

Carotid Webs in Cryptogenic Ischemic Strokes: A Matched Case-Control Study

Song J. Kim, MD,* Jason W. Allen, MD, PhD,*† Mehdi Bouzlama, MD,*
Fadi Nahab, MD,* Michael R. Frankel, MD,* Raul G. Nogueira, MD,* and
Diogo C. Haussen, MD*

Background: Young individuals with symptomatic carotid webs may be predisposed to ischemic strokes. However, evidence remains scarce. This investigation reports the frequency of carotid webs among patients with cryptogenic strokes compared to a control group. *Methods:* Consecutive cryptogenic ischemic strokes and trauma patients were identified. Additional inclusion criteria required age 18-60 years and availability of head/neck computed tomography (CT) angiography. CT angiogram (CTA) neck images were evaluated independently by 2 fellowship-trained specialists. A carotid web was defined by a shelf-like, linear filling defect in the posterior internal carotid artery bulb. *Results:* Of 1877 patients presenting with ischemic strokes in 2015-2017, 165 were diagnosed with cryptogenic strokes, 51 of whom met the inclusion criteria of age and CTA availability. Fifty one trauma cases were matched for age and sex. After imaging analysis, 13 carotid webs (25%) were identified in the 51 cryptogenic stroke group versus 0 (0%; $P < .001$) in trauma subjects. Thirty-nine of the 51 cryptogenic ischemic stroke patients were found with carotid anterior distribution infarcts, of which 9 (23%) were found with ipsilateral carotid webs. There were more proximal large vessel occlusions in the cryptogenic patients with carotid webs, compared to those without ($P = .04$). All carotid webs led to less than 30% degree of stenosis. *Conclusions:* Carotid webs were found at a significantly higher frequency in patients with cryptogenic ischemic strokes compared to controls, indicating a potentially thrombogenic nature of these lesions in young patients. Additionally, intracranial large vessel occlusions were more common in patients with symptomatic carotid webs, presenting with ipsilateral strokes.

Key Words: Stroke in young—cryptogenic strokes—fibromuscular dysplasia—carotid web

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From the *Department of Neurology, Emory University School of Medicine, Marcus Stroke and Neuroscience Center, Grady Memorial Hospital, Atlanta, Georgia; and †Department of Radiology and Imaging Sciences, Emory University School of Medicine, Marcus Stroke and Neuroscience Center, Grady Memorial Hospital, Atlanta, Georgia.

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Address correspondence to Diogo C. Haussen, MD, Department of Neurology, Emory University School of Medicine, Marcus Stroke and Neuroscience Center, Grady Memorial Hospital, 80 Jesse Hill Jr. Drive SE, Box 036, Atlanta, GA 30303. E-mails: diogo.haussen@emory.edu, dhaussen@med.miami.edu.

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Introduction

Carotid web (CaW) is a shelf-like lesion located on the posterior aspect of the internal carotid artery (ICA) bulb (Fig 1 A), first reported in 1968 in a young patient presenting with recurrent left middle cerebral artery territory strokes.¹ It is thought to be an intimal variant of fibromuscular dysplasia, with predominant fibroplasia and proliferative changes in the intimal layer on histopathology.¹⁻⁴ These lesions may predispose to recurrent thromboembolism due to flow stasis and thrombus formation in the pocket of the CaW, with subsequent anterior circulation strokes.⁵

As a relatively newly recognized vascular entity, CaWs could account for a significant portion of cryptogenic ischemic strokes (CIS), particularly in young adults. Indeed, recent studies have further described the prevalence of CaW among CIS patients less than 60 years of age, at rates

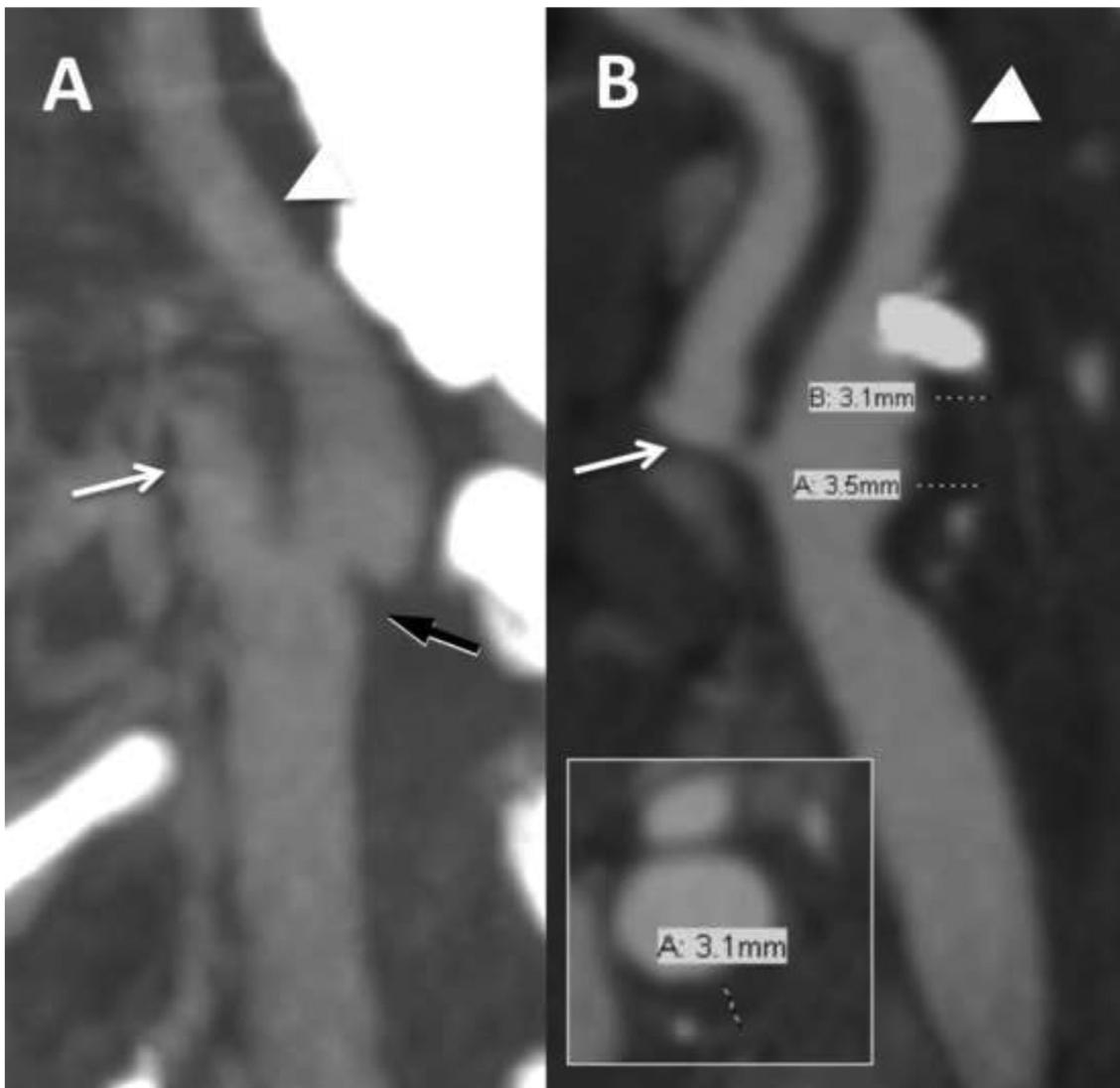


Figure 1. Carotid web versus carotid atherosclerotic plaque. Sagittal neck CTA demonstrating (A) carotid webs and (B) carotid atherosclerosis. Dotted lines and corresponding labels of A and B in the gray boxes indicate the thickness of the atherosclerotic plaque, with inset from axial CTA cut. Black arrow: carotid web; arrowhead: internal carotid artery; white arrow: external carotid artery. Abbreviation: CTA, CT angiogram.

ranging between 9.4%-37%,^{4,6,7} suggesting that CaW may be an independent risk factor in cerebrovascular ischemia in the young.

In this retrospective study, we aim to study the prevalence of CaW in a cohort of young CIS compared to controls.

Methods

This is a matched case-control study conducted across 2 comprehensive stroke centers. The study received approval by Emory University Institutional Review Board. As this was a retrospective chart review with protected patient data, the study qualified for a waiver of informed consent by the IRB.

Patient Selection

Of 1877 patients with ischemic strokes from 2015 to 2017, 165 patients with CIS (undetermined stroke

etiology - negative investigation subtype) were identified by TOAST criteria (Trial of Org 10172 in Acute Stroke Treatment classification), through the Get with the Guidelines) American Heart Association/American Stroke Association) database.⁸ Minimum stroke workup included noncontrast brain computed tomography (CT) and MRI Brain, vessel imaging with either head and neck CT angiogram (CTA), head and neck MR angiogram, coagulation tests, inpatient telemetry, electrocardiogram, plus transthoracic, and/or transesophageal echocardiography in accordance with AHA Stroke Council and Stroke Association guidelines.^{9,10} Inclusion criteria for the study consisted of availability of neck CTA imaging and age range of 18-60, leading to 51 patients selected for the CIS study cohort (Fig 2). Demographics and baseline characteristics (including risk factors and history of previous strokes) were collected.

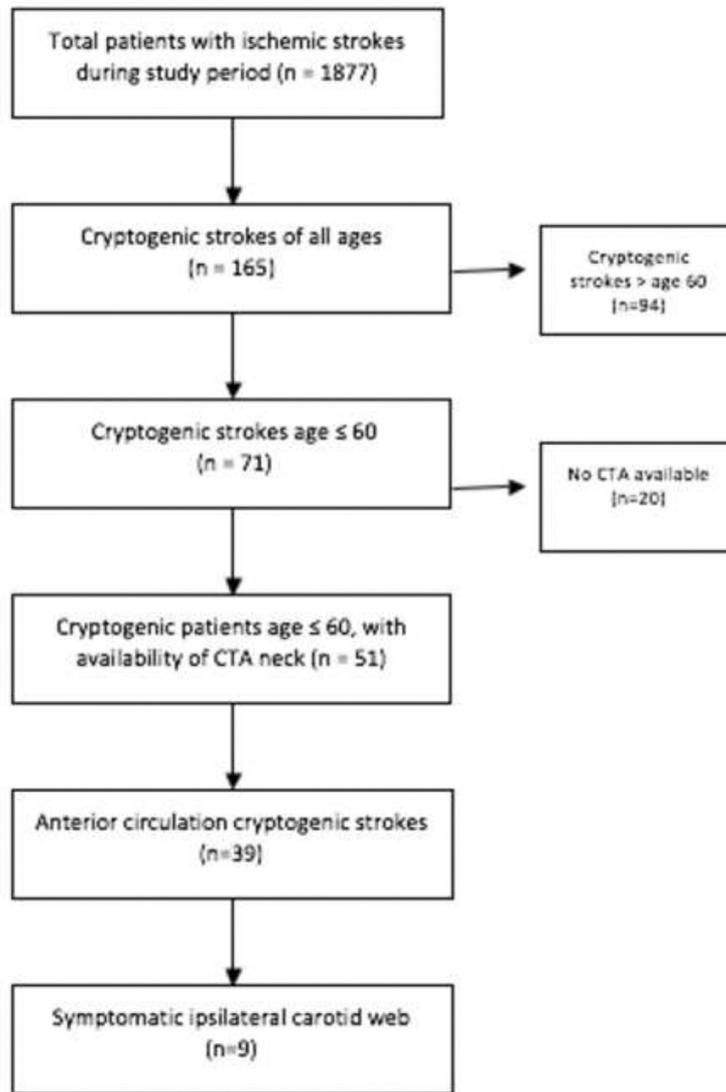


Figure 2. Algorithmic representation of patient selection for CIS, and frequency of symptomatic CaW. Abbreviations: CaW, carotid web; CIS, cryptogenic ischemic strokes.

The control group was derived from a database containing 391 consecutive patients from 2011 to 2013 who underwent neck CTA to assess for blunt cerebrovascular injury in the setting of trauma. Exclusion criteria of the database included penetrating injury or a follow-up study for known vascular injury. Patients with blunt neck trauma were not excluded after age and gender matching, in order to capture all possible carotid etiologies including asymptomatic incidental CaW.

Imaging Analysis

All vascular images were evaluated independently and blindly by a fellowship trained neuroradiologist (11 years postfellowship experience) and interventional neuroradiologist (4 years postfellowship experience). Discrepancies were resolved with a consensus read. CaW was defined as

a shelf-like linear filling defect in the posterior aspect of the carotid bulb. In addition, degree of stenosis per North American Symptomatic Carotid Endarterectomy Trial criteria, presence of superimposed thrombus, and presence of atherosclerotic changes (defined by the presence of calcification or by a segment of maximal vessel wall thickness greater than or equal to 2.2 mm; in case of a focal linear endoluminal projectile lesion, adjacent areas were also assessed)¹¹ were evaluated (Fig 1 B). The endoluminal projectile length of the CaW was measured using a sagittal CTA maximum intensity projection in a perpendicular plane to the web.¹² In the stroke patients, proximal large vessel occlusion strokes were identified by CTA, defined as intracranial ICA, middle cerebral artery (MCA M1 or M2 segment), or basilar artery occlusions. Echocardiography was used to determine ejection fraction and the presence of patent foramen ovale.

Matching Methodology

A matching method based on weighted Euclidean distances was used to obtain a pair of subjects considered to be the nearest neighbors in a 2-dimensional space of age and gender. The distance between each Cryptogenic/trauma pair was computed using the %FIND_NEIGHBORS Macro in SAS University Edition (SAS Institute, Cary, NC). Each patient with cryptogenic stroke was matched with nearest trauma patient (having the smallest Euclidian distance). After matching, the distribution of Euclidian distances was studied to identify outliers and a threshold was determined as follows: $\text{Threshold} = Q75 + 1.5 * (Q75 - Q25)$, where Q25 and Q75 are, respectively, the 25th and 75th percentile. Pairs with distances greater than the threshold were considered extreme values at the tail of the distribution and eliminated from further consideration.

Statistical Analysis

The Shapiro-Wilk test was used to assess the normality of the variables. Continuous variables were reported as mean \pm SD if normally distributed or median (interquartile range - IQR) if nonparametric. Categorical variables were reported as proportions. Between groups, comparisons for continuous/ordinal variables were made with paired t test, rank sum test, as appropriate. Categorical variables were compared by Mc Nemar test for discordant pairs. Significance was set at $P < .05$ and all P values were 2-sided. Statistical analysis was performed using IBM SPSS Statistics 24 (IBM-Armonk, NY, USA) and SAS University Edition (SAS Institute).

Results

Cryptogenic Ischemic Strokes

Out of 1877 patients with ischemic strokes treated within the study period, a total of 165 were diagnosed with cryptogenic strokes after standard inpatient workup. From the total CIS cohort, 51 met the inclusion criteria per age 18 to less than or equal to 60 years, and availability of CTA (Fig 2). Fifty-one corresponding controls were identified by matching for gender and age, out of the total 391 trauma patients included in the database; CIS and trauma cohorts had comparable mean age (46.4 ± 9.2 versus 46.4 ± 9.2 years; $P = 1.00$), and male gender frequency (39% versus 39%; $P = 1.00$).

Prevalence

Of the 51 patients in the CIS group, 13 (25%) CaW were identified versus 0 (0%) in the trauma control group ($P = .001$). The Inter-rater agreement for identification of CaW was highly positive ($\kappa = .78$; $P < .001$). The mean web length was 1.76 mm (± 0.47 SD), measuring $2.0 \pm .6$ mm in patients with concordant reads versus $1.4 \pm .8$ mm in discordant reads ($P = .22$). We did not find a statistically significant difference in the prevalence of atherosclerosis (39% versus 33%; $P = .54$), or superimposed carotid thrombus (5.8% versus 0%; $P = .24$), in the CIS versus trauma groups, respectively (Fig 3). The inter-rater agreement for the diagnosis of atherosclerosis ($\kappa = .87$; $P < .001$) and superimposed thrombus ($\kappa = .86$; $P < .001$) were strong.

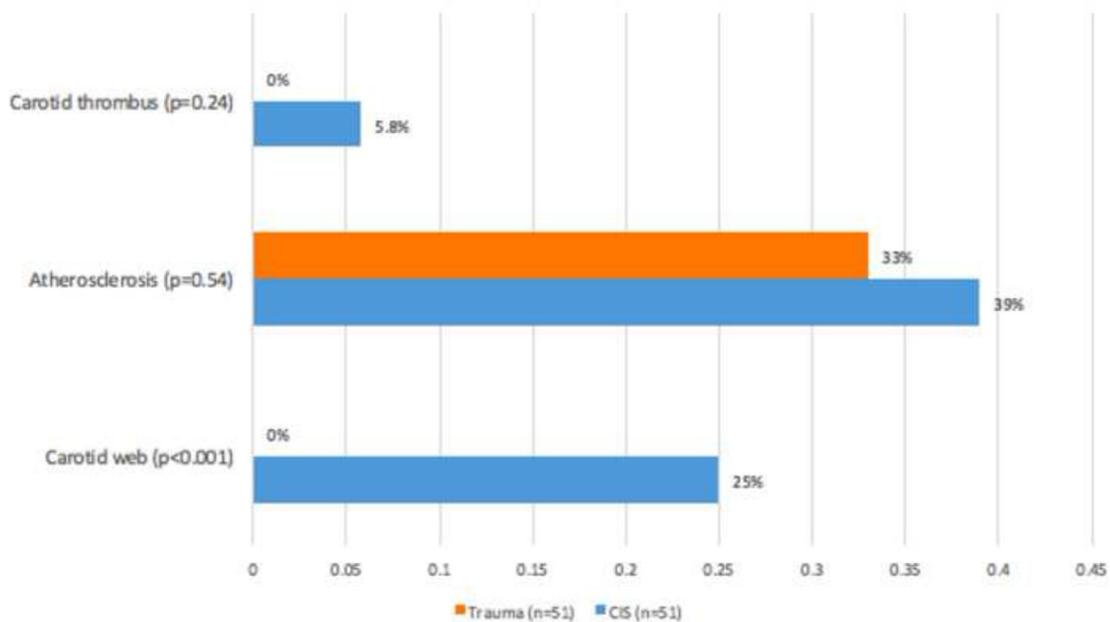


Figure 3. Frequency of carotid lesions – thrombus, atherosclerosis, and web – in patients with cryptogenic patients versus trauma.

CaW Patient Characteristics

Thirty-nine of the 51 patients had anterior circulation ischemic strokes, of which 9 (23%) were found with ipsilateral CaWs. None of the posterior circulation stroke patients had incidental CaW seen on imaging. Four other CaWs were found contralateral to the affected anterior circulation strokes. The 9 patients with anterior circulation strokes attributed to CaW had a mean age of 42.7 ± 7.5 years and 66% were male. Two of these patients (22%) had hypertension, 3 (33%) hyperlipidemia, 1 (11%) diabetes, and 2 (22%) reported greater than or equal to 10-pack-year cigarette use. Comparison of CIS patients with CaW ($n = 9$) to the remainder of the CIS patients without webs ($n = 42$) did not reveal a statistically significant difference with regards to the frequency of vascular risk factors and stroke severity, as well as history of prior stroke and concurrent antiplatelet use at the time of the stroke (Table 1).

Proximal LVOs were observed in all 9 symptomatic CaW – 2 in the supraclinoid ICA (22%), 5 MCA-M1 (56%), and 2 MCA-M2 (22%) – at a rate more significant compared to the LVOs in the remaining CIS patients (100% versus 55%, $P = 0.02$, Table 1).

Discussion

This investigation adds to the growing body of literature on CaW, strengthening the association between

this vascular entity and ischemic strokes in young patients.

Our analysis shows 17.6% frequency of 9 symptomatic CaW among 51 young (18-60 years of age) cryptogenic stroke patients, statistically significant compared to 0% presence among age and gender-matched controls. This is comparable to the prevalence of webs found in other retrospective age and gender-matched case-control analyses of young CIS patients: 37% in a series of 27 patients conducted in the Martiniques,⁶ 21% in a population of 33 patients from the United States,⁴ and 9% in 53 cases in a Canadian study.^{4,7} Although limited by the study design investigating only the CIS patients, and unavailability of CTA in a substantial number therein, out of 165 CIS patients and 1877 total consecutive ischemic strokes, 9 symptomatic webs translates to 5.4% frequency among all cryptogenic strokes, and ~.5% frequency in all ischemic strokes in our study. Taken altogether, these findings indicate that CaW may be an independent risk factor for ischemic strokes at large.

The likely pathophysiology of CaW in ischemic strokes may relate to flow stasis and thrombus formation in the pocket of the CaW, which may be the source of ipsilateral embolism.^{13,14} Even though this was not observed in the present series, multiple reports have demonstrated superimposed thrombus along the rostral surface of the septum in patients with ipsilateral acute stroke.^{3,12,15,16}

Table 1. Comparison of symptomatic CaW with ipsilateral strokes versus CIS patients without webs

	Web (n = 9)	All Nonweb CIS (n = 42)	P value
Age (y)	42.7 ± 7.5	47.2 ± 9.5	.19
Male sex	6 (66%)	25 (59%)	.49
Black ethnicity	8 (89%)	31 (74%)	.31
Hypertension	2 (22%)	21 (50%)	.12
Hyperlipidemia	3 (33%)	22 (52%)	.25
Diabetes (HbA1c > 6.5%)	1 (11%)	13 (31%)	.22
Smoking (active or 10-pack year)	2 (22%)	12 (28%)	.55
Cocaine	0 (0%)	3 (7%)	.32
History of prior strokes	0 (0%)	10 (24%)	.18
History of concurrent antiplatelet use	0 (0%)	6 (14%)	.57
Atrial fibrillation	0 (0%)	0 (0%)	-
Ejection fraction (%)	57 ± 2.6	56 ± 5.7	.61
Patent foramen ovale	0 (0%)	3 (7%)	.32
Hemoglobin A1c	6.2 ± 2.3	6.3 ± 2.1	.89
LDL cholesterol (mg/dL)	91 ± 27	106 ± 33	.22
NIHSS	13.8 ± 6.6	10.1 ± 6.7	.14
IV thrombolysis	66.1 ± 24.3	73.3 ± 20.2	.35
Thrombectomy	6 (67%)	18 (43%)	.27
THRIVE score	6 (67%)	14 (33%)	.13
All vessel occlusions	9 (100%)	27 (64%)	.04
Proximal LVOs	9 (100%)	23 (55%)	.02
Modified Rankin scale	2.3 (1.9)	1.8 (1.5)	.47

Abbreviations: CaW, carotid web; CIS, cryptogenic ischemic strokes; LDL, low-density lipoprotein; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; Proximal LVOs, large vessel occlusion stroke; THRIVE, totaled health risks in vascular events.²³

Note: Internal carotid artery, middle cerebral artery M1 and M2, or basilar artery; All vessel occlusions: any visible occlusion including MCA-M3, anterior cerebral or posterior artery occlusions.

Statistically significant values depicted in bold.

Although lacunar infarcts have been reported in events attributed to CaW,¹⁷ embolic strokes may be more common.¹⁸ Interestingly, we were able to demonstrate that patients with stroke attributable to CaW presented with proximal LVOs more commonly so than non-CaW-related cryptogenic strokes, indicating that the thrombotic potential and resultant emboli originating from CaW can be substantial.

Although CaW's have a unique radiological appearance, there is considerable variability in morphology (e.g., length, thickness, and angulation). These lesions may be missed or mistaken for radiological mimics such as dissections or atherosclerotic plaques. Finally, it is possible that lesions coexist in some patients.¹⁹ Nevertheless, the present study demonstrated a highly positive inter-rater coefficient ($\kappa = .78$), comparable to previous reports ($\kappa = .72-1.00$).^{4,6,7,18} The web length was numerically more pronounced in patients with concordant reads, although the difference was not statistically significant, potentially due to the limited sample size.

This study has limitations inherent to retrospective analysis. We have not included patients with strokes of "other determined etiology" TOAST subtype, which likely included cases attributed to CaW and therefore may have attenuated the observed frequency of CaW in CIS. Twenty CIS patients aged 18-60 were excluded due to lack of available CTA, which may have led to underestimation of the overall frequency of CaW within the ischemic stroke population. Regarding the selection of CIS patients, the lack of data on outpatient cardiac monitoring and transesophageal echocardiogram for all patients in determination of stroke etiology is a potential bias. Although TEE in cryptogenic strokes may rarely demonstrate left appendage thrombus, it is not included in the proposed criteria definition or mandated work-up of embolic strokes of undetermined source.^{20,21} Additionally, we have used comparable methodology as those in trials evaluating patients with embolic strokes of undetermined source, which have utilized greater than 20 hours of cardiac monitoring.²²

Conclusions

CaWs were found at a greater frequency in patients with CIS compared to controls, and were found associated with higher rates of proximal large vessel intracranial occlusions. Prospective controlled studies are warranted to better understand the natural history and impact of treatment options for these patients.

Conflicts of Interest

S.J.K., J.W.A., M.B., F.N., M.R.F.: No relevant disclosures. D.C.H.: Stryker-Neurovascular (consultant), Vesalio (consultant). R.G.N.: Stryker-Neurovascular (Trevor-2&DAWN/Trial PI), Covidien (SWIFT&SWIFT-PRIME/Steering-Committee, STAR Trial/Core-Lab), Penumbra (3-D Separator Trial/Executive-Committee).

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