Original Article

Associations between carotid atherosclerotic plaque characteristics determined by magnetic resonance imaging and improvement of cognition in patients undergoing carotid endarterectomy

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Background: To determine the predictive value of carotid plaque characteristics for the improvement of cognition in patients with moderate-to-severe carotid stenosis after carotid endarterectomy (CEA), using vessel wall magnetic resonance imaging (MRI).

Methods: This was a prospective cohort study. Patients with unilateral, moderate-to-severe carotid stenosis referred to the Peking University Third Hospital for CEA were prospectively recruited and underwent carotid vessel wall MRI within 1 week before CEA. We performed Montreal Cognitive Assessment (MoCA) within 1 week before and 3–4 days after CEA. The morphological and compositional characteristics of carotid plaques on MRI were evaluated. Improvement of cognition was defined as >10% increase of the total MoCA score after CEA compared with baseline. Carotid plaque characteristics were compared between patients with and without cognitive improvement.

Results: In total, 105 patients (91 males; mean age, 65.5±8.4 years) were included. The volume {48.0 [interquartile range (IQR), 21.0 to 91.6] *vs.* 16.3 (IQR, 8.1 to 53.1) mm^3; P=0.005} and cumulative slice [4.0 (IQR, 3.0 to 7.0) *vs.* 3.0 (IQR, 2.0 to 5.0); P=0.019] of carotid calcification, and maximum percentage of calcification area [13.1% (IQR, 6.0% to 19.8%) *vs.* 6.2% (IQR, 3.7% to 10.8%); P=0.004] were significantly smaller in participants with cognitive improvement compared to those without. Univariate logistic regression analysis showed that volume [odds ratio (OR) =0.994; 95% confidence interval (CI): 0.989 to 1.000; P=0.043] and cumulative slice (OR =0.823; 95% CI: 0.698 to 0.970; P=0.020) of carotid calcification, and maximum percentage of calcification area (OR =0.949; 95% CI: 0.909 to 0.991; P=0.018) were significantly correlated with cognitive improvement. After adjusting for confounding factors, these associations remained statistically

or marginally significant (volume: OR =0.994; 95% CI: 0.988 to 1.000; P=0.057; maximum percentage of calcification area: OR =0.937; 95% CI: 0.890 to 0.987; P=0.014; and cumulative slice: OR =0.791; 95% CI: 0.646 to 0.967; P=0.022). No significant associations were found between other plaque characteristics and cognitive improvement (all P>0.05).

Conclusions: More than half of the participants with unilateral, moderate-to-severe carotid atherosclerotic stenosis had cognitive improvement. The size of calcification might be an effective indicator of cognitive improvement after CEA.

Keywords: Carotid artery; atherosclerosis; cognitive function; vessel wall magnetic resonance imaging (vessel wall MRI); carotid endarterectomy (CEA)

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Introduction

Stroke is one of the leading causes of death worldwide (1,2). Ischemic stroke accounts for 80% of strokes, of which 25–30% are attributed to carotid atherosclerotic stenosis (AS) (3). Carotid stenosis or occlusion is significantly associated with decreased cerebral blood flow (CBF). Previous studies have shown that a reduction of CBF by 40–50% causes ischemic damage, including degeneration of neurons, increase in cerebral oxygen uptake fraction, and damage to the cerebral vascular reserve (4-6). Persistent chronic cerebral ischemia caused by carotid AS stenosis will eventually lead to vascular-related cognitive impairment (7-9).

Vascular-related cognitive impairments exist as a dynamic continuum involving 3 stages: brain-at-risk (intact cognitive function), cognitive impairment-without dementia, and vascular dementia (10). Therefore, early intervention for vascular-related cognitive impairment is critical. Timely and effective treatment of carotid AS might delay or even curb the progression of cognitive impairment to a certain extent. Carotid endarterectomy (CEA) has been shown to be an effective treatment for plaque removal and recanalization (9,11). Previous studies have demonstrated the associations between plaque characteristics, such as morphological and compositional features, and cognitive function in patients with carotid AS stenosis (12-14). A clinical study including 99 patients with carotid AS stenosis showed that carotid intraplaque hemorrhage (IPH) increased the risk of cerebral infarction and cognitive impairment (15). Another study reported that carotid calcification was negatively correlated with cognitive function score, which might be an effective predictor for early cognitive impairment (13,16). However, evidence is scarce regarding the association between carotid plaque characteristics and the improvement of cognitive function after CEA. A better understanding of the relationship between carotid plaque characteristics and cognitive improvement after CEA will facilitate precise prediction of the cognition-related prognosis in patients referred to CEA, and thus refine treatment strategy formulation.

The high resolution vessel wall magnetic resonance imaging (MRI) technique has been largely used to accurately evaluate the morphological and compositional characteristics of carotid AS plaques (17). The aim of this study was to determine the predictive value of carotid plaque characteristics for the improvement of cognition in patients with moderate-to-severe carotid stenosis after CEA, using vessel wall MRI.

We present the following article in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-21-981/rc).

Methods

Study sample

Patients with unilateral symptomatic or asymptomatic moderate-to-severe carotid stenosis (50–99%) determined by computed tomography angiography (CTA) who were >40 years old and referred to CEA at the Department of Neurosurgery of the Peking University Third Hospital were prospectively enrolled from May 2019 to December 2020. All participants underwent carotid artery vessel wall MRI within 1 week before CEA. The assessment of cognition was performed within 1 week before and 3–4 days after CEA.

The exclusion criteria were as follows: (I) large artery atherosclerotic stroke and cardio-embolic stroke; (II) hemorrhagic stroke; (III) cerebral neoplasms; (IV) history of vascular intervention treatment, including CEA, carotid stenting, clips or coils of aneurysms; (V) intracranial vasculature (intracranial segment of internal carotid artery or middle cerebral artery) stenosis ≥50% on CTA; (VI) any contraindications to MRI examination, such as claustrophobia; (VII) previous psychosis; (VIII) dementia or difficulties in complying with cognitive assessment, such as severe hearing or language impairment; and (IX) refusal to sign informed consent. Clinical information, including age, gender, education attainment, height, weight, history of hypertension, hyperlipidemia, diabetes, smoking, drinking, stroke, transient ischemic attack, and coronary heart disease and medication was collected. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Medical Ethics Committee of Peking University Third Hospital. All patients provided written informed consent before participating in this study.

Surgical procedures

All participants underwent CEA under general anesthesia conducted by the same senior neurosurgeon (T Wang) with 30 years' experience in standardized surgical procedures. Manipulation of the vessels was performed under microscope. The vital signs and neurological function of all participants were closely monitored, and blood pressure and heart rate were strictly controlled.

MRI protocol

All participants underwent carotid vessel wall MRI on a 3.0-T MR scanner (uMR780, United Imaging Healthcare, Shanghai, China) with an 8-channel dedicated carotid coil. The imaging protocol and parameters were as follows: 3D time-of-flight (TOF) image using gradient echo (GRE) with repeat time (TR)/echo time (TE) of 17.6/6.7 ms, flip angle of 8°, and slice thickness of 2 mm; 2D T1-weighted (T1W) image using MATRIX (Modulated flip Angle Technique in Refocused Imaging with eXtended echo train) and fast spin echo (FSE) with TR/TE of 850/13.44 ms and slice thickness of 2 mm; 2D T2-weighted image using MATRIX and FSE with TR/TE of 2,000/96.6 ms and slice thickness of 2 mm; and simultaneous non-contrast angiography intraplaque hemorrhage (SNAP) imaging using GRE with TR/TE of 9.6/4.0 ms, flip angle of 12°, and slice thickness of 1 mm. All of the above imaging sequences were acquired with an identical field of view (140×140 mm^2), in-plane spatial resolution (0.55×0.55 mm^2), and longitudinal coverage (32 mm). The carotid vessel wall MRI was centered on the index-side of the plaque, which was defined as the carotid artery with moderate-to-severe stenosis referred to CEA.

All participants underwent brain MRI on a 3.0-T MR scanner (Discovery 750, General Electric, Milwaukee, WI, USA) with an 8-channel dedicated brain coil within the 48 hours before the CEA. Table S1 provides the imaging protocol and parameters.

Assessment of cognition

All participants underwent neuropsychological testing with the Beijing version of the Montreal Cognitive Assessment (MoCA) for evaluating cognitive function, which was applied by the same trained observer (R Huo) with more than 2 years' experience who was blinded to the patients' clinical information and findings of carotid MRI. Educational level was assessed according to the maximum educational time and categorized into 2 levels: a lower educational level comprising ≤12 years and a higher educational level comprising >12 years. The final total MoCA score of patients with the lower educational level was corrected to the actual score plus 1 point. The improvement of cognition was defined as a >10% increase in total MoCA score after CEA compared to that at baseline (18). A follow-up assessment of cognition was performed at 3–4 days after CEA.

MR data analysis

All the carotid vessel wall MR images were independently interpreted by another 2 trained radiologists (Y Liu and H Xu) with more than 5 years' experience in cerebrovascular imaging, using a commercialized software (Vessel Explorer 2, TSimaging Healthcare, Beijing, China). In the case of inconsistency in the interpretation of results between the 2 observers, another senior radiologist (X Zhao) with more than 10 years' experience in neurovascular imaging was invited to arbitrate. All observers were blinded to the participants' clinical information and results of cognitive assessment. The image quality (IQ) was assessed using a 4-point scale (19): 1 = poor, low signal-to-noise ratio (SNR) with unidentifiable arterial wall and vessel margins; 2 = marginal, marginal SNR with identifiable wall structure

but more than half of the lumen and outer boundaries indistinct; 3 = good, high SNR with minimal artifacts, well-defined vessel wall, lumen and adventitial boundary; and 4 = excellent, high SNR without artifacts, clear wall architecture, lumen and adventitial boundary. Only images with an IQ ≥2 were included in further analysis. The lumen, wall, and plaque component boundaries at each axial MR image of carotid artery on the index side were outlined manually. The plaque burden, including the mean values of wall area (WA), lumen area (LA), total vessel area (TVA), normalized wall index (NWI = WA/TVA ×100%) and maximal wall thickness (Max WT), was measured. The presence of plaque components, including calcification, lipid-rich necrotic core (LRNC), IPH, ulcer, and fibrous cap rupture (FCR), was evaluated using published criteria (17,20,21). Briefly, calcification within the plaque was defined as low signal intensity (SI) on all multi-contrast carotid vessel wall images. The LRNC was identified as iso-SI on both T1W and TOF images and lower SI on T2W images within the plaque. The IPH was determined when there was a region appearing as high SI on T1W, TOF, and SNAP images within the plaque. Ulceration showed a disrupted luminal surface on T1W images and the formation of a niche on TOF images. A FCR had 2 manifestations: ulcer and minor FCR which is defined when the hyperintensity of an IPH extended into the lumen and the hypointensity of a band between the high signal of the lumen and juxta-luminal hemorrhage was absent on TOF images. The volume and cumulative slice of each plaque component, and maximum percentage of each plaque component area were also measured.

The white matter hyperintensity characteristics of all the brain MR images were independently identified by another 2 trained radiologists (J Li and R Xin) with more than 3 years' experience in brain imaging. The total Fazekas scale was evaluated using published criteria (22,23).

Statistical analysis

Continuous variables with normal distribution were presented as mean and standard deviation, whereas those with abnormal distribution were expressed as median and interquartile range (IQR). Categorical variables were described as count and percentage. Clinical variables and plaque characteristics were compared between patients with and without improvement of cognition using the independent *t*-test, Mann-Whitney U test, or chi-square test. The predictive value of baseline carotid plaque characteristics for the improvement of cognitive function after CEA was analyzed using a logistic regression model. During univariate and multivariate logistic regression analyses, the odds ratio (OR), risk difference (RD), adjusted risk difference (ARD), and corresponding 95% confidence interval (CI) of plaque characteristics were calculated in predicting the improvement of cognition. In multivariate logistic regression model 1, we adjusted for age (24-26), gender (26,27), educational level (24), and Fazekas score (28). In multivariate logistic regression model 2, we adjusted for age, gender, educational level, Fazekas score, and clinical variables with P<0.100 in the comparison analysis (*Table 1*), including luminal stenosis, coronary heart disease, and antihypertensive treatment. These clinical variables had been demonstrated to be associated with cognitive function in previous studies (24,29,30). A P value <0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed using the software SPSS 26.0 (SPSS, Inc., IBM Corp., Chicago, IL, USA) and Stata SE 15.0. (StataCorp, College Station, TX, USA).

Results

Clinical characteristics of the study population

A total of 126 patients were enrolled in this study from May 2019 to December 2020. Of the 126 patients, 21 were excluded from the analysis due to the following reasons (*Figure 1*): (I) loss to cognitive follow-up (n=9); (II) moderate or severe stenosis or occlusion of the intracranial artery (n=5); (III) poor carotid MR IQ due to motion (IQ <2; n=2); and (IV) history of vascular intervention treatment (n=5). Of the remaining 105 patients (65.5±8.4 years old), 91 (86.7%) were male, 92 (87.6%) had symptomatic stenosis, and 35 (33.3%) had a high educational level. Demographic and clinical characteristics of this study population are summarized in *Table 1*. There were no significant differences in age (65.5±8.4 *vs.* 64.7±8.3 years; P=0.529), male gender (86.7% *vs.* 90.5%; P=0.905), and educational level (>12 years, 33.3% *vs.* 26.8%; P=0.671) between the included and excluded patients (Table S2).

In the present study, cognitive improvement was observed in 56.2% (59/105) of participants {MoCA score: before CEA, 18 [15–21]; after CEA, 23 [20–26]}. A total of 46 (43.8%) participants did not have cognitive improvement {MoCA score: before CEA, 20 [17–23]; after CEA, 21 [18–24]}. Domain scores of the MoCA for each group in the study population are shown in Table S3.

Table 1 Clinical characteristics of the study population

Characteristics	Mean ± SD or n (%)			P value
	All patients (n=105)	Cognitive unimprovement (n=46)	Cognitive improvement (n=59)	
Age, years	65.5±8.4	66.5±8.8	64.6±8.1	0.347
Gender, male	91 (86.7)	43 (93.5)	48 (81.4)	0.070
BMI, kg/m^2	24.9±2.7	25.0±2.7	24.9±2.8	0.804
Education level, >12 years	35 (33.3)	17 (37.0)	18 (30.5)	0.487
Hypertension	76 (72.4)	35 (76.1)	41 (69.5)	0.453
SBP, mmHg	134.0±16.2	132.2±17.1	135.3±15.5	0.179
DBP, mmHg	79.4±9.8	78.6±10.1	80.0±9.6	0.245
BPD, mmHg	54.6±13.9	53.7±15.0	55.3±13.2	0.355
Hyperlipidemia	59 (56.2)	27 (58.7)	32 (54.2)	0.648
HDL, mmol/L	1.0±0.2	1.04±0.25	0.99±0.24	0.292
LDL, mmol/L	2.1±0.8	2.2±0.7	2.1±0.8	0.744
TC, mmol/L	3.7±0.9	3.7±0.8	3.7±1.0	0.539
TG, mmol/L	1.6±0.8	1.6±0.8	1.5±0.7	0.366
Diabetes	42 (40.0)	19 (41.3)	23 (39.0)	0.810
Glu, mmol/L	6.2±1.6	6.4±1.9	6.0±1.4	0.446
Smoke	69 (65.7)	30 (65.2)	39 (66.1)	0.925
Alcohol	70 (66.7)	32 (69.6)	38 (64.4)	0.578
Coronary heart disease	19 (18.1)	12 (26.1)	7 (11.9)	0.060
Stroke	31 (29.5)	13 (28.3)	18 (30.5)	0.802
TIA	48 (45.7)	20 (43.5)	28 (47.5)	0.685
Antiplatelet	86 (81.9)	38 (82.6)	48 (81.4)	0.869
Anticoagulation	2 (1.9)	1 (2.2)	1 (1.7)	0.687
Statin use	86 (81.9)	38 (82.6)	48 (81.4)	0.869
Hypoglycemic treatment	34 (32.4)	18 (39.1)	16 (27.1)	0.192
Antihypertensive treatment	62 (59.0)	32 (69.6)	30 (50.8)	0.053

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BPD: blood pressure difference; HDL, high density lipoprotein; LDL, low density lipoprotein; TC, total cholesterol; TG, triglyceride; Glu, glucose; TIA, transient ischemic attack; SD, standard deviation.

Comparison of clinical and carotid plaque characteristics

The mean cognitive follow-up time was 3.4±0.5 days. Of the 105 participants, 59 (56.2%) had improved cognition after CEA. No significant differences were found in clinical characteristics between participants with and without improvement of cognition (all P>0.05).

The results for the comparison of carotid plaque characteristics between participants with and without improvement of cognition are shown in *Table 2*. Compared to participants with improvement of cognition, those without improvement of cognition showed significantly larger calcification volume [48.0 (IQR, 21.0 to 91.6) *vs.* 16.3 (IQR, 8.1 to 53.1) mm^3; P=0.005], larger maximum percentage of calcification area [13.1% (IQR, 6.0% to 19.8%) *vs.* 6.2% (IQR, 3.7% to 10.8%); P=0.004], and more cumulative slices of calcification [4.0 (3.0 to 7.0) *vs.* 3.0 (2.0

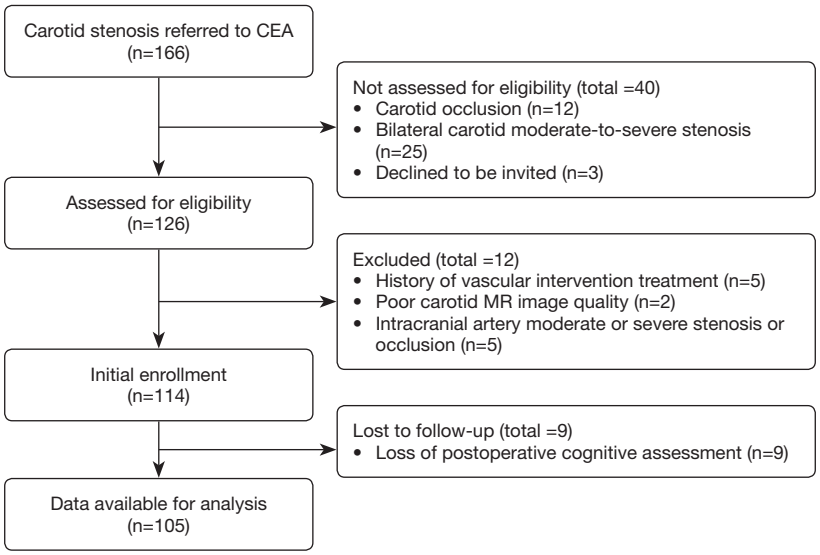

Figure 1 Flow diagram of patient recruitment.

to 5.0); P=0.019]. Other carotid plaque components and morphological measurements did not significantly differ between the 2 groups (all P>0.05).

Carotid plaque characteristics predict the improvement of cognition

Table 3 shows the results of univariate and multivariate regression analyses. In the univariate logistic regression analysis, significant associations between improvement of cognition and calcification volume (OR =0.994; 95% CI: 0.989 to 1.000; P=0.043), maximum percentage of calcification area (OR =0.949; 95% CI: 0.909 to 0.991; P=0.018), and cumulative slices of calcification (OR =0.823; 95% CI: 0.698 to 0.970; P=0.020) were detected (*Figure 2*). After adjusting for confounding factors of age, gender, educational level and Fazekas score, the associations remained statistically significant (calcification volume: OR =0.994; 95% CI: 0.988 to 1.000; P=0.043; maximum percentage of calcification area: OR =0.945; 95% CI: 0.901 to 0.990; P=0.017; and cumulative slice of calcification: OR =0.802; 95% CI: 0.670 to 0.961; P=0.017). After further adjusting for the above confounding factors and stenosis, history of coronary heart disease, and anti-hypertension treatment, the associations of cognitive function with maximum percentage of the calcification area (OR =0.937; 95% CI: 0.890 to 0.987; P=0.014) and cumulative slice (OR =0.791; 95% CI: 0.646 to 0.967; P=0.022) of calcification remained statistically significant, but the volume of calcification was no longer significantly associated with cognitive function (OR =0.994; 95% CI: 0.988 to 1.000; P=0.057). No significant associations were found between other carotid plaque characteristics and improvement of cognition (all P>0.05).

The values for absolute risk of the measurements of carotid morphology and plaque characteristics on MRI in predicting improvement of cognitive function are shown in Table S4.

Discussion

This study investigated the relationships between carotid plaque characteristics determined by vessel wall MRI and the improvement of cognition in patients with moderate-to-severe unilateral carotid stenosis after CEA. We found that patients who experienced improvement of cognitive function after CEA had a smaller size of carotid calcification. Our findings suggest that for patients with a smaller size of calcification in a carotid atherosclerotic plaque, CEA may provide a benefit for their cognitive function.

This study demonstrated that the size of carotid calcification was negatively associated with improvement of cognitive function in patients with moderate-to-severe unilateral carotid stenosis after CEA. This finding suggests that patients with calcified plaque in a carotid artery benefit less from CEA with respect to restoration of cognitive function. Calcium deposition occurs in the advanced stage of AS (31). A larger size of calcification indicates the long-

Table 2 Characteristics of carotid plaque characteristics in the study population

Characteristics	All patients (n=105)	Unimprovement (n=46)	Improvement (n=59)	P value
Morphology, median (IQR)				
Mean lumen area, mm^2	26.1 (21.6, 32.0)	26.7 (21.7, 32.3)	26.0 (21.5, 31.6)	0.675
Mean wall area, mm^2	40.7 (32.2, 52.0)	41.5 (32.8, 54.2)	40.4 (30.7, 47.1)	0.568
Mean total vessel area, mm^2	67.4 (57.8, 79.6)	68.0 (57.8, 85.1)	66.7 (57.2, 77.6)	0.633
Maximum wall thickness, mm	6.0 (4.9, 7.4)	6.1 (4.9, 7.2)	5.9 (4.8, 7.4)	0.689
Mean normalized wall index, %	60.6 (54.6, 66.3)	61.0 (56.5, 66.3)	59.6 (51.9, 66.4)	0.354
Stenosis, %	75.5 (69.7, 83.5)	74.2 (69.9, 81.4)	75.7 (69.5, 85.5)	0.342
Presence of plaque components, n (%)				
LRNC	96 (91.4)	41 (89.1)	55 (93.2)	0.695
IPH	56 (53.3)	25 (54.3)	31 (52.5)	0.854
Calcification	87 (82.9)	38 (82.6)	49 (83.1)	0.952
Ulcer	29 (27.6)	14 (30.4)	15 (25.4)	0.569
FCR	59 (56.2)	26 (56.5)	33 (55.9)	0.952
Volume of plaque components*, median (IQR)				
LRNC, mm^3	267.6 (95.8, 541.6)	274.6 (104.9, 564.4)	217.1 (87.8, 538.6)	0.349
IPH, mm^3	193.1 (45.0, 384.4)	159.5 (22.3, 408.3)	210.4 (82.5, 383.7)	0.387
Calcification, mm^3	28.1 (11.4, 75.8)	48.0 (21.0, 91.6)	16.3 (8.1, 53.1)	0.005
Ulcer, mm^3	21.0 (9.6, 55.2)	26.8 (7.2, 64.7)	20.6 (14.7, 44.3)	0.747
Maximum percentage of plaque component area*, median (IQR)				
LRNC, %	62.2 (40.6, 73.8)	60.6 (36.6, 75.4)	62.5 (41.4, 73.3)	0.731
IPH, %	47.2 (19.0, 61.8)	47.0 (14.6, 60.1)	50.4 (20.6, 61.9)	0.644
Calcification, %	8.0 (4.3, 15.8)	13.1 (6.0, 19.8)	6.2 (3.7, 10.8)	0.004
Ulcer, %	9.8 (4.1, 18.7)	13.1 (4.1, 19.9)	8.9 (3.9, 17.9)	0.683
Cumulative slice of plaque components*, median (IQR)				
LRNC	8.0 (5.0, 10.0)	8.0 (5.50, 9.50)	8.0 (4.00, 10.00)	0.958
IPH	6.0 (4.0, 8.8)	6.0 (3.0, 8.5)	6.0 (4.0, 9.0)	0.829
Calcification	4.0 (2.0, 6.0)	4. 0 (3.0, 7.0)	3.0 (2.0, 5.0)	0.019
Ulcer	3.0 (2.0, 3.0)	2.50 (1.0, 3.0)	3.0 (2.0, 3.0)	0.451

*, only patients with the corresponding component present were included in the comparison. LRNC, lipid-rich necrotic core; IQR, interquartile range; IPH, intraplaque hemorrhage; FCR, fibrous cap rupture.

term progression of a carotid plaque, in which various compensatory mechanisms, including the redistribution of CBF via the circle of Willis and collateral vessels, gradually mature. Improvement of cognitive function might be bolstered by the recovery of CBF at the unilateral side of moderate-to-severe carotid stenosis after CEA (18,32). However, the compensatory process of CBF is initiated when chronic carotid stenosis occurs. In cases with chronic carotid stenosis and sufficient blood flow compensation, cognitive function can be sustained (33). In addition, neurodegeneration during cerebral gliosis mediated by oxidative stress in patients with long-term carotid stenosis

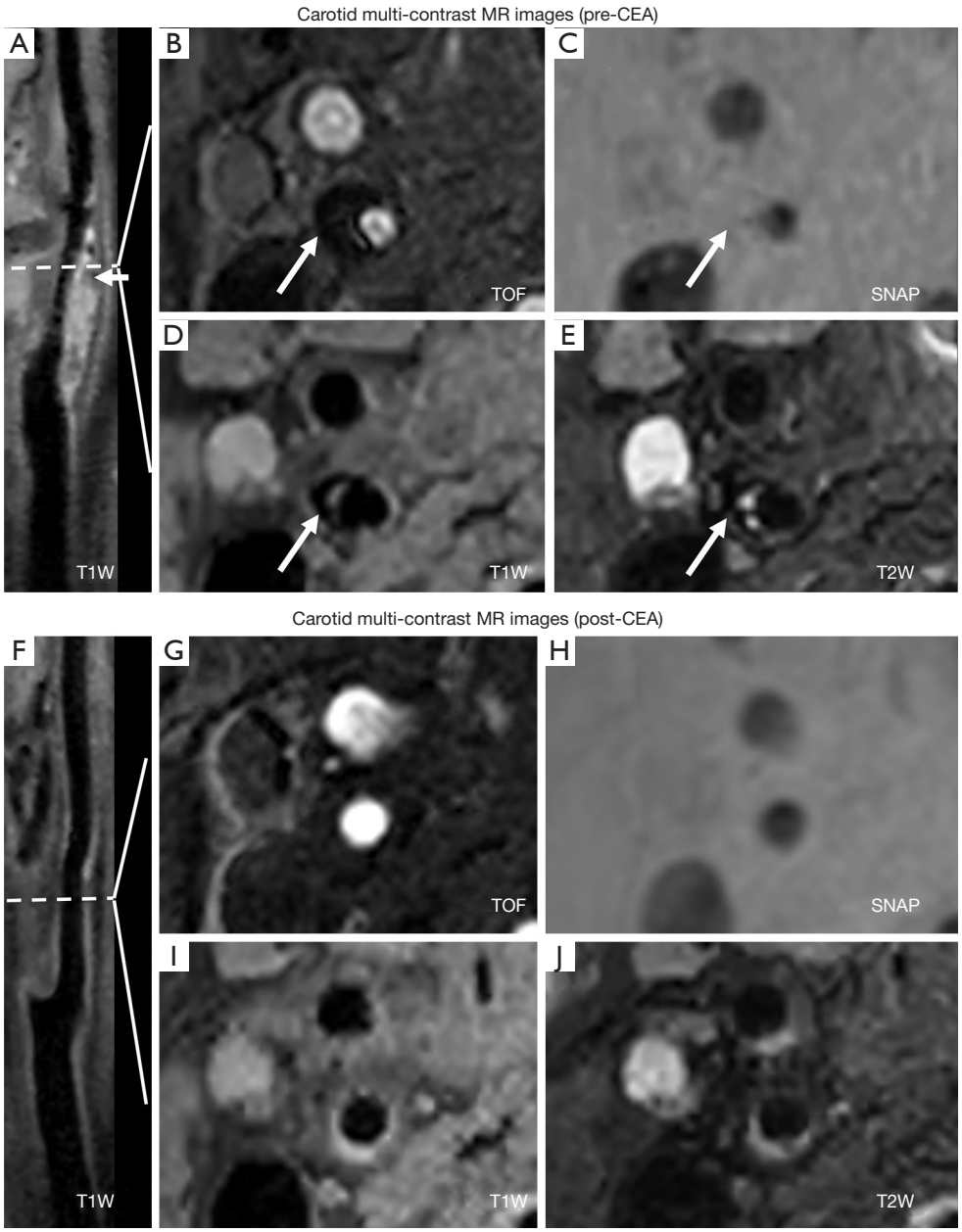

Figure 2 A 76-year-old male patient had a calcific plaque in the right internal carotid artery and underwent revascularization pre- and post-CEA. The patient's scores of pre-MoCA and post-MoCA were 17 and 20, respectively. Calcification can be seen in the multi-contrast MR images (white arrows). (A) 3D T1W curved planar reconstruction image before CEA; (B) 3D TOF image before CEA; (C) SNAP image before CEA; (D) 2D T1W image before CEA; (E) 2D T1W image before CEA; (F) 3D T1W curved planar reconstruction image after CEA; (G) 3D TOF image after CEA; (H) SNAP image after CEA; (I) 2D T1W image after CEA; and (J) 2D T1W image after CEA. CEA, carotid endarterectomy; MR, magnetic resonance; MoCA, Montreal Cognitive Assessment; T1W, T1-weighted; TOF, time-of-flight; SNAP, simultaneous non-contrast angiography intraplaque hemorrhage; T2W, T2-weighted.

Table 3 Associations between carotid plaque characteristics and changes of MoCA

Characteristics	Univariate regression			Multivariate regression (model 1)			Multivariate regression (model 2)		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Morphology									
Mean lumen area, mm^2	1.006	0.970, 1.043	0.762	1.005	0.967, 1.044	0.792	1.008	0.967, 1.050	0.706
Mean wall area, mm^2	0.999	0.977, 1.022	0.935	1.007	0.982, 1.032	0.591	1.005	0.980, 1.031	0.684
Mean total vessel area, mm^2	1.001	0.984, 1.018	0.935	1.005	0.987, 1.024	0.595	1.005	0.986, 1.024	0.629
Maximum wall thickness, mm	0.954	0.777, 1.170	0.649	0.995	0.803, 1.233	0.962	0.996	0.792, 1.253	0.974
Mean normalized wall index, %	0.988	0.949, 1.030	0.575	1.005	0.961, 1.052	0.814	0.993	0.945, 1.043	0.775
Stenosis, %	1.015	0.982, 1.050	0.376	1.020	0.984,1.058	0.271	–	–	–
Presence of plaque components									
LRNC	1.677	0.424, 6.636	0.461	2.800	0.619, 12.665	0.181	3.674	0.738, 18.288	0.112
IPH	0.930	0.429, 2.015	0.854	1.151	0.510, 2.598	0.735	1.363	0.568, 3.275	0.488
Calcification	1.032	0.371, 2.866	0.952	1.348	0.450, 4.033	0.593	1.263	0.387, 4.125	0.699
Ulcer	0.799	0.330, 1.840	0.569	0.891	0.363, 2.183	0.800	1.160	0.438, 3.076	0.765
FCR	0.976	0.449, 2.124	0.952	1.210	0.533, 2.746	0.648	1.553	0.638, 3.780	0.332
Volume of plaque components*									
LRNC, mm^3	0.999	0.998, 1.001	0.344	0.999	0.998, 1.001	0.462	1.000	0.998, 1.001	0.802
IPH, mm^3	1.001	0.999, 1.003	0.473	1.001	0.999, 1.003	0.435	1.002	0.999, 1.004	0.214
Calcification, mm^3	0.994	0.989, 1.000	0.043	0.994	0.988, 1.000	0.043	0.994	0.988, 1.000	0.057
Ulcer, mm^3	0.993	0.971, 1.015	0.528	0.995	0.971, 1.020	0.688	0.996	0.969, 1.023	0.748
Maximum percentage of plaque component area*									
LRNC, %	1.005	0.985, 1.025	0.643	1.007	0.986, 1.028	0.532	1.006	0.982, 1.030	0.645
IPH, %	1.007	0.983, 1.031	0.576	1.008	0.982, 1.033	0.565	1.014	0.985, 1.044	0.353
Calcification, %	0.949	0.909, 0.991	0.018	0.945	0.901, 0.990	0.017	0.937	0.890, 0.987	0.014
Ulcer, %	0.965	0.892, 1.044	0.377	0.966	0.879, 1.061	0.467	0.972	0.882, 1.071	0.561
Cumulative slice of plaque components*									
LRNC	1.010	0.905, 1.127	0.858	1.038	0.925, 1.164	0.528	1.000	0.881, 1.135	1.000
IPH	1.053	0.901, 1.230	0.515	1.067	0.898, 1.268	0.459	1.119	0.909, 1.376	0.288
Calcification	0.823	0.698, 0.970	0.020	0.802	0.670, 0.961	0.017	0.791	0.646, 0.967	0.022
Ulcer	1.440	0.691, 3.000	0.330	1.678	0.741, 3.798	0.215	1.947	0.763, 4.968	0.163

*, only patients with the corresponding component present were included in the comparison. Model 1: adjusted for age, gender, educational level and Fazekas score; Model 2: adjusted for age, gender, educational level, Fazekas score, stenosis, coronary heart disease and antihypertensive treatment. MoCA, Montreal Cognitive Assessment; LRNC, lipid-rich necrotic core; IPH, intraplaque hemorrhage; FCR, fibrous cap rupture; CI, confidence interval; OR, odds ratio.

may partially offset the improvement of cognitive function after CEA. An animal study demonstrated an increase in the superoxide anion and the activation of microglia and astrocytes in the hippocampus in mice with carotid AS (34). The activation of microglia and astrogliosis are considered key mechanisms contributing to neurodegeneration and leading to cognitive impairment (35,36). Coexisting cerebral lacunar infarction and white matter lesions in carotid stenosis patients with calcification might partially account for lesser improvement of cognitive function after removing the plaques by CEA. Previous studies have shown that the incidence of small vessel disease in patients with carotid AS stenosis significantly increases, and is one of the important risk factors of dementia (37,38). A community-dwelling population study showed that calcification in intracranial and extracranial arteries is associated with the increase of white matter lesion volume (39). Finally, arterial calcification has been shown to increase artery wall shear stress, which is a risk factor for cognitive decline and dementia (14,40). Briefly, cerebral damage that has already occurred due to the long-term presence of plaques with more calcium may account for reduced safeguard in the future. However, the safeguard in patients with softer plaques without calcium may be effective.

In the present study, the compositional features of IPH, LRNC, and ulcer were not found to be associated with changes of cognitive function. Histologically, the IPH, large LRNC, and ulcer of a carotid plaque are key risk features of a vulnerable plaque (41). An autopsy study suggested that presence of IPH is a potent atherogenic stimulus via promotion of plaque progression, including cholesterol deposition, macrophage infiltration, and the expansion of the necrotic core (42). Takaya *et al.* (43) found that repeated intraplaque bleeding accelerated lipid core volume in a longitudinal clinical study conducted over an 18-month period. In addition, Cui *et al.* (21) reported that the size of fresh IPH was independently associated with minor fibrous cap disruption in patients with carotid plaque. Minor disruption of vulnerable plaques with IPH, large LRNC, or ulcer may occur asymptomatically but will contribute to obstruction of the micro-circulation by episodic micro-emboli. Previous studies have shown that cerebral perfusion is correlated with cognitive function in patients with carotid plaques (18,33). As such, we speculate that cognitive impairment may not be subsequently improved after removing the plaque due to the existing obstruction of the micro-circulation.

We also found that there was no significant association between carotid AS stenosis and cognitive improvement after CEA. The present results might be attributed to the compensatory mechanisms from contralateral vessels accompanied by progression of a carotid plaque with a certain degree of stenosis. Collateral circulation has been understood to play a key role in maintaining CBF in patients with severe extracranial carotid artery stenosis (3,44,45). In carotid AS stenotic patients, decreased CBF on the ipsilateral side is compensated via the circle of Willis (46-48). Our findings suggest that the improvement of cognitive function in patients with carotid AS stenosis after CEA might be independent of the degree of stenosis.

This study had several limitations. First, patients with a carotid occlusion were not included in the present study. Carotid occlusion is one of the main factors related to vascular-related cognitive impairment due to reduction of CBF, damaged cerebral vascular reserve, as well as carotid stenosis. Second, only short-term cognitive function was analyzed. A previous study reported that there was a fluctuation in cognitive function recovery between short-term (3 days after CEA) and long-term (3 months) periods (49). Therefore, long-term evaluation of postoperative cognitive function after CEA is warranted in future studies. Third, in the present study, only 32 mm of extracranial carotid artery centered to the bifurcation was analyzed. Lesions in more proximal or distal segments of the extracranial carotid artery were not assessed. This may have led to underestimation of the calcification volume in some cases. Fourth, the lesion of the intracranial segment of the internal carotid artery and middle cerebral artery was not evaluated due to the unavailability of the corresponding vessel wall imaging data. Intracranial artery disease with lower grade stenosis may play a role in the recovery of cognitive function after CEA. Fifth, we did not adjust for the information of lacunar and cortical infarcts and cerebral microbleeds in the multivariate regression analysis, which might be associated with cognitive function.

Conclusions

More than half of the patients with moderate-to-severe unilateral carotid AS exhibited cognitive improvement. Calcification size might be an effective indicator for cognitive improvement after CEA.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-21-981/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-981/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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was supported by the Medical Ethics Committee of Peking University Third Hospital, and all participants provided written informed consent.

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Supplementary

Table S1 Protocol and parameters of brain MR imaging

Parameters	T1W	T2W	FLAIR	DWI
Sequence	FSE	FSE	FSE	EPI
TR/TE, ms	2374/24	5972/70	8400/140	3000/71
Flip angle, degree	111	142	111	–
FOV, mm^2	250×250	250×250	250×250	250×250
Matrix	352×256	384×384	284×224	160×160
Slice thickness, mm	5	5	5	5
Slice number	24	24	24	24
b value	–	–	–	0/1,000
Scanning time	1’24”	1’18”	1’42”	0’24”

DWI, diffusion weighted imaging; EPI, echo planar imaging; FLAIR, fluid-attenuated inversion recovery; FSE, fast spin echo; FOV, field of view; MR, magnetic resonance imaging; TR, repetition time; TE, echo time; T1W, T1-weighted; T2W, T2-weighted.

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Table S2 Comparison between included and excluded patients in the study

Characteristics	Mean ± SD or n (%)		P value
	Included (n=105)	Excluded (n=21)	
Age	65.5±8.4	64.7±8.3	0.529
Gender, male	91 (86.7)	19 (90.5)	0.905
BMI, kg/m^2	24.9±2.7	24.5±2.4	0.633
Education level, >12 years	35 (33.3)	6 (28.6)	0.671
Hypertension	76 (72.4)	16 (76.2)	0.720
SBP, mmHg	134.0±16.2	134.3±22.1	0.394
DBP, mmHg	79.4±9.8	83.33±7.6	0.064
BPD, mmHg	54.6±13.9	51.0±20.8	0.158
Hyperlipidemia	59 (56.2)	8 (38.1)	0.129
HDL, mmol/L	1.0±0.2	1.1±0.3	0.313
LDL, mmol/L	2.1±0.8	2.2±0.8	0.966
TC, mmol/L	3.7±0.8	3.8±0.9	0.594
TG, mmol/L	1.6±0.8	1.5±0.7	0.839
Diabetes	42 (40.0)	11 (52.4)	0.294
Glu, mmol/L	6.2±1.6	6.4±1.6	0.471
Smoke	69 (65.7)	14 (66.7)	0.933
Alcohol	70 (66.7)	13 (61.9)	0.674
Coronary heart disease	19 (18.1)	3 (14.30	0.916
Stroke	31 (29.5)	14 (66.7)	0.001
TIA	48 (45.7)	8 (38.1)	0.521
Antiplatelet	86 (81.9)	16 (76.2)	0.761
Anticoagulation	2 (1.9)	0 (0)	0.693
Statin use	86 (81.9)	12 (57.1)	0.028
Hypoglycemic treatment	34 (32.4)	9 (42.9)	0.355
Antihypertensive treatment	62 (59.0)	14 (66.7)	0.515

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BPD, blood pressure difference; HDL, high density lipoprotein; LDL, low density lipoprotein; SD, standard deviation; TC, total cholesterol; TG, triglyceride; Glu, glucose; TIA, transient ischemic attack.

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Table S3 Domain scores of MoCA in the study population

Domain of MoCA	All patients (n=105)		Cognitive unimprovement (n=46)		Cognitive improvement (n=59)	
	Pre-CEA	Post-CEA	Pre-CEA	Post-CEA	Pre-CEA	Post-CEA
Visuospatial/executive	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
Naming	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)
Attention	5.0 (4.0, 6.0)	6.0 (5.0, 6.0)	6.0 (4.75, 6.0)	6.0 (5.0, 6.0)	5.0 (4.0, 6.0)	6.0 (5.0, 6.0)
Language	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	2.0 (1.0, 2.0)
Abstraction	0.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.0 (0.0, 1.0)	1.0 (0.0, 1.0)
Delayed recall	0.0 (0.0, 1.0)	2.0 (0.0, 4.0)	0.0 (0.0, 2.0)	1.0 (0.0, 3.0)	0.0 (0.0, 1.0)	3.0 (1.0, 4.0)
Orientation	5.0 (5.0, 6.0)	6.0 (5.0, 6.0)	6.0 (5.0, 6.0)	5.0 (5.0, 6.0)	5.0 (5.0, 6.0)	6.0 (5.0, 6.0)

All the measurements were described as median and interquartile range. CEA, carotid endarterectomy; MoCA, Montreal Cognitive Assessment.

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Table S4 Absolute risk for associations between carotid plaque characteristics and changes of MoCA

Characteristics	Univariate regression			Multivariate regression (model 1)			Multivariate regression (model 2)		
	RD	95% CI	P value	ARD	95% CI	P value	ARD	95% CI	P value
Morphology									
Mean lumen area, mm^2	0.0014	−0.0078, 0.0106	0.7638	0.0012	−0.0079, 0.0104	0.7929	0.0017	−0.0072, 0.0106	0.7078
Mean wall area, mm^2	−0.0002	−0.0057, 0.0053	0.9345	0.0016	−0.0041, 0.0073	0.5850	0.0011	−0.0043, 0.0066	0.6843
Mean total vessel area, mm^2	0.0002	−0.0041, 0.0045	0.9350	0.0012	−0.0031, 0.0054	0.5862	0.0010	−0.0031, 0.0051	0.6256
Maximum wall thickness, mm	−0.0111	−0.0555, 0.0333	0.6236	−0.0012	−0.0513, 0.0489	0.9620	−0.0008	−0.0492, 0.0476	0.9744
Mean normalized wall index, %	−0.0024	−0.0080, 0.0033	0.4133	0.0013	−0.0091, 0.0117	0.8108	−0.0014	−0.0102, 0.0073	0.7486
Stenosis, %	0.0038	−0.0043, 0.0118	0.3558	0.0048	−0.0035, 0.0131	0.2604	–	–	–
Presence of plaque components									
LRNC	0.1285	−0.2109, 0.4679	0.4581	0.2340	−0.0785, 0.5464	0.1422	0.2647	−0.0263, 0.5556	0.0746
IPH	−0.0179	−0.2080, 0.1723	0.8540	0.0329	−0.1573, 0.2232	0.7344	0.0651	−0.1168, 0.2470	0.4831
Calcification	0.0077	−0.2444, 0.2598	0.9525	0.0703	−0.1873, 0.3279	0.5928	0.0498	−0.2028, 0.3024	0.6994
Ulcer	−0.0617	−0.2748, 0.1514	0.5703	−0.0273	−0.2390, 0.1845	0.8008	0.0313	−0.1723, 0.2348	0.7635
FCR	−0.0059	−0.1971, 0.1853	0.9518	0.0447	−0.1465, 0.2358	0.6468	0.0919	−0.0900, 0.2738	0.3222
Volume of plaque components*									
LRNC, mm^3	−0.0002	−0.0004, 0.0001	0.3154	−0.0001	−0.0004, 0.0002	0.4464	−0.0000	−0.0004, 0.0003	0.8007
IPH, mm^3	0.0002	−0.0003, 0.0007	0.4735	0.0002	−0.0003, 0.0008	0.4326	0.0003	−0.0002, 0.0009	0.1948
Calcification, mm^3	−0.0014	−0.0028, −0.0000	0.0455	−0.0014	−0.0026, −0.0002	0.0255	−0.0011	−0.0022, −0.0000	0.0433
Ulcer, mm^3	−0.0018	−0.0070, 0.0035	0.5099	−0.0013	−0.0073, 0.0048	0.6828	−0.0009	−0.0061, 0.0044	0.7454
Maximum percentage of plaque component area*									
LRNC, %	0.0012	−0.0039, 0.0063	0.6437	0.0016	−0.0033, 0.0065	0.5227	0.0012	−0.0038, 0.0062	0.6465
IPH, %	0.0017	−0.0042, 0.0077	0.5732	0.0019	−0.0044, 0.0081	0.5592	0.0028	−0.0028, 0.0084	0.3248
Calcification, %	−0.0109	−0.0181, −0.0038	0.0026	−0.0114	−0.0187, −0.0042	0.0021	−0.0109	−0.0178, −0.0040	0.0020
Ulcer, %	−0.0084	−0.0250, 0.0083	0.3263	−0.0083	−0.0285, 0.0120	0.4227	−0.0056	−0.0236, 0.0125	0.5455
Cumulative slice of plaque components*									
LRNC	0.0025	−0.0248, 0.0297	0.8595	0.0087	−0.0182, 0.0357	0.5255	−0.0000	−0.0258, 0.0258	0.9995
IPH	0.0129	−0.0253, 0.0511	0.5089	0.0161	−0.0248, 0.0569	0.4403	0.0222	−0.0150, 0.0594	0.2419
Calcification	−0.0382	−0.0607, −0.0156	0.0009	−0.0408	−0.0631, −0.0186	0.0003	−0.0382	−0.0619, −0.0144	0.0016
Ulcer	0.0891	−0.0807, 0.2589	0.3038	0.1252	−0.0649, 0.3153	0.1968	0.1159	−0.0203, 0.2521	0.0953

*, only patients with the corresponding component present were included in the comparison. Model 1: adjusted for age, gender, education level and Fazekas score; Model 2: adjusted for age, gender, education level, Fazekas score, stenosis, coronary heart disease and antihypertensive treatment. MoCA, Montreal Cognitive Assessment; LRNC, lipid-rich necrotic core; IPH, intraplaque hemorrhage; FCR, fibrous cap rupture; RD, risk difference; ARD, adjusted risk difference.

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