Plaque morphology in acute symptomatic intracranial atherosclerotic disease

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ABSTRACT

Background Intracranial atherosclerotic disease (ICAD) is globally a major ischaemic stroke subtype with high recurrence. Understanding the morphology of symptomatic ICAD plaques, largely unknown by far, may help identify vulnerable lesions prone to relapse.

Methods We prospectively recruited patients with acute ischaemic stroke or transient ischaemic attack attributed to high-grade ICAD (60%–99% stenosis). Plaque morphological parameters were assessed in three-dimensional rotational angiography, including surface contour, luminal stenosis, plaque length/thickness, upstream shoulder angulation, axial/longitudinal plaque distribution and presence of adjoining branch atheromatous disease (BAD). We compared morphological features of smooth, irregular and ulcerative plaques and correlated them with cerebral ischaemic lesion load downstream in MRI.

Results Among 180 recruited patients (median age=60 years; 63.3% male; median stenosis=75%), plaque contour was smooth (51 (28.3%)), irregular (101 (56.1%)) or ulcerative (28 (15.6%)). Surface ulcers were mostly at proximal (46.4%) and middle one-third (35.7%) of the lesions. Most (84.4%) plaques were eccentric, and half had their maximum thickness over the distal end. Ulcerative plaques were thicker (medians 1.6 vs 1.3 mm; p=0.003), had steeper upstream shoulder angulation (56.2° vs 31.0°; p<0.001) and more adjoining BAD (83.3% vs 57.0%; p=0.033) than non-ulcerative plaques. Ulcerative plaques were significantly associated with coexisting acute and chronic infarcts downstream (35.7% vs 12.5%; adjusted OR 4.29, 95% CI 1.65 to 11.14, p=0.003). Sensitivity analyses in patients with anterior-circulation ICAD lesions showed similar results in the associations between the plaque types and infarct load.

Conclusions Ulcerative intracranial atherosclerotic plaques were associated with vulnerable morphological features and had a higher cumulative infarct load downstream.

INTRODUCTION

Intracranial atherosclerotic disease (ICAD) is a major ischaemic stroke subtype of high recurrence.1 In the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, risk of recurrent stroke or death for patients with high-grade ICAD was 12.6% in the first year despite optimal medical treatment.2 In the Chinese Intracranial Atherosclerosis study, a population-based cohort, 15% of ICAD patients with multiple vascular risk factors had stroke recurrence over 1 year.3

In contrast to coronary/carotid artery plaques where established imaging features might predict a myocardial or cerebral ischaemic event,4–9 the morphology of ICAD lesions immediately after or portending a stroke was largely unknown. The sole parameter forecasting stroke relapse in symptomatic ICAD had been ‘luminal stenosis’ which, however, might imply distal perfusion deficit alone but would not account for stroke mechanisms like artery-to-artery thromboembolism, lacunar syndrome from junctional atheroma or branch hypoperfusion.10 11 Of note, luminal narrowing in a third of ICAD lesions was only moderate at stroke onset, suggesting that factors beyond stenotic severity might also govern the stroke risks in patients with ICAD.

Therefore, a study on plaque morphology in acute symptomatic ICAD might improve our understanding of stroke occurrence/recurrence and inform treatment strategy.5 12 13 In this study, we assessed ICAD plaque morphology by three-dimensional rotational angiography (3DRA), a catheter-based technique that enabled angiarchitectural evaluation from a near-infinite number of planes and could reveal plaque morphology and further subordinate branch/perforator patency in a superior spatial resolution compared with conventional digital subtraction angiography.14 15 We compared morphological features of plaques with smooth, irregular and ulcerative contour and correlated the plaque morphological features with downstream cerebral ischaemic lesion load in MRI.

MATERIALS AND METHODS

Study design and subjects

This was a prospective, investigator-initiated multicentre-referral study. We recruited adult patients with acute ischaemic stroke or transient ischaemic attack (TIA) within 4 weeks of symptom onset, attributed to...
high-grade ICAD (60%–99% stenosis) as confirmed in 3DRA. TIA was defined as a transient episode of neurological dysfunction caused by focal brain or retinal ischaemia that completely resolved within 24 hours. All patients underwent brain MRI. The stroke aetiology and relevance to ICAD were determined by neurologists, based on clinical syndrome, imaging features and concurrent cardiovascular risk factors. We excluded patients with probable non-atherosclerotic stenosis (eg, moyamoya disease, vasculitis or dissection), evidence of cardioembolism (eg, atrial fibrillation, valvular heart disease or myocardial infarction within 6 weeks), concurrent tandem >70% extracranial carotid or vertebral artery (VA) stenosis and contradictions to MRI and 3DRA. In this observational study, all patients received guideline-based treatment that evolved with emerging evidence. Of note, participants recruited before SAMMPRIS received lifelong single antiplatelet treatment (aspirin), whereas those recruited after SAMMPRIS had short-term dual antiplatelets (aspirin plus clopidogrel) immediately after the index stroke, followed by lifelong aspirin. All patients received statins with a low-density lipoprotein target of <70 mg/dL (1.8 mmol/L). Other goals of cardiovascular risk control, if applicable, included an HbA1c <6.5% and a systolic blood pressure <140 mm Hg.

3DRA and plaque morphology evaluation
In a neuroangiographic unit (Integris BN 3000 Neuro; Philips Medical Systems, Best, the Netherlands), we performed 3DRA within 4 weeks from the index stroke/TIA. A total volume of 20–25 mL Iopamiro300 was injected by an automated machine (2.0–2.5 mL/s) through a 4F endovascular catheter perching at the internal carotid artery (ICA)-C2 segment for distal ICA or middle cerebral artery (MCA)-M1 lesions, or at VA-V2 segment for vertebrobasilar lesions. 3DRA images were then reconstructed from 200 non-subtracted images captured during a 4s 180° rotation of the C-arm around the lesion of interest with a maximal matrix of 512×512×512. One investigator (XL) with over 8 years’ experience in interpreting and researching neurovascular images evaluated the culprit ICAD lesions in 3DRA in a Philips Allura Xper FD20/20 biplane neuro X-ray system (Koninklijke Philips N.V.). The plaque surface contour was classified into smooth, irregular (undulating plaque surface lining) or ulcerative subtype (figure 1A,B,C). An ulcerative plaque was characterised by invagination of contrast beneath the endoluminal lining or have an upstream or downstream slope >90°. In a plane that maximally displayed the luminal stenotic severity, we measured lesion length, per cent luminal stenosis, maximum plaque thickness, upstream plaque shoulder angulation and eccentricity index (figure 1). Whereas the assessment of surface contour, adjoining branch atheromatous disease (BAD) and axial plaque load distribution was based on 360° rotatory full-profile views of the target lesion. In patients with more than one spatially separated qualifying ICAD lesions, the lesion with the highest degree of luminal stenosis was assessed. Uncertainties in classification and measurement were resolved by consulting a senior neurologist. The plaque surface lining) or ulcerative subtype (figure 1A,B,C). An ulcerative plaque was characterised by invagination of contrast beneath the endoluminal lining or have an upstream or downstream slope >90°. In a plane that maximally displayed the luminal stenotic severity, we measured lesion length, per cent luminal stenosis, maximum plaque thickness, upstream plaque shoulder angulation and eccentricity index (figure 1). Whereas the assessment of surface contour, adjoining branch atheromatous disease (BAD) and axial plaque load distribution was based on 360° rotatory full-profile views of the target lesion. In patients with more than one spatially separated qualifying ICAD lesions, the lesion with the highest degree of luminal stenosis was assessed. Uncertainties in classification and measurement were resolved by consulting a senior neurologist and a neurointerventionalist with 15 years’ experience in neurointervention (TWL). We tested intrarater (XZ) and inter-rater (XZ and YP) reproducibility for the 3DRA measurements in 24 cases. We measured percent luminal stenosis by Warfarin-Aspirin Symptomatic Intracranial Disease method. Maximum plaque thickness was the height from the stenotic throat down to an extrapolated vessel wall drawn from both ends of the plaque, assuming natural tapering of the artery (figure 1D). Upstream plaque shoulder angulation was the angle between the proximal vessel wall and the extrapolated vessel wall (figure 1E,F). We recorded the maximal plaque load over proximal, middle and distal one-thirds of the plaque in a longitudinal view (figure 1G,H,I). In a cross-sectional axial view, we assessed the plaque load over the superior, inferior, ventral and dorsal walls of MCA-M1 lesions, or the lateral, ventral and dorsal walls of basilar artery (BA) lesions. The circumferential plaque distribution was numerically expressed by eccentricity index, calculated as (maximum plaque thickness – minimum plaque thickness) / maximum plaque thickness. Plaques were eccentric if eccentricity index was >0.5 or concentric if <0.5 (figure 1J,K).

Orificial narrowing of an adjacent branch/perforator >50% by a contiguous and morphologically inseparable plaque extending from the parent artery plaque defined ‘adjointing BAD’ (figure 1G,J). For MCA lesions, we scrutinised lenticulostrate artery, anterior temporal artery and, occasionally, an early M2 branch emanating from the horizontal MCA segment. For BA lesions, we examined superior cerebellar artery and anterior inferior cerebellar artery.

Cerebral ischaemic lesion assessment in MRI
Each participant received a brain MRI examination on a 1.5 tesla (Siemens Sonata, Germany) or 3.0 tesla MR scanner (Achieva 3.0T Philips, Netherlands), including axial T1-weighted and T2-weighted imaging, diffusion-weighted imaging (DWI), apparent diffusion coefficient mapping, T2 fluid-attenuated inversion recovery and time-of-flight MR angiography within a week from the index stroke/TIA. One investigator (XL) assessed
Cerebrovascular disease

the cerebral ischaemic lesion load over the corresponding territory of a diseased intracranial artery. Evaluation of the MR images was at least 1 month after the 3DRA assessments, and the reviewer was blinded to the plaque morphological features except for the location of the culprit ICAD lesion. Acute infarct(s) was defined by high signal in DWI with low signal in apparent diffusion coefficient maps, and chronic infarct(s) was defined by high signal in T2 fluid-attenuated inversion recovery imaging and iso-intensity or high-intensity signal in apparent diffusion coefficient maps. We classified the infarct load in the corresponding territory as: (A) no infarct, (B) acute infarct(s) only or chronic infarct(s) only or (C) coexisting acute and chronic infarcts. We correlated cerebral ischaemic lesion load with clinical and 3DRA findings.

Statistical analysis

We used IBM SPSS Statistics V.24.0 for statistical analyses. A two-sided p<0.05 was considered statistically significant. Continuous variables were expressed in medians (IQR) and categorical variables in numbers (percentages). Missing data were presented intrarater and inter-rater correlation coefficients represented intrarater and inter-rater reproducibility for categorical and continuous variables. We used Wilcoxon rank-sum tests or Kruskal-Wallis tests for univariable comparisons of continuous variables and χ2 tests or Fisher’s exact tests for categorical variables, in patients with different plaque types and in those with different infarct loads. Following a significant Kruskal-Wallis test, pairwise comparisons were conducted using the Dunn-Bonferroni post hoc method.

In univariable binary logistic regression analyses, we tested the associations of coexisting acute and chronic infarcts with demographics, clinical features and lab testing results, and culprit ICAD plaque types. In a multivariable binary logistic regression model, we tested for an independent relationship between plaque types and coexisting acute and chronic infarcts after adjusting for factors with p<0.10 in univariable logistic regression analyses. Crude and adjusted ORs with the 95% CIs were obtained. The logistic regression analyses were performed among all patients, and in patients with anterior circulation ICAD (sensitivity analysis).

Data availability

Anonymised data that support the findings of this study are available from the corresponding author on reasonable request from qualified investigators.

RESULTS

Demographics and clinical features

From May 2007 to February 2018, we recruited 180 acute stroke patients with high-grade, symptomatic ICAD. The median age was 60 years (IQR 54–68), and 114 patients (63.3%) were male; 143 (79.4%), 123 (68.3%) and 64 (35.6%) patients, respectively, had a history of dyslipidaemia, hypertension and diabetes; 84 (46.7%) patients were smokers. The qualifying events were ischaemic strokes in 141 (78.3%) and TIA in 39 patients (21.7%). The median National Institutes of Health Stroke Scale on admission was 1 (IQR 1–3).

ICAD plaque morphology

The median interval between stroke onset and 3DRA was 23 days (IQR 13–32). Table 1 summarises the morphological features of the 180 ICAD plaques. Among the 180 lesions, 132 were in MCA-M1, 26 in terminal ICA, 6 spanning across terminal ICA and MCA-M1, 14 in BA and 2 in VA. Intrarater (0.82–0.87) and inter-rater reproducibility (0.76–0.81) for the measurements were moderate to good in 24 cases.

The median luminal stenosis was 75% (IQR 71–84). Plaque contour was smooth (n=51; 28.3%), irregular (n=101; 56.1%) or ulcerative (n=28; 15.6%). There were 30 plaque surface ulcers identified in 28 ulcerative plaques. These surface ulcers indicative of fibrous cap rupture was found most frequently at the proximal (n=13; 46.4%) and middle one-third (n=10; 35.7%) of the plaques and relatively less at the distal end (n=7).

Table 1  Morphological characteristics of all plaques and comparisons of different plaque types

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall (N=180)</th>
<th>Smooth (n=51)</th>
<th>Irregular (n=101)</th>
<th>Ulcerative (n=28)</th>
<th>P value †</th>
<th>Smooth and irregular plaques (n=152)</th>
<th>P value †</th>
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<tr>
<td>Location of the qualifying ICAD lesions</td>
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<tr>
<td>MCA-M1</td>
<td>132 (73.3)</td>
<td>45 (88.2)</td>
<td>72 (71.3)</td>
<td>15 (53.6)</td>
<td>0.035</td>
<td>117 (77.0)</td>
<td>0.048</td>
</tr>
<tr>
<td>Terminal ICA</td>
<td>26 (14.4)</td>
<td>4 (15.4)</td>
<td>14 (13.9)</td>
<td>8 (28.6)</td>
<td>0.003</td>
<td>26 (13.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>Across terminal ICA and proximal MCA</td>
<td>6 (3.3)</td>
<td>0 (0)</td>
<td>4 (4.0)</td>
<td>2 (7.1)</td>
<td>0.007</td>
<td>4 (2.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>VA-V4 or BA</td>
<td>16 (8.9)</td>
<td>2 (12.5)</td>
<td>11 (10.9)</td>
<td>3 (10.7)</td>
<td>0.007</td>
<td>13 (6.8)</td>
<td>0.007</td>
</tr>
<tr>
<td>Arterial luminal stenosis, %</td>
<td>75 (71–84)</td>
<td>73 (70–79)</td>
<td>78 (72–86)</td>
<td>77 (72–81)</td>
<td>0.027</td>
<td>75 (70–85)</td>
<td>0.876</td>
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<tr>
<td>Maximal plaque thickness, mm</td>
<td>1.3 (1.2–1.6)</td>
<td>1.3 (1.1–1.5)</td>
<td>1.3 (1.2–1.6)</td>
<td>1.6 (1.3–1.9)</td>
<td>0.007</td>
<td>1.3 (1.1–1.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Plaque length, mm</td>
<td>9.0 (6.9–11.6)</td>
<td>7.0 (5.8–8.7)</td>
<td>10.1 (8.0–13.2)</td>
<td>9.0 (6.2–14.9)</td>
<td>&lt;0.001</td>
<td>9.0 (6.9–11.6)</td>
<td>0.873</td>
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<tr>
<td>Eccentricity index</td>
<td>0.87 (0.63–1.00)</td>
<td>0.87 (0.68–1.00)</td>
<td>0.83 (0.59–1.00)</td>
<td>1.00 (0.80–1.00)</td>
<td>0.164</td>
<td>0.85 (0.62–1.00)</td>
<td>0.107</td>
</tr>
<tr>
<td>Eccentric plaque</td>
<td>152 (84.4)</td>
<td>44 (86.3)</td>
<td>83 (82.2)</td>
<td>25 (89.3)</td>
<td>0.599</td>
<td>127 (83.6)</td>
<td>0.442</td>
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<tr>
<td>Upstream plaque shoulder angulation,°</td>
<td>33.4 (23.4–46.4)</td>
<td>28.0 (21.1–43.6)</td>
<td>33.1 (24.5–43.4)</td>
<td>56.2 (30.6–94.2)</td>
<td>&lt;0.001</td>
<td>31.0 (22.5–43.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>Maximal stenosis distribution in the longitudinal axis of the lesion</td>
<td>0.416</td>
<td>0.321</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Values are medians (IQR) or numbers (%); Kruskal-Wallis tests or Wilcoxon rank-sum tests were used for comparison of continuous variables and χ2 tests for categorical variables. †P values for comparisons among smooth, irregular and ulcerative plaques. ‡P values for comparisons between ulcerative plaques and other plaques.

ICAD, intracranial atherosclerotic disease; MCA-M1, M1 middle cerebral artery; ICA, internal carotid artery; VA-V4, V4 vertebral artery; BA, basilar artery.
and were more frequently associated with adjoining BAD (83.3\% vs 57.0\%; p=0.033). Table 1 summarises the morphological characteristics of smooth, irregular and ulcerative plaques.

**Cerebral ischaemic lesion load and plaque types**

The median interval between symptom onset and the MRI exam was 3 days (IQR 2–7). Of the infarct load in the corresponding territory, 26 patients (14.4\%) had no infarct; 125 patients (69.4\%) had acute infarct(s) only or chronic infarct(s) only; and 29 (16.1\%) patients had coexisting acute and chronic infarcts.

Univariable and multivariable analyses for predictors of coexisting acute and chronic infarcts, in all patients and in patients with an anterior circulation lesion, are shown in tables 2 and 3 and online supplemental table 2 and 3. Comparing the three patterns of progressive infarct load, plaque morphology and clinical parameters (age, hypertension, diabetes, glycosylated haemoglobin and fasting blood glucose at the index stroke and plaque type) differed among the groups. Compared with the remaining patients, those with coexisting acute and chronic infarcts were more likely to have a history of hypertension (89.7\% vs 64.2\%; p=0.007) and ulcerative plaques (34.5\% vs 11.9\%; p=0.007) (table 2).

In univariable logistic regression analyses, history of hypertension (crude OR=4.83; 95\% CI 1.40 to 16.68; p=0.013) and ulcerative plaques (crude OR vs otherwise=3.89; 95\% CI 1.57 to 9.66; p=0.003) were significantly associated with coexisting acute and chronic infarcts in the corresponding territory (online supplemental table 3). In multivariable logistic regression analysis, patients harbouring ulcerative plaques were significantly more likely to have coexisting acute and chronic infarcts in the downstream vascular territory (35.7\% vs 12.5\%; crude OR=3.89, 95\% CI 1.57 to 9.66, p=0.003; adjusted OR=4.29, 95\% CI 1.65 to 11.14, p=0.003) than those with smooth or irregular plaques (table 3). Sensitivity analyses among patients with an anterior circulation lesion (n=164) showed similar results in univariable analyses (online supplemental table 2) and multivariable analyses (table 3). Figure 3 shows the MRI and 3DRA images of a patient with an ulcerative MCA-M1 plaque and coexisting acute and established infarcts in the corresponding cortical and subcortical regions, including the internal and posterior borderzones.

**DISCUSSION**

In a prospective multicentre-referral study, we reported the morphology of acute symptomatic intracranial atherosclerotic plaques by 3DRA and correlated the plaque morphology with the downstream cerebral ischaemic lesion load. In summary, plaque contour was mostly irregular or ulcerative at the acute stage. Surface ulcers indicative of plaque rupture were mostly present over the upstream plaque region. By axial view, over 80\% of the plaques were noted to be eccentric. By longitudinal view, the luminal plaque load was found disproportionally skewed to the distal end in half of the lesions. Compared with non-ulcerative plaques, ulcerative lesions had a significantly higher luminal plaque load, a steeper upstream shoulder and more adjoining BAD. Of note, ulcerative plaque was independently associated with more cumulative (ie, chronic plus acute) infarcts at the downstream regions.

As an imaging marker of fibrous cap rupture, plaque ulcer and the associated morphological features are potential clues to lesion vulnerability. In terms of atherosclerosis burden, a larger plaque volume may increase stroke risk by causing more severe luminal narrowing or perforator/branch jailing. Plaque rupture

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**Figure 2** Maximal stenosis distribution in 132 MCA-M1 plaques and 14 BA plaques by axial and longitudinal views. A darker colour indicates a higher frequency. Upper panel: frequencies of cases with the maximum plaque thickness located over the superior, inferior, ventral and dorsal walls of MCA-M1 (left) or over the ventral, dorsal and lateral walls of BA (right). Lower panel: frequencies of cases with the maximum plaque thickness located at the proximal, middle or distal one-third along the longitudinal axis of MCA-M1 (left) and BA (right) plaques. BA, basilar artery; MCA-M1, M1 middle cerebral artery.

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**Morphological differences of smooth/irregular/ulcerative plaques**

Demographics, history of vascular risk factors or lab results did not differ between patients with or without ulcerative plaques; yet, patients harbouuring ulcerative plaques had a higher fasting blood glucose level (medians 6.7 vs 5.7 mmol/L; p=0.047; online supplemental table 1). Overall, smooth, irregular and ulcerative plaques had different luminal stenosis (p=0.027); specifically, irregular plaques had significantly higher luminal stenosis than smooth plaques (medians 78\% vs 73\%; p=0.021), while there was no significant difference in luminal stenosis in other pairwise comparisons. Compared with non-ulcerative plaques, ulcerative plaques were thicker (medians 1.6 vs 1.3 mm; p=0.003), of a steeper upstream shoulder (medians 56.2\° vs 31.0\°; p<0.001)
stress at the upstream zone of the plaques. These adverse ulcerality and ulcers were also associated with enhanced wall shear downstream. In coronary and carotid vasculature, surface irregularities were maximal and, concordantly, the presence of more infarcts at the proximal stenotic throats where flow jets and shear stress mechanisms might explain why most plaque ulcers were found ulcerative plaques might suggest repetitive artery-to-artery thromboembolism. This observation might explain the efficacy of dual antiplatelet regimen during acute stage of ICAD and a potential therapeutic application of blood flow augmentation in clearing the stranded emboli at the watershed regions. Basal ganglia or brainstem lacunar syndrome had been common in ICAD patients with infarct topography resembling small vessel disease. However, confirmation of branch/perforator disease in vivo had not been feasible with conventional angiographic techniques. With 3DRA, we revealed the frequent coexistence of adjoining BAD within the perforator-rich stenotic segments, constituting a competing stroke mechanism: parent artery atherosclerosis occluding branch/perforator. In fact, understanding the spatial relationship between parent artery and branches/perforators might have further clinical implications. First, ostial involvement of branches/perforators might highlight the risk of branch jailing by ‘snow-plow effect’ during intracranial angioplasty/stenting. As perforator stroke frequently

### Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>None (n=26)</th>
<th>Acute infarct(s) only or chronic infarct(s) only (n=125)</th>
<th>Coexisting acute and chronic infarcts (n=29)</th>
<th>P value †</th>
<th>P value ‡</th>
</tr>
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<tr>
<td>Age, years</td>
<td>55 (51–62)</td>
<td>61 (55–69)</td>
<td>62 (57–69)</td>
<td>0.004</td>
<td>0.255</td>
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<td>Male</td>
<td>19 (73.1)</td>
<td>76 (60.8)</td>
<td>19 (65.5)</td>
<td>0.480</td>
<td>0.790</td>
</tr>
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<td>Current smoker</td>
<td>15 (57.7)</td>
<td>52 (41.6)</td>
<td>17 (58.6)</td>
<td>0.121</td>
<td>0.159</td>
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<td>History of dyslipidaemia</td>
<td>18 (69.2)</td>
<td>100 (80.0)</td>
<td>25 (86.2)</td>
<td>0.287</td>
<td>0.325</td>
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<td>History of hypertension</td>
<td>13 (50.0)</td>
<td>84 (67.2)</td>
<td>26 (89.7)</td>
<td>0.006</td>
<td>0.007</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>4 (15.4)</td>
<td>46 (36.8)</td>
<td>14 (48.3)</td>
<td>0.034</td>
<td>0.118</td>
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<td>Systolic blood pressure, mm Hg</td>
<td>152 (133–169)</td>
<td>150 (136–165)</td>
<td>159 (138–172)</td>
<td>0.527</td>
<td>0.259</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>85 (76–93)</td>
<td>80 (70–90)</td>
<td>82 (71–94)</td>
<td>0.317</td>
<td>0.556</td>
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<td>Laboratory test results</td>
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<tr>
<td>Glycosylated haemoglobin, %</td>
<td>6.0 (5.3–6.4)</td>
<td>6.2 (5.7–7.5)</td>
<td>6.4 (5.9–7.5)</td>
<td>0.030</td>
<td>0.353</td>
</tr>
<tr>
<td>Fasting blood glucose, mmol/L</td>
<td>5.1 (4.9–5.9)</td>
<td>5.8 (5.1–7.3)</td>
<td>6.4 (5.2–7.4)</td>
<td>0.031</td>
<td>0.293</td>
</tr>
<tr>
<td>Low-density lipoprotein, mmol/L</td>
<td>3.3 (2.4–4.6)</td>
<td>3.4 (2.7–4.1)</td>
<td>3.3 (2.8–3.9)</td>
<td>0.859</td>
<td>0.582</td>
</tr>
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<td>High-density lipoprotein, mmol/L</td>
<td>1.3 (1.0–1.5)</td>
<td>1.1 (0.9–1.3)</td>
<td>1.2 (0.9–1.5)</td>
<td>0.091</td>
<td>0.277</td>
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<td>Triglycerides, mmol/L</td>
<td>1.3 (0.9–1.6)</td>
<td>1.5 (1.2–2.0)</td>
<td>1.6 (1.2–2.1)</td>
<td>0.143</td>
<td>0.890</td>
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<td>Location of the qualifying ICAD lesions</td>
<td></td>
<td></td>
<td></td>
<td>0.286</td>
<td>0.447</td>
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<tr>
<td>MCA-M1</td>
<td>20 (76.9)</td>
<td>91 (72.8)</td>
<td>21 (72.4)</td>
<td>0.286</td>
<td>0.447</td>
</tr>
<tr>
<td>Terminal ICA</td>
<td>1 (3.8)</td>
<td>20 (16.0)</td>
<td>5 (17.2)</td>
<td>0.286</td>
<td>0.447</td>
</tr>
<tr>
<td>Across terminal ICA and proximal MCA</td>
<td>2 (7.7)</td>
<td>2 (1.6)</td>
<td>2 (6.9)</td>
<td>0.286</td>
<td>0.447</td>
</tr>
<tr>
<td>VA-V4 or BA</td>
<td>3 (11.5)</td>
<td>12 (9.6)</td>
<td>3 (1.4)</td>
<td>0.286</td>
<td>0.447</td>
</tr>
<tr>
<td>Plaque types</td>
<td></td>
<td></td>
<td></td>
<td>0.032</td>
<td>0.007</td>
</tr>
<tr>
<td>Smooth</td>
<td>8 (30.8)</td>
<td>38 (30.4)</td>
<td>5 (17.2)</td>
<td>0.286</td>
<td>0.447</td>
</tr>
<tr>
<td>Irregular</td>
<td>15 (57.7)</td>
<td>72 (57.6)</td>
<td>14 (48.3)</td>
<td>0.286</td>
<td>0.447</td>
</tr>
<tr>
<td>Ulcerative</td>
<td>3 (11.5)</td>
<td>15 (12.0)</td>
<td>10 (34.5)</td>
<td>0.286</td>
<td>0.447</td>
</tr>
<tr>
<td>Arterial luminal stenosis, %</td>
<td>78 (72–83)</td>
<td>75 (71–85)</td>
<td>75 (70–82)</td>
<td>0.781</td>
<td>0.519</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Characteristics (n=180)</th>
<th>Infarct loads in the relevant territory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcerative</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>Smooth</td>
<td>8 (30.8)</td>
</tr>
<tr>
<td>Irregular</td>
<td>15 (57.7)</td>
</tr>
<tr>
<td>Ulcerative</td>
<td>3 (11.5)</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=180)</th>
<th>Patients with anterior circulation ICAD (n=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of hypertension</td>
<td>5.27 (1.48 to 18.75)</td>
<td>5.74 (1.60 to 20.65)</td>
</tr>
<tr>
<td>Plaque types</td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Smooth/irregular</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Ulcerative</td>
<td>4.29 (1.65 to 11.14)</td>
<td>4.88 (1.80 to 13.22)</td>
</tr>
</tbody>
</table>

ICAD, intracranial atherosclerotic disease;
Sclerosis in pathogenesis (i.e., BAD), whereas truncal or distal and Caplan et al, ostial perforator disease favoured athero- 
alinosis.31 32 Therefore, by stringent risk factor control, orifical low signal in apparent diffusion coefficient maps) at left posterior corona 
symptom onset showed a cluster of early infarcts (high signal in DWI and 
complicated intracranial stenting, 2 a careful angiographic eval-
uation prior to endovascular intervention is warranted in this 
subgroup.30 Second, based on the postmortem studies by Fisher and Caplan et al, ostial perforator disease favoured athero-
sclerosis in pathogenesis (i.e., BAD), whereas truncal or distal perforator disease might suggest fibrinoid degeneration/lipohyalinosis.31 32 Therefore, by stringent risk factor control, orifical stenoses of branches/perforators might stand a chance to regress if they were predominantly atherosclerotic or simply extensions of parent large-vessel atheroma.15 20 23 On the contrary, in the 
truncal form of perforator disease that entailed fibrinoid degen-
eration, lipohyalinosis and small haemorrhagic extravasations at the arterial walls, use of intensive antithrombotics should be
judicious given the non-atherothrombotic stroke mechanism and probable presence of microbleeds.31 32

Our study has the following limitations: first, the median interval from index stroke/TIA onset to 3DRA exam was 23 days. Plaque morphology might evolve during this period under treatments with antiplatelet(s) and statins. Second, vessel opaci-
fication in 3DRA was flow-dependent. Therefore, small vessels that were completely occluded, grossly hypoperfused, or of minute calibre (e.g., vertebrobasilar perforators) might not be evident in our study, leading to misjudgement of branches/perfo-
rators ostium locations. There were cases when orifices of lentic-
ulostriate arteries (rising from the dorsal-superior wall of MCA 
stem) were invisible even when the MCA plaque was predomin-
anty located over the inferior wall of MCA stem (e.g., figure 1G). A plausible explanation could be the Venturi effect, in which the 
perfusion pressure to the perforators might abruptly drop due to 
the accelerated jet across the index high-grade stenosis. 34 35 Third, some plaque morphological assessments were susceptible to subjective judgement. We attempted to minimise this potential bias by employing experienced investigators who had moderate to good intrarater and inter-rater reliability in reviewing 3DRA. Further validation of this technique at other centres is warranted. Fourth, 3DRA revealed protruding luminal plaques, while posi-
tively remodelled plaques (i.e., outward compensatory growth of 
arterial wall to maintain a constant lumen diameter) required vessel-wall MRI for diagnosis and evaluation.36 37 Moreover, vessel wall MRI might also provide critical information on plaque components, vessel wall characteristics and the spatial relationship between parent plaque and orifices of penetrating arteries. Coregistration of 3DRA images with vessel wall MRI may provide complementary information in plaque evaluation.38 As plaque instability is a summation of morphology, plaque components and adverse haemodynamic parameters, a rheology study across the symptomatic ICAD lesions is also crucial to supplement and explain stroke recurrence.

CONCLUSIONS

3DRA allowed evaluation of morphological traits of intracranial atherosclerotic plaques. Symptomatic high-grade ICAD plaques were mostly eccentric with stenosis most severe over the distal portion. Morphological features differed between smooth, irregular and ulcerative plaques: ulcerative ICAD plaques entailed more vulnerable morphological attributes, adjoining BAD and were associated with a higher incidence of acute-and-chronic infarctions downstream. Further longitudinal studies on the dynamic evolution of plaque morphology, composition and global/focal rheological characteristics will deepen our understand-
ing of stroke mechanisms in the presence of ICAD.

Figure 3   MRI and 3DRA images of a patient with an ulcerative MCA-M1 plaque and coexisting acute and chronic infarcts in cortical and subcortical regions. A patient with a history of hypertension presented with sudden dysphasia. The MRI exam conducted 1 day after symptom onset showed a cluster of early infarcts (high signal in DWI and low signal in apparent diffusion coefficient maps) at left posterior corona radiata (internal borderzone) and left temporal–parietal cortical and subcortical regions (including the posterior borderzone). There were also older small infarcts (high signal in T2 fluid-attenuated inversion recovery imaging and iso-intensity signal in apparent diffusion coefficient maps) in the same regions. The 3DRA exam conducted 4 weeks after the index stroke showed 80% stenosis of the left MCA-M1 with an ulcer in the plaque surface, that is, contrast appearing beneath the surface outline of the plaque (arrow). The patient received aspirin and clopidogrel treatment for 4 weeks since admission followed by lifelong aspirin treatment, in conjunction with stringent vascular risk factor control. The patient had no recurrent ischaemic stroke within 1 year after the index stroke. A repeated 3DRA exam at 1 year showed healing of the previously ulcerated MCA-M1 plaque. 3DRA, 3-dimensional rotational angiography; DWI, diffusion-weighted imaging; MCA-M1, M1 middle cerebral artery.

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Cerebrovascular disease

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Contributors  TWL, SCHY and XL planned the study, analysed the data, interpreted the findings and wrote the manuscript; LW, XZ, YS and YP contributed to data collection and analyses; HLI, AC, LWCA, FF, SHM, BI, KM, AM-L, LH, KF, RL, SHL, MF and WCF contributed to data collection; JL, VM, KSLW, ZM and NM provided critical comments/ revisions of the manuscript. TWL and XL are responsible for the overall content.

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Data availability statement  Data are available on reasonable request.

Supplemental material  Anonymised data that support the findings of this study are available from the corresponding author on reasonable request from qualified investigators.

References