Prevalence of Nonstenotic Carotid Plaque in Stroke Due to Atrial Fibrillation Compared to Embolic Stroke of Undetermined Source

James E. Siegler, MD,*[,1] Jesse M. Thon, MD,*[,1] John H. Woo, MD,† David Do, MD,* Steven R. Messé, MD,* and Brett Cucchiara, MD*

Background: Embolic stroke of undetermined source (ESUS) accounts for about 20% of strokes. Nonstenotic cervical arterial plaque may be a mechanism of stroke in a subset of these patients. *Methods:* A cohort of consecutive patients with ischemic stroke was retrospectively identified from a stroke registry. Patients with unilateral anterior circulation embolic stroke due to atrial fibrillation (AF) or consistent with ESUS who underwent computed tomographic neck angiography were included. The prespecified primary outcome was a comparison of the prevalence of carotid plaque greater than or equal to 3 mm thickness ipsilateral versus contralateral to the infarct side. *Results:* Of 772 screened patients, 96 patients with ESUS and 99 patients with AF were included. Plaque greater than or equal to 3 mm was more frequently ipsilateral than contralateral to the infarct in patients with ESUS (41% versus 29%, $P = .03$), and plaque thickness was greater ipsilateral compared to contralateral (median 2.5 versus 2.2 mm, $P = .02$). No significant differences in plaque characteristics ipsilateral compared to contralateral were found in patients with AF. The prevalence of ipsilateral versus contralateral plaque was greater in ESUS patients less than or equal to 65 years old (48% versus 19%, $P < .01$), but no different in patients greater than 65 years old (35% versus 39%, $P = .57$). *Conclusions:* Nonstenotic cervical carotid plaque is more common ipislateral to the infarction in patients with ESUS, but not in patients with AF, supporting an underlying atheroembolic mechanism in a subset of ESUS patients. This association might be greater in younger ESUS patients.

Key Words: Cryptogenic stroke—carotid stenosis—atherosclerosis—ischemic stroke—paroxysmal atrial fibrillation—atrial fibrillation—cardioembolic stroke

Background

Prevention of stroke recurrence is dependent on recognition of the proximate mechanism of cerebral infarction. Unfortunately, an underlying stroke mechanism is not identified in many patients with ischemic stroke despite a thorough diagnostic evaluation.[1] In patients with embolic appearing stroke of undetermined source (ESUS), which comprises about 20% of stroke, underlying etiologies that increase the risk of cardiac thrombus formation, such as paroxysmal atrial fibrillation (AF), occult malignancy, or atrial cardiopathy, may be common.[1-5] In these circumstances, optimal secondary stroke prevention might include therapeutic anticoagulation instead of antiplatelet therapy.

From the *Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; and †Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

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Address correspondence to James E. Siegler, MD, Department of Neurology, Hospital of the University of Pennsylvania, 3400 Spruce St., 3W Gates, Philadelphia, Pennsylvania 19104. E-mail: siegler.james@gmail.com.

[1]Authors contributed equally to the production of this manuscript.

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Recent clinical trial data, however, indicate that anticoagulation is no more effective than antiplatelet therapy in unselected ESUS patients.[6,7] This suggests that mechanisms other than paroxysmal AF or occult hypercoagulable states, such as nonstenotic atherosclerotic plaque, may play a more important role in ESUS than previously recognized. Nonstenotic plaque has been implicated as a stroke mechanism in ESUS based on observational cohorts demonstrating greater prevalence of such plaque ipsilateral as opposed to contralateral to stroke location.[8-10] In the present study, we sought to validate prior observations of a greater prevalence of nonstenotic carotid plaque ipsilateral to the side of cerebral infarction in a cohort of ESUS patients, to confirm that the association is not present in non-ESUS patients, and to identify patient groups in which this association might be magnified.

Methods

Patient Selection

We conducted a retrospective observational cohort study of consecutive patients with a diagnosis of acute ischemic stroke admitted to 3 hospitals within a single integrated hospital system between October 1, 2015 and April 1, 2017. Only patients older than or equal to 18 years of age with unilateral anterior circulation ischemic stroke due to ESUS or AF were included. Patients were excluded from final analyses if there were multiple possible mechanisms of cerebral infarction; if they had evidence of simultaneous, acute cerebral infarction in more than 1 vascular territory; if the patient had prior carotid endarterectomy or stenting; if there was occlusion of either cervical internal carotid artery (ICA); or if computed tomographic angiography (CTA) of the neck was not performed within 10 days of the time the patient was last known normal. This study was approved by our local institutional review board.

Stroke Mechanisms

Patients with stroke due to AF were classified based on a documented history of AF, or presence of AF on electrocardiographic monitoring at any point during their evaluation. To meet criteria for ESUS, patients had to experience a stroke greater than 1.5 cm in diameter confirmed on neuroimaging (or with a clear vessel occlusion on angiographic imaging); undergo electrocardiography and a minimum of 24 hours of cardiac telemetry without evidence of myocardial infarction or AF; undergo transthoracic echocardiogram without an obvious source of cardioembolism; and undergo vessel imaging without intracranial or extracranial atherosclerosis causing greater than or equal to 50% luminal stenosis in the territory of the infarct; and have no other cause of stroke identified.[1] At our center, among patients over the age of 50 who have no other suspected stroke mechanism, a minimum of 7 days of outpatient telemetry monitoring is recommended by providers to exclude the possibility of paroxysmal AF. Any AF lasting longer than 6 minutes was considered clinically relevant.

Imaging and Laboratory Data

CTA of the neck was acquired in the axial plane using a fourth-generation, helical CT scanner. Slice thickness ranged from 0.625 mm to 1.5 mm (77% were acquired using 1.5 mm sections), depending on the available scanner. At all sites, per institutional protocol, iodinated contrast (100 mL Isovue-370) was administered intravenously through a 20-gauge (or larger) right antecubital catheter. A half dose of Isovue-370 was administered if the patient was anticipated to undergo perfusion CT following the CTA.

Each neck CTA was reviewed by a neuroradiologist blinded to all clinical information, including the location of cerebral infarction. The reader was not permitted to view any additional neuroimaging other than the neck CTA. The reader first viewed axial CTA source images, and then reconstructed images in TeraRecon for 3-dimensional viewing. Using TeraRecon, the reader calculated the degree of ICA stenosis on each side using North American Symptomatic Carotid Endarterectomy Trial methodology.[11] Next, the reader measured ICA plaque thickness of each carotid. The reader was only permitted to view the common and ICAs 2 cm above or below the carotid bifurcation, using a methodology similar to that reported by Coutinho et al.[8] Maximum axial plaque thickness, measured from the outermost wall of the plaque to the outer wall of the ICA, was recorded at these levels, and the level of the plaque need not have corresponded to the level with maximum luminal stenosis. Overall plaque thickness and calcified plaque thickness were recorded from each side. Finally, the reader assessed whether the plaque was ulcerated, using a combination of axial source images and 3D projections. Given the excellent inter-rater reliability previously demonstrated using this methodology, all CTA images were reviewed by a single neuroradiologist.[8]

Results of low-density lipoprotein and hemoglobin A1c blood testing performed within 1 week of acute stroke as part of routine clinical care were collected.

Outcome Measures

The prespecified, primary outcome measure was the presence of cervical ICA plaque greater than or equal to 3 mm comparing the side ipsilateral to the cerebral infarction to the contralateral side. The 3 mm threshold was selected based on prior data indicating this threshold optimized discrimination between the 2 sides in ESUS patients.[8] Additional exploratory thresholds for plaque thickness were also compared as had been done previously.[8] Prespecified secondary outcomes included overall cervical ICA plaque thickness, thickness of calcified ICA plaque, the presence of plaque ulceration, and the degree of ICA luminal stenosis by North American Symptomatic Carotid Endarterectomy Trial criteria.[11]

Sample Size

Using prior data showing a 20% absolute difference in ipsilateral versus contralateral plaque greater than or equal to 3 mm (35% ipsilateral to stroke versus 15% contralateral), a minimum sample size of 67 patients with ESUS would provide 80% power to detect a 20% absolute difference between paired arteries at the 5% significance level.[8] Assuming ESUS represents 20% of the stroke population, 80% of whom experienced anterior circulation infarctions, and half of whom would be expected to undergo CTA of the neck at our center, we anticipated a need to screen a total of 850 patients with acute ischemic stroke.[1] We did not perform a sample size calculation for the comparison AF group, but included all qualifying AF subjects identified during the screening process.

Statistical Analysis

The presence of plaque above dichotomized plaque thickness thresholds was compared ipsilateral versus contralateral to the infarction side using McNemar's test. Plaque ulceration was evaluated similarly. The degree of luminal stenosis was compared between ipsilateral and contralateral sides using the Wilcoxon signed-rank test. A paired *t* test was used to compare total and calcified plaque thickness ipsilateral versus contralateral to the infarction side. Patients with ESUS were evaluated separately from those with stroke due to AF. Post hoc exploratory analysis was undertaken comparing the proportion of ESUS patients with ipsilateral versus contralateral ICA plaque greater than or equal to 3 mm in various subgroups. Age was dichotomized at the median age for the ESUS population, and thresholds for low-density lipoprotein and hemoglobin A1c were defined based on our hospital laboratory's standard definitions for abnormal values. Missing data were not imputed. Analyses were performed using JMP version 14.0 (SAS Institute Inc., Cary, NC). An association was considered significant if $P < .05$. All tests were 2-sided. This study was approved by the local institutional review board with waiver of informed consent due to the retrospective nature of data abstraction. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Among 772 screened patients with confirmed mechanism of infarction, 171 were diagnosed with ESUS, 96 of whom met inclusion criteria. In this group, 31 of 96 (32%) had prolonged mobile cardiac outpatient telemetry for greater than or equal to 7 days (median duration 27 days, IQR 19-28). Of 213 patients with suspected cardioembolism, 99 had AF and were included. Study flowchart is shown in Figure 1. Baseline characteristics of the ESUS and

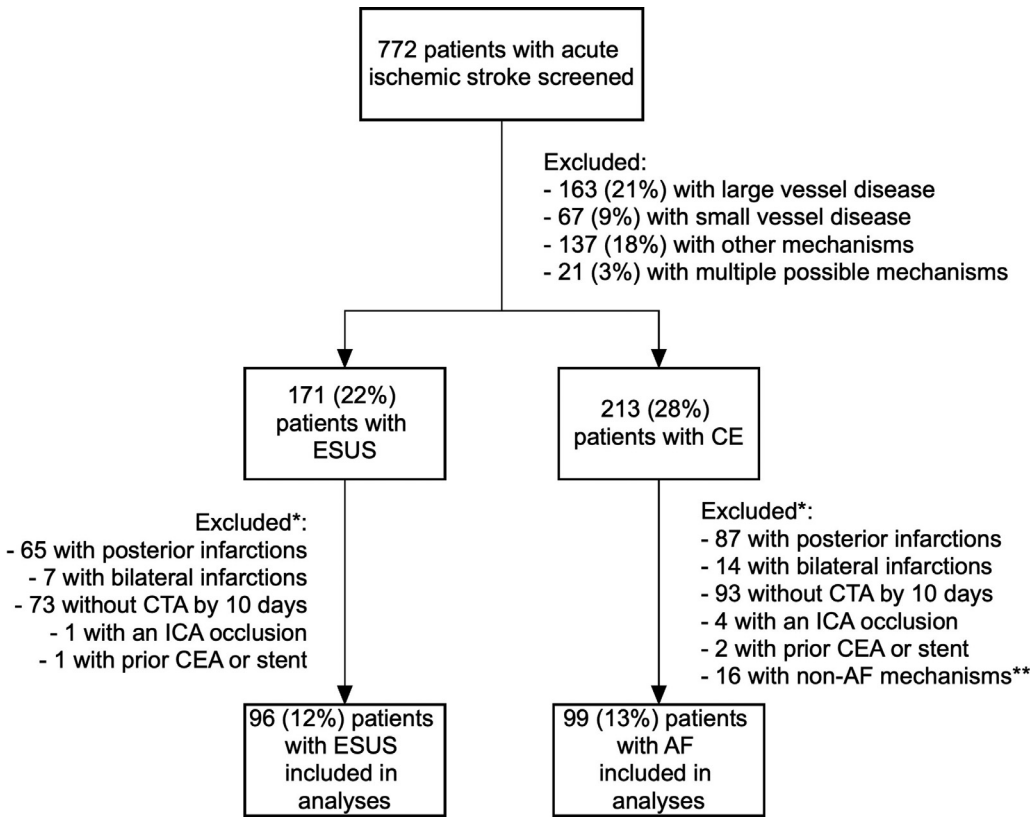

Figure 1. *Study flowchart. *Patients could be excluded for more than 1 reason. Abbreviations: CE, cardiombolic source of infarction; CEA, carotid endarterectomy; CTA, computed tomography angiography; ESUS, embolic stroke of undetermined source; ICA, internal carotid artery.*

Table 1. *Baseline characteristics*

	ESUS (n = 96)	AF (n = 99)
Age, median y (IQR)	66 (57-75)	78 (68-84)
Sex, no. female (%)	53 (55%)	48 (48%)
Race, no. (%)		
Caucasian	45 (47%)	59 (60%)
Black	45 (47%)	30 (30%)
Other	6 (6%)	10 (10%)
Past medical history, no. (%)		
Stroke	15 (16%)	21 (21%)
Hypertension	67 (70%)	76 (76%)
Diabetes mellitus	26 (27%)	31 (31%)
Dyslipidemia	33 (34%)	45 (45%)
Coronary artery disease	22 (23%)	33 (33%)
Any prior tobacco use	21 (22%)	12 (12%)
Baseline NIHSS, median (IQR)	8 (3-16)	12 (6-18)
IV tPA administered, no. (%)	38 (40%)	45 (45%)
Thrombectomy attempted, no. (%)	15 (16%)	41 (41%)
Left hemispheric (only) infarction, no. (%)	52 (54%)	55 (56%)

Abbreviations: AF, atrial fibrillation; ESUS, embolic stroke of undetermined source; IQR, interquartile range; IV tPA, intravenous tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale.

AF patients are shown in Table 1. For the patients with AF, 89% were in persistent AF and 11% had paroxysmal AF.

Regarding the primary outcome, ipsilateral ICA plaque greater than or equal to 3 mm was more common than contralateral ICA plaque in ESUS patients (41% versus 29%, $P = .03$). Plaque thickness was also greater ipsilateral to the infarction compared to contralateral in ESUS patients (median 2.5 versus 2.2 mm, $P = .02$), largely driven by the thickness of calcified plaque (median 1.4 versus 1.1 mm, $P = .01$). There was no significant difference in the degree of luminal stenosis or the prevalence of ulcerated plaque between the 2 sides among patients with ESUS. In patients with AF, there was no significant difference in any plaque feature or degree of stenosis between the 2 sides. Table 2 shows detailed results of plaque features between groups. Exploratory dichotomous analysis of alternative plaque thresholds for both patient groups is shown in Table 3.

In subgroup analysis of the ESUS cohort dichotomized by median age, younger patients (age ≤65) had substantially higher prevalence of ipsilateral compared to contralateral greater than equal to 3 mm ICA plaque (48% versus 19%, $P = .0005$), whereas no significant difference was seen in patients over age 65 (35% versus 39%, $P = .57$). Analysis in the AF cohort using this same age threshold showed no significant difference between ipsilateral and contralateral ICA plaque in either younger (32% versus 21%, $P = .49$) or older (43% versus 39%, $P = .58$) patients. The prevalence of ipsilateral compared to contralateral plaque in subgroups in the ESUS cohort is shown in Figure 2.

Discussion

We found that the presence of nonstenotic carotid plaque greater than or equal to 3 mm thickness on CTA was more common ipsilateral to the side of infarction compared to contralateral in patients with anterior circulation ESUS. Absolute plaque thickness was also greater ipsilateral to stroke. These findings, in conjunction with prior studies[8-10] (Table 4), strongly support nonstenotic carotid plaque being the underlying stroke mechanism in some patients with ESUS. Our study was deliberately designed to use methods similar to the study of Coutinho et al,[8] which demonstrated that 35% of ESUS patients had greater than or equal to 3 mm of carotid artery plaque ipsilateral to their stroke, as compared to 15% of patients

Table 2. *Carotid plaque imaging findings*

	Ipsilateral cervical ICA	Contralateral cervical ICA	*P* value*
ESUS (n = 96)			
Plaque thickness ≥ 3 mm, no. (%)	40 (42%)	28 (29%)	0.03
Stenosis (%), median (IQR)	0 (0-2.5)	0 (0-2.5)	0.76
Total plaque thickness, mean (SD)	2.5 ± 1.5	2.2 ± 1.6	0.02
Calcified plaque thickness, mean (SD)	1.4 ± 1.5	1.1 ± 1.5	0.01
Plaque ulceration, no. (%)	1 (1%)	5 (5%)	0.10
Atrial fibrillation (n = 99)			
Plaque thickness ≥ 3 mm, no. (%)	40 (40%)	35 (35%)	0.41
Stenosis (%), median (IQR)	0 (0-15)	0 (0-10)	0.45
Total plaque thickness, mean (SD)	2.6 ± 1.5	2.4 ± 1.5	0.30
Calcified plaque thickness, mean (SD)	1.8 ± 1.6	1.7 ± 1.6	0.92
Plaque ulceration, no. (%)	3 (3%)	2 (2%)	0.65

Abbreviations: ESUS, embolic stroke of undetermined source; ICA, internal carotid artery; IQR, interquartile range; SD, standard deviation.

*All tested using paired comparisons.

Table 3. *Prevalence of plaque according to plaque thickness and stroke mechanism*

	Ipsilesional cervical ICA	Contralesional cervical ICA	*P* value
ESUS (n = 96)			
Plaque ≥2 mm	63 (66%)	56 (58%)	.20
Plaque ≥3 mm	40 (42%)	28 (29%)	.03
Plaque ≥4 mm	17 (18%)	13 (14%)	.35
Plaque ≥5 mm	4 (4%)	4 (4%)	1.0
AF (n = 99)			
Plaque ≥2 mm	68 (69%)	65 (66%)	.53
Plaque ≥3 mm	40 (40%)	35 (35%)	.41
Plaque ≥4 mm	13 (13%)	13 (13%)	1.0
Plaque ≥5 mm	4 (4%)	5 (5%)	.74

Abbreviations: AF, atrial fibrillation; ESUS, embolic stroke of undetermined source; ICA, internal carotid artery.

in the contralateral artery. Compared to these findings, we demonstrated a slightly greater absolute prevalence of plaque ipsilateral to stroke side, but also a greater prevalence in the contralateral side. Whether this reflects differences in our patient population or in the precise methodology used to measure plaque thickness is unclear. Other smaller studies using carotid ultrasound to measure plaque thickness have also found greater prevalence of plaque ipsilateral compared to contralateral to stroke side.[9,10] Further supporting nonstenotic carotid plaque as a mechanism in patients with ESUS is the recent observation that those with nonstenotic carotid plaque are less likely to be subsequently diagnosed with AF than those without carotid plaque.[12]

From a clinical perspective, determining whether nonstenotic carotid plaque is the stroke mechanism in an individual patient is a major challenge. In the ESUS Global Registry, 79% of ESUS patients had some degree of nonstenotic cervical artery plaque,[5] indicating that the mere presence of carotid plaque is extremely common and often likely incidental. In some respects, this situation is similar to that of determining whether patent foramen ovale is relevant to cryptogenic stroke in younger patients or an innocent bystander. To this end, we sought to identify subgroups of ESUS patients in whom nonstenotic carotid plaque might be more likely to be the stroke mechanism.

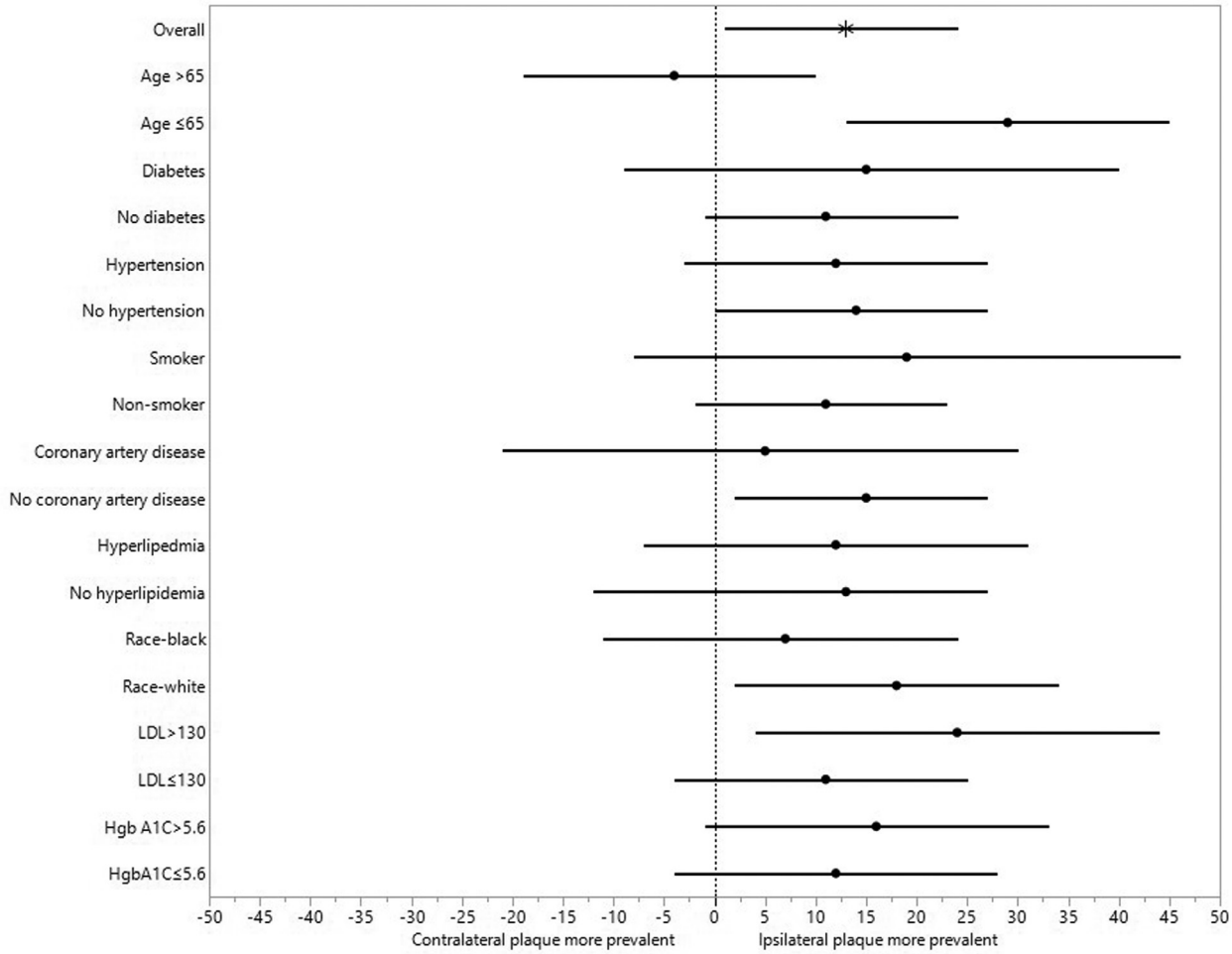

Figure 2. *Subgroup analysis showing proportional difference (with 95% confidence intervals) in prevalence of plaque ≥3 mm ipsilateral compared to contralateral in ESUS patients.*

Table 4. *Relevant previous literature*

Study	Design	Sample size	Stroke type	Imaging modality	Plaque thickness thresholds	Prevalence of ipsilateral versus contralateral nonstenotic ICA plaque (% patients)
Coutinho et al[8]	Retrospective observational cohort	85	ESUS	CTA	≥3 mm	35% versus 15%, $P = .001$
					≥4 mm	19% versus 5%, $P = .002$
					≥5 mm	11% versus 1%, $P = .008$
Komatsu et al[9]	Retrospective observational cohort	53	ESUS	Carotid Ultrasound	≥1.5 mm	59% versus 42%, $P = .049$
					≥2.0 mm	32% versus 19%, $P = .039$
					≥3.0 mm	15% versus 4%, $P = .07$
Buon et al[10]	Prospective observational cohort	44	Cryptogenic	Carotid Ultrasound	>2 mm	50% versus 34%, $P = .023$

Abbreviations: CTA, computed tomography angiography; ESUS, embolic stroke of undetermined source.

Within our cohort, the differential prevalence between ipsilateral and contralateral plaque was much greater in younger ESUS patients, suggesting that nonstenotic plaque plays a greater role in this group. This finding is biologically plausible given strong evidence of an age-related increase in the prevalence of paroxysmal AF, such that younger patients would be less likely to have this alternative mechanism for ESUS. This is also consistent with the recent study showing that AF is more commonly detected among ESUS patients without carotid plaque and the RESPECT-ESUS trial, which found a possible benefit to oral anticoagulation in older but not younger subjects.[7,12] We did not find any other subgroup with a particular differential prevalence of plaque ipsilateral to or contralateral to stroke location, though our sample size was likely underpowered to identify clinically relevant associations.

Some preliminary evidence suggests that plaque imaging features, such as intraplaque high-intensity signal on MR angiography, might be useful in identifying patients with ESUS in whom nonstenotic carotid plaque is the culprit mechanism.[13,14] Aside from ulceration, which was infrequent and did not vary between ipsilateral and contralateral sides, we did not investigate detailed plaque imaging features. Additional studies of plaque composition in the context of ESUS patients with nonstenotic plaque are warranted.

In addition to the ESUS cohort, we also evaluated the prevalence of carotid plaque in patients with atrial fibrillation as the mechanism of stroke. As opposed to the ESUS group, these patients had no significant difference in carotid plaque prevalence or thickness between the ipsilateral and contralateral carotid artery. This argues against a major role of nonstenotic plaque as an unrecognized etiology in patients with a cardioembolic mechanism. It also serves as a negative control, lending further support to the validity of our findings in the ESUS group. That said, there may still be a small risk of coexisting paroxysmal AF in patients with nonstenotic plaque ipsilateral to the side of infarction, as demonstrated in the observational cohort by Ntaios et al.[12]

Limitations of our study include its retrospective nature, which may have led to selection bias, and lack of power to fully assess the differential prevalence of ipsilateral and contralateral plaque in specific subgroups. Measurement of plaque thickness may also be imprecise, particularly when heavily calcified plaque is present, although this would have biased our study toward the null. Finally, our ESUS cohort may have included some patients with unrecognized paroxysmal AF, as only one third of patients underwent prolonged mobile cardiac outpatient telemetry. This would likewise be expected to bias our results toward the null.

In summary, nonstenotic carotid plaque is likely the causative stroke mechanism in some ESUS patients, or at minimum could represent a biomarker indicating a heightened risk of ipsilateral cerebrovascular events due to unclear mechanisms. Future studies to define which patients are most likely to have had a stroke due to nonstenotic plaque

could be useful. In a similar fashion, it is probable that some patients with ESUS may have experienced stroke due to nonstenotic intracranial atherosclerosis. This should be evaluated further. Regardless of the location of nonstenotic plaque (cervical or intracranial), the optimal treatment of patients with nonstenotic plaque is unclear. Based on the results of the NAVIGATE and RESPECT-ESUS trials, full-dose oral anticoagulation appears no better than antiplatelet therapy in unselected ESUS patients.[6,7] Alternative antithrombotic regimens, such as dual antiplatelet therapy or a single antiplatelet agent plus low-dose anticoagulation with a direct oral anticoagulant, such as was used in the COMPASS trial of patients with atherosclerotic vascular disease, might be worth exploration in future trials.[15-17]

Conflict of Interest

The authors report no competing financial interests exist.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.07.005.

References

1. Hart RG, Catanese L, Perera KS, et al. Embolic stroke of undetermined source: a systematic review and clinical update. Stroke 2017;48:867-872.
2. Hart RG, Diener H-C, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol 2014;13:429-438.
3. Kamel H, Bartz TM, Elkind MSV, et al. Atrial cardiopathy and the risk of ischemic stroke in the CHS (cardiovascular health study). Stroke 2018;49:980-986.
4. Yaghi S, Kamel H, Elkind MSV. Atrial cardiopathy: a mechanism of cryptogenic stroke. Expert Rev Cardiovasc Ther 2017;15:591-599.
5. Perera KS, Vanassche T, Bosch J, et al. Embolic strokes of undetermined source: prevalence and patient features in the ESUS global registry. Int J Stroke Off J Int Stroke Soc 2016;11:526-533.
6. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. N Engl J Med 2018;378:2191-2201.
7. Diener H-C, Sacco RL, Easton JD, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. N Engl J Med 2019;380:1906-1917.
8. Coutinho JM, Derkatch S, Potvin AR, et al. Nonstenotic carotid plaque on CT angiography in patients with cryptogenic stroke. Neurology 2016;87:665-672.
9. Komatsu T, Iguchi Y, Arai A, et al. Large but nonstenotic carotid artery plaque in patients with a history of embolic stroke of undetermined source. Stroke 2018;49:3054-3056.
10. Buon R, Guidolin B, Jaffre A, et al. Carotid ultrasound for assessment of nonobstructive carotid atherosclerosis in young adults with cryptogenic stroke. J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc 2018;27:1212-1216.
11. North American Symptomatic Carotid Endarterectomy Trial Collaborators, HJM Barnett, Taylor DW, et al. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991;325:445-453.
12. Ntaios G, Perlepe K, Sirimarco G, et al. Carotid plaques and detection of atrial fibrillation in embolic stroke of undetermined source. Neurology 2019;92:e2644-e2652.
13. Gupta A, Gialdini G, Lerario MP, et al. Magnetic resonance angiography detection of abnormal carotid artery plaque in patients with cryptogenic stroke. J Am Heart Assoc 2015;4:e002012.
14. Gupta A, Gialdini G, Giambrone AE, et al. Association between nonstenosing carotid artery plaque on MR angiography and acute ischemic stroke. JACC Cardiovasc Imaging 2016;9:1228-1229.
15. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med 2011;365:993-1003.
16. Derdeyn CP, Chimowitz MI, Lynn MJ, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. Lancet Lond Engl 2014;383:333-341.
17. Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet Lond Engl 2018;391:219-229.