ORIGINAL

Lipoprotein (a) is a risk factor of aortic valve calcification in patients with a risk of atherosclerosis

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Abstract : Aortic valve calcification (AVC), which causes aortic stenosis (AS), is more common in elderly persons. Controlling for conventional risk variables did not, however, reduce the incidence of AS. Thus, residual risk factors of AS should be identified. We enrolled 513 patients who underwent coronary angiography with computed tomography because of suspicion of coronary artery disease (CAD) or ruling out of CAD before aortic valve replacement. Calcium volume was calculated with a commercially available application. Conventional and lipid-related risk factors including serum levels of Lp(a) were evaluated for all patients. Calcium volume and Lp(a) levels were significantly higher in patients who underwent aortic valve replacement than in those who did not. A single regression analysis showed that the calcium volume was positively associated with age and the Lp(a) levels and negatively associated with the estimated glomerular filtration rate. No statistical significance was observed for other risk factors, including oxidized low-density lipoprotein, omega-3 fatty acids levels. The multiple regression analysis revealed that age (P<0.001), female sex (P<0.05), Lp(a) (P<0.01), and hemoglobin A1c (P<0.01) were determinants of the calcium volume. The area under the curve in receiver operating characteristic analysis of Lp(a) for implementation of AVR was 0.65 at an Lp(a) cut-off level of 16 mg/dL. In conclusion, the serum Lp(a) level is a potent risk factor of AVC in patients with high risk of atherosclerosis. J. Med. Invest. 70 : 450-456, August, 2023

Keywords **:** *Calcium volume, Aortic stenosis, Lipoprotein*

The development of aortic calcification leads to aortic stenosis (AS), which is one of the most common and serious valve diseases in the elderly population (1). Delayed treatment for AS, including aortic valve replacement (AVR) and transcatheter aortic valve implantation, results in heart failure and sudden cardiac death ; thus, the prevention of aortic valve calcification (AVC) is needed, and clinical risk factors for AVC should be identified (2). According to epidemiological research, AS is linked to common atherogenic risk factors as hypertension, smoking, diabetes, and hyperlipidemia (1). Risk factors for AS overlap with those for vascular atherosclerosis, such as male sex, hypertension, dyslipidemia, diabetes mellitus, and the coexistence of atherosclerosis and valvular calcification (3, 4). AS develops through initial endothelial injury and dysfunction, immune cell infiltration, the myofibroblastic/osteoblastic differentiation of valvular interstitial cells (VICs), and subsequent calcification (5). AS is partially caused by the infiltration of lipids and the production of oxidatively derived products in the aortic valve (6). However, controlling conventional risk factors has not prevented the development of AS ; thus, residual risk factors for AVC should be identified. Lipoprotein (Lp) (a), omega 3- and 6-fatty acids like eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA), and oxidized low-density lipoprotein (LDL) are lipid-related candidates of residual risk factors (6-8). However, the most contributable risk factor for AVC has not been identified. Thus, we investigated the residual risk factors for AVC in patients at a high risk of atherosclerotic disease.

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METHODS

We retrospectively enrolled 2,378 patients who underwent coronary angiography with computed tomography (CT) because of suspicion of coronary artery disease (CAD) or ruling out of CAD before AVR at the Department of Cardiovascular Medicine at Tokushima University Hospital between January 2016 and November 2022. Figure 1 shows the selection of eligible patients and the enrollment process. Young AS patients included those

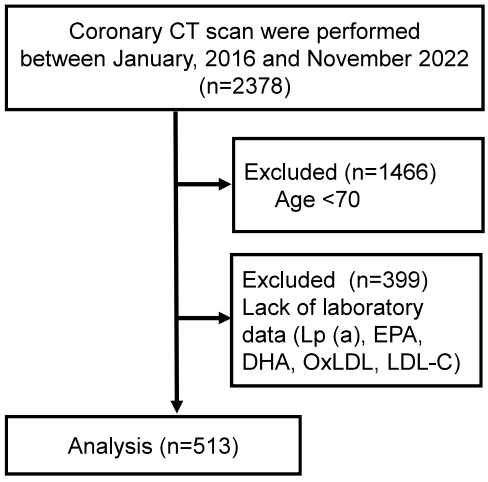

Figure 1. Flow diagram of the study population.

with congenital disorders (e.g., bicuspid aortic valve), many of which lacked laboratory data. To explore the influence of Lp(a) on atherosclerotic aortic valve calcification, we enrolled relatively older patients age 70 and older. Thus, after excluding patients younger than 70 years of age, to eliminate heterogeneity in the study population, as well as patients lacking laboratory data on Lp(a), EPA, oxidized LDL, and LDL-cholesterol (LDL-C), we finally evaluated the data of 513 patients.

We calculated calcium volume using the commercially available 3 mensio Structural Heart 10.1 (Pie Medical Imaging ; Maastricht, The Netherlands), which were expressed as mm^3. We defined aortic valve calcification as calcification within the aortic valve leaflets, aortic annulus, or aortic wall, below the sinotubular junction and excluded calcification of the coronary arteries and mitral annulus from the region of interest (Figure 2). A threshold of 650 HU (Hounsfield Unit) was chosen for AVC assessment in all patients to distinguish between calcium and the contrast agent (9, 10).

Plasma Lp(a) levels were measured via latex agglutination immunoassays at a commercial laboratory (SRL ; Tokyo, Japan). Serum fatty acid composition, including the levels of EPA, DHA, and arachidonic acid (AA), was measured using gas-liquid chromatography at a commercial laboratory (SRL, Tokyo, Japan). Oxidized LDL was measured as malondialdehyde-modified LDL using enzyme-linked immunosorbent assays at a commercial laboratory (SRL). In addition, other conventional biochemical parameters, including LDL-C, triglycerides, high-density lipoprotein cholesterol (HDL-C), hemoglobin A1c (HbA1c), and the serum estimated glomerular filtration rate (eGFR), were measured. All laboratory data were collected from blood tests within 1 year of the date of the CT scan.

Because the study was retrospective, written informed consent was not necessary. The study protocol was approved by the Tokushima University Hospital Ethics Committee in conformity with the Helsinki Declaration (No. 3913).

STATISTICAL ANALYSES

Continuous variables are defined as mean ± standard deviation, whereas categorical variables are expressed as numbers and percentages. The patient characteristics classified by the presence or absence of AVR were compared using the t-test for continuous variables and chi-squared test for discrete variables. After stratification according to age and quartiles of lipid-related biomarkers, differences in clinical characteristics were determined using one-way analysis of variance. A Pearson correlation analysis was performed to determine the association between the calcium volume and biomarkers of AS, including Lp(a). A multiple regression analysis was used to assess the dependence of a set of variables on the calcium volume. A receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off level for implementation of AVR. Calcium volume was natural log transformed due to non-normally distributed parameter for the multiple regression analysis. JMP 10 software (SAS ; Cary, NC, USA) was used to conduct all statistical analyses. $P < 0.05$ was used to determine statistical significance.

RESULTS

A total of 513 individuals highly at risk of atherosclerosis and aged 79.6 ± 6.1 years participated in this study. Representative cases of AVC are shown in Figure 2. The characteristics of all patients stratified based on the presence or absence of AVR are shown in Table 1. The calcium volume and serum Lp(a) level were significantly higher in patients with AVR than in those without AVR. The prevalence of elderly age was higher in patients with AVR, and the prevalence of male sex, and the levels of HbA1c and eGFR were lower in patients with AVR. There was no difference in the serum levels of triglycerides, HDL-C, LDL-C, oxidized LDL, and fatty acid concentrations, including EPA,

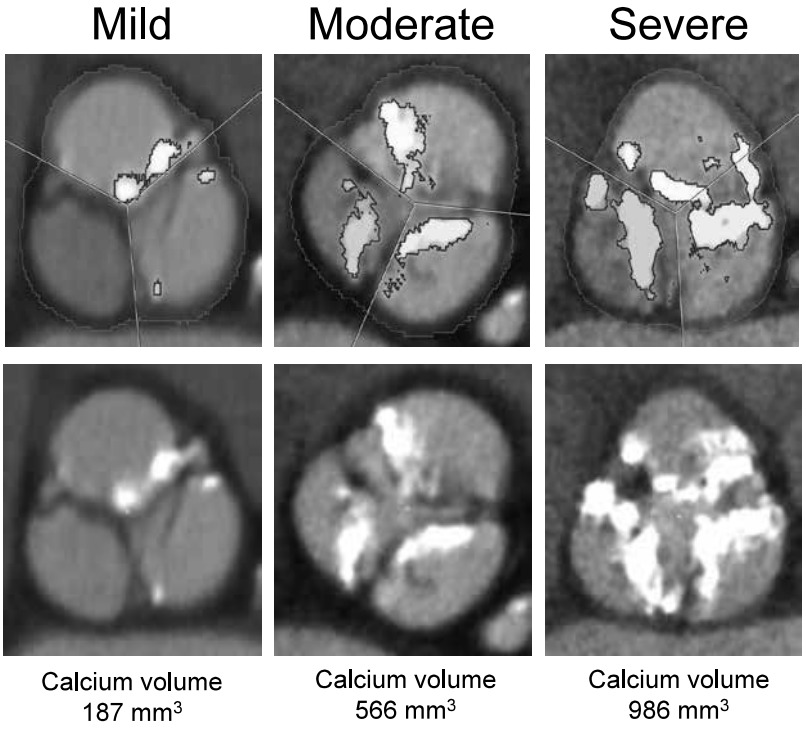

Figure 2. Representative images of mild, moderate, and severe aortic valve calcification.

DHA, and AA, as well as the prevalence of statin use between these two groups.

The level of calcium volume was significantly associated with age and quartiles of Lp(a), but not with the quartiles of oxidized LDL, EPA, and DHA (Figure 3).

A single regression analysis showed that the calcium volume was positively associated with age and the Lp(a) level and negatively associated with the eGFR and HbA1c levels. No statistical significance was observed for other risk factors, including triglyceride, LDL-C, HDL-C, oxidized LDL, EPA, DHA, and AA levels (Table 2).

The multiple regression analysis revealed that age ($P<0.001$), female sex ($P<0.05$), Lp(a) ($P<0.01$), and HbA1c ($P<0.01$) were determinants of the calcium volume, but not eGFR (Table 3).

The area under the curve in ROC analysis of Lp(a) for implementation of AVR was 0.65 at an Lp(a) cut-off level of 16 mg/dL (Figure. 4).

Table 1. Clinical characteristics of patients with/without aortic valve replacement

Variables	All patients	AVR(-)	AVR (+)	P-value
Number of patients	513	421	92	
Age (years)	79.6 ± 6.1	77.9 ± 0.2	87.2 ± 0.5	<0.001
Male sex, n (%)	271 (53%)	244 (58%)	27 (29%)	<0.001
Calcium volume (mm^3)	113 ± 198	40 ± 6	442 ± 13	<0.001
Lipoprotein (a) (mg/dL)	17.2 ± 21.0	14.8 ± 0.9	27.7 ± 2.1	<0.001
eGFR (mL/min/1.73 m^2)	62.0 ± 16.7	64.4 ± 0.7	51.5 ± 1.6	<0.001
HbA1c (%)	6.1 ± 0.7	6.1 ± 0.1	5.8 ± 0.1	<0.01
Triglyceride (mg/dL)	129.6 ± 70.5	131.8 ± 3.4	119.3 ± 7.3	0.12
HDL-C (mg/dL)	61.1 ± 16.4	61.2 ± 0.8	60.7 ± 1.7	0.82
LDL-C (mg/dL)	105.6 ± 28.9	106.7 ± 1.4	100.5 ± 2.9	0.06
Oxidized LDL (U/I)	99.4 ± 34.4	100.5 ± 1.7	94.8 ± 3.6	0.15
Fatty acid concentrations				
EPA (μg/mL)	66.7 ± 46.7	67.9 ± 2.3	61.2 ± 4.8	0.22
DHA (μg/mL)	130.6 ± 40.5	130.1 ± 1.9	133.1 ± 4.2	0.52
AA (μg/mL)	194.9 ± 47.4	194.9 ± 2.3	194.9 ± 4.9	0.99
Medication use				
Statins, n (%)	240 (47%)	190 (45%)	50 (54%)	0.14
Ezetimibe, n (%)	32 (6%)	27 (6%)	5 (5%)	0.70
ACEI/ARB, n (%)	178 (35%)	129 (31%)	49 (53%)	<0.001
β-blockers, n (%)	185 (36%)	154 (37%)	31 (33%)	0.54
Calcium channel blockers, n (%)	269 (52%)	210 (50%)	59 (63%)	0.02
Antidiabetics, n (%)	113 (22%)	94 (22%)	19 (20%)	0.68
Anticoagulants, n (%)	167 (33%)	155 (37%)	12 (13%)	<0.001
Antiplatelets, n (%)	248 (48%)	169 (40%)	79 (85%)	<0.001
Complications				
Coronary artery disease, n (%)	227 (44%)	197 (47%)	30 (32%)	0.01
Diabetes mellitus, n (%)	145 (28%)	126 (30%)	19 (20%)	0.06

Data are presented as the median ± standard deviation.
Abbreviations : AVR ; aortic valve replacement ; eGFR, estimated glomerular filtration rate ; HbA1c, hemoglobin A1c ; TG, triglyceride ; HDL-C, high- density lipoprotein cholesterol ; LDL-C, low- density lipoprotein cholesterol ; EPA, eicosapentaenoic acid ; DHA, docosahexaenoic acid ; AA, arachidonic acid ; ACEI, angiotensin- converting enzyme inhibitors ; ARB, angiotensin II receptor blockers.

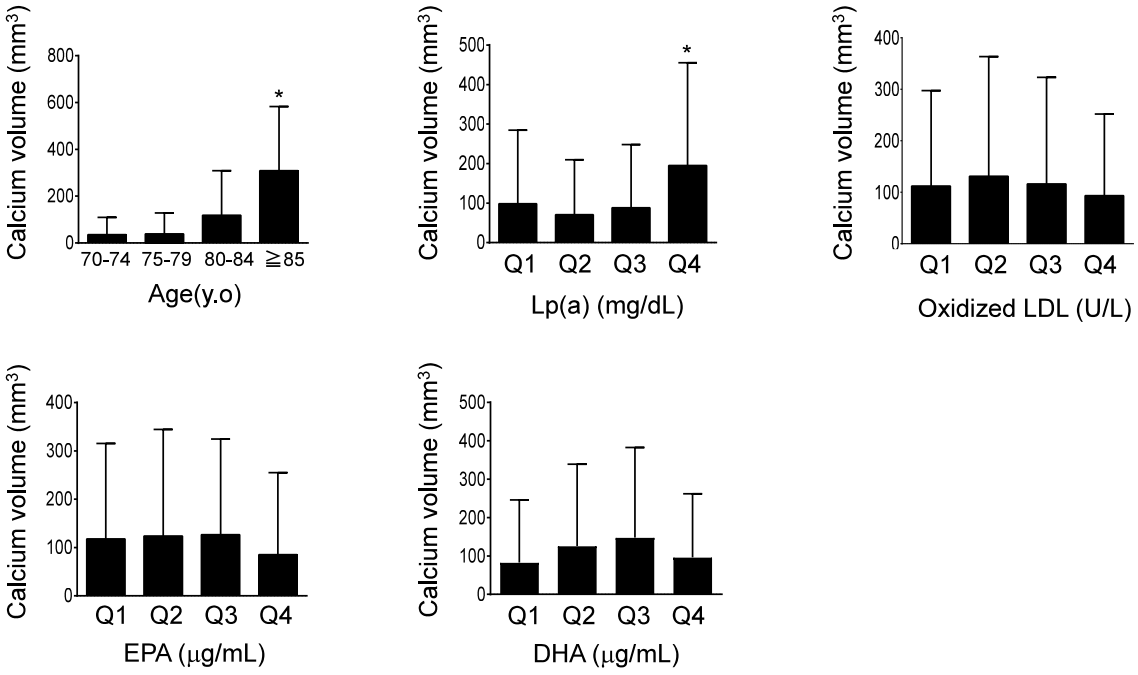

Figure 3. Calcium volume stratified by age groups, and stratified by quartiles of Lp(a), oxidized low-density lipoprotein (LDL), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) ; expressed as mean ± standard deviation (*P < 0.001).

Table 2. Single regression analysis for the determinant association of the calcium volume and risk factors of aortic valve calcification

Variables	β	P-value
Age (years)	18.4	<0.001
Lipoprotein (a) (mg/dL)	2.3	<0.001
eGFR (mL/min/1.73 m^2)	-2.9	<0.001
HbA1c (%)	-28.1	0.02
Triglyceride (mg/dL)	-0.05	0.66
HDL-C (mg/dL)	-0.58	0.27
LDL-C (mg/dL)	-0.47	0.12
Oxidized LDL (U/L)	-0.19	0.45
EPA (μg/mL)	-0.22	0.24
DHA (μg/mL)	0.08	0.70
AA (μg/mL)	0.03	0.86

Abbreviations : eGFR, estimated glomerular filtration rate ; HbA1c, hemoglobin A1c ; HDL-C, high- density lipoprotein cholesterol ; LDL-C, low- density lipoprotein cholesterol ; EPA, eicosapentaenoic acid ; DHA, docosahexaenoic acid ; AA, arachidonic acid

Table 3. Multiple regression analysis for the determinant association of the calcium volume and risk factors of aortic valve calcification

	β (95% CI)	P-value
Age (years)	0.16 (0.13, 0.19)	<.0001
Female sex	0.20 (0.03, 0.36)	0.02
Lipoprotein (a) (mg/dL)	0.01 (0.01, 0.02)	<0.01
eGFR (mL/min/1.73 m^2)	-0.01 (-0.02, 0.01)	0.08
HbA1c (NGSP%)	0.35 (0.13, 0.58)	<0.01

Abbreviations : eGFR, estimated glomerular filtration rate ; HbA1c, hemoglobin A1c

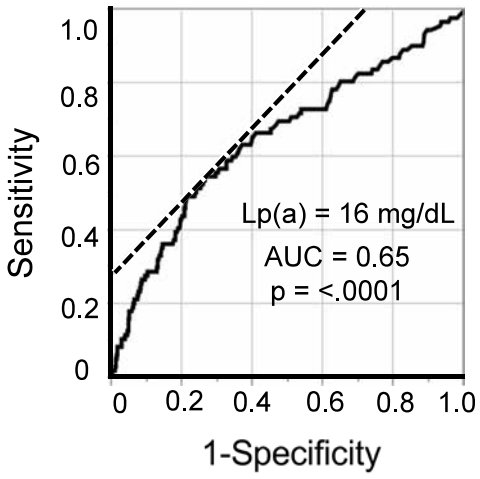

Figure 4. The area under the curve in receiver operating characteristic analysis of Lp(a) for implementation of AVR.

DISCUSSION

The present study demonstrated that the serum levels of Lp(a) contribute to an increase in AVC in patients at a high risk of CAD. The result indicates that a high Lp(a) level is a residual risk factor for AVC in high-risk patients of CAD.

We showed that female sex is a determining factor for calcium volume. AS shows a female predominance in the Japanese registry (11). This study contained many older female AS patients with a high calcium volume. This may be due to the longer life expectancy of women. The skewed prevalence of AS toward older females in our subjects might have influenced the results. In addition, we showed that the use of anticoagulants was lower, but antiplatelet use was higher in patients with than in patients without AVR. The predominance of antiplatelet use in patients with AVR was thought to be related to perioperative use in those with AVR. It has been reported that anticoagulant and antiplatelet use might influence aortic valve calcification (12, 13). Thus, we could not exclude the possibility of effects of anti-coagulant and anti-platelet use on aortic valve calcification, which was a limitation of this cross-sectional study.

Lp(a) has been recognized as a risk factor for CAD based on abundant evidence (14) ; however, whether Lp(a) is a risk factor for AVC has not been established, although some papers have reported that the serum Lp(a) level is a risk factor for AVS (7). A genome-wide association study showed that *LPA* single nucleotide polymorphisms were associated with aortic valve calcium, as evaluated by CT (15). The ASTRONOMER trial showed that elevated Lp(a) levels were associated with the progression of AS, as well as the need for AVR (16). Thus, Lp(a) could be a novel biomarker for AS and a target for the prevention of AS.

The AVS process is as follows : the aortic valve is exposed to powerful mechanical/shear stress according to the cardiac output, leading to valvular endothelial cell (VEC) damage, following lipoprotein infiltration, including LDL and Lp(a). Damaged VECs evoke the extravasation of immune cells into the interstitium of the valve leaflets and a decreased endothelial nitric oxide synthase (eNOS) activation. Reduced eNOS induces the production of reactive oxygen species, which stimulate the oxidation of infiltrated lipids into oxidized LDL and oxidized phospholipids, resulting in transformation into lysophosphatidylcholine, promoting VIC apoptosis and the release of inflammatory cytokines, such as tumor necrosis factor-α, interleukin (IL)-6, IL-1β, and the receptor activator of nuclear factor kappa B^5. These cytokines activate inflammatory cells, including macrophages and T cells, and lead to the osteogenic differentiation of VICs, resulting in AVC (17).

Lp(a) is a plasma lipoprotein composed of an LDL-like particle containing cholesteryl esters and triglycerides as a central core, which was ringed by many particles, including phospholipids and free cholesterol. Lp(a) also contains a single apo B-100 molecule linked via a single disulfide bond to a large polymorphic glycoprotein apo (a) (18). The lipoprotein component apo (a) can bind to exposed fibrin on areas of injured endothelium subjected to mechanical stress and can easily accumulate in aortic valve leaflets, leading to a substrate of AVC (19).

In addition, the lysine site of Kringle domain IV type 10 on Lp(a) is where Lp(a) covalently binds to oxidized phospholipids (oxPLs) in the plasma, contributing to the progression of AVC (20). oxPLs on Lp(a) play a pivotal role in the calcification of VICs by increasing IL-6 and bone morphogenetic protein 2. Thus, Lp(a) is susceptible to oxidation and inflammatory and proatherogenic processes (21). The direct effect of oxPL on Lp(a) leading to valvular inflammation may explain the association between a high Lp(a) level and AVC.

n-3 polyunsaturated fatty acids (PUFAs) are another candidate for preventing aortic calcification (8). Human stenotic aortic valves have been found to have lower amounts of n-3 PUFAs, and n-3 PUFA therapy has been shown to reduce AVC in mouse models, improving the hemodynamics of the aortic valve. A genetic variation in the fatty acid desaturase 1/2 locus, which is responsible for manufacturing the essential enzyme for synthesizing PUFAs has been linked to AS by genome-wide association and Mendelian randomization studies (22). It has been proposed that the proresolving lipid mediator resolvin E1, derived from the n-3 PUFA EPA, exerts protective effects against VIC calcification and valvular inflammation through its receptor ChemR23 (8). In addition, higher systemic levels of AA, having pro-inflammatory properties, are associated with AVC (23). However, our results indicate that the serum levels of n-3 PUFAs and n-6 PUFAs did not contribute to AVC. Furthermore, oxidized LDL is associated with pro-inflammatory and growth-stimulating properties and is involved in the initiation and progression of atherosclerosis (6, 24). A previous study revealed that oxidized LDLs are present in AS valves and colocalize with calcium nodules and inflammatory infiltrates (25). Additionally, oxidized LDL-C can easily be taken up by macrophages. However, our results indicate that the serum levels of oxidized LDL did not contribute to AS. This may be due to a discrepancy between the serum level of oxidized LDL and tissue levels of oxidized LDL.

Lp(a) is a genetically determined by LDL particle ; however, a reduction in Lp(a) is recommended to reduce cardiovascular events (26). It is estimated that one in seven cases of AS could be prevented by marked Lp(a) reduction (27). Clinical studies that used intensive lipid-lowering therapy with atorvastatin did not halt the progression of calcific AS or induce its regression (28). Additionally, proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors lowered Lp(a) concentrations by approximately 25%, although clinical trials remain underway (NCT04968509) (29, 30). Niacin also reduces Lp(a) levels by approximately 20%. Although no proven effect on cardiovascular endpoints was revealed in two major studies (31, 32), niacin could be a currently available agent in Japan. Inclisiran, a small interfering RNA (siRNA) that inhibits the hepatic synthesis of the PCSK9 protein (33), the antisense oligonucleotide AKCEA-APO(a)-LRx (Pelacarsen) that reduces Lp(a) levels by impairing the synthesis of apo(a) (34), and siRNA against apo(a) under phase 2 trials (NCT04270760) may contribute to a potential strategy for preventing the progression of AS. The development of Lp(a)-lowering agents is awaited, and randomized controlled studies are needed.

CONCLUSION

The serum Lp(a) level is a potent risk factor for AVC in patients at a high risk of atherosclerosis. Lowering Lp(a) levels may be a potential strategy for the prevention of AVC. Intervention studies involving methods of lowering Lp(a) levels are needed to confirm the results.

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