Nonstenotic carotid plaque on CT angiography in patients with cryptogenic stroke

Jonathan M. Coutinho,
MD, PhD*
Sheldon Derkatch, MD*
Alphonse R.J. Potvin, BSc
George Tomlinson, PhD
Tim-Rasmus Kiehl, MD
Frank L. Silver, MD
Daniel M. Mandell, MD,
PhD

Correspondence to
Dr. Mandell:
danny.mandell@uhn.ca

ABSTRACT

Objective: To determine whether large (≥ 3 mm thick) but nonstenotic ($< 50\%$) carotid artery atherosclerotic plaque predominantly occurs ipsilateral rather than contralateral to cryptogenic stroke.

Methods: This was a cross-sectional observational study. Using a stroke registry, we identified consecutive patients with anterior circulation embolic stroke of undetermined source (ESUS). Using CT angiography, we measured carotid plaque size (thickness, mm) and carotid artery stenosis (North American Symptomatic Carotid Endarterectomy Trial method) for each patient. We dichotomized plaque size at several predefined thresholds and calculated the frequency of plaque size above each threshold ipsilateral vs contralateral to stroke.

Results: We included 85 patients with ESUS. Plaque with thickness ≥ 5 mm was present ipsilateral to stroke in 11% of patients, and contralateral in 1% (9/85 vs 1/85; $p = 0.008$). Plaque with thickness ≥ 4 mm was present ipsilateral to stroke in 19% of patients, and contralateral in 5% (16/85 vs 4/85; $p = 0.002$). Plaque with thickness ≥ 3 mm was present ipsilateral to stroke in 35% of patients, and contralateral in 15% (30/85 vs 13/85; $p = 0.001$). There was no difference in percentage stenosis ipsilateral vs contralateral to stroke ($p = 0.98$), and weak correlation between plaque size and stenosis ($R^2 = 0.26$, $p < 0.001$).

Conclusions: Large but nonstenotic carotid artery plaque is considerably more common ipsilateral than contralateral to cryptogenic stroke, suggesting that nonstenotic plaque is an underrecognized cause of stroke. We measured plaque size using CT angiography, a method that could be easily implemented in clinical practice. *Neurology*® 2016;87:665–672

GLOSSARY

CTA = CT angiography; **ESUS** = embolic stroke of undetermined source; **IQR** = interquartile range; **NASCET** = North American Symptomatic Carotid Endarterectomy Trial.

Secondary prevention of ischemic stroke depends on determining the cause of an initial TIA or stroke. However, in 25% of cases, standard investigations fail to identify a cause.^{1,2} Many of these cryptogenic strokes are embolic strokes of undetermined source (ESUS).³

A widely adopted stroke etiology classification system⁴ requires at least 50% narrowing of the carotid artery lumen to attribute a stroke to carotid atherosclerotic disease. More recent classification schemes^{5,6} include the possibility that carotid atherosclerotic plaque with less than 50% luminal narrowing is a potential source of thromboembolic stroke.

CT angiography (CTA) is a first-line investigation for patients with acute ischemic stroke. Physicians interpreting CTA typically assess carotid atherosclerotic disease by measuring the degree of carotid artery stenosis. This approach was established using catheter angiography,^{7,8} before the current era of cross-sectional vascular imaging, and it ignores the possibility of using CTA to directly measure atherosclerotic plaque size, not only its secondary effect on the lumen. A recent study demonstrated that greater carotid plaque size, measured using CTA, correlates with high-risk plaque features diagnosed using high-resolution plaque MRI.⁹

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*These authors contributed equally to this work.

From the Division of Neuroradiology, Department of Medical Imaging (J.M.C., S.D., D.M.M.), Division of Neurology, Department of Medicine (A.R.J.P., F.L.S.), and Department of Pathology (T.-R.K.), University Health Network and the University of Toronto; Dalla Lana School of Public Health (G.T.), University of Toronto; and Department of Medicine (G.T.), University Health Network and Mount Sinai Hospital, Toronto, Canada. Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

We measured carotid plaque size using CTA in patients with cryptogenic stroke. We hypothesized that large (≥ 3 mm thick), nonstenotic ($< 50\%$) carotid plaque predominantly occurs ipsilateral rather than contralateral to cryptogenic stroke.

METHODS Patients. Using a prospectively maintained stroke registry at a regional stroke center, we identified consecutive patients admitted for acute ischemic stroke between January 1, 2012, and March 15, 2015. Within this cohort, we identified patients with a carotid territory, nonlacunar infarct who fulfilled the recently proposed diagnostic criteria for ESUS.³ At minimum, the diagnostic assessment for ESUS had to include a CT or MRI of the brain showing the infarct, imaging of the cervical and intracranial arteries, a 12-lead ECG, a transthoracic or transesophageal echocardiogram, and automated cardiac rhythm monitoring for at least 24 hours. Additional investigations, such as prolonged cardiac rhythm monitoring, or hematologic screening, were performed if deemed clinically indicated and at the discretion of the treating physician. For diagnosis of ESUS, none of the investigations could show a major risk factor for cardioembolic stroke (such as atrial fibrillation, intraventricular thrombus, or left ventricular ejection fraction of less than 30%), ipsilateral carotid artery stenosis $\geq 50\%$, intracranial atherosclerotic stenosis $\geq 50\%$, or other specific causes of stroke such as arterial dissection or arteritis.³ As the aim of this study relates to identification of carotid plaque using CTA, we required that patients had a CTA within 10 days of hospital admission. We excluded patients with acute stroke in multiple vascular territories.

CT angiography. The imaging was performed using Aquilion ONE and Aquilion 64 CT scanners (Toshiba Medical Systems, Tokyo, Japan). IV iodinated contrast was iodixanol (Visipaque, 320 mg iodine/mL; GE Healthcare, Cleveland, OH) 60–80 mL injected at 5 mL/s. Acquisition was triggered automatically by attenuation of 100 Hounsfield units in the aortic arch. The scan was helical with 0.5-mm section thickness (100–120 kV, auto-mA), gantry speed 0.5 s/rotation, and table speed 25.5 mm/rotation. Coverage was from the aortic arch to the vertex. Images were reconstructed in the axial plane with 0.5-mm slice thickness.

Image analysis. Images were viewed using the software Coral Workstation (University Health Network, Toronto, Canada). Each CTA was reviewed by a neuroradiologist who was blinded to the side of the stroke and all other clinical information. Blinding was ensured by masking all CT and CTA images above the skull base. The reader viewed axial CTA source images, and also generated sagittal oblique maximum intensity projection images at the workstation. The reader first assessed image quality and determined whether there was an artifact (such as patient motion) that would impede evaluation of one or both carotid arteries, and these patients were recorded and censored from further analysis. The reader then recorded the degree of carotid artery stenosis on each side using North American Symptomatic Carotid Endarterectomy Trial (NASCET)-type measurement.^{7,8} The reader then viewed the common and internal carotid arteries from 2 cm proximal to the common carotid bifurcation to 2 cm distal to the bifurcation to directly assess carotid plaque. Using the source images and the sagittal oblique projections, the neuroradiologist measured plaque thickness approximately perpendicular to the long axis of the artery, at the location of greatest plaque thickness. The level of plaque thickness measurement did not necessarily correspond with the level of maximal luminal stenosis.

The neuroradiologist was free to adjust the window and level settings to demonstrate the inner and outer margin of the plaque, and to reduce beam-hardening artifact from calcification. The reader measured total plaque thickness (in millimeters with 1 decimal point) from the margin of the contrast column to the outer margin of the vessel wall. If no arterial wall was visible, or if the measured diameter was less than 1.0 mm, the plaque was scored as no plaque and recorded as 0 mm. At this location of maximum plaque thickness, the reader also recorded the maximum thickness of noncalcified plaque. The reader recorded whether the plaque was ulcerated or not, using a 1 mm or greater focal outpouching of the contrast-filled lumen into the plaque as the criterion for ulceration.⁹

To evaluate interobserver variability, a second radiologist repeated the plaque thickness measurement on each side, for all patients, using the same technique. The second reader was blinded in the same manner as the first reader and, in addition, was blinded to the results of the first reader.

Statistical analysis. We compared the degree of luminal stenosis ipsilateral vs contralateral to ischemic stroke using a Wilcoxon signed-rank test. We measured the correlation between percentage luminal stenosis and carotid plaque thickness by calculating Pearson correlation coefficient. We dichotomized plaque thickness at predefined thresholds (2 mm, 3 mm, 4 mm, 5 mm) and calculated the frequency of carotid plaque thickness above the threshold ipsilateral vs contralateral to ischemic stroke. To determine whether these frequencies differed ipsilateral vs contralateral to ischemic stroke, we used McNemar test. We repeated this analysis for total plaque thickness and noncalcified plaque thickness. We also compared plaque thickness ipsilateral vs contralateral to ischemic stroke among all patients using a paired Student *t* test. We calculated an intraclass correlation coefficient to determine interobserver variability between the 2 readers.^{10,11} Interobserver variability might differ between the carotid plaques ipsilateral vs contralateral to ischemic stroke (due to differences in plaque characteristics), and so we calculated the correlation coefficient separately for each side. All analyses were performed using SPSS version 22 and *p* values less than 0.05 were considered statistically significant.

Standard protocol approvals, registrations, and patient consents. This research study was approved by the Research Ethics Board of the University Health Network, Toronto, Canada.

RESULTS Patient characteristics. There were 1,038 patients admitted with an acute ischemic stroke during the study period, and 128 (12.3%) of these patients met the criteria for ESUS. After excluding patients with posterior circulation stroke (*n* = 15), infarcts in multiple vascular territories (*n* = 11), no CTA within 10 days of acute ischemic stroke (*n* = 11), or motion artifact on the CTA (*n* = 6), we had a final study population of 85 patients. The median age of patients at the time of stroke was 70 years (interquartile range [IQR] 58–79) and 52% were women. Table 1 provides additional details of patient characteristics, diagnostic investigations, clinical management, and disposition.

Degree of carotid artery stenosis. Median (IQR) carotid artery stenosis was 0% (0%–0%) both ipsilateral and

Table 1 Clinical characteristics, investigations, management, and disposition for 85 patients with embolic stroke of undetermined source

Variable	All patients (n = 85)
Age, y, median (IQR)	70 (58–79)
Female sex, n (%)	44/85 (52)
NIHSS, median (IQR) ^a	7 (3–14)
Left-sided stroke, n (%)	49/85 (58)
Cardiovascular risk factors, n (%)	
Hypertension	51/85 (60)
Diabetes mellitus	24/85 (28)
Dyslipidemia	29/85 (34)
Coronary artery disease	17/85 (20)
Previous stroke or TIA	15/85 (18)
Investigations, n (%)	
CT brain and CT angiogram from aortic arch to vertex	85/85 (100)
Diffusion-weighted MRI brain	63/85 (74)
Magnetic resonance angiogram from aortic arch to circle of Willis	19/85 (22)
Transthoracic echocardiogram	85/85 (100)
Transesophageal echocardiogram	13/85 (15)
Intracranial vessel wall MRI	8/85 (9)
Time from admission to CT angiogram, d, median (IQR)	0 (0–1)
Management and disposition, n (%)	
IV thrombolysis	40/85 (47)
Endovascular reperfusion therapy	12/85 (14)
Carotid endarterectomy	6/85 (7)
Duration of hospital admission, d, median (IQR)	6 (4–12)
Discharge, n (%)	
Home	47/85 (55)
Rehabilitation center/long-term facility	36/85 (42)
Deceased	2/85 (2)
Antiplatelet use at discharge	81/85 (95)
Oral anticoagulation use at discharge	5/85 (6)

Abbreviations: IQR = interquartile range; NIHSS = NIH Stroke Scale.

^aNIHSS score was not available for 1 patient.

contralateral to ischemic stroke, with no difference in the degree of stenosis ipsilateral vs contralateral to stroke ($p = 0.98$) (table 2). Ipsilateral to stroke, carotid artery stenosis was less than 30% in 89% (76/85) of patients. Contralateral to stroke, stenosis was less than 30% in 92% (78/85) of patients.

There was a weak correlation between degree of carotid artery stenosis and carotid plaque thickness ($R^2 = 0.26$, $p < 0.001$).

Carotid plaque. Dichotomizing carotid plaque size at the predetermined thresholds, we found that plaque with thickness ≥ 5 mm was present ipsilateral to the stroke in 11% of patients, and present contralateral to the stroke in only 1% of patients (9/85 vs 1/85 patients, $p = 0.008$). Plaque with thickness ≥ 4 mm was present ipsilateral to the stroke in 19% of patients, and present contralateral to the stroke in only 5% of patients (16/85 vs 4/85 patients, $p = 0.002$). Plaque with thickness ≥ 3 mm was present ipsilateral to the stroke in 35% of patients, and present contralateral to the stroke in 15% of patients (30/85 vs 13/85 patients, $p = 0.001$). Plaque with thickness ≥ 2 mm had the same prevalence ipsilateral (59%) and contralateral (58%) to the stroke (50/95 vs 49/95 patients, $p = 1.0$).

When the noncalcified component of the plaque was analyzed instead of the total plaque thickness, the results were similar (table 2). Figure 1 shows imaging and histopathologic correlation of a representative case.

Scatterplots of carotid plaque thickness ipsilateral vs contralateral to ischemic stroke (figure 2) demonstrate that in patients with plaque thickness ≥ 3 mm on only one side, the ischemic stroke was much more commonly on that same side (21 patients vs 4 patients, $p = 0.0009$). The results were similar for plaque thickness ≥ 4 mm (13 patients vs 1 patient, $p = 0.0018$) and for plaque thickness ≥ 5 mm (8 patients vs 0 patients, $p = 0.0078$).

Among all 85 patients, mean carotid plaque thickness was minimally greater ipsilateral than contralateral to ischemic stroke (2.2 vs 1.8 mm, $p = 0.009$) (table 2). Similarly, the noncalcified component of plaque thickness was minimally greater ipsilateral than contralateral (1.8 vs 1.3 mm, $p = 0.016$). The frequency of plaque ulceration did not differ between the ipsilateral and contralateral sides (24% vs 18%, $p = 0.33$).

There was almost perfect correlation^{10,11} between the 2 readers on plaque thickness measurements (intraclass correlation coefficient ipsilateral carotid 0.86 [95% confidence interval 0.79–0.91], contralateral carotid 0.81 [95% confidence interval 0.72–0.87]).

DISCUSSION This study evaluated the importance of nonstenotic carotid atherosclerotic plaque in patients with cryptogenic stroke. Specifically, we studied patients who fulfilled the recently proposed diagnostic criteria for ESUS.³ We found that larger (≥ 3 mm thick), nonstenotic carotid plaque was prevalent in patients with ESUS, and considerably more common ipsilateral than contralateral to ischemic stroke. Together, these findings suggest that nonstenotic carotid plaque is likely an important source of

Table 2 Carotid plaque characteristics

Variable	Ipsilateral carotid artery (n = 85)	Contralateral carotid artery (n = 85)	p Value
Percentage luminal stenosis, ^a median (IQR)	0 (0-0)	0 (0-0)	0.98
Plaque size, n (%)			
Thickness ≥5 mm	9/85 (11)	1/85 (1)	0.008
Thickness ≥4 mm	16/85 (19)	4/85 (5)	0.002
Thickness ≥3 mm	30/85 (35)	13/85 (15)	0.001
Thickness ≥2 mm	50/85 (59)	49/85 (58)	1.0
Noncalcified plaque size, n (%)			
Thickness ≥5 mm	8/85 (9)	1/85 (1)	0.039
Thickness ≥4 mm	14/85 (17)	4/85 (5)	0.013
Thickness ≥3 mm	25/85 (29)	11/85 (13)	0.007
Thickness ≥2 mm	42/85 (49)	37/85 (44)	0.36
Total plaque thickness, mm, mean (SD)	2.2 (1.9)	1.8 (1.4)	0.009
Noncalcified plaque thickness, mm, mean (SD)	1.8 (1.9)	1.3 (1.5)	0.016
No measurable plaque, n (%)	27/85 (32)	26/85 (31)	1.0
Plaque ulceration, n (%)	20/85 (24)	15/85 (18)	0.33

Abbreviation: IQR = interquartile range.

^aAccording to North American Symptomatic Carotid Endarterectomy Trial-type measurement.¹¹

embolism in patients with cryptogenic stroke. We measured nonstenotic plaque using routine CTA, a method that could be easily implemented in clinical practice.

We found that 3-mm plaque thickness is the threshold above which there is an association with ipsilateral ESUS. This is consistent with a previous CTA study¹² that found that a threshold of 2.2-mm plaque thickness discriminated between symptomatic and asymptomatic status in patients with moderate carotid artery stenosis, and another CTA study¹³ that found that a threshold of 3.5 mm discriminated between symptomatic and asymptomatic status in patients with severe stenosis. It is also consistent with a high-resolution carotid plaque MRI study that found that complicated plaque features were only present with soft plaque thickness ≥ 2.2 mm.⁹

There are several potential thromboembolic sources in patients with ESUS. Previous studies have focused on cardiac sources such as unrecognized paroxysmal atrial fibrillation, systolic dysfunction, mitral valve calcification, and patent foramen ovale.^{3,14-16} More than one-third of the patients in our ESUS cohort had a carotid plaque with thickness ≥ 3 mm ipsilateral to the ischemic stroke, suggesting that nonstenotic carotid plaque is potentially a common cause of ESUS.

Greater plaque size is associated with higher risk of thromboembolism, but plaque size is only

a secondary marker of the underlying pathophysiology, which may include plaque rupture resulting in thromboembolism, or possibly thrombus formation within a superficial erosion of a nonruptured plaque.¹⁷ High-resolution carotid plaque MRI^{18,19} is a technique that enables more detailed characterization of plaque composition than CTA, with identification of vulnerable plaque features such as intraplaque hemorrhage, lipid-rich necrotic core, and thinned or disrupted fibrous cap.²⁰⁻²² A study²³ using high-resolution MRI to examine nonstenotic carotid plaque in a smaller series of patients with cryptogenic stroke found high-risk imaging features indicative of type VI plaque (American Heart Association²⁴) in 38% (12/32) of carotid arteries ipsilateral to ischemic stroke, and no type VI plaque on the contralateral side. The absence of high-risk plaque on the contralateral side differs from our study, which found bilateral plaque ≥ 3 mm in 15% of patients with ESUS, and bilateral plaque ≥ 4 mm in 5% of patients. This discordance between the studies may reflect higher specificity of high-resolution carotid plaque MRI compared with CTA for plaque characterization. However, the difference could also reflect the larger sample size of our study. Despite the evidence that high-resolution plaque MRI features predict recurrent stroke,^{18,22} widespread clinical adoption has been slow. This partly reflects a lack of randomized controlled trials that incorporate plaque imaging, and partly reflects the need for specialized hardware (carotid surface coil), pulse sequences, and interpretive expertise that are not yet widely available, although improving with time.^{18,19}

A simpler approach to carotid plaque MRI is to use routine hardware (head and neck coil) and focus on more easily evaluated parameters such as the presence vs absence of intraplaque hemorrhage. Studies using widely available 3D T1-weighted²⁵ and time-of-flight²⁶ pulse sequences have shown an association between intraplaque hemorrhage and ipsilateral cryptogenic ischemic events in patients with less than 50% carotid artery stenosis.

Carotid ultrasound is widely available, and large prospective population studies using carotid ultrasound²⁷ have shown that nonstenotic plaque is a marker for increased risk of cerebrovascular and cardiovascular events in general, but data on the role of carotid ultrasound for determining the cause of cryptogenic stroke or ESUS is lacking.

Our study used routine CTA to evaluate carotid atherosclerotic plaque. The advantages of this approach are that CTA is already widely performed for patients presenting with transient ischemic attack or ischemic stroke, the images are nearly always of adequate quality to measure plaque size, plaque

Figure 1 Imaging and histopathologic correlation for a representative patient

Sagittal-oblique reformat (A.a, A.b) of CT angiogram source images demonstrates mild narrowing of the proximal left internal carotid artery (40% according to North American Symptomatic Carotid Endarterectomy Trial). The upper image (A.a) was used to measure the arterial diameter distal to the stenosis and the lower image (A.b) was used to measure the arterial diameter at the stenosis. Axial CT angiogram source image (B) demonstrates a large atherosclerotic plaque (long arrows) adjacent to the carotid artery lumen (short arrow). Axial T1-weighted double inversion recovery black-blood MRI (C) shows a corresponding hyperintense plaque (long arrows) and the carotid lumen (short arrow). Carotid endarterectomy specimen (D, E) demonstrates an approximately 5-mm-thick atherosclerotic plaque (D), and histopathologic section (E) through the plaque with a Movat pentachrome stain at 10 $\times$ magnification demonstrates features of American Heart Association type VI plaque including disruption (d) of the fibrous cap (fc), presence of erythrocytes indicating acute hemorrhage (arrows), and acute intramural thrombus (t).

measurement does not require specialized software or extensive training, and the time required to assess the plaque is approximately the same amount of time it takes to perform NASCET-type measurement of percentage luminal stenosis. Use of CTA for patients presenting with acute ischemic symptoms may increase even further as recent guidelines recommend

CTA to facilitate selection of patients for endovascular therapy.^{28–30} One of our readers had no previous experience measuring carotid plaque, and we found almost perfect interobserver agreement on plaque thickness measurements. This high reproducibility is consistent with previous studies of stenotic plaques using CTA.^{9,31}

Figure 2 Scatterplots of carotid atherosclerotic plaque thickness ipsilateral vs contralateral to cryptogenic stroke for 85 patients

Each of the 4 scatterplots dichotomizes plaque thickness at a different threshold: 2 mm (A), 3 mm (B), 4 mm (C), or 5 mm (D). Each dot represents a patient. The top left quadrant of each scatterplot shows patients with plaque thickness above the threshold only in the carotid artery ipsilateral to ischemic stroke. The bottom right quadrant of each scatterplot shows patients with plaque thickness above the threshold only in the carotid artery contralateral to ischemic stroke. The other 2 quadrants (which have red dots rather than black dots) show patients with bilaterally concordant plaque thickness, either below (bottom left) or above (top right) the threshold. The scatterplots illustrate that in patients with plaque thickness above a threshold of 3 mm on 1 side, the ischemic stroke is more commonly on that same side (21 vs 4, $p = 0.0009$). The scatterplots illustrate similar results for a 4-mm threshold (13 vs 1, $p = 0.0018$) and 5-mm threshold (8 vs 0, $p = 0.0078$).

We also used CTA to diagnose plaque ulceration, but did not find an association between ulceration and ipsilateral ischemic stroke. Our definition of ulceration was a focal outpouching of the arterial lumen by at least 1 mm,⁹ and we recognize that other definitions^{32,33} may have yielded different results. Previous studies have used an automated computer algorithm to quantify lipid content of carotid plaque from CTA,^{34,35} but our goal was to evaluate a method that could be more easily translated into clinical practice. Our 2 readers did observe that there was a hypoattenuating region in some of the carotid plaques,

suggesting a lipid-rich necrotic core, but we did not score this feature as part of this study.

The NASCET trial and European Carotid Surgery Trial both included patients with less than 50% carotid artery stenosis, and a pooled analysis of this data suggested that endarterectomy was not beneficial.³⁶ In patients with less than 30% stenosis, endarterectomy was harmful. However, both of these studies used catheter angiography to assess luminal narrowing, and there was no attempt to identify a subset of patients with plaque that was nonstenotic but large.^{7,37} If a patient with ESUS has an ipsilateral

nonstenotic but large (≥ 3 mm thick) carotid plaque, we will optimize lifestyle and risk factors and implement antiplatelet therapy. We may also perform high-resolution plaque MRI to further characterize the plaque. For patients who have a nonstenotic large carotid plaque, and recurrent ischemic events in the territory of the artery despite optimized medical therapy, and extensive investigations fail to identify an alternative cause, we will consider endarterectomy.³⁸ We do this with the explicit recognition that the previous clinical trials did not demonstrate therapeutic value of endarterectomy for nonstenotic plaque, and there are not yet clinical trials proving that plaque CTA and MRI are able to select a subset of patients who will benefit from surgical treatment.

A study limitation is that we attempted to measure plaque thickness perpendicular to the long axis of the artery, but we did not use advanced 3D rendering software to maximize the accuracy of this measurement. We decided to use CTA source images and simple reformats as we sought a method that other physicians could easily replicate in clinical practice.

Assessment of carotid plaque thickness using CTA easily yields quantitative measurements that may enable risk stratification; however, the clinical significance of specific plaque thickness thresholds (such as the 3-mm threshold arising from our data) will require validation in a large prospective observational study or clinical trial setting. Also, the interobserver and intraobserver reproducibility of these measurements, and the dependence of these measurements on technical factors such as CT scanner hardware and CTA acquisition parameters, warrants further evaluation. Assessment of MRI plaque features such as presence vs absence of intraplaque hemorrhage may be viewed as a simpler means of characterizing plaque, but dichotomous observations also require a threshold (such as relative signal intensity of putative hemorrhage or size of hemorrhage) to differentiate between 2 conditions.

We found that large, but nonstenotic, carotid artery plaque is considerably more common ipsilateral than contralateral to cryptogenic stroke, suggesting that nonstenotic plaque is an underrecognized cause of stroke. We measured plaque size using CTA, a method that could be easily implemented in clinical practice.

AUTHOR CONTRIBUTIONS

J.M.C. contributed to the study design, data acquisition, and data analysis (including statistical analysis) and wrote the initial draft of the report with D.M.M. J.M.C.'s professional affiliation is academic (University of Toronto). S.D. contributed to the study design, data acquisition, data analysis, and revision of the final report, and was 1 of 2 readers of CTA images. A.R.J.P. contributed to the data acquisition and revision of the final report. G.T. contributed to the data analysis (including statistical analysis) and revision of the final report. G.T.'s professional affiliation is academic (University of Toronto). T.-R.K.

contributed to the data acquisition and revision of the final report. F.L.S. was the domain expert on vascular neurology, and contributed to the study design and revision of the final report. D.M.M. was the principal investigator of the study, and was responsible for the study conception and design, interpretation of data, writing of the initial draft of the report with J.M.C., and was 1 of 2 readers of CTA images obtained during the study.

STUDY FUNDING

J.M.C. was supported by The Netherlands Organisation for Scientific Research (NWO), grant number 021.001.045, the Dutch Thrombosis Society, grant number 2012-2, and the Remmert Adriaan Laan Foundation. D.M.M. was supported by the AUR-GE Radiology Research Academic Fellowship Award.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received October 28, 2015. Accepted in final form March 21, 2016.

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