(%)	88.9 ± 8.1	86.3 ± 13.5	0.20
Lesion length (mm)	54.6 ± 26.6	49.8 ± 25.3	0.29
IVUS findings			
Fibrous plaque,(%)	3.7	4.7	0.78
Calcified plaque,(%)	94.4	89.4	0.30
Lipid plaque,(%)	48.1	44.7	0.69
Attenuated plaque,(%)	14.8	10.6	0.46
MLA,mm^2	2.4 ± 0.6	2.5 ± 0.7	0.41
Area of stenosis at the MLA,(%)	82.1 ± 5.3	80.1 ± 7.4	0.08
Maximum calcium angle	166.4[102.1, 260.5]	118.4[83.4,169.7]	**0.007**
Maximum calcium arch ≥ 90°,(%)	85.2	80.0	0.59
Maximum calcium arch ≥ 180°,(%)	42.6	18.8	**0.002**
Thick calcification,(%)	40.7	21.2	**0.013**
Calcium arch ≥ 180° +Thick calcification, (%)	35.2	11.8	**0.001**

Data are presented as mean ± standard deviation, number (%), or median (25th–75th percentile), as appropriate..

IVUS: intravascular ultrasound; MLA: minimal lumen area.

3.2 Quantitative Ivus Analysis

A total of 139 culprit lesions in 123 patients were analyzed. The IVUS analysis were presented in Table 2.There were no significant differences in minimum lumen area and plaque burden between the two groups.There was no significant difference in the culprit plaque type (fibrous,lipid,calcified and attenuated lesions) between the groups.Calcification was detected by IVUS in 91.4% (127 of 139) of lesions. The median maximum calcification angle(166.4°[102.1, 260.5] versus 118.4° [83.4,169.7], P = 0.007) (Fig. 3) and the prevalence of thick calcification(40.7% versus 21.2%, P = 0.013) were significantly greater in low Lp(a) group compared with high Lp(a) group. Plaques with a maximum calcification angle of ≥ 180° were more frequently observed in the low Lp(a) group (42.6% versus 18.8%, P = 0.002) (Fig. 4A).The calcification lesions of maximum arc ≥ 180° plus thick calcification were larger in the low Lp(a) group (35.2% versus 11.8%, P = 0.001) (Fig. 4B).

3.3 Univariate And Multivariate Logistic Regression Analysis

The univariate and multivariate logistic regression analysis were shown in Table 3 and Table 4. In the multivariate model, low Lp(a) level was significantly associated with a greater calcification angle ≥ 180° (OR 4.43, 95%CI 1.93–10.13;P < 0.001). The low Lp(a) level were also independently associated with the features of calcification maximum arc ≥ 180° plus thick calcification(OR 5.92, 95% CI 2.36–14.82; P < 0.001). The multivariate logistic regression analysis demonstrated that low Lp(a) level was independently associated with greater calcification angle and thicker plaque calcification.

Table 3
Multivariate logistic regression analysis for the factors that affect maximum calcium arch ≧ 180°

Univariate analysis	**Odds ratios (95 % CI)**	**P**
LP(□) < 150mg/L	3.45 [1.61, 7.41]	**0.001**
LDL(mmol/L)	0.94 [0.56, 1.57]	0.81
Age	0.99 [0.95, 1.02]	0.49
Diabetes	1.46 [0.68, 3.13]	0.33
Statin use	1.45 [0.68, 3.07]	0.34
Multivariate analysis	**Odds ratios (95 % CI)**	**P**
LP(□) < 150mg/L	4.43 [1.93, 10.13]	**< 0.001**
LDL(mmol/L)	1.55 [0.85, 2.84]	0.16
Age	1.02 [0.98, 1.06]	0.27
Diabetes	1.95 [0.84, 4.55]	0.12
Statin use	1.92 [0.82, 4.51]	0.13
Data are presented as estimate (95% confidence interval).		
Odds ratios (OR) and 95% confidence intervals (CI) investigating the association between low Lp(a) level and coronary artery calcification.		

Table 4
Multivariate logistic regression analysis for the factors that affect thick calcification + maximum calcium arch ≥ 180°

Univariate analysis	**Odds ratios (95 % CI)**	**P**
LP(□) < 150mg/L	4.77 [2.03, 11.25]	**< 0.001**
LDL(mmol/L)	0.99 [0.57, 1.74]	0.98
Age	0.98 [0.94, 1.02]	0.29
Diabetes	0.91 [0.39, 2.14]	0.84
Statin use	1.57 [0.69, 3.98]	0.29
Multivariate analysis	**Odds ratios (95 % CI)**	**P**
LP(□) < 150mg/L	5.92 [2.36, 14.82]	**< 0.001**
LDL(mmol/L)	1.45 [0.74, 2.83]	0.28
Age	1.04 [0.99, 1.08]	0.12
Diabetes	1.14 [0.44, 2.92]	0.79
Statin use	1.99 [0.77, 5.11]	0.16
Data are presented as estimate (95% confidence interval).		
Odds ratios (OR) and 95% confidence intervals (CI) investigating the association between low Lp(a) level and coronary artery calcification.		

4. Discussion

The main findings of the study were:1).In the low Lp(a) group were more likely to have a greater calcification angle. 2).The characteristics of calcification plaque with a greater maximum arc and thicker calcification were more frequently observed in the low Lp(a) group.

Lp(a) is composed of an LDL-like particle in which apoB is bound by a single disulfide bond to apolipoprotein(a) (apo[a]), the pathognomonic component of Lp(a)[10].Elevated Lp(a) is defined as lipid disorders.Multiple studies have reported that elevated plasma concentrations of Lp(a) are strongly and causally linked with an increased risk of atherosclerotic cardiovascular disease (ASCVD)[11,12].Lp(a) contributes to CVD risk through multiple, nonredundant mechanisms. Lp(a) may potentiate atherothrombosis through additional mechanisms such as inflammation through its content of oxidized phospholipids (OxPL)[13].Statins can effectively lower LDL-cholesterol, but have no impact on plasma Lp(a) concentrations.Plasma Lp (a) concentration may partly account for the residual risk of ASCVD in statin-treated patients[14].There was an approximately linear correlation between elevated baseline Lp(a) level and cardiovascular disease risk. In previous study, 150mg/L was used as the median value of the concentration of lipoprotein(a)[8].

Coronary artery calcification developments as atherosclerotic lesions progress. CAC has been strongly established as an independent predictor of cardiovascular adverse events[15].A prospective study show that higher Lp(a) levels are associated with larger annual increases in CAC volume via calcification scoring using computed tomography (CT)[5]. In the study, IVUS detected the calcifications in 91.4% (127 of 139) of lesions. However, the Wang Xiao et al study showed that IVUS detected lesion-associated calcification in 83%[6].The higher prevalence of IVUS calcification in the present study (91% vs 83%) could be due to higher plaque burden in the culprit lesions, whereas there was no difference in the calcified plaque between the two groups.Most studies are lack of plaque burden(calcification angle and thick) measurement, moreover, calcification-scoring via CT has a much lower resolution compared with IVUS[16].Previously studies have suggested that the relationship between calcification and lesion stability is much more complicated[17]. Although calcification is a maker which represents greater atheromatous plaque and more coexistence diseases[18], stable lesions have much more extensive calcification compared to unstable lesions.In addition, spotty(calcification angle < 90°) and thin calcifications represent a lower density calcified lesions[17,18].Furthermore, spotty calcification is associated with more extensive and diffuse coronary atherosclerosis and accelerated disease progression[19].In the present study, we demonstrated that the low Lp(a) group was associated with the incidence of greater calcification arc(166.4°[102.1, 260.5] vs 118.4° [83.4,169.7], P = 0.007) and thicker calcification (40.7% versus 21.2%, P = 0.013).Of note, in the multivariate model, including terms for baseline age,diabetes mellitus, baseline LDL, and baseline statin use, did not change the results. The current analysis might provide a new view to explore the effect of Lp(a) on plaque-stabilizing effects via transforming calcification density in coronary atheroma plaque.

5. Study Limitation

Our study has several limitations.First,this study was a retrospective analysis at a single center,selection bias could not be excluded, and the number of patients was small. Further multicenter and large sample size studies to to prove the results in a larger number of patients. Second,conventional grayscale IVUS was used in the current study, and the optical coherence tomography(OCT) might have improved the diagnostic performance of IVUS.Finally,there have no any vitro experiments that would help support the results of the present study. Further studies are required to improve our understanding of the association between low Lp(a) levels and coronary calcification.

6. Conclusion

In patients with coronary artery disease, low Lp(a) level was associated with high burden of coronary artery calcification. Our findings might provide a new perspective of Lp(a) level on plaque-stabilizing effects in coronary atherosclerotic plaque.

7. Declarations

Acknowledgement: We are grateful for the Cardiology of the Third Xiangya Hospital, Central South University.

Statement of Ethics: The study was approved by local institutional review boards and adheres to the principles of the Declaration of Helsinki.

Conflict of Interest Statement : All authors have no conflict of interest.

Funding Sources: None of any relationship with Profit Organization.

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Figures

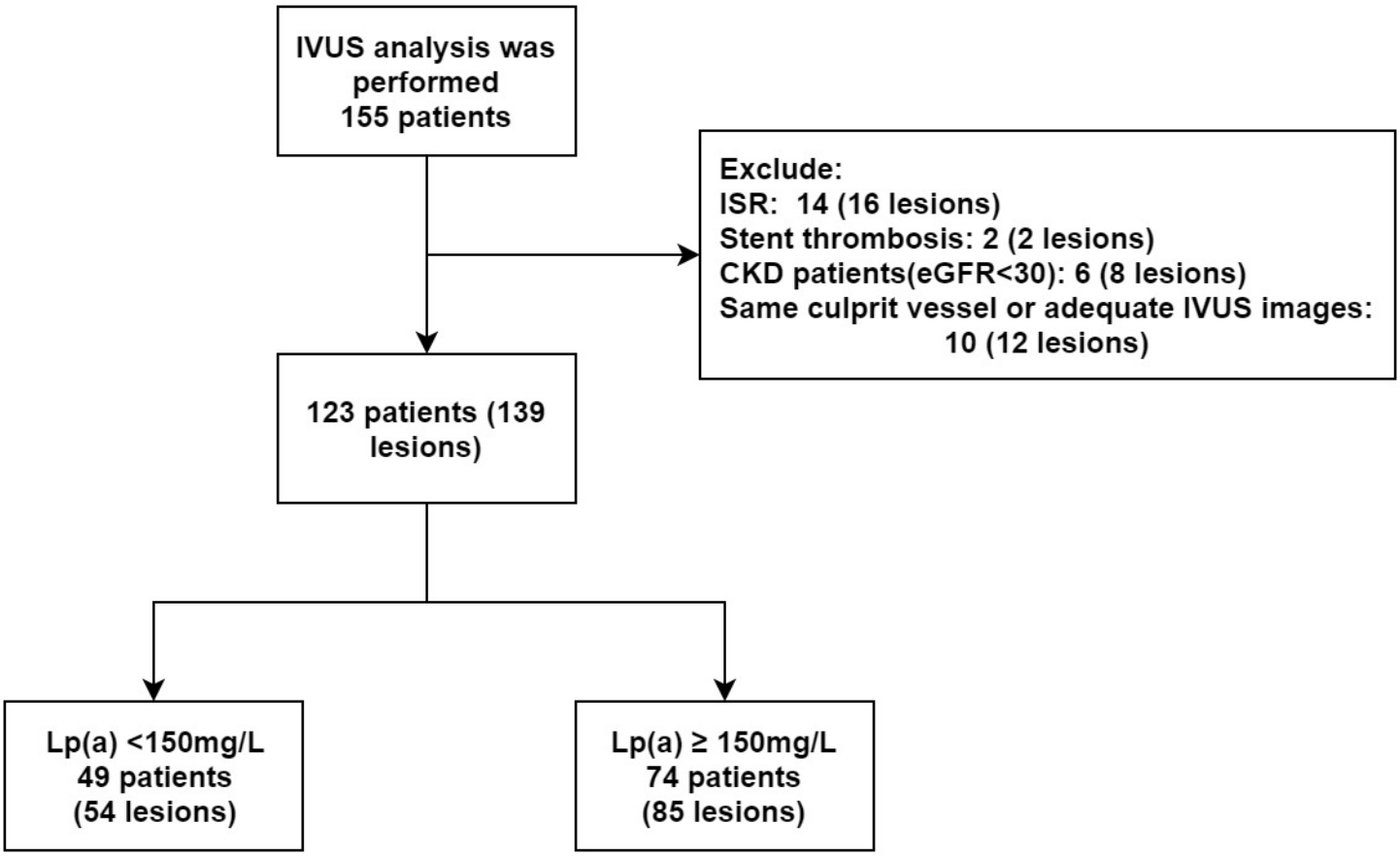

Figure 1

Flow chart of patient selection. ISR:in-stent restenosis;CKD:chronic kidney disease.

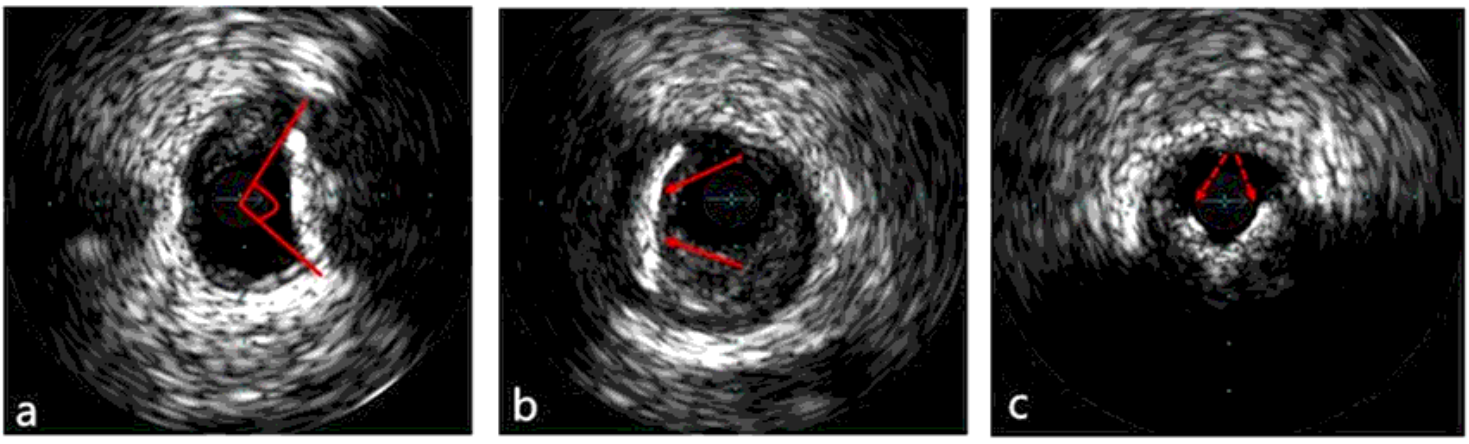

Figure 2

a, The IVUS-detected imaging: shows the maximum calcification angle of calcified plaque. IVUS:intravascular ultrasound; b, The feature of thin calcification(red arrows):smooth hyperechoic leading edge with reverberation; c, Thick calcification(red dotted-arrows): irregular surface without reverberation behind.

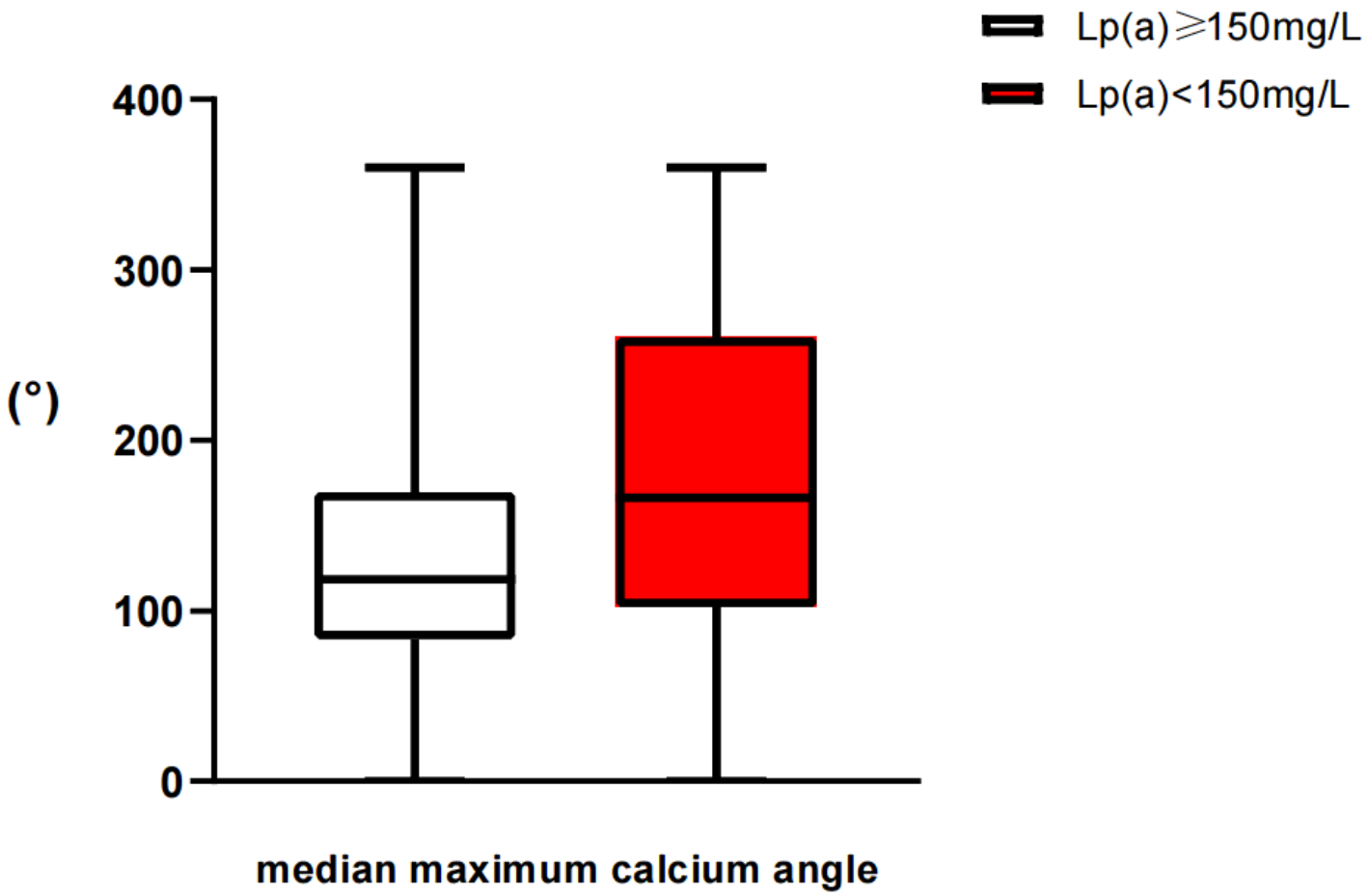

Figure 3

Comparison between the maximum calcification angle in two groups(low Lp(a) group and high Lp(a) group): the median maximum calcification angle was significantly greater in low Lp(a) group(P=0.007).

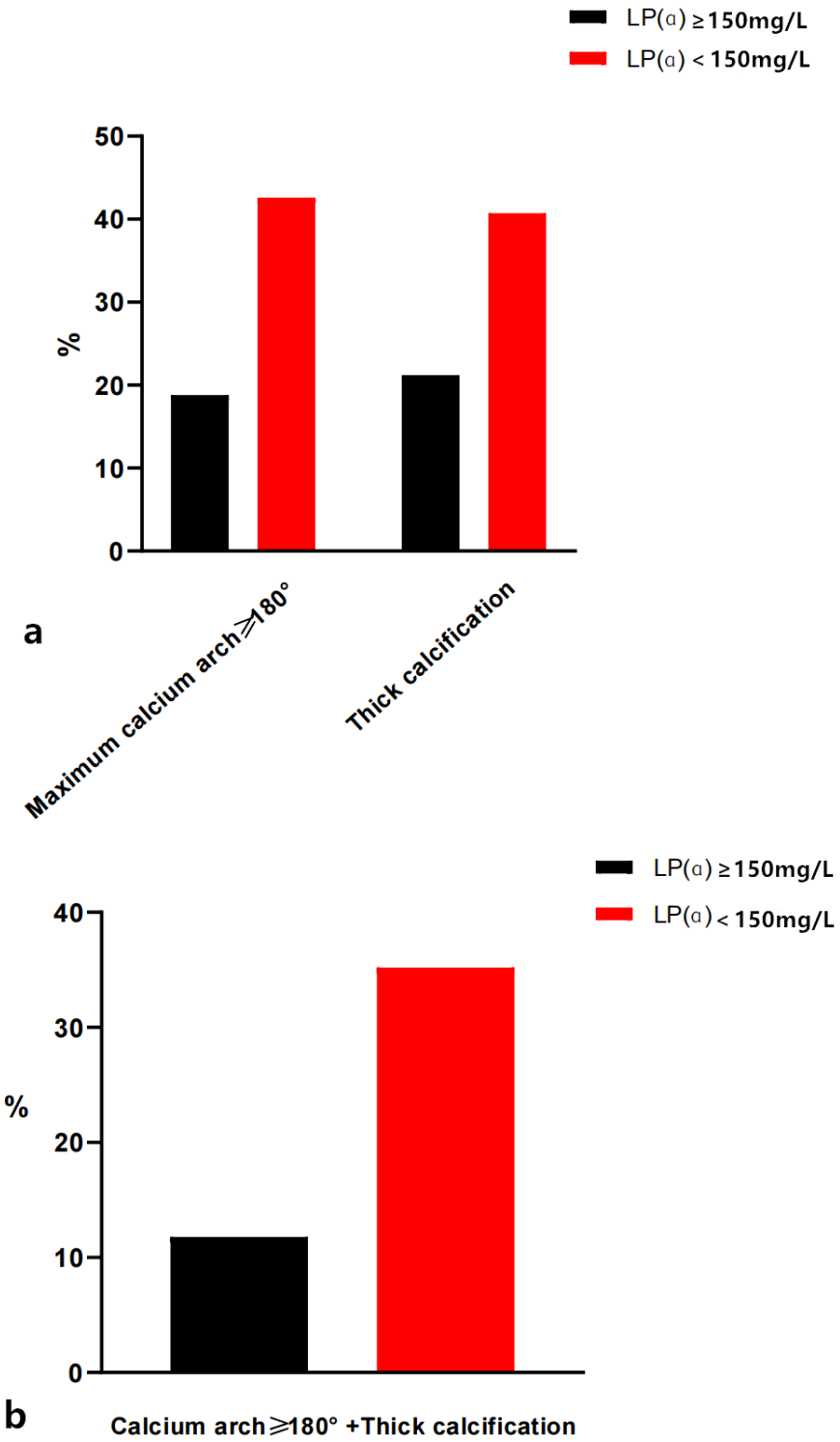

Figure 4

a, Comparison between frequency of maximum calcification angle of ≥180° and thick calcificationas assessed in intravascular ultrasound in two groups; b, The prevalence of maximum calcified angle ≥180° thick calcification was larger in the low Lp(a) group(P=0.001).