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Complicated Carotid Artery Plaques as a Cause of Cryptogenic Stroke

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ABSTRACT

BACKGROUND The underlying etiology of ischemic stroke remains unknown in up to 30% of patients.

OBJECTIVES This study explored the causal role of complicated (American Heart Association–lesion type VI) nonstenosing carotid artery plaques (CAPs) in cryptogenic stroke (CS).

METHODS CAPIAS (Carotid Plaque Imaging in Acute Stroke) is an observational multicenter study that prospectively recruited patients aged older than 49 years with acute ischemic stroke that was restricted to the territory of a single carotid artery on brain magnetic resonance imaging (MRI) and unilateral or bilateral CAP (≥2 mm, NASCET [North American Symptomatic Carotid Endarterectomy Trial] <70%). CAP characteristics were determined qualitatively and quantitatively by high-resolution, contrast-enhanced carotid MRI at 3T using dedicated surface coils. The pre-specified study hypotheses were that that the prevalence of complicated CAP would be higher ipsilateral to the infarct than contralateral to the infarct in CS and higher in CS compared with patients with cardioembolic or small vessel stroke (CES/SVS) as a combined reference group. Patients with large artery stroke (LAS) and NASCET 50% to 69% stenosis served as an additional comparison group.

RESULTS Among 234 recruited patients, 196 had either CS (n = 104), CES/SVS (n = 79), or LAS (n = 19) and complete carotid MRI data. The prevalence of complicated CAP in patients with CS was significantly higher ipsilateral (31%) to the infarct compared with contralateral to the infarct (12%; p = 0.0005). Moreover, the prevalence of ipsilateral complicated CAP was significantly higher in CS (31%) compared with CES/SVS (15%; p = 0.02) and lower in CS compared with LAS (68%; p = 0.003). Lipid-rich and/or necrotic cores in ipsilateral CAP were significantly larger in CS compared with CES/SVS (p < 0.05).

CONCLUSIONS These findings substantiate the role of complicated nonstenosing CAP as an under-recognized cause of stroke. (Carotid Plaque Imaging in Acute Stroke [CAPIAS]; NCT01284933) (J Am Coll Cardiol 2020;76:2212–22) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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Stroke is a major cause of death and the leading cause of permanent disability (1). Defining the underlying etiology is important because strategies for secondary prevention, both early and long-term, vary depending on stroke mechanism (2). The importance of a precise ascertainment of stroke mechanisms has been further illustrated by the recent NAVIGATE-ESUS (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source) and RE-SPECT ESUS (Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source) trials, which found no benefit of anticoagulant treatment in patients with embolic stroke of undetermined source (ESUS) (3,4).

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The widely used TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification of ischemic stroke distinguishes 5 major categories of stroke: large artery atherosclerosis, cardioembolism, small vessel occlusion, other determined etiology, and undetermined etiology (5). However, even in settings with extensive diagnostic workup, up to 30% of stroke cases are classified as undetermined, leaving these patients without specific treatment (6).

Although a diagnosis of large artery stroke (LAS) typically requires stenosis >50% (5), there are obvious limitations to a definition of stroke etiology based on a strict cutoff of a single variable. Specifically, there is growing recognition of the importance of atherosclerotic plaque composition and morphology in determining stroke risk (7,8). For example, histological studies on arteries from patients who underwent carotid endarterectomy showed features of plaque vulnerability to be more frequent in patients with symptomatic compared with asymptomatic carotid artery stenosis (9) and in recently symptomatic plaques compared with those removed late after the ischemic event (10).

High-resolution, black-blood carotid magnetic resonance imaging (MRI) enables noninvasive characterization of atherosclerotic carotid artery plaques (CAPs), including features of plaque vulnerability (11). It enables assessment of plaque size, plaque morphology, and plaque composition with good correlation to histopathology (12). Recent meta-analyses on prospective single- and multicenter MRI studies have shown that the presence of intraplaque hemorrhage (IPH), a thin and/or ruptured fibrous cap, or a large lipid-rich and/or necrotic core (LRNC) are associated with increased risk of cerebrovascular events (13,14). Specifically, a meta-analysis of individual patient data found the presence of IPH at baseline increased the risk of ipsilateral stroke in both symptomatic and asymptomatic patients (15).

In a pilot study on 32 patients with cryptogenic stroke (CS) with nonstenosing CAP, we previously found that complicated American Heart Association–lesion type (AHA-LT) VI CAP (cCAP), as defined by IPH, a ruptured fibrous cap, or the presence of a mural thrombus (12), was more frequent ipsilateral to ischemic stroke compared with that of the contralateral side (16). These findings suggested a possible causal role of nonstenosing cCAP in patients with CS. However, the study was conducted as an explorative single-center study with a limited sample size and without inclusion of patients with defined stroke etiologies.

To better define the causal involvement of nonstenosing cCAP in ischemic stroke, we initiated the CAPIAS (Carotid Plaque Imaging in Acute Stroke; NCT01284933) study as a prospective, observational, multicenter study. This study tested the following pre-specified hypotheses: 1) that in patients with CS, the prevalence of cCAP would be higher ipsilateral to the infarct versus contralateral to the infarct; and 2) that the prevalence of ipsilateral cCAP would be higher in CS compared with patients with either cardioembolic stroke (CES) or small vessel stroke (SVS) as a combined reference group, with LAS with NASCET (North American Symptomatic Carotid Endarterectomy Trial) 50% to 69% stenosis serving as an additional comparison group. To address these hypotheses, we used high-resolution MRI at 3T with dedicated surface coils and use of contrast enhancement to allow for both qualitative and detailed quantitative plaque analyses.

ABBREVIATIONS AND ACRONYMS

AHA-LT = American Heart Association–lesion type

cCAP = complicated carotid artery plaque

CES = cardioembolic stroke

CS = cryptogenic stroke

DWI = diffusion-weighted imaging

ESUS = embolic stroke of undetermined source

IPH = intraplaque hemorrhage

LAS = large artery stroke

LRNC = lipid-rich/necrotic core

MRI = magnetic resonance imaging

NWI = normalized wall index

SVS = small vessel stroke

METHODS

STUDY DESIGN. CAPIAS is an observational, prospective, multicenter study conducted at 4 study sites in Germany: Ludwig-Maximilians-Universität Munich, Technical University Munich, University of Tübingen, and University of Freiburg. The study was approved by the local ethics committees. All participants provided written informed consent. The study design, including inclusion and exclusion criteria, was previously reported (17).

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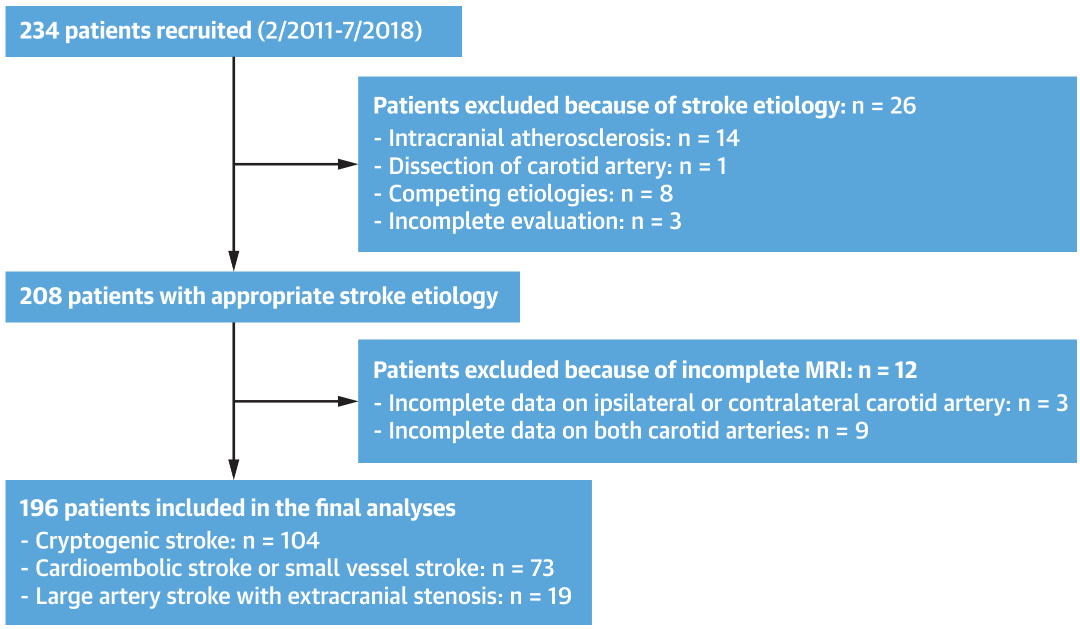
FIGURE 1 **Study Profile**



Study profile detailing the reasons for exclusion. MRI = magnetic resonance imaging.

STUDY POPULATION. Study participants had to meet all of the following criteria for study inclusion: age older than 49 years; an acute ischemic stroke within the last 7 days, including patients with a symptom duration of <24 h (i.e., patients who met the World Health Organization definition of a transient ischemic attack but had a documented acute ischemic infarct); a corresponding unilateral infarct restricted to the territory of a single carotid artery as defined by a diffusion-weighted imaging (DWI)-positive lesion on brain MRI at 3T; and unilateral (independent of side) or bilateral CAP with a thickness of ≥2 mm as determined by duplex ultrasound. Patients with carotid artery stenosis ≥70% (NASCET) (18) were excluded. The recruitment period was from February 2011 to July 2018. The study originally aimed to recruit 300 patients but was terminated prematurely after inclusion of 234 patients due to slow recruitment. This decision was made before initiation of data cleaning and any statistical analyses.

STUDY WORKFLOW. All patients underwent comprehensive diagnostic workup, including laboratory investigations, 12-lead electrocardiography, continuous electrocardiography monitoring for at least 24 h, transthoracic echocardiography, transesophageal echocardiography (when indicated), duplex ultrasound of the extracranial and intracranial vessels, and brain MRI. Additional tests (e.g., cerebrospinal fluid analysis, conventional angiography, screening for prothrombotic conditions) were performed as clinically indicated. Stroke etiology was classified according to TOAST categories (5). Classification was done centrally by trained raters (A.K. and M.L.K.), who were blinded to the plaque imaging data.

Based on the preceding information, patients were divided into the following 3 groups: 1) patients with CS, that is, stroke of undetermined origin with negative evaluation despite complete diagnostic workup and excluding patients with competing etiologies; 2) patients with either CES or SVS as a combined reference group; and 3) patients with LAS and NASCET 50% to 69% stenosis. Patients with other stroke etiologies were excluded from further analyses.

CAROTID PLAQUE IMAGING. All study participants underwent high-resolution, black-blood carotid MRI within 10 days of symptom onset. Imaging was done on 3T MRI scanners (Magnetom Verio, Magnetom Skyra, Magnetom Tim Trio, Magnetom Prisma, and

Biograph mMR, all from Siemens Healthineers, Erlangen, Germany) with a dedicated 4-channel surface coil (Machnet B.V., Eelde, the Netherlands). The MRI protocol consisted of a time-of-flight MR angiography, axial pre- and post-contrast black-blood T1-, PD-, and T2-weighted sequences with fat suppression (best in-plane resolution 0.5×0.5 mm^2) as previously reported (19). Post-contrast T1w imaging was performed 5 min after intravenous injection of 0.1 mmol/kg of body weight gadolinium-DO3A-butrol (Gadovist, Bayer Schering, Leverkusen, Germany).

The carotid plaque MRI data were reviewed in a consensus reading by 2 experienced radiologists (A.S. and T.S.) who were blinded to the clinical status following previously published criteria (12,19). In case of disagreement, a third expert radiologist (A.H.) was consulted, and a consensus decision was made.

Atherosclerotic plaques were classified separately for the ipsilateral and contralateral carotid artery applying the modified AHA criteria (12). MRI allowed differentiation of the following lesion types: AHA-LT I/II (initial lesion with near-normal wall thickness and without calcification); AHA-LT III (diffuse intimal thickening or small eccentric plaque without calcification); AHA-LT IV/V (plaque with a LRNC surrounded by fibrous tissue with possible calcification); AHA-LT VI (complicated plaque with possible surface defect, hemorrhage, or thrombus); AHA-LT VII (calcified plaque); and AHA-LT VIII (fibrotic plaque without lipid core and with possible small calcifications) (12).

For the primary comparisons, we focused on complicated (AHA-LT VI) plaques as pre-specified in the study protocol (17). We further performed area measurements of the lumen, wall, outer wall, and tissue components for all plaques using a custom-designed semiautomatic image analysis tool (CASCADE, University of Washington, Seattle, Washington). The normalized wall index (NWI) was calculated by dividing the wall area by the total vessel area. Tissue components (LRNC, calcification, and IPH; all in relation to the wall area and displayed as a percentage of the vessel wall), the status of the fibrous cap, and presence of juxtaluminal hemorrhage and/or mural thrombus were identified based on previously published criteria (20).

PRIMARY STUDY COMPARISONS. The 2 pre-specified primary comparisons were: 1) the prevalence of nonstenosing cCAPs in patients with CS ipsilateral to the infarct compared with contralateral to the infarct; and 2) the prevalence of ipsilateral cCAPs in patients with CS compared with patients with either CES or SVS as the combined reference group. Patients with LAS and NASCET 50% to 69% stenosis served as an additional comparison group.

TABLE 1 Patient Characteristics

	CS (n = 104)	CES/SVS (n = 73)	p Value*	LAS (n = 19)	p Value†
Demographic characteristics					
Age, yrs	71.8 ± 9.1	76.3 ± 9.5	**0.002**	72.5 ± 10.9	0.767
Male	83 (79.8)	45 (61.6)	**0.010**	13 (68.4)	0.364
NIHSS					
0–5	80 (76.9)	49 (67.1)	0.149	16 (84.2)	0.480
6–10	16 (15.4)	15 (20.5)	0.373	3 (15.8)	0.964
>10	8 (7.7)	9 (12.3)	0.303	0 (0.0)	0.356
Vascular risk factors					
Hypertension	73 (70.2)	54 (74.0)	0.615	14 (73.7)	0.844
Hypercholesterolemia	34 (33.0)	25 (34.7)	0.703	6 (35.3)	0.878
Diabetes mellitus	21 (20.4)	19 (26.0)	0.466	4 (21.1)	0.694
BMI, kg/m^2	26.8 ± 3.6	25.6 ± 3.5	**0.037**	28.6 ± 4.1	**0.046**
Current smoker	20 (32.3)	11 (33.3)	0.225	3 (23.1)	0.233
Ever smoker	62 (59.6)	33 (45.2)	0.076	13 (68.4)	0.076
History of cardiovascular disease					
Coronary heart disease	19 (18.5)	17 (23.3)	0.217	2 (11.8)	0.289
Myocardial infarction	12 (11.8)	11 (15.3)	0.190	0 (0.0)	0.214
TIA‡	9 (8.8)	4 (5.6)	0.738	2 (11.1)	0.738
Stroke‡	14 (13.5)	14 (19.2)	0.573	4 (21.1)	0.509
Previous medication					
Antihypertensives	65 (63.1)	65 (89.0)	**<0.001**	11 (57.9)	0.426
Statins	30 (29.1)	27 (37.0)	0.250	9 (47.4)	0.099
Oral anticoagulants	1 (1.0)	19 (26.0)	**<0.001**	0 (0.0)	0.844
Antiplatelet drugs	34 (33.0)	27 (37.0)	0.271	10 (52.6)	0.086
Stroke-related interventions					
Thrombolysis	18 (17.5)	17 (23.3)	0.341	3 (15.8)	1.000
Thrombectomy	5 (5.1)	11 (15.1)	**0.031**	0 (0.0)	1.000

Values are mean ± SD and n (%). **Bold** p values are statistically significant. *p value, group comparisons between patients with cryptogenic stroke (CS) and patients with cardioembolic/small vessel stroke (CES/SVS). †p value, group comparisons between patients with CS and large artery stroke (LAS). ‡Previous to a qualifying event.

BMI = body mass index; NIHSS = National Institute of Health Stroke Scale; TIA = transient ischemic attack.

STATISTICAL ANALYSES. Categorical variables are presented as absolute and relative frequencies; continuous variables are presented as mean ± SD. Subject characteristics were calculated with Student's *t*-test for numerical variables. Categorical variables were analyzed with chi-square or Fisher exact tests. Prevalence of cCAPs and differences between stroke etiologies were calculated with Fisher's exact test. For adjustments of p values, we used logistic regression analysis with age, body mass index, and sex as covariates. Prevalence of cCAPs and differences between ipsilateral and contralateral cCAPs within 1 etiology were calculated using McNemar's test.

Plaques characteristics were analyzed with the chi-square or Fisher exact tests. Differences in plaque burden and in plaque composition were assessed with Student's *t*-test for normally distributed variables.

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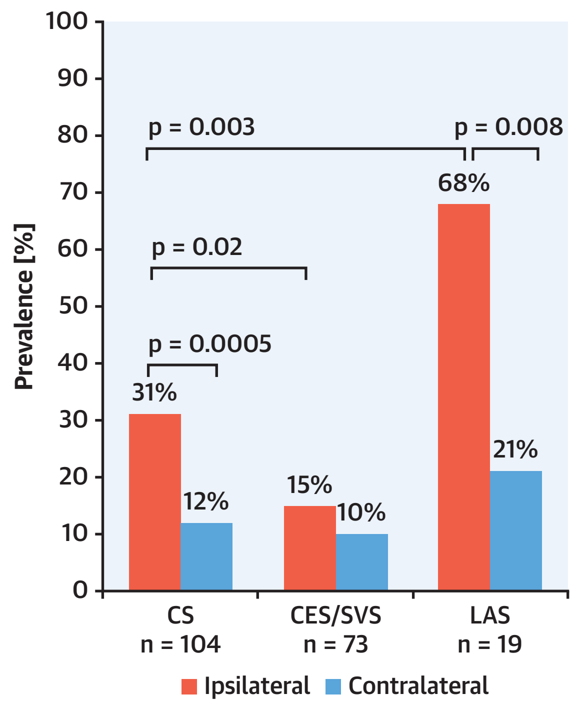
FIGURE 2 **Prevalence of Complicated AHA-LT VI CAPs in Patients With Acute Ischemic Stroke**



Statistical analyses between groups were performed with the Fisher exact test. Analyses within groups were performed using McNemar's test. Only significant unadjusted p values ($p < 0.05$) are shown. AHA-LT = American Heart Association–lesion type. CAP = carotid artery plaque; CES/SVS = cardioembolic/small vessel stroke; CS = cryptogenic stroke; LAS = large artery stroke.

Otherwise, the Mann-Whitney *U* test was applied. Equality of variance was tested with the Levene's test. If equality of variance was not granted, the Welch test, instead of Student's *t*-test, was applied. When indicated, false discovery rate correction was performed across all p values to account for multiple testing (Supplemental Appendix).

All analyses were performed using R version 3.5.3 (R Project for Statistical Computing, Vienna, Austria). A p value of <0.05 was considered statistically significant.

RESULTS

PATIENTS. A total of 234 patients were recruited into the study. Thirty-eight patients were excluded based on nonqualifying stroke etiology or incomplete MRI data, which left 196 patients (mean age: 73.5 ± 9.6 years; median National Institute of Health Stroke Scale: 3 [interquartile range: 1 to 6]) for the final analysis (Figure 1). Of these, 169 patients had stroke symptoms that lasted ≥24 h, and 27 patients had stroke symptoms that lasted <24 h, all with a corresponding DWI-positive lesion. Among the 196 patients with a qualifying stroke etiology, 104 had CS, 73 had either CES or SVS (CES: n = 54; SVS: n = 19), and 19 had LAS. The mean interval from symptom onset to carotid MRI was 4.1 ± 1.5 days, with no significant differences among the diagnostic groups (all $p > 0.1$).

Compared with patients in the reference group, patients with CS were younger (CS: 71.8 ± 9.1 years; CES/SVS: 76.3 ± 9.5 years; p = 0.002), were more frequently men (CS: 79.8%; CES/SVS: 61.6%; p = 0.01), and had a higher body mass index (CS: 26.8 ± 3.6 kg/m^2; CES/SVS: 25.6 ± 3.5 kg/m^2; p = 0.037) (Table 1). Patients with LAS did not differ from patients with CS with respect to age (LAS: 72.5 ± 10.9 years) and sex (LAS: 68.4% male) ($p > 0.05$ for both comparisons) but had a higher body mass index (LAS: 28.6 ± 4.1 kg/m^2; p = 0.046) (Table 1).

PREVALENCE OF COMPLICATED PLAQUES IN PATIENTS WITH CS AND OTHER STROKE ETIOLOGIES. Focusing on patients with CS, nonstenosing cCAPs were approximately 3 times more frequent in carotid arteries ipsilateral to the infarct compared with the contralateral side (31% vs. 12%; p = 0.0005; first pre-specified comparison) (Figure 2, Supplemental Table 1). In contrast, there was no significant side-to-side difference in the prevalence of cCAPs in the reference group (CES/SVS) (ipsilateral: 15%; contralateral 10%; $p > 0.05$) (Figure 2, Supplemental Table 1). Patients with LAS showed a substantially higher prevalence of cCAPs ipsilateral to the infarct compared with contralateral to the infarct (68% vs. 21%; p = 0.008).

Comparisons across stroke etiologies revealed that ipsilateral cCAPs were more frequent in CS (31%) than that in the reference group (CES/SVS: 15%; p = 0.02; second pre-specified analysis) but less frequent than that of LAS (68%, p = 0.003) (Figure 2, Supplemental Tables 1 and 2).

Figure 3 shows the distribution of individual AHA-LTs of CAPs ipsilateral to the infarct stratified by stroke etiology. The most frequent lesion types in CS were complicated AHA-LT VI plaques (31%), followed by AHA-LT III (28%) and calcified AHA-LT VII (20%) plaques (Figure 3, Supplemental Table 3). In contrast, the most frequent lesion types in the reference group (CES/SVS) were calcified AHA-LT VII plaques (42%), followed by AHA-LT III (26%) and AHA-LT IV/V (15%) plaques. Most ipsilateral lesions in LAS were complicated AHA-LT VI plaques (68%), with AHA-LT III plaques being the second most frequent lesion type

(16%), thus resembling the overall distribution of ipsilateral CAPs in CS.

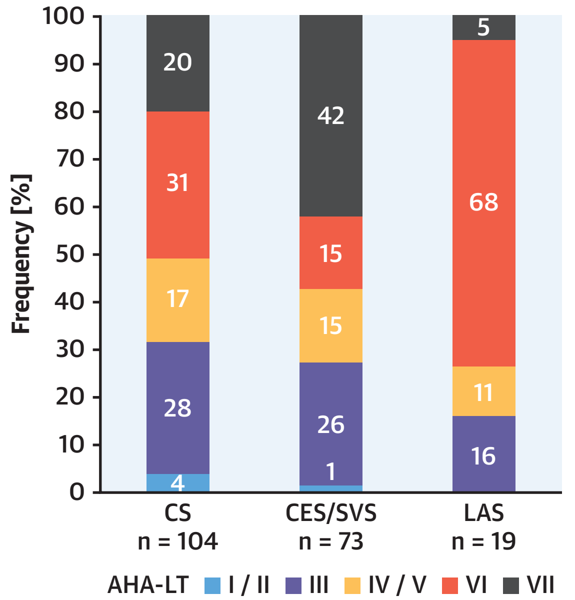
PREVALENCE OF INDIVIDUAL MRI CHARACTERISTICS DEFINING IPSILATERAL cCAP. MRI characteristics of complicated (AHA-LT VI) plaques that may be present in isolation or combination are IPH, a ruptured fibrous cap, and a mural thrombus indicating juxtaluminal hemorrhage (**Figure 4**). The most frequent characteristic of ipsilateral cCAP was IPH (**Figure 5**). Specifically, the frequency of IPH in ipsilateral cCAPs was 28 of 32 (88%) in patients with CS and 50 of 56 (89%) in the total sample of 196 patients (Supplemental Table 4).

PLAQUE BURDEN AND PLAQUE COMPOSITION IN DIFFERENT STROKE ETIOLOGIES. The quality of images obtained from plaque MRI was sufficient to quantify plaque burden and plaque composition in 191 (97.4%) of the 196 patients included in the final analyses (CS: 102 [98.1%]; CES/SVS: 72 [98.6%]; LAS: 17 [89.5%]).

Minimum lumen area and maximum NWI did not differ between patients with CS and the reference group (all $p > 0.05$) (**Table 2**). Maximum wall area and maximum total vessel area were larger in CS compared with the reference group (**Table 2**), but none of the plaque burden parameters remained significant after adjustment and correction for multiple testing (Supplemental Table 5). Plaque composition differed between CS and the reference group in that patients with CS had a larger maximum LRNC ($p = 0.006$) (**Table 2**) that remained significant after adjustment and correction for multiple testing (Supplemental Table 5).

As expected, minimum lumen area was smaller in LAS compared with CS ($p < 0.001$) (**Table 2**). Also, maximum NWI was higher in LAS compared with that of CS ($p = 0.001$). There was no significant difference in maximum wall area, total vessel area, and calcification area between patients with CS and LAS (all $p > 0.05$). Maximum IPH area was nominally higher in LAS compared with that in CS (17% vs. 9%) but did not reach statistical significance (**Table 2**, Supplemental Table 5). Maximum LRNC was higher in LAS compared with that of CS ($p = 0.038$) but did not remain significant after adjustment and correction for multiple testing ($p > 0.05$). Data on plaque burden and plaque composition in contralateral CAP are shown in Supplemental Table 6.

FIGURE 3 **Frequency Distribution of Individual AHA-LT in Ipsilateral CAPs in Patients With Acute Ischemic Stroke**



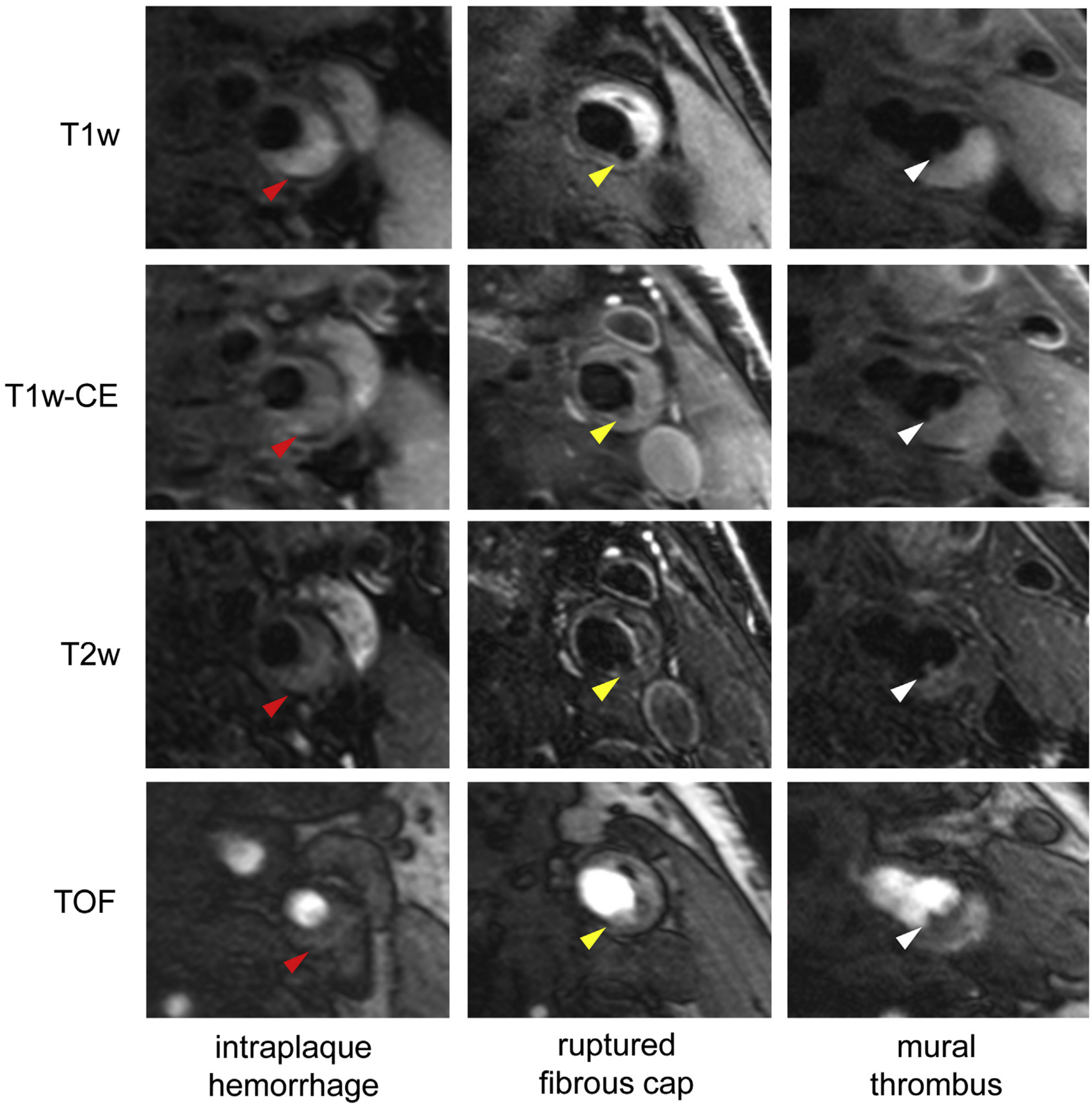
Type I/II: near-normal wall thickness; type III: diffuse intimal thickening or small eccentric plaque; type IV/V: plaque with a lipid or necrotic core surrounded by fibrous tissue with possible calcification; type VI: complicated plaque with possible surface defect, hemorrhage or thrombus; type VII: calcified plaque; and type VIII: fibrotic plaque without lipid core and with possible small calcifications. There were no fibrotic type VIII plaques detected in the sample. Abbreviations as in **Figure 2**.

DISCUSSION

The 2 main findings of this study were that nonstenosing complicated (AHA-LT VI) CAPs in patients with CS were significantly more frequent ipsilateral to the infarct compared with contralateral to the infarct and that nonstenosing ipsilateral cCAPs were significantly more frequent in CS compared with patients with CES/SVS as the combined reference group (**Central Illustration**). Patients with LAS and NASCET 50% to 69% stenosis had the highest prevalence of ipsilateral cCAPs and largest side-by-side differences in cCAP prevalence, which underscored the importance of ipsilateral cCAPs in anterior circulation stroke. We also found ipsilateral LRNCs, a feature of plaque vulnerability that is not part of the AHA-LT VI definition, were larger in CS compared with the reference group. The most frequent feature of ipsilateral cCAP was IPH. We believe these findings add to the understanding of stroke etiologies and have potential implications for the development of diagnostic algorithms.

Our data, which were obtained in a prospective multicenter study and used cutting-edge MRI technology, substantiated recent evidence for nonstenosing cCAP being an under-recognized cause of

FIGURE 4 MRI Characteristics of Complicated AHA-LT VI Plaques



Illustrative examples of MRI plaque imaging data from the CAPIAS (Carotid Plaque Imaging in Acute Stroke) study demonstrating characteristics of complicated AHA-LT VI plaques. The presence of at least 1 of the following criteria defines plaques as AHA-LT VI plaques: intraplaque hemorrhage **(left panel, red arrowhead)**, ruptured fibrous cap **(middle panel, yellow arrowhead)**, or mural thrombus indicating juxtaluminal hemorrhage **(right panel, white arrowhead)**. T1w = T1-weighted; T1w-CE = contrast-enhanced T1-weighted; T2w = T2-weighted; TOF = time of flight.

stroke. Since our initial report (16), there have been several studies on nonstenosing CAP with high-risk features in patients with CS (21-24) or ESUS (25,26). These studies used variable methods for plaque imaging, including MR angiography (22–24), computed tomography angiography (21), and carotid ultrasound using variable definitions of high-risk plaques (25). All of them were single-center studies, mostly on small samples. Most of them found the prevalence of CAPs with high-risk features to be significantly higher ipsilateral compared with contralateral to stroke (24,25). In addition to demonstrating a side-to-side asymmetry, we found the prevalence of ipsilateral cCAP to be higher in patients with CS compared with a carefully selected reference group, which provided additional evidence for a causal role of cCAP in CS. This conclusion was further supported by our findings in patients with LAS and moderate carotid artery stenosis who had the highest prevalence of ipsilateral cCAPs while likewise showing a pronounced side-to-side asymmetry.

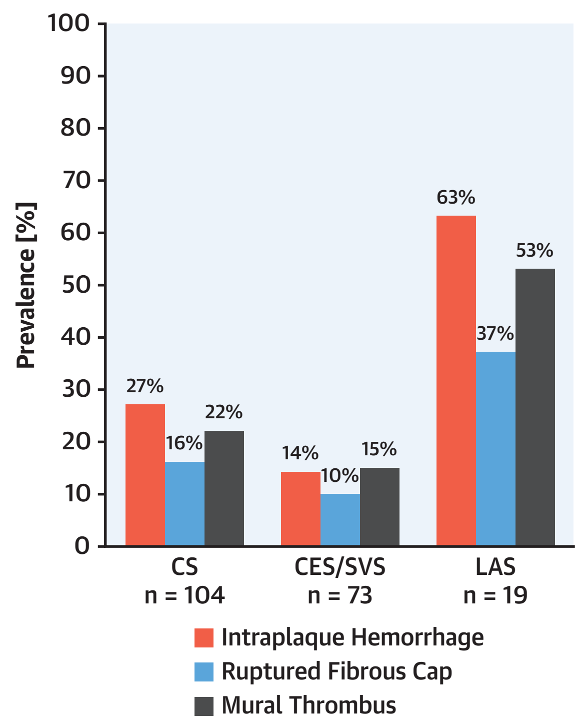
Our entry criteria required a DWI-positive lesion restricted to the territory of a single carotid artery and either unilateral or bilateral CAP. This enabled meaningful analyses while avoiding bias for the 2 main comparisons: the exclusion of patients with infarcts in the posterior circulation avoided selection of patients in whom CAP could be excluded as a possible stroke etiology. The exclusion of patients with bilateral DWI-positive lesions enabled side-to-side comparisons and avoided enriching for patients with a high a priori probability of having a proximal source of embolism from the heart or aortic arch. The requirement for either ipsilateral or contralateral CAP might have enriched for patients with some degree of atherosclerosis. However, this applied equally for patients in the reference group.

As a notable result, we found the prevalence of contralateral cCAP to range between 10% in the reference group and 21% in the LAS group. These percentages compared well with a study in asymptomatic individuals that found the prevalence of cCAP to be 8.1% in subjects with a 1% to 15% stenosis (27). By design, none of our patients had a contralateral DWI-positive lesion. Hence, all contralateral cCAPs in our patients could be considered truly silent. This also implied that a substantial proportion of cCAPs were asymptomatic. We found no significant side-to-side asymmetry in the prevalence of cCAP in the reference group. Thus, cCAP should be interpreted in the context of clinical findings, infarct patterns, and alternative stroke etiologies.

The prevalence values for cCAP and other AHA lesion types reported here could not be generalized to the broader population of patients with stroke. The requirement for both a cranial MRI and a carotid MRI examination with injection of contrast agent might have enriched for patients with less severe stroke and less comorbidity. However, the distribution of National Institute of Health Stroke Scale scores resembled that of large population-based studies (28).

The use of high-resolution, contrast-enhanced MRI enabled us to assess various aspects of plaque morphology. LRNCs, which can reliably be detected by MRI (20), represent heterogeneous tissue composed of cholesterol crystals, debris from apoptotic cells, and calcium particles (8). We found ipsilateral LRNCs to be significantly larger in CS compared with that of the reference group, which emphasized the importance of vulnerable CAP in CS. LRNCs on MRI were shown to correlate with plaque remodeling (29), to be larger in symptomatic patients compared with asymptomatic patients (30), and to be predictive of both plaque rupture (31) and risk of ipsilateral stroke (8,13). We also found LRNCs to be largest in LAS. Collectively, these findings emphasize the role of MRI-defined LRNCs in atherosclerotic stroke.

FIGURE 5 **Prevalence of Individual MRI Characteristics Defining Ipsilateral Complicated AHA-LT VI Plaques in Patients With Acute Ischemic Stroke**



The prevalence of MRI characteristics such as intraplaque hemorrhage **(red)**, ruptured fibrous cap **(blue)**, or mural thrombus indicating juxtaluminal hemorrhage **(gray)** in ipsilateral CAPs. Presence of at least 1 of these MRI characteristics define complicated AHA-LT VI plaques. Abbreviations as in **Figures 1 and 2**.

FUTURE WORK. Carotid MRI studies in patients with symptomatic carotid artery stenosis found high-risk features of CAPs were associated with an increased risk of recurrent ipsilateral stroke or transient

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TABLE 2 Plaque Burden and Plaque Composition of Ipsilateral CAPs in Acute Ischemic Stroke

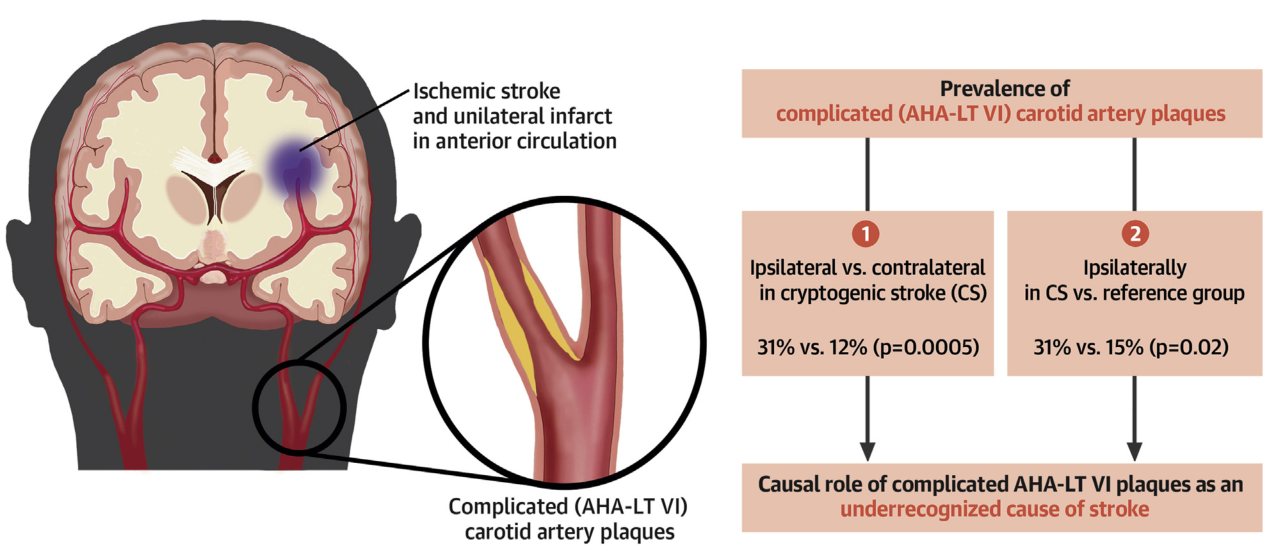
	CS (n = 102)	CES/SVS (n = 72)	p Value*	LAS (n = 17)	p Value†
Plaque burden					
Minimum lumen area, mm^2	15.3 ± 8.3	15.4 ± 7.0	0.946	10.6 ± 3.3	**<0.001**
Maximum wall area, mm^2	52.3 ± 23.2	45.8 ± 16.1	**0.041**	54.9 ± 18.8	0.664
Maximum total vessel area, mm^2	107.2 ± 38.1	96.8 ± 27.0	**0.035**	90.0 ± 25.7	0.075
Maximum normalized wall index	0.63 ± 0.13	0.60 ± 0.11	0.123	0.73 ± 0.12	**0.001**
Plaque composition					
Maximum LRNC, %	20 ± 23	11 ± 18	**0.006**	32 ± 22	**0.038**
Maximum calcified area, %	5 ± 8	6 ± 6	**0.015**	7 ± 9	0.061
Maximum hemorrhage area, %	9 ± 21	2 ± 7	**0.024**	17 ± 24	0.092

Values are mean ± SD. **Bold** p values are statistically significant. *p value, group comparisons between patients with CS and patients with CES/SVS. †p value, group comparisons between patients with CS and LAS. The unadjusted and uncorrected p values are shown.
CAPs = carotid artery plaques; LRNC = lipid-rich/necrotic core; other abbreviations as in Table 1.

ischemic attack (8,13,14). Whether high-risk features of nonstenosing CAPs are likewise associated with an increased risk of stroke recurrence is poorly investigated (13,14). However, our present findings in patients with acute stroke identified ipsilateral nonstenosing cCAPs to be high-risk lesions. Aspects that need to be addressed by future studies include the risk of stroke recurrence and other vascular events, as well as strategies for secondary prevention (32).

Integrating multisequence high-resolution, contrast-enhanced MRI into the standard diagnostic workflow of acute stroke could prove difficult, thus, we are calling for simpler imaging protocols. Unlike other features of cCAPs, IPH can be reliably detected by standard coils and conventional native T1-weighted sequences (33). We found IPH present in 89% of ipsilateral nonstenosing cCAPs. Hence, IPH might serve as a surrogate marker for cCAPs, although this would need to be formally investigated by comparing conventional imaging with high-resolution, contrast-enhanced MRI, ideally in the setting of acute stroke. Recent studies found a significant side-to-side difference for IPH in patients

CENTRAL ILLUSTRATION Study Concept and Main Study Results



Kopczak, A. et al. J Am Coll Cardiol. 2020;76(19):2212-22.

The 2 key comparisons exploring the role of complicated American Heart Association–lesion type (AHA-LT) VI plaques in cryptogenic stroke (CS).

with CS or ESUS using conventional MRI (24,25). Accounting for IPH was further shown to reclassify stroke etiologies of up to 15% of patients with anterior circulation infarction (24). However, whether integration of carotid MRI into the diagnostic workflow for anterior circulation stroke would eventually influence individual therapeutic options remains to be investigated.

STUDY STRENGTHS. Our study had several strengths. First, CAPIAS was a prospective, multicenter study with plaque imaging obtained within 10 days after symptom onset. Second, all patients had imaging-confirmed stroke with an infarct pattern that was related to the primary study comparisons. Third, sample size by far exceeded that of previous CAP imaging studies with high-resolution carotid MRI (16,25), which enhanced power and enabled comparisons across etiological groups. Fourth, all patients entering the final analysis received comprehensive diagnostic workup, thus minimizing the risk of misclassification with regard to TOAST category. Fifth, we used high-resolution carotid MRI at 3T using dedicated carotid surface coils and a standardized imaging protocol that included contrast-enhanced sequences (19), which enabled detailed assessment of plaque characteristics. Sixth, evaluation of the high-resolution carotid MRI images was done centrally by readers blinded to the clinical data. Finally, the primary comparisons were specified before study onset.

STUDY LIMITATIONS. Our study also had limitations, in particular, the long recruitment period. This mostly related to our entry criteria and the requirement for a study-related MRI with injection of a contrast agent. The number of patients with LAS was relatively low. This mostly related to a substantial proportion of patients with a NASCET of 50% to 69% carotid artery stenosis who underwent early carotid endarterectomy or stenting following European guidelines (34). As per our entry criteria, these patients were excluded from study participation. However, and despite the low number of patients with LAS, we found a significantly higher prevalence of ipsilateral cCAPs in LAS compared with CS and a significant side-to-side difference in LAS that further validated our primary comparisons and substantiated the causal role of cCAP in acute stroke. Additional limitations included a relatively low proportion of female patients, the limited age range, and a minimum duration of continuous electrocardiographic monitoring of only 24 h. Also, we excluded patients with CAP <2 mm, which limited the results to stroke patients with some degree of atherosclerosis.

CONCLUSIONS

Our findings substantiate the role of nonstenosing ipsilateral cCAP as an underrecognized cause of stroke. Whether integration of carotid MRI into the diagnostic workflow for anterior circulation stroke would eventually influence therapeutic strategies remains to be investigated.

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AUTHOR RELATIONSHIP WITH INDUSTRY

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Nonstenotic cCAPs are under-recognized as a potential cause of ischemic stroke.

TRANSLATIONAL OUTLOOK: Additional studies are needed to determine how characterization of atherosclerotic carotid artery lesions by MRI during evaluation of patients with cryptogenic anterior circulation ischemic stroke could influence management.

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KEY WORDS AHA–lesion type, carotid artery, complicated plaque, plaque imaging, stroke, stroke etiology

APPENDIX For an expanded Methods section and supplemental tables, please see the online version of this paper.