



Effect of moderate-intensity statin on carotid intraplaque neovascularization of coronary artery disease: a retrospective cohort study

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Background: Statin treatment can reduce atherosclerotic plaque as detected via invasive intracoronary methods. However, few studies have evaluated the effect of moderate-intensity statin therapy on carotid intraplaque neovascularization (IPN) using semiquantitative indices. This study thus aimed to assess the effect of statin on the carotid IPN of coronary artery disease with contrast-enhanced ultrasound (CEUS).

Methods: In this noncontrol, retrospective, cohort study, 35 inpatients who underwent coronary angiography, serial CEUS, and laboratory evaluations were consecutively enrolled from June 2020 to December 2022 at the Department of Cardiology, Chinese PLA General Hospital. All patients were administered moderate-intensity statin during serial CEUS, and continuous and categorical assessment of IPN and maximum plaque height (MPH) of carotid plaque was performed. Patients with a target low-density lipoprotein cholesterol (LDL-C) <1.8 mmol/L at 12-month follow-up were compared with those who did not reach the LDL-C 1.8 mmol/L target.

Results: From baseline to 12-month follow-up, there were significant differences in the LDL-C levels between patients (2.71 ± 1.29 vs. 1.35 ± 0.83 mmol/L), those with 12-month follow-up LDL-C <1.8 mmol/L (2.58 ± 1.24 vs. 1.08 ± 0.52 mmol/L), and those with 12-month follow-up LDL-C ≥ 1.8 mmol/L (3.24 ± 1.44 vs. 2.56 ± 0.85 mmol/L) all P values <0.05, with decreases of 41%, 49%, and 11% from baseline, respectively. The mean MPH (12 months to baseline) decreased from 2.47 ± 0.63 to 2.22 ± 0.60 mm (P<0.05), and the IPN also decreased from 1.15 ± 0.62 to 0.58 ± 0.56 , representing a reduction of 0.57 ± 0.59 from baseline (P<0.001). In the LDL-C <1.8 mmol/L patients, there were significant differences between baseline and 12 months in MPH (2.37 ± 0.56 vs. 2.03 ± 0.52 mm; P<0.05) and IPN (1.32 ± 0.77 vs. 0.54 ± 0.63 ; P<0.05) compared with those with a follow-up LDL-C ≥ 1.8 mmol/L. Patients with a follow-up LDL-C <1.8 mmol/L, compared with those with a follow-up LDL-C ≥ 1.8 mmol/L, showed a significantly greater reduction in MPH (-0.34 ± 0.46 vs. -0.13 ± 0.39 ; P<0.05) and IPN (-0.79 ± 0.63 vs. -0.57 ± 0.79 ; P<0.05). Additionally, patients with carotid IPN regression showed a higher percent change in LDL-C compared with those without carotid IPN regression (-53.31 ± 23.20 vs. -29.55 ± 19.47 ; P<0.05).

Conclusions: Controlling the LDL-C to <1.8 mmol/L under moderate-intensity statin can stabilize and reduce carotid IPN as detected by the semiquantitative noninvasive CEUS.

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Introduction

Coronary artery disease (CAD) and consequent cardiovascular events (CVEs) are the leading causes of morbidity and mortality worldwide, and there is a positive correlation between CAD and blood cholesterol levels (1). Statin therapy is the treatment mainstay for reducing low-density lipoprotein cholesterol (LDL-C) and further decreasing the risk of CVEs (2). The relevant guidelines recommend high-intensity statin therapy for reducing the level of LDL-C to a target level of <1.8 mmol/L (70 mg/mL) and a $\geq 50\%$ reduction from baseline for patients with high-risk atherosclerotic cardiovascular disease (3). Recent clinical studies have shown that more intensive lipid-lowering therapy for high-risk patients can further reduce the incidence of CVEs, but these results were not derived from a Chinese population (4,5).

Decreasing the LDL-C level can halt the progression of coronary plaque in patients with CAD (6). It is important to reduce the LDL-C level in patients with premature CAD with carotid plaque. Previous studies have demonstrated that the regression of coronary plaque is associated with the lowering LDL-C levels and is a key indicator for evaluating the effect of statin therapeutics as detected by coronary angiography (CAG), intravascular ultrasound (IVUS), or optical coherence tomography (OCT) (7). However, these intracoronary methods are invasive, expensive, and increase the incidence of contrast-induced nephropathy and the clinical burden of patients. Atherosclerosis is a systemic disease that can occur in some vessels such as the coronary artery and carotid artery (8). Intraplaque neovascularization (IPN) is positively associated with plaque vulnerability (9). Most recently available studies support contrast-enhanced ultrasound (CEUS) as capable of noninvasively assessing IPN; in turn, IPN can be used to indicate the progression and regression of atherosclerotic plaque, predict future CVEs, and reclassify patients with high cardiovascular risk (10-13).

Research has also shown that statin treatment can reduce neovascularization in atherosclerotic plaque according to

CEUS quantitative evaluation (14). Only a few studies have evaluated the effect of moderate-intensity statin therapy on carotid IPN using semiquantitative indices, and of these studies, none have included patients with severe CAD from a Chinese populations. Thus, in this study, we examined the potential role of noninvasive CEUS to semiquantitatively assess the impact of moderate-intensity statin therapy on carotid IPN in Chinese patients with CAD. We present this article in accordance with the STROBE reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1104/rc>).

Methods

Study design and population

In this single-center retrospective cohort study, 108 patients with angina symptoms who had undergone CAG and serial CEUS and whose baseline and follow-up laboratory evaluations [including lipid profile and LDL-C:high-density lipoprotein cholesterol (HDL-C)] were available were screened from June 2020 to December 2022 at the Department of Cardiology, Chinese PLA General Hospital. After being diagnosed with severe CAD via CAG, each enrolled patient was administered moderate-intensity lipid-lowering therapy including rosuvastatin calcium tablets (10 mg/day) or atorvastatin calcium tablets (20 mg/day) according to the 2023 Chinese Guidelines for Lipid Management (15); only those patients who adhered to their medication regimen were included. All patients underwent phone visits at 1, 3, and 6 months and clinical visits at months 12.

The full set of inclusion criteria for patients were as follows: (I) at least 18 years of age, (II) absence of contraindication to CAG and diagnosed with severe CAD via CAG due to a change in angina symptoms, (III) at least one carotid atherosclerotic plaque, and (IV) a period of CEUS examination of at least 12 months.

Severe CAD was defined as stenosis $\geq 50\%$ of the left main stem or that of $\geq 70\%$ in the proximal to mid left anterior

descending artery, proximal left circumflex, or proximal to mid right coronary artery as detected by CAG (16).

The exclusion criteria for patients were as follows: (I) any statin therapy or administration of other lipid-lowering drugs (such as niacin or fibric acid derivatives) before diagnosis of severe CAD; (II) administration of combined ezetimibe-statin lipid-lowering therapy during the serial CEUS; (III) a coexisting condition that reduced life expectancy by at least 2 years; (IV) a history of percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG); (V) serious heart, hepatic, or kidney diseases; (VI) unexplained high elevation in creatine kinase level (>3 times the upper limit of normal) not related to myocardial infarction; (VII) complete absence of clinical laboratory and CEUS data at baseline or follow-up; (VIII) a history of carotid endarterectomy and myocardial infarction, stroke, or transient ischemic attack; and (IX) participation in other clinical trials.

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Research Ethics Committee of Chinese PLA Hospital (No. S2021-679-02). Individual consent for this retrospective analysis was waived.

Carotid CEUS protocol and analysis

All patients underwent standard carotid ultrasound and CEUS at baseline before initiation of moderate-intensity statins, and these same examinations were performed after at least 12 months of treatment. Standard carotid ultrasound and CEUS were performed by an experienced physician blinded to the patients' characteristics using the Acuson S2000 ultrasound system (Siemens Healthineers, Mountain View, CA, USA) at a transducer frequency of 4–9 MHz. Before the second examination, the physician reviewed the previous examination imaging of all patients to ensure that the assessed plaque was the same as the previously assessed plaque. The protocol and analysis of the carotid CEUS have been previously described (17). Briefly, maximum plaque height (MPH), was defined as the maximum distance from the intima-lumen interface to the media-adventitia interface after the vessel walls of both the left and right carotid arteries were compared; meanwhile, atherosclerotic plaques were defined as a focal structure encroaching into the arterial lumen by >0.5 mm or a thickness of the surrounding intima-media complex $>50\%$ or demonstrating a thickness >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface. In each patient, we selected

atherosclerotic plaques for CEUS-IPN analyses. IPN was identified according to the appearance and distribution of microbubbles in each plaque. Native raw data (baseline and follow-up) were stored in the scanner's hard drive for later analysis, and the cine clips were later assessed offline. Intraplaque contrast enhancement was classified as follows: IPN grade 0, no visible microbubbles within the plaque; IPN grade 1, mild microbubbles confined to the shoulder and/or adventitial side of the plaque; IPN grade 2, linear microbubbles that extended into the plaque; and IPN grade 3, extensive microbubbles throughout the plaque (Figure 1) (17). The scans were analyzed by two experienced physicians in CEUS (L.R. and X.F., each with more than 10 years of experience in vascular CEUS), who were blinded to the clinical information and each other's results. Any inconsistent gradings were discussed, and the final result was determined via discussion between both physicians consensus. Cohen's Kappa was used in a subset of 50 carotid plaques to assess intraobserver and interobserver agreement. For the grade of neovascularization, intraobserver and interobserver agreement was 0.81 and 0.83 (k coefficient), respectively, both of which corresponded with good confidence.

Study endpoint

The primary endpoint was a change in IPN on serial CEUS as expressed by categorical variables and continuous variables. The second endpoint was a change in MPH on serial CEUS and the occurrence of CVEs, including coronary revascularization, nonfatal myocardial infarction, heart failure, stroke, or cardiac death.

Sample size calculation

A previous study reported that strict controlling of LDL-C using very high-intensity statin resulted in the regression of coronary atherosclerosis in 78.1% of patients (6). With an α value of 0.1, a power of 0.8, and a noninferiority difference of -0.15 , it was determined that 31 participants from a population of 108 patients were needed.

Statistical methods

All data analyses were performed with SPSS 20.0 software (IBM Corp.). Categorical variables are described as frequencies (percentage). Continuous variables that were normally distributed are expressed as the mean and

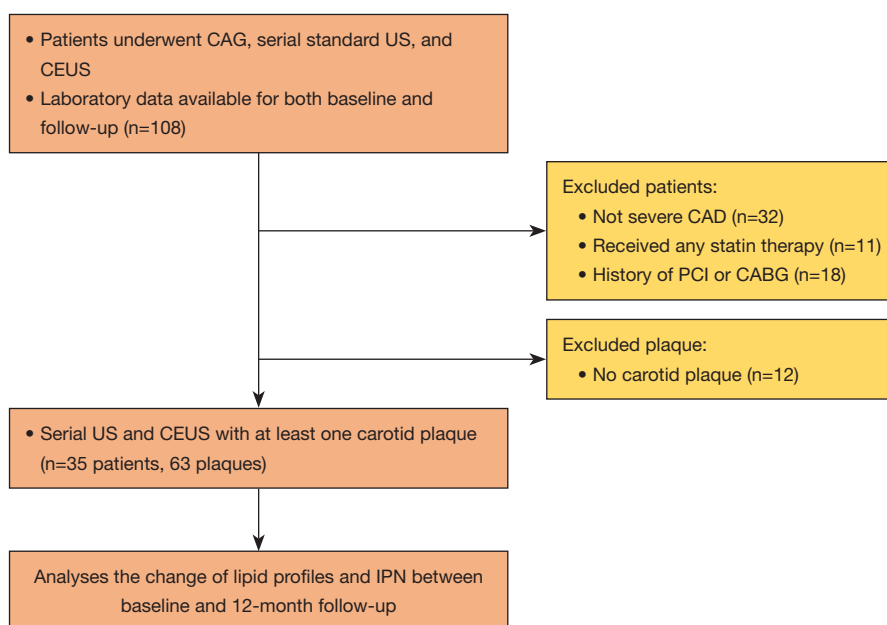


Figure 1 Enrollment of the study population. CAG, coronary angiography; US, ultrasound; CEUS, contrast-enhanced ultrasound; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; IPN, intraplaque neovascularization.

standard deviation (SD), while those that were nonnormally distributed are reported as the median and interquartile range (IQR). Differences between categorical variables were analyzed with the Chi-squared test, while differences between continuous variables were analyzed with the Wilcoxon rank-sum test or *t*-test. A paired sample *t*-test or a paired sample Wilcoxon rank-sum test was used to compare measures from baseline to those at 12-month follow-up within-groups. Univariate and multivariate regression analyses were applied to identify factors associated with carotid IPN regression. All statistical tests were two-tailed, with $P < 0.05$ being considered statistically significant.

Results

Patient population

A total of 108 patients were initially screened in our study. Patients were excluded for the following reasons: without severe CAD ($n=32$), a history of any statin therapy ($n=11$), a history of PCI or CABG ($n=18$), and without carotid plaque ($n=12$). Ultimately, 35 patients (comprising 63 plaques) with at least one carotid plaque according to CEUS were enrolled into this study with a scan period of at least 1 year (median: 12.0 months, IQR: 12.0–12.0 months)

(Figure 1). All patients were treated with dual-antiplatelet therapy and β -blocker inhibitor. There were no contraindications for CAG or CEUS in any patients. The baseline clinical characteristics of the 35 patients are displayed in Table 1. The mean age was 49.54 (SD: 10.77) years, and 82.9% of the patients were male; 37.1%, 22.9%, and 17.1% of patients had a history of hypertension, diabetes mellitus, and a family history of CAD, respectively; and 16 patients had a history of smoking or had quit smoking. The mean LDL-C level at baseline was 2.71 (SD: 1.29) mmol/L. Compared with patients with a follow-up LDL-C (F/U LDL-C) ≥ 1.8 mmol/L, those with a F/U LDL-C < 1.8 mmol/L were more likely to be younger, male, and have a history of hypertension or diabetes mellitus or a family history of CAD (all P values > 0.05). Three patients with F/U LDL-C ≥ 1.8 mmol/L underwent revascularization (PCI), and none of the patients with F/U LDL-C < 1.8 mmol/L experienced CVEs.

Changes in lipid profile

The changes of lipid parameters from baseline to 12 months are summarized in Tables 2,3. At 12 months, the mean LDL-C level was 1.35 (SD: 0.83) mmol/L, representing a

Table 1 Baseline characteristics of patients divided according to F/U LDL-C level

Characteristics	Total (n=35)	F/U LDL-C <1.8 mmol/L (n=28)	F/U LDL-C ≥1.8 mmol/L (n=7)	P value
Age (years), mean (SD)	49.54 (10.77)	48.57 (11.74)	53.43 (3.95)	0.293
Men, n (%)	29 (82.9)	25 (89.3)	4 (57.1)	0.079
BMI (kg/m ²), mean (SD)	26.11 (3.58)	26.12 (3.91)	26.09 (1.95)	0.983
History of hypertension, n (%)	13 (37.1)	10 (35.7)	3 (42.9)	>0.99
History of diabetes mellitus, n (%)	8 (22.9)	6 (21.4)	2 (28.6)	0.648
History of smoking, n (%)	16 (45.7)	15 (53.6)	1 (14.3)	0.200
Family history of CAD, n (%)	6 (17.1)	6 (21.4)	0	0.311
Moderate-intensity statin therapy, n (%)				0.594
Atorvastatin (20 mg)	14 (40.0)	11 (39.3)	3 (42.9)	
Rosuvastatin (10 mg)	21 (60.0)	17 (60.7)	4 (57.1)	
Lipid profile, mean (SD)				
TC (mmol/L)	4.12 (1.48)	3.97 (1.42)	4.73 (1.66)	0.226
TG (mmol/L)	1.52 (0.61)	1.43 (0.57)	1.90 (0.67)	0.066
Apo A-I (mmol/L)	1.18 (0.26)	1.14 (0.22)	1.33 (0.37)	0.091
Apo B (mmol/L)	0.77 (0.31)	0.75 (0.32)	0.84 (0.27)	0.495
Apo B/A-I ratio	0.70 (0.36)	0.71 (0.37)	0.67 (0.31)	0.836
HDL-C (mmol/L)	1.04 (0.30)	1.03 (0.30)	1.08 (0.33)	0.683
LDL-C (mmol/L)	2.71 (1.29)	2.58 (1.24)	3.24 (1.44)	0.234

F/U, follow-up; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; BMI, body mass index; CAD, coronary artery disease; TC, total cholesterol; TG, triglyceride; Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol.

decrease of 41% from baseline ($P<0.05$). Compared with patients with F/U LDL-C ≥ 1.8 mmol/L, those with F/U LDL-C <1.8 mmol/L exhibited a greater percent change in apolipoprotein (Apo) A-I, a lower Apo B:Apo A-I ratio, and lower Apo B and LDL-C levels (all P values <0.05).

Impact of statins on the regression of carotid plaque

All patients safely underwent serial CEUS. *Table 4* shows the serial changes in CEUS variables. The mean MPH decreased from 2.47 mm at baseline to 2.22 mm in all patients ($P<0.05$), and there were significant differences in the change of MPH between the two groups ($P<0.05$). The mean IPN also decreased from 1.15 to 0.58, representing a reduction of 0.57 from baseline ($P<0.001$). There was an also significant difference in the change of the IPN between the two groups according to both continuous and categorical variables (all P values <0.05). On baseline CEUS, the distribution of IPN grades was as follows: 3 (8.6%)

patients with IPN grade 0, 17 (48.6%) patients with IPN grade 1, 13 (37.1%) patients with IPN grade 2, and 2 (5.7%) patients with IPN grade 3 (*Figure 2*). After 12 months, IPN regressed in 24 (69%) patients (*Figure 3*). In the univariate analysis, variables associated with carotid IPN regression were percent change in LDL-C level (beta: -0.071 ; $P=0.01$) and percent change in LDL-C:HDL-C ratio (beta: -0.033 ; $P=0.03$). Only percent change in LDL-C was associated with carotid IPN regression in the multivariate analysis that was adjusted according other clinical characteristics (beta: -0.177 ; $P=0.03$) (*Tables S1,S2*). Patients with carotid IPN regression showed a higher percent change in LDL-C compared with patients without carotid IPN regression (-53.31 ± 23.20 vs. -29.55 ± 19.47 ; $P<0.05$), while there was no difference in the percent change of HDL-C between these two groups in *Figure 4*. The lowest LDL-C reduction was 21% in a 58-year-old man without any clinical risk factors, for whom the baseline and 12-month LDL-C levels were 1.88 and 1.48 mmol/L, respectively.

Table 2 Lipid parameters results from baseline to 12 months

Characteristics	Total (n=35)			F/U LDL-C <1.8 mmol/L (n=28)			F/U LDL-C ≥1.8 mmol/L (n=7)			P value [†]
	After 12 months, mean (SD)	Change from baseline to 12 months (95% CI) [†]	Percent change (%)	After 12 months, mean (SD)	Change from baseline to 12 months (95% CI) [†]	Percent change (%)	After 12 months, mean (SD)	Change from baseline to 12 months (95% CI) [†]	Percent change (%)	
TC (mmol/L)	2.83 (1.00)	-1.30 (-1.84 to -0.76)	-25	2.51 (0.67)	-1.39 (-2.05 to 0.73)	-31	3.90 (1.42)	-0.82 (-2.18 to 0.53)	-10	0.104
TG (mmol/L)	1.30 (0.58)	-0.23 (-0.41 to -0.05)	-10	1.32 (0.61)	-0.12 (-0.31 to 0.07)	-6	1.26 (0.31)	-0.64 (-1.16 to -0.12)	-28	0.180
Apo A-I (mmol/L)	1.37 (0.30)	0.20 (0.09 to 0.30)	20	1.36 (0.29)	0.22 (0.10 to 0.34)	24	1.27 (0.47)	-0.05 (-0.28 to 0.17)	-5	0.047
Apo B (mmol/L)	0.47 (0.20)	-0.30 (-0.41 to -0.18)	-31	0.42 (0.15)	-0.32 (-0.46 to -0.17)	-37	0.69 (0.19)	-0.15 (-0.38 to 0.08)	-12	0.046
Apo B/A-I ratio	0.36 (0.16)	-0.34 (-0.47 to -0.21)	-38	0.32 (0.13)	-0.38 (-0.53 to -0.22)	-45	0.63 (0.24)	-0.05 (-0.22 to 0.13)	-2	0.001
HDL-C (mmol/L)	1.21 (0.33)	0.17 (0.06 to 0.27)	20	1.17 (0.29)	0.15 (0.03 to 0.27)	20	1.44 (0.55)	0.36 (-0.13 to 0.85)	39	0.301
LDL-C (mmol/L)	1.35 (0.83)	-1.36 (-1.84 to -0.88)	-41	1.08 (0.52)	-1.44 (-2.02 to -0.86)	-49	2.56 (0.85)	-0.68 (-1.64 to 0.28)	-11	0.008

[†], P<0.05 according to the paired t-test between baseline and 12-month follow-up; [†], analysis of variance was used to analyze lipid parameters. To convert from milligrams per deciliter (mg/dL) to millimoles per liter (mmol/L) multiply by 0.0259 for cholesterol, 0.0113 for triglyceride, and 0.01 for apolipoproteins. SD, standard deviation; CI, confidence interval; F/U, follow-up; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol.

Table 3 Number of patients with the target LDL-C lowering

Target LDL-C lowering	Total (n=35), n (%)	F/U LDL-C <1.8 mmol/L (n=28), n (%)	F/U LDL-C ≥1.8 mmol/L (n=7), n (%)
≥50%	12 (34.3)	12 (42.9)	0
30–49%	12 (34.3)	9 (32.1)	3 (42.9)
<30%	11 (31.4)	7 (25.0)	4 (57.1)

LDL-C reduction <30%: 11 patients, including 7 patients with lowered target LDL-C and baseline LDL <1.8 mmol/L, 3 patients without lowered target LDL-C and baseline LDL ≥1.8 mmol/L, and 1 patient with lowered target LDL-C but baseline LDL ≥1.8 mmol/L. LDL-C, low-density lipoprotein cholesterol; F/U, follow-up.

Table 4 Baseline and follow-up CEUS result

Characteristics	Total (n=35)	F/U LDL-C <1.8 mmol/L (n=28)	F/U LDL-C ≥1.8 mmol/L (n=7)	P value
Maximum plaque height (mm)				
Baseline				
Mean (SD)	2.47 (0.63)	2.37 (0.56)	2.86 (0.77)	0.086
Median (IQR)	2.30 (2.00 to 2.80)	2.20 (2.00 to 2.75)	2.80 (2.30 to 3.70)	
After 12 months				
Mean (SD)	2.22 (0.60)	2.03 (0.52)	2.73 (0.54)	0.006
Median (IQR)	2.10 (1.70 to 2.70)	1.90 (1.60 to 2.40)	2.70 (2.20 to 3.00)	
Nominal change				
Mean (SD)	-0.24 (0.42)	-0.34 (0.46)	-0.13 (0.39)	
Median (95% CI)	-0.20 (-0.39 to -0.10)	-0.35 (-0.51 to -0.16)	-0.10 (-0.49 to 0.24)	
P value compared with baseline	0.004	0.001	0.422	
Intraplaque neovascularization				
Baseline				
Mean (SD)	1.15 (0.62)	1.32 (0.77)	1.71 (0.49)	0.160
Median (IQR)	1.00 (1.00 to 1.50)	1.00 (1.00 to 2.00)	2.00 (1.00 to 2.00)	
After 12 months				
Mean (SD)	0.58 (0.56)	0.54 (0.63)	1.14 (0.38)	0.048
Median (IQR)	0.50 (0.00 to 1.00)	0.00 (0.00 to 1.00)	1.00 (1.00 to 1.00)	
Nominal change				
Mean (SD)	-0.57 (0.59)	-0.79 (0.63)	-0.57 (0.79)	
Median (95% CI)	-0.50 (-0.77 to -0.37)	-0.50 (-1.03 to -0.54)	-0.67 (-1.30 to 0.16)	
P value compared with baseline	<0.001	<0.001	0.103	
Intraplaque neovascularization				
Baseline, n				
Grade 0–1	20	18	2	
Grade 2–3	15	10	5	
After 12 months, n				
Grade 0–1	32	26	6	
Grade 2–3	3	2	1	
P value compared with baseline	0.001	0.009	0.103 (Fisher)	
Number of regressions, n [%]	24 [69]	19 [68]	5 [71]	

Imputed change in parameters for the whole cohort is expressed as the least square mean (95% CI). CEUS, contrast-enhanced ultrasound; F/U, follow-up; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; IQR, interquartile range; CI, confidence interval.

Discussion

We conducted a noncontrol cohort study using CEUS to semiquantitatively evaluate the effect of moderate-intensity statin therapy on serial changes of carotid MPH and IPN in Chinese patients with severe CAD. In our study, 12-month moderate-intensity statin treatment significantly decreased the mean LDL-C levels to 1.35 mmol/L (−41% from baseline) and reduced the carotid MPH and IPN as

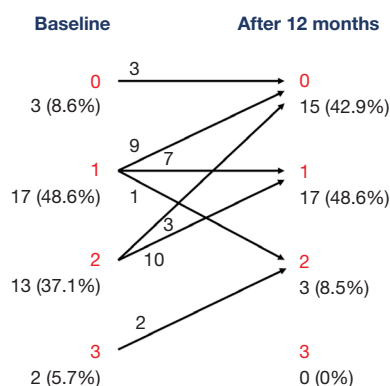


Figure 2 The change of IPN according to grade. At baseline, the number of patients with IPN grades 0, 1, 2, and 3 was respectively 3 (8.6%), 17 (48.6%), 13 (37.1%), and 2 (5.7%). After 12 months of moderate-intensity statin treatment, the number of carotid IPN regression patients was 24 (69%): 9 patients with IPN grade 1 were downgraded to IPN grade 0, 3 patients with IPN grade 2 were downgraded to IPN grade 0, 10 patients with IPN grade 2 were downgraded IPN grade 1, and 2 patients with IPN grade 3 were downgraded to IPN grade 2. IPN, intraplaque neovascularization.

detected by noninvasive CEUS. Furthermore, achieving an LDL-C level of <1.8 mmol/L was associated with a higher prevalence of carotid IPN regression. Our findings suggest that moderate lipid-lowering therapy can stabilize atherosclerotic plaque or even contribute to its regression.

Traditionally, CAG has been used to diagnose CAD and coronary stenosis. Vulnerable plaque is a major mechanism underlying the occurrence of CVEs (18). Thus, specific characteristics of vulnerable plaque are more significant than is the severity of the lumen occlusion (19). Recent IVUS and OCT trials of high-intensity statin therapy have demonstrated that a greater decrease in percent atheroma volume and a greater fibrous cap thickness—which are characteristics of vulnerable plaque—are associated with fewer CVEs (20,21). However, IPN is also a marker of vulnerable plaque (22) and is difficult to observe on IVUS or OCT, but not on noninvasive CEUS. Atherosclerosis is a systemic disease, and previous studies have reported that carotid IPN is associated with the severity of coronary stenosis and can be used to assess cardiovascular risk (10,23). A recent cross-sectional CEUS-IPN study in asymptomatic patients demonstrated an association of high level of LDL-C with higher IPN and suggested that statins can influence plaque vulnerability via their effect on IPN (24). In subgroup analysis of Deyama *et al.*'s study, there was a regression of IPN in 46% of plaques after 6 months of statin treatment in patients with stable CAD (10). In our study, IPN regression occurred in 19 patients with LDL-C <1.8 mmol/L (54% of all patients) after 12-month moderate-intensity statin treatment, with none of these

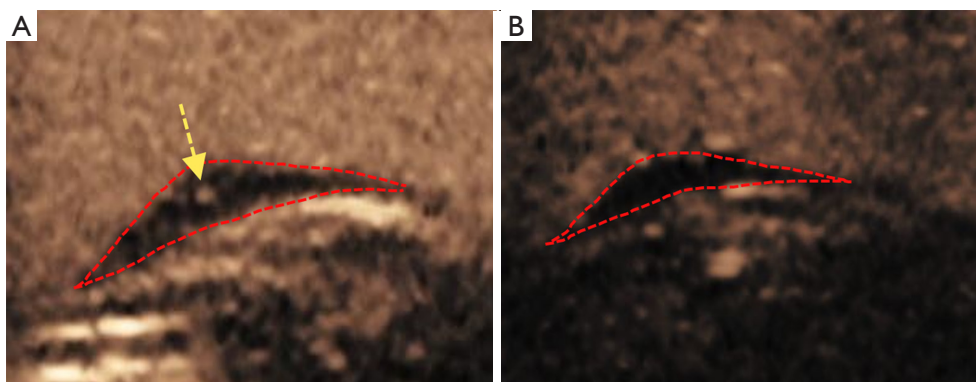


Figure 3 Carotid IPN regression on CEUS. A 37-year-old male patient had IPN grade 1 of the right internal carotid artery as detected on CEUS at baseline. (A) After 1 year of regular moderate-intensity statin therapy, the neovascularization of the same carotid plaque regressed to IPN grade 0 (B). The red dotted lines indicate the carotid plaque, and the yellow arrow indicates the intraplaque contrast microbubbles. IPN, intraplaque neovascularization; CEUS, contrast-enhanced ultrasound.

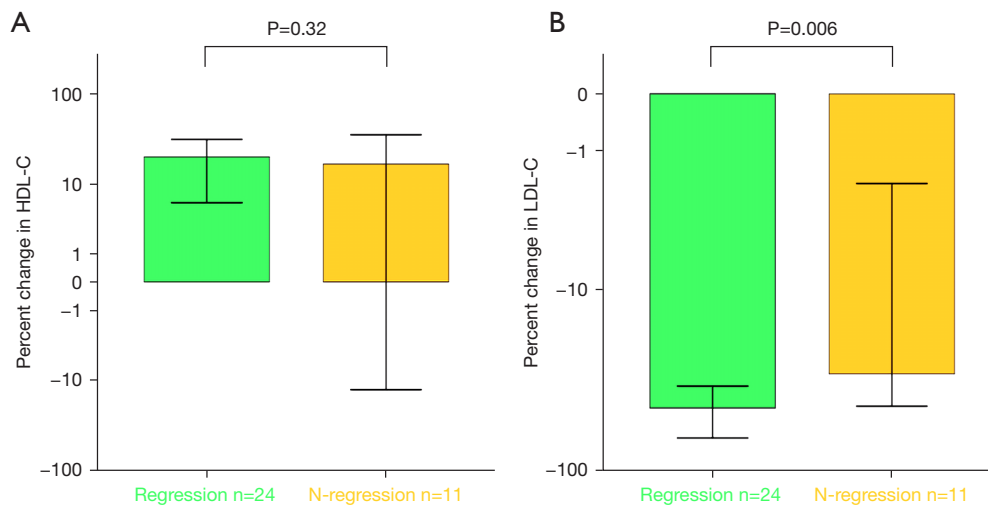


Figure 4 Correlations between the regression of carotid IPN and the percent change of lipid profiles at 12 months. (A) There was no significant difference in percent change in HDL-C between the Regression and N-regression groups (23.63 ± 36.94 vs. 11.47 ± 20.85 ; $P=0.32$). (B) Patients with carotid IPN regression showed a higher percent change in LDL-C compared with patients without carotid IPN regression mean \pm standard deviation: -53.31 ± 23.20 vs. -29.55 ± 19.47 ; $P<0.05$. N-regression: patients without regression of carotid neovascularization. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; IPN, intraplaque neovascularization.

patients experiencing CVEs. Statin treatment can reduce the IPN, and the reduction of IPN indicates plaque stability. Thus, the effect of statin on the change of IPN could be monitored via CEUS in patients with severe CAD.

Carotid plaque is one of the markers of target organ damage, and the presence of carotid plaque increases the overall cardiovascular risk of patients (15). In clinical practice, it is difficult to determine whether to initiate statin therapy for low-risk or moderate-risk patients. If carotid plaque is detected in these patients, they should be treated as high-risk patients (15). In our study, all patients with F/U LDL-C <1.8 mmol/L were at high risk but did not experience CVEs; however, three patients with F/U LDL-C ≥ 1.8 mmol/L underwent revascularization. This thus suggests that in high-risk patients with carotid plaque, the LDL-C levels should be lowered, but further research is needed to confirm this.

Many clinical studies have shown that the LDL-C-lowering effect of high-intensity statin is more prominent than that of low- and moderate-intensity statin therapy (2,4,5,25). However, these studies did not examine Chinese patients. The CHILLAS (China Intensive Lipid Lowering with Statins in Acute Coronary Syndrome) study showed that the reduction of LDL-C levels via intensive statin therapy does not demonstrate significant clinical effectiveness in Chinese patients (26). A retrospective

study reported that moderate-intensity statin in Korean patients with diabetes mellitus resulted in a higher LDL-C reduction rate than it did in White patients due to the different pharmacokinetics between Asian and Western populations (27). In the HPS2-THRIVE (Heart Protection Study 2-Treatment to Reduce the Incidence of Vascular Events), the rate of myopathy in Chinese participants was higher than that in European participants (28). Given the difference in statin pharmacokinetics and dose-related side effects (29,30), treatment with moderate-intensity statin in all patients in our study lowered the LDL-C levels by 41% from baseline, with 80% of the patients achieving an LDL-C level <1.8 mmol/L and none experiencing CVEs. The LDL-C reduction rate was similar to that of a study of White patients (42.6%) treated with 20 mg of atorvastatin but lower than that of a study of White patients (52.1%) treated with 10 mg of rosuvastatin (31). None of patients in our study experienced statin-related side effects. Given the above-mentioned relevant factors and results, for the Chinese population, it may be reasonable to control the level of LDL-C by prescribing moderate-intensity statins.

Higher levels of HDL-C or its associated molecule Apo A-I are generally considered beneficial for reducing CVEs. Conversely, elevated levels of LDL-C and its associated molecules Apo B and Apo B:Apo A-I ratio may increase the risk for CVEs (32-34). Measuring both Apo

A-I and Apo B can provide information about the total amount of potentially antiatherogenic and atherogenic lipoproteins (35). Previous studies have shown that higher levels of HDL-C or Apo A-I can induce regression or reduction in carotid atherosclerotic plaque (36-38). Moreover, the Apo B:Apo A-I ratio is associated with carotid intima-media thickness and atherosclerotic plaque (34,39). However, we observed that patients with F/U LDL-C <1.8 mmol/L had a lower average level of HDL-C but exhibited greater regression in carotid plaque after 12 months of moderate-intensity statin treatment, with the levels of Apo A-I being higher; meanwhile, the absolute values of Apo B and the Apo B:Apo A-I ratio were lower in patients with F/U LDL-C <1.8 mmol/L. Moreover, the univariate and multivariate analysis showed that the levels of HDL-C and Apo B, along with the Apo B:Apo A-I ratio, were not associated with the carotid IPN regression. The explanation for this observation in our study may be attributed to the number of patients who did not achieve the target LDL-C lowering level and the small sample size. Therefore, multicenter and large-sample studies are needed to further confirm the results. Furthermore, it is worth exploring whether the combination of proprotein convertase subtilisin kexin type-9 inhibitor and moderate-intensity statin can provide further benefits in controlling lipoprotein levels and reducing atherosclerotic plaque on CEUS.

Some limitations to this study should be mentioned. First, we employed a single-center, cohort study, and the number of participants in this study was very small, consisting of only 35 patients with severe CAD and carotid plaque. Of the initial patients screened, 29.63% (32/108) had no severe coronary artery stenosis while 11.11% (12/108) had no carotid plaque; these patients were excluded, and the mean age of these patients was 50.97±11.93 years, which suggests that the progression of atherosclerosis could be associated with age (8). Our results may not be representative of the general clinical phenomenon, and future studies with larger populations from multiple centers are needed. Second, some interfering factors, such as quitting smoking and losing weight, could not be eliminated in our study. Previous studies indicate that smoking is associated with the progression of atherosclerosis. However, IPN regressed in 13 previous smokers and 11 nonsmokers, and there was no significant difference in IPN regression between the groups. This study suggests that smoking may not be associated with carotid IPN regression, which may be related to the small sample size in our study. Third, there was no control

arm in this study because it would have been unethical to treat patients with a placebo instead of statin for severe CAD. Fourth, because of the acoustic shadows in calcified or hyperechoic plaques, the comparative subjectivity of CEUS, the limitations of available techniques, and the relatively high costs and expertise needed, we only analyzed the largest carotid plaque and did not assess plaque volume or other variables, such as IPN microbubbles. Thus, further multicenter, large-scale, prospective trials in patients with severe CAD conducted with techniques for detecting a wider array of variables related to plaque and IPN are required.

Conclusions

In Chinese patients with severe CAD, CEUS could represent a helpful tool for assessing the effect of statin on neovascularization of carotid atherosclerotic plaques and determining patient vulnerability. Furthermore, we demonstrated that the lipid-lowering target level of LDL-C <1.8 mmol/L via rosuvastatin (10 mg) and atorvastatin (20 mg) is associated with the stabilization or regression of carotid IPN, which could be observed via serial carotid CEUS.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1104/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Research Ethics Committee of Chinese PLA Hospital (No. S2021-679-02). Individual consent for this retrospective analysis was waived.

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