Association of Plaque Morphology With Stroke Mechanism in Patients With Symptomatic Posterior Circulation ICAD

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Abstract

Background and Objectives
Although the main mechanisms of stroke in patients with intracranial atherosclerotic disease (ICAD)—perforating artery occlusion (PAO) and artery-to-artery embolism (AAE)—have been identified and described, relatively little is known about the morphology of the symptomatic plaques and how they differ between these 2 mechanisms.

Methods
We prospectively recruited patients with acute ischemic stroke in the posterior circulation that was attributable to ICAD. Fifty-one eligible patients were enrolled and underwent magnetic resonance imaging before being assigned to the PAO or AAE group according to probable stroke mechanism. Plaque morphological properties including plaque length, lumen area, outer wall area, plaque burden, plaque surface irregularity, vessel wall remodeling, and plaque enhancement were assessed using high-resolution MRI. Plaque morphological parameters of both PAO and AAE groups were compared using nonparametric tests. A binary logistic regression model was used to identify independent predictors while a receiver operating characteristic curve tested the sensitivity and specificity of the model.

Results
Among patients who met the imaging eligibility criteria, 38 (74.5%) had PAO and 13 (25.5%) had AAE. Plaque length was shorter (6.39 interquartile range [IQR, 5.18–7.7] mm vs 10.90 [IQR, 8.18–11.85] mm, \( p < 0.01 \)) in patients with PAO. Plaque burden was lower in PAO group (78.00 [IQR, 71.94–86.35] % vs 86.37 [IQR, 82.24–93.04] %, \( p = 0.04 \)). The proportion of patients with plaque surface irregularity was higher in patients with AAE than in patients with PAO (19/38, 50.00% vs 12/13, 92.30%, \( p = 0.008 \)). Plaque length was significantly associated with the PAO mechanism (adjusted OR 0.57, 95% CI, 0.41–0.79).

Discussion
Intracranial atherosclerotic plaque morphology differs between patients with PAO and those with AAE. Plaque with shorter length, lower plaque burden, and regular surface is more likely to cause PAO.

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Intracranial atherosclerotic disease (ICAD) is one of the leading causes of ischemic stroke worldwide, particularly in East Asian, Hispanic, and African American populations with high rates of morbidity and mortality. In contrast to symptomatic carotid artery stenosis where artery-to-artery embolism (AAE) has long been regarded as the main mechanism for stroke in the setting of moderate-to-severe internal carotid artery plaque, less is known about perforating artery occlusion (PAO) which may play a more important role in patients with ICAD. In the posterior circulation, ICAD is frequently present in the distal vertebral artery (VA) and the basilar artery (BA). In clinical practice, diffusion-weighted imaging (DWI) is used to explore the association between ischemic lesions responsible for stroke and intracranial atheromatous disease. It has been widely accepted that intracranial occlusive diseases often cause pontine or medullary infarcts in the supply zone of one of the paramedian branches of the BA or distal VA. Otherwise, artery-to-artery emboli from ICAD could potentially lead to cortical infarcts in the cerebellum or tempo-occipital lobe, or to multiple infarcts, including the “top of the basilar” syndrome. Despite a variety of possibilities, the specific properties that determine whether intracranial atherosclerotic plaques will be occlusive or embolic remains unclear.

Methods

Study Population
For this multicenter, observational study, we prospectively recruited patients with acute stroke with ICAD in the posterior circulation within 7 days of symptom onset. All patients underwent head HRMRI, MRA, and DWI. The etiologic origins of each stroke and its relevance to ICAD were determined by clinical neurologists using the ASCO (Atherosclerosis, Small vessel disease, Cardiac source, Other cause) stroke subtype classification. Patients were considered for inclusion if within the preceding week (1) they had an ischemic stroke in the distribution of posterior circulation, (2) a hyperintense signal was seen on DWI while an associated decrease in signal was seen on the apparent diffusion coefficient (ADC) map, and (3) symptomatic eccentric atherosclerotic plaques were identified within the intracranial posterior circulation, including the intracranial segment of VA (ICVA), the BA, and P1 segment of the posterior cerebral artery (PCA) on HRMRI. We then classified the mechanisms of ICAD into 2 groups—PAO and large-artery occlusive disease AAE based on previously published criteria (Figures 1 and 2). Patients with any of the following features were excluded from the analysis: (1) probable nonatherosclerotic vasculopathy, such as Moyamoya disease, vasculitis, or dissection; (2) evidence of cardioembolism; (3) coexistent > 50% extracranial VA stenosis or luminal irregularity.

Standard Protocol Approvals, Registrations, and Patient Consents
The Shanghai General Hospital Clinical Research Ethics Committee approved the study (Reference No. 2016KY164–3), and each participant provided written informed consent.

MRI Protocol
MRI was performed with a 3.0 Tesla MR Achieva scanner (Philips Healthcare, Best, Netherlands) and an eight-channel phased array coil within 7 days from the index stroke. All patients initially underwent conventional brain MRI, which included T1-weighted and T2-weighted imaging, T2 fluid-attenuated inversion recovery, DWI, ADC, and 3-dimensional (3D) time-of-flight (TOF) MRA. DWI was performed with the following parameters: a slice thickness of 5 mm (no gap between slices) with a matrix size of 128 × 128 mm, 24–30 axial slices, a field of view (FOV) of 240 mm, a standard spin echo echo-planar imaging sequence with a repetition time/echo time (TR/TE) = 4,528/103 ms. The 3D TOF MRA images were obtained using the following parameters: TR/TE = 23.0/3.5 ms,
HRMRI was obtained on the stenotic lesions identified by TOF-MRA. The 3D high-resolution black-blood (BBMRI) sequence was performed using a volumetric isotropic turbo spin echo acquisition (VISTA; Philips Healthcare, Best, Netherlands) in a coronal plaque (40-mm thick slab) optimized for flow suppression and intracranial vessel wall delineation. The BBMRI sequence were acquired using the following parameters: FOV = 200 × 167 × 45 mm, acquired resolution 0.6 × 0.6 × 1.0 mm, reconstructed resolution = 0.5 × 0.5 × 0.5 mm, TR/TE = 1500 ms/36 ms; turbo spin echo factor 56 echoes, echo spacing 4.0ms, sense factor 1.5 (right-left direction), scan time of 6.51 minutes. Before the acquisition of the contrast-enhanced T1 VISTA sequence, a gadolinium-containing contrast agent (Dotarem, Gadoteric acid 0.5 mmol/mL; Guerbet, Roissy CdG Cedex, France) was introduced intravenously (0.1 mmol per kilogram of body weight) and BBMRI was repeated 5 minutes after contrast material administration.

MRI Analysis

The lesion sites for evaluation of symptomatic atheromatous plaques were determined by 1 neurologist (Q.W.) and 1 neuroradiologist (J.Z.) with more than 25 years’ experience in interpreting and researching neurovascular images. In patients with more than 1 spatially separated, qualifying ICAD lesion, the plaque with the highest degree of luminal stenosis was measured. If any disagreements arose between the 2 senior clinicians, a third senior neuroradiologist’s decision was obtained. In this study, an acute infarct was defined as a hyperintense signal on DWI with an associated hypointense signal on the ADC map. Based on their size and number, infarcts were categorized as (1) small lesions (diameter <20 mm) or large lesions (diameter ≥20 mm); (2) single infarct (only 1 contiguous acute lesion identified on DWI) or multiple infarcts. Patients were assigned to 1 of 2 group according to probable stroke mechanism: PAO or AAE (Figures 1 and 2). The PAO group included patients with acute infarct(s) within the territory of the perforating artery that correlated with infarcts distributed in multiple distal branches where atherosclerotic plaque had occluded the oriifice (Figures 3 and 4). Plaque length was defined as plaque slices × slice thickness. Plaque length was calculated as WA/OWA × 100%. The OWAs at the reference sites (the distal and proximal sites) were also measured. The reference OWA (OWAreference) was defined as the mean of those sites (the distal and proximal sites) were also measured. The reference OWA (OWAreference) was defined as the mean of those sites (the distal and proximal sites) were also measured. The ratio (RR) was calculated as OWA/OWAreference. RR ≥ 0.95 was considered as positive remodeling, RR ≤ 0.95 negative remodeling, and 0.95 < RR < 1.05 as intermediate remodeling. Plaque surface was classified as irregular if there was a discontinuity of the plaque surface margin or a disruption of the plaque inner wall (Figures 2 and 4).

Figure 1 Flowchart of Participant Recruitment and Criteria for Imaging Analysis

Quantitative data were expressed as median (interquartile range [IQR]) and compared using a between-groups Mann-Whitney test. Categorical variables were summarized as count (percentage) and analyzed using the χ² test or the Fisher exact test. Furthermore, in a multiple binary logistic regression model, we tested for an independent relationship between plaque features and the stroke mechanisms of PAO and AAE after adjusting for factors with p < 0.10 in univariable logistic regression analyses. Variables with p values less than 0.1 from
univariate analyses were considered candidate predictors, and Forward: LR was used to select variables including plaque length, plaque burden, and stenosis degree. The receiver operating characteristic (ROC) curve was calculated based on the logistic regression model. The highest value of the Youden index was used to determine the cut-off point for the model-predicted probability that reported the sensitivity and specificity of the model. A p value of less than 0.05 indicated statistical significance. Inter-reader reliability was assessed by using intraclass correlation coefficients (ICCs) with a two-way random effects model for continuous variables. Reliabilities less than 0.4 were considered as poor, 0.4–0.75 as fair, and above 0.75 as excellent. All statistical analyses were performed using SPSS 23.0 (IBM SPSS Inc, Chicago, IL).

Results

Participant Characteristics

From March 2017 to May 2019, we recruited 51 patients with acute stroke with symptomatic ICAD in the posterior circulation; 38 with PAO, and 13 with AAE (see Table 1 for patient demographic data). Traditional stroke risk factors were similar between the 2 groups. In the PAO group, most of the infarcts were detected in the pons (36/46, 78.3%), yet in AAE group, the 34 infarcts seen in the group’s images were located in numerous different regions within the posterior circulation, with larger concentrations in the cerebellum (9/34, 26.5%) and occipital lobe (6/34, 17.6%).
Plaque Morphology and Infarct Patterns

Plaque morphological characteristics are summarized in Table 2. In the PAO group, we found that symptomatic plaques were commonly located in the BA (30/38, 78.9%), while in the AAE group, most of the lesions were found in the intracranial VA (5/13, 38.5%) and the BA (6/13, 46.2%). Compared with the PAO group, the degree of stenosis was significantly higher (55 [48–66] % vs 69 [65–77]%, p = 0.001) in the AAE group, and the degree of plaque burden in the PAO group was significantly lower than that in the AAE group (78.00 [71.94–86.35]% vs 96.37 [82.24–93.04]%, p = 0.04). Of the 51 symptomatic plaques, 33 (64.7%) showed contrast enhancement, and no significant differences were identified between the PAO and AAE groups in this area. Plaque length in patients with PAO was significantly shorter than that seen in patients with AAE (6.39 [5.18–7.71] mm vs 10.90 [8.18–11.85] mm, p < 0.01). Among the 51 ICAD plaques detected in the posterior circulation, positive remodeling was identified in 31 (60.8%) plaques and negative remodeling was seen in 18 (35.3%). There were no significant differences between the 2 groups in the positive to negative ratio of remodeling in plaque areas (Table 2).

Figure 3 High-Resolution MRI (HRMRI) of Basilar Artery Plaque With Perforating Artery Infarct

A transverse MRI showed an acute left pontine infarct (arrow) on DWI (A) with mild stenosis (arrow) in basilar artery on MRA (B). HRMRI showed an eccentric wall thickening (arrow) in corresponding site with contrast enhancement in cross-section imaging (C and D, the plaque enclosed by blue contour represents the outer wall area and yellow contour represents lumen area). Arrow showed regular plaque surface in long axis of HRMRI (E). Abbreviation: DWI = diffusion-weighted imaging.

Figure 4 High-Resolution MRI (HRMRI) of Basilar Artery Plaque With Artery-to-Artery Emboli

A patient with multiple acute infarcts in cerebellum and bilateral occipital lobe (arrow) on DWI (A) with severe stenosis (arrow) in basilar artery on MRA (B). HRMRI showed an eccentric wall thickening (arrow) in corresponding site with contrast enhancement in cross-section imaging (C), the plaque enclosed by blue (outer wall area) and yellow (lumen area) contour. Arrow showed irregular plaque surface in long axis of HRMRI (D). Abbreviation: DWI = diffusion-weighted imaging.
Plaque surface irregularity was identified in 31 (60.8%) patients and was more likely to be found in the AAE group (19/38, 50.0% vs 12/13, 92.3%, p = 0.008). Irregular plaque surface was more common in patients with multiple infarcts (19/27, 70.4% vs 12/24, 50.0%, p = 0.161) (Table 3). Among the 51 patients with ICAD in the posterior circulation, we found small-size infarcts in 42 (82.4%) patients and a single infarction in 24 (47.1%). The proportion of small-size infarctions (34/38, 89.5% vs 8/13, 61.5%, p = 0.003) and single infarction (23/38, 60.5% vs 1/13, 7.7%, p = 0.001) were significantly higher in PAO group (Table 2).

A binary logistical regression was used to identify independent predictors of plaques related to PAO. We found that plaque length was independently associated with the PAO mechanism (adjusted OR 0.573, 95% CI, 0.41–0.79, p = 0.001). The area under the ROC curve was 0.86 (95% CI, 0.74–0.92), which provided a sensitivity of 76.3% and a specificity of 92.3% in predicting PAO. No evidence of multicollinearity was found in our regression analyses.

**Measurement Reliability**

The inter-reader reliability for LA, OWA, RR, and plaque length with ICC (95% CI) were 0.90 (0.80–0.95), 0.84 (0.70–0.92), 0.893 (0.79–0.94), and 0.76 (0.54–0.87), respectively.

**Discussion**

In this hospital-based multicenter study, we reported the morphological features of symptomatic plaques in the intracranial posterior circulation and their possible correlation with stroke mechanisms. Our study provided evidence that plaque features differ between patients with PAO and patients with AAE. Compared with plaques in the AAE group, plaques in the PAO group had a shorter length, a lower plaque burden, and a relatively regular surface. Plaque length was independently associated with PAO.

For several decades, lumen stenosis has been the primary object studied in many investigations focused on symptomatic ischemic events. However, with the recent advances in neuroimaging technology, some factors have been both verified and shown to be at least equally (if not more) effective in the evaluation of ischemic stroke than the older methods.

The vessel wall imaging using HRMRI is sensitive enough to enable the delineation of vessel wall changes caused by intracranial atherosclerosis or other etiologies, such as vasculitis or dissection. For stroke patients with intracranial atherosclerosis, adding a group of measurable morphological features (e.g., plaque burden, plaque length, lesion eccentricity, and remodeling ratio) to the time-tested lumen stenosis identification may improve clinician’s ability to detect the presence of ICAD in the posterior circulation, categorize symptomatic plaque, and quantitatively assess the degree of stroke risk and/or recovery potential.

Apart from predicting the occurrence of ischemic events, the new imaging features could also be used to infer the underlying mechanism, together with other information such as location, size, or number of brain infarcts. PAO could be the result of atherosclerotic plaques without causing lumen narrowing >50% identified on MRA. In a HRMRI study among patients with paramedian pontine infarction, HRMRI detected a plaque in 61.5% of patients, whereas only 35% had BA lumen stenosis on conventional TOF MRA. Therefore, ASCO (Atherosclerosis, Small vessel disease, Cardiac source, Other cause) stroke subtype classification proposed HRMRI as a useful method to identify stroke phenotype characterization and mechanism.

In the PAO group, most of these infarcts were found in the pons close to the responsible vessels. Furthermore, isolated lesions are commonly detected in this type of infarct. By contrast, in the AAE group, multiple infarcts were common and often found in distal regions of the posterior circulation, especially the cerebellum and the occipital lobe. This result is consistent with a previous study that found the cerebellum is often involved in atherosclerotic strokes when there are multiple infarcts. We also found that in both groups, half of the responsible vessels were in the BA. Studies indicated that in strokes caused by intracranial atherosclerosis, symptomatic plaques were most often detected in the middle BA. Of note, the authors of a study also found that plaques located at this site presented at a higher rate in recurrent strokes or death.
Regarding plaque burden, a larger plaque volume may increase stroke risk due to more severe lumen narrowing or PAO. Our study indicated that a higher atherosclerosis burden was more likely to cause AAE, which concurs with studies of symptomatic carotid artery stenosis.6,7 A study of Hong Kong Chinese who had acute strokes with moderate-to-severe middle cerebral artery stenosis (>50-99%) showed that (1) multiple cerebral emboli is an important mechanism of cerebral infarcts and (2) microembolic signals were detected in 9 (60%) patients with multiple infarcts and in 1 (6.6%) patient with a single infarct.34 In previous studies of anterior circulation, researchers suggested that in MCA strokes, plaque burden tended to be lower in deep perforator infarctions in asymptomatic atherosclerotic plaque.28,35 Similarly, we also observed that the plaque burden appeared significantly lower in cases of PAO of posterior circulation.

As for plaque length, we found that it was significantly shorter in patients with PAO compared with those with AAE. A logistic regression model also showed that plaque length may serve as an independent predictor of PAO or AAE as a mechanism for stroke. Knowledge from an extracranial carotid atherosclerosis (>65% stenosis) study indicated that carotid plaque length was a significant variable (in addition to

<table>
<thead>
<tr>
<th>Location of symptomatic plaques</th>
<th>PAO (n = 38)</th>
<th>AAE (n = 13)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial vertebral artery</td>
<td>7 (18.4%)</td>
<td>5 (38.5%)</td>
<td></td>
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<tr>
<td>Basilar artery</td>
<td>30 (78.9%)</td>
<td>6 (46.2%)</td>
<td></td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>1 (2.6%)</td>
<td>2 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>LA (mm²)</td>
<td>5 (3–10)</td>
<td>4 (2–19)</td>
<td>0.115</td>
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<tr>
<td>OWA (mm²)</td>
<td>25 (19–45)</td>
<td>20 (17–70)</td>
<td>0.252</td>
</tr>
<tr>
<td>Plaque burden (%)</td>
<td>78.00 (71.94–86.35)</td>
<td>86.37 (82.24–93.04)</td>
<td>0.04²</td>
</tr>
<tr>
<td>Stenosis degree (%)</td>
<td>55 (48–66)</td>
<td>69 (65–77)</td>
<td>0.001²</td>
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<tr>
<td>Plaque enhancement</td>
<td>22 (57.89%)</td>
<td>11 (84.61%)</td>
<td>0.103</td>
</tr>
<tr>
<td>Plaque length (mm)</td>
<td>6.39 (5.18–7.71)</td>
<td>10.90 (8.18–11.85)</td>
<td>&lt;0.01²</td>
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<tr>
<td>Remodeling ratio</td>
<td>1.14 (0.88–1.40)</td>
<td>1.12 (0.87–1.99)</td>
<td>0.489</td>
</tr>
<tr>
<td>Vessel wall remodeling</td>
<td></td>
<td></td>
<td>0.626</td>
</tr>
</tbody>
</table>

| Positive                                              | 23 (60.5%)   | 8 (61.5%)    |         |
| Intermediate                                          | 1 (2.6%)     | 1 (7.7%)     |         |
| Negative                                              | 14 (36.8%)   | 5 (30.8%)    |         |
| Small-size infarct                                     | 34 (89.5%)   | 8 (61.5%)    | 0.036²  |
| Single infarct                                         | 23 (60.5%)   | 1 (7.7%)     | <0.01²  |

PAO, perforating artery occlusion; AAE, artery-to-artery embolism; LA, lumen area; OWA, outer wall area.
² Mann-Whitney U test.
² Fisher exact test.

### Table 3 Plaque Surface Irregularity

<table>
<thead>
<tr>
<th></th>
<th>Multiple infarcts</th>
<th>Single infarct</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Irregularity</td>
</tr>
<tr>
<td>PAO</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>AAE</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>19/27 (70.4%)³</td>
</tr>
</tbody>
</table>

PAO = perforating artery occlusion; AAE = artery-to-artery embolism.
³ PAO vs AAE (p = 0.008, Fisher exact test).
² Multiple vs single (p = 0.161, Pearson chi-square).
degree of stenosis), in predicting compromise of ipsilateral carotid blood flow in patients undergoing carotid revascularization. Similar findings were obtained in another study in patients with symptomatic carotid artery atherosclerosis whose carotid plaque length was independently associated with microembolic signals. This mechanism may help explain why increasing plaque length is related to AAE.

In addition, we noted significant plaque surface irregularity in the AAE group compared with the PAO group. A study defined surface irregularity as a discontinuity of the surface or disruption of the plaque inner wall. Another study reported that such surface irregularity was strongly related to symptomatic stroke and multiple infarcts. Multiple infarcts, usually refer to artery-to-artery emboli and present the most common pattern in both anterior and posterior circulation. As we speculate, atherosclerosis with surface irregularity may indicate the presence of plaque ulceration. Several studies have reported that plaque ulceration was the main source of microemboli and had an association with recent ischemic symptoms.

The problem of vessel wall remodeling has been investigated in numerous studies. Positive remodeling is a term describing the compensated enlargement of a vessel wall in response to changing hemodynamics or other factors. Generally speaking, enlarged arteries provide greater volume/blood supply in the presence of atherosclerotic plaques. However, in many cases, that volume can actually be considered as a red flag for unstable plaque which is not only inclined to rupture but also can occlude arteries downstream and thus lead to more damaging ischemic events. In our study, we found that positive remodeling happened with equal frequency in both the PAO and AAE groups. Several studies indicated that symptomatic plaques had higher remodeling ratios and frequency of positive remodeling. Beyond that, positive remodeling is generally related to other aspects of ischemic stroke. The authors of a study proposed that positive remodeling is related to serious clinical symptoms. They measured the NIHSS scores of patients with stroke and found that scores were higher in patients with positive remodeling than in those with negative remodeling. Through the use of transcranial color Doppler, the authors of a study found that greater numbers of microemboli were detected in patients with positive remodeling. In our research, while the prevalence of positive remodeling proved to be similar between the PAO and AAE groups, the remodeling ratio was higher in the AAE group but not statistically significant.

Of note, our study has indicated that plaques with longer length and irregular surfaces present a greater risk for artery-to-artery emboli. With this in mind, we hypothesize that, the greater the plaque burden, the more unstable the inner substance and the more likely it would be to damage the plaque surface and form thrombin that could embolize downstream. Considering that intracranial plaques with long length, greater plaque burden, and irregular surface may be responsive to dual antiplatelet therapy, and antiplatelet therapy has been shown to reduce microemboli in carotid stenosis, we believe our findings have therapeutic implications for early detection with HRMRI and treatment with dual antiplatelet therapies.

Our study has several limitations. First, previous studies found that atherosclerosis affected both the extracranial VA (ECVA) and the intracranial posterior circulation equally. The main mechanism of symptomatic ECVA is AAE. In our series, patients with ECVA stenosis were not recruited, which leads to fewer patients in the AAE group. Second, when evaluating the vessel wall with HRMRI, the interpreters were not blind for the ICAD stroke subtype, which may have influenced their views of the data analysis. Fourth, in our study, all intracranial posterior circulation arteries, including ICVA, BA, and PCA, were analyzed together to explore the mechanism of stroke. In different cohorts, the proportion of vessels may be variable, which may, in turn, have some degree of influence on our results. Owing to the limited sample size, no vessel-specific studies on BA or ICVA were performed. Finally, plaque morphology data on HRMRI such as intraplaque hemorrhage, calcification, and plaque volume were not included as outcome variables here and thus will be targets for analysis in future studies.

Overall, our findings showed that HRMRI is helpful for exploring symptomatic atherosclerotic plaque morphology in the posterior circulation with PAO or AAE. Plaque with short length and a regular surface was associated with PAO, while plaque with long length, greater plaque burden, and an irregular surface was highly suggestive of an unstable lesion that might lead to AAE. Further longitudinal studies are required to evaluate the plaque morphology dynamically, which is likely to be helpful in providing individualized therapies as we gain a clearer and deeper understanding of the mechanisms of ischemic stroke caused by symptomatic ICAD.

Acknowledgment
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