

BRIEF COMMUNICATION

Sex Differences in Carotid Plaque Composition in Patients With Embolic Stroke of Undetermined Source

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BACKGROUND: We examined sex differences in nonstenotic carotid plaque composition in patients with embolic stroke of undetermined source (ESUS).

METHODS AND RESULTS: Patients with anterior circulation ischemic stroke imaged with neck computed tomographic angiography who met criteria for ESUS or had atrial fibrillation were identified. Patients with atrial fibrillation were included as a negative control. Semiautomated plaque quantification software analyzed carotid artery bifurcations. Plaque subcomponent (calcium, intraplaque hemorrhage [IPH], and lipid rich necrotic core) volumes were compared by sex and in paired analyses of plaque ipsilateral versus contralateral to stroke. Multivariate linear regressions tested for associations. Ninety-four patients with ESUS (55% women) and 95 patients with atrial fibrillation (47% women) were identified. Men with ESUS showed significantly higher volumes of calcified plaque (63.9 versus 19.6 mm³, $P < 0.001$), IPH (9.4 versus 3.3 mm³, $P = 0.008$) and a IPH/lipid rich necrotic core ratio (0.17 versus 0.07, $P = 0.03$) in carotid plaque ipsilateral to stroke side than women. The atrial fibrillation cohort showed no significant sex differences in plaque volumes ipsilateral to stroke. Multivariate analyses of the ESUS cohort showed male sex was associated with IPH_{ipsi} ($\beta = 0.49$; 95% CI, 0.11–0.87) and calcium_{ipsi} ($\beta = 0.78$; 95% CI, 0.33–1.23). Paired plaque analyses in men with ESUS showed significantly higher calcified plaque (63.9 versus 34.1 mm³, $P = 0.03$) and a trend of higher IPH_{ipsi} (9.4 versus 7.5 mm³, $P = 0.73$) and lipid rich necrotic core_{ipsi} (59.0 versus 48.4 mm³, $P = 0.94$) volumes.

CONCLUSIONS: Sex differences in carotid plaque composition in ESUS suggest the possibility of a differential contribution of nonstenosing carotid plaque as a stroke mechanism in men versus women.

Key Words: atherosclerosis ■ carotid artery ■ computed tomographic angiography ■ embolic stroke

In patients with embolic stroke of undetermined source (ESUS), a subset have atheroembolism from nonstenotic carotid plaque.^{1,2} However, at present there is limited ability to determine in which individual patients this is the operative mechanism. An inflammatory plaque phenotype with vulnerable plaque components could suggest a higher likelihood of carotid atheroembolism, and if this were the case, an inflammatory plaque phenotype would be expected to be seen more often in the carotid artery ipsilateral to the side of stroke compared with the contralateral carotid artery.

To this point, studies evaluating patients with ESUS have shown morphologic differences between carotid arteries ipsilateral versus contralateral to the side of stroke.^{1,2} Carotid arteries ipsilateral to the stroke side have higher noncalcified plaque thickness compared with the contralateral side. This noncalcified plaque component may reflect intraplaque hemorrhage (IPH) or lipid rich necrotic cores (LRNC), which are associated with increased plaque rupture risk and subsequent embolization.³ In addition to the presence of IPH, the IPH/LRNC ratio may also reflect

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a higher plaque rupture risk suggesting quantification may also be an important feature of the biomarker.⁴ Detection and quantification of noncalcified plaque components may increase diagnostic confidence in identifying carotid atheroembolism. Although sex differences in vascular biology are recognized, how sex affects carotid plaque composition in patients with ESUS remains unexplored. Histologic studies of carotid endarterectomy specimens suggest plaque composition in men more frequently shows inflammatory plaque phenotypes compared with fibrous phenotypes in women.⁵ We examined sex differences in carotid plaque composition in an ESUS cohort to investigate whether men had higher volumes of vulnerable plaque components.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. A retrospective observational cohort study was conducted at a single integrated hospital system at a comprehensive stroke center between October 1, 2015 to April 1, 2017. This cohort was previously used by Siegler et al.² Patients 18 years or older with unilateral anterior circulation ischemic stroke and imaged with computed tomographic angiography (CTA) of the neck were included. Patients were excluded if there were multiple possible mechanisms of ischemic infarction, acute infarction in more than 1 vascular territory, if a patient had prior carotid endarterectomy or stenting, if there was occlusion of either cervical internal carotid artery, or if the CTA neck was performed >10 days since patient was last known normal. Demographic, clinical, and laboratory data were collected from electronic medical records.

Stroke etiology due to atrial fibrillation (AF) was identified based on documented history or presence of AF on electrocardiographic monitoring during diagnostic evaluation. ESUS criteria were met with neuroimaging confirmation of an ischemic infarct >1.5 cm in diameter, electrocardiography and cardiac telemetry without evidence of myocardial infarction or AF, transthoracic echocardiogram without an obvious source of cardioembolism, and vessel imaging without ≥50% luminal stenosis of the intracranial or extracranial arteries supplying the infarct territories, and no other cause of stroke identified. At our institution, for patients older than 50 years with no other suspected stroke mechanism, a minimum of 7 days of outpatient telemetry monitoring is recommended to exclude the possibility of paroxysmal AF. Any AF lasting 6 minutes or longer was considered clinically relevant. Stroke mechanism was determined by a vascular neurologist. Patients with AF served

as a negative control group; as these patients had a cardioembolic stroke mechanism, it was expected that there would be little if any contribution of non-stenosing plaque as a stroke mechanism and thus no significant difference in plaque ipsilateral versus contralateral to the side of stroke.

CT imaging details were previously described.⁴ Briefly, technical parameters included section thickness 0.625 to 1.5 mm, matrix size 512×512, and field of view 20 to 33 cm. Per institutional protocol, iodinated contrast (100 mL Isovue-370) was administered intravenously through a 20-gauge or larger right antecubital catheter. Half dose of Isovue-370 was administered if the patient was anticipated to undergo CT perfusion following the CTA. A neuroradiologist blinded to the clinical data and side of cerebral infarction segmented each carotid artery (2 cm above/below the bifurcation) using a semiautomated plaque quantification software (Elucid Bioimaging, Wenham, MA) (Figure S1).⁶ Additional details are expanded in Data S1. All segmentations were manually checked and edited by the neuroradiologist. Automated outcomes used for analysis included volumes of plaque subcomponents (calcium, IPH, and LRNC) and total plaque (eg, sum of calcium, IPH, LRNC, and matrix volumes). IPH/LRNC volume ratios were calculated.

Statistical Analysis

Descriptive analyses are reported as medians and interquartile ranges for continuous variables; frequency and proportions are reported for categorical variables. Normality for all outcomes was tested using the Kolmogorov-Smirnov Z-test. Cubic B-spline polynomial lines fit to examine the difference in association between IPH and LRNC by sex were projected on scatterplots. Plaque subcomponent volumes ipsilateral versus contralateral to stroke side between men and women were tested using Wilcoxon signed-rank tests. Correlations were tested by Spearman rank-order correlation. To determine associations between each plaque subcomponent and covariates of interest, multivariate linear regressions were performed using age, sex, body mass index (BMI), and vascular risk factors as predictors, adjusting for the contralateral carotid plaque subcomponent. A natural log transformation of the IPH and calcium volumes in regression models was used because of nonnormality of the residuals. Forward selection with the Akaike information criterion as an optimization criterion was used to select the best predictors. Coefficients and CIs are reported for significant outcome measures ($P<0.05$). As this was an exploratory analysis, there was no adjustment for multiple hypothesis testing. SPSS (v19 IBM, Chicago) and R statistical software were used. This study was approved by the local institutional review board with waiver of informed consent because of the retrospective design.

RESULTS

Among 772 screened patients, 94 met inclusion criteria for ESUS and 95 had confirmed AF. Six CTs were excluded owing to poor contrast opacification or motion degradation limiting software quantification accuracy. Table 1 shows baseline characteristics between men and women in the ESUS and AF cohorts. Women had significantly higher BMIs compared with men in the ESUS cohort ($P=0.02$). The baseline National Institutes of Health Stroke Scale score was significantly higher in women than men in the AF cohort. Otherwise, there were no significant differences in baseline characteristics by sex in the ESUS and AF cohorts.

In the ESUS cohort, there were significant sex differences in plaque composition of carotid plaque ipsilateral to stroke side (Figure 1A through 1C). Men with ESUS showed significantly higher calcium_{ipsi} (63.9 versus 19.6 mm³, $P<0.001$) and IPH_{ipsi} (9.4 versus 3.3 mm³, $P=0.008$) volumes (Table 2). Men also showed higher LRNC_{ipsi} volumes than women though this did not reach statistical significance (59.0 versus 51.1 mm³, $P=0.84$). The IPH/LRNC_{ipsi} ratio of plaque ipsilateral to stroke side in men was also significantly higher than in women (0.17 versus 0.07, $P=0.03$). By contrast, in the AF cohort, there was no significant difference by sex in carotid plaque composition ipsilateral to stroke side.

Multivariate analysis of the ESUS cohort evaluated associations between plaque subcomponent volumes and age and sex, accounting for the contralateral

plaque subcomponent volume, and comorbidities (Table S1). Plaque volume contralateral to stroke side served as an internal control in the model to account for within-subject correlation. Analyses showed male sex was associated with a 63% increase in mean IPH_{ipsi} volume compared with female sex ($\beta=0.49$; 95% CI, 0.11–0.87). Male sex ($\beta=0.78$; 95% CI, 0.33–1.23), age ($\beta=0.02$; 95% CI, 0–0.04), and hypertension ($\beta=0.57$; 95% CI, 0.09–1.05) were significantly associated with higher calcium_{ipsi} volumes. Age ($\beta=1.65$; 95% CI, 0.40–2.90) and BMI ($\beta=5.56$; 95% CI, 3.04–8.08) were significantly associated with higher LRNC_{ipsi} volumes.

Paired analyses of plaque volumes ipsilateral versus contralateral to stroke side were compared to examine the potential of nonstenotic carotid atheroembolic stroke mechanism in patients with ESUS (Figure 1A; Table S2). Carotid plaque ipsilateral to stroke side in men showed a trend in higher volumes of all plaque subcomponents although only calcified plaque volume was significantly higher (ipsilateral, 63.9 versus contralateral, 34.1 mm³, $P=0.03$). IPH (ipsilateral, 9.4 versus contralateral, 7.5 mm³, $P=0.73$) and LRNC (ipsilateral, 59.0 versus contralateral, 48.4 mm³, $P=0.94$) volumes and IPH/LRNC (ipsilateral, 0.17 versus contralateral, 0.15, $P=0.45$) were also higher compared with contralateral plaque though not statistically significant. Women with ESUS did not show significant differences in carotid subcomponent plaque volumes ipsilateral versus contralateral to stroke side. In an exploratory analysis of the ESUS cohort, there were no significant differences between men and women

Table 1. Baseline Characteristics

	Embolic Stroke of Undetermined Source (n=94)			Atrial Fibrillation (n=95)		
	Men (n=42)	Women (n=52)	P Value	Men (n=50)	Women (n=45)	P Value
Age, y (IQR)	65.5 (53.8–74.0)	65.0 (57.0–75.0)	0.83	78.0 (62.8–84.0)	78.0 (70.0–85.0)	0.64
Race, no. (%)			0.19			0.42
White	24 (57%)	20 (39%)		33 (66%)	24 (53%)	
Black	16 (38%)	29 (56%)		12 (24%)	16 (36%)	
Other*	2 (5%)	3 (6%)		5 (10%)	5 (11%)	
Baseline National Institutes of Health Stroke Scale score, median (IQR)	7 (4, 17)	8 (3, 15)	0.97	11 (5, 16)	14 (7, 21)	0.05
Body mass index, median (IQR)	26.2 (23.0–30.6)	29.2 (25.4, 33.0)	0.02	28.6 (24.8, 32.3)	27.1 (24.0, 33.5)	0.83
Past medical history, n (%)						
Diabetes mellitus	14 (33%)	12 (23%)	0.35	17 (34%)	13 (29%)	0.66
Hypertension	27 (64%)	39 (75%)	0.27	37 (74%)	36 (80%)	0.63
Coronary artery disease	13 (20%)	9 (17%)	0.15	18 (36%)	14 (31%)	0.67
Dyslipidemia	11 (26%)	21 (40%)	0.19	23 (46%)	22 (49%)	0.84
Stroke	7 (17%)	8 (15%)	1.0	9 (18%)	12 (27%)	0.33
Transient ischemic attack	3 (7%)	7 (13%)	0.50	3 (6%)	3 (7%)	1.0
Any prior tobacco use	8 (19%)	13 (25%)	0.62	6 (12%)	5 (11%)	1.0

IQR indicates interquartile range.

*Other includes Not Reported and Asian.

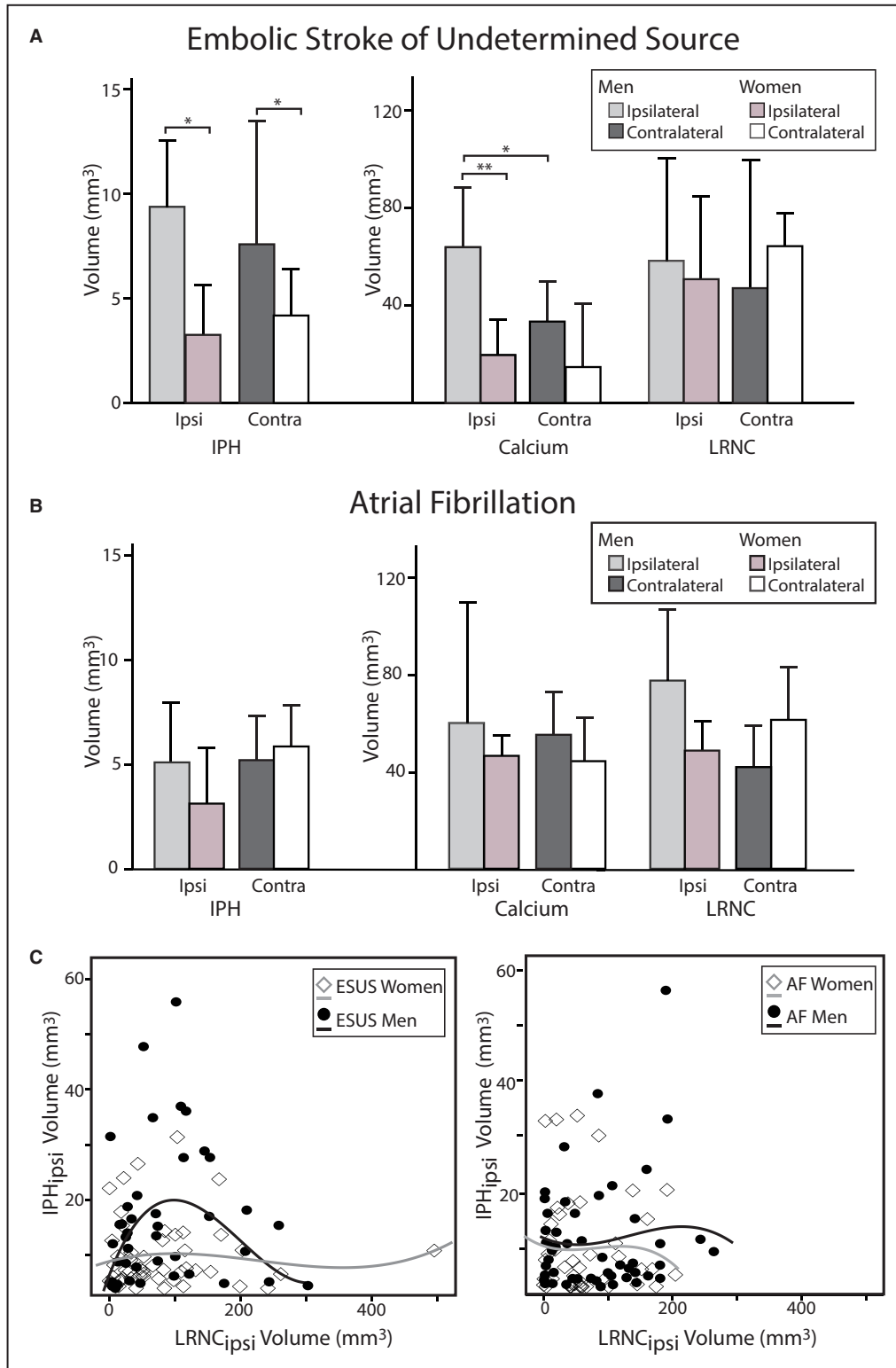


Figure 1. Plaque subcomponent volumes by sex.

A and **B**, Median volumes of each plaque subcomponent by sex for carotid plaque ipsilateral and contralateral to stroke side in the **(A)** ESUS and **(B)** AF cohorts are compared using Wilcoxon signed-rank tests. Bar graphs represent medians with 95% CIs. Significant results are labeled with asterisks. * $P < 0.05$; ** $P < 0.001$. **C**, Scatterplots show associations of plaque IPH_{ipsi} to LRNC_{ipsi} volumes by sex. Cubic B-spline polynomial lines are fit to examine the differences in association between IPH and LRNC by sex. AF indicates atrial fibrillation; ESUS, embolic stroke of undetermined source; IPH, intraplaque hemorrhage; and LRNC, lipid rich necrotic core.

Table 2. Comparisons of Plaque Volumes of Carotid Arteries Ipsilateral to the Stroke by Sex

Volumes of Plaque Subcomponent (mm ³)	Embolic Stroke of Undetermined Source (n=94)			Atrial Fibrillation (n=95)		
	Men (n=42)	Women (n=52)	P Value	Men (n=50)	Women (n=45)	P Value
Carotid arteries ipsilateral to stroke						
Calcium _{ipsi}	63.9 (27.9–116.3)	19.6 (8.1–64.0)	<0.001	59.8 (25.2–149.8)	46.3 (10.3–87.3)	0.10
IPH _{ipsi}	9.4 (2.5–15.3)	3.3 (1.8–8.3)	0.008	5.1 (1.6–12.6)	3.2 (3.2–11.8)	0.08
LRNC	59.0 (23.3–117.9)	51.1 (19.3–111.6)	0.84	77.6 (13.5–139.2)	48.0 (22.7–97.6)	0.52
IPH/LRNC _{ipsi}	0.17 (0.05–0.38)	0.07 (0.03–0.16)	0.03	0.14 (0.02–0.50)	0.07 (0.004–0.40)	0.09
Carotid arteries contralateral to stroke						
Calcium _{contra}	34.1 (12.6–99.2)	14.7 (2.5–63.7)	0.06	55.0 (8.0–115.9)	44.1 (17.7–83.3)	0.87
IPH _{contra}	7.5 (3.7–17.4)	4.3 (1.4–12.5)	0.03	5.2 (1.0–10.0)	6.0 (1.6–9.6)	0.87
LRNC _{contra}	48.4 (16.0–117.5)	63.3 (14.7–105.5)	0.79	42.6 (21.4–79.2)	61.1 (24.0–104.8)	0.43
IPH/LRNC _{contra}	0.15 (0.05–0.43)	0.09 (0.03–0.21)	0.08	0.11 (0.02–0.34)	0.09 (0.02–0.18)	0.09

Contra indicates contralateral; IPH, intraplaque hemorrhage; Ipsi, ipsilateral; and LRNC, lipid rich necrotic core.

in low-density lipoprotein, hemoglobin A1C, or erythrocyte sedimentation rate (Table S3). Low-density lipoprotein, hemoglobin A1C and erythrocyte sedimentation rate also did not significantly correlate with ipsilateral carotid LRNC, IPH, or calcified plaque volumes in men or women with ESUS (Table S4).

DISCUSSION

The results suggest sex differences in carotid plaque composition in men versus women with ESUS. Male sex was independently associated with higher IPH and calcified plaque volumes ipsilateral to stroke side adjusting for contralateral plaque volumes and BMI, indicating the association is not only due to larger vessel size in men. Men with ESUS also had a trend of higher IPH_{ipsi} volumes and IPH/LRNC_{ipsi} ratios compared with plaque contralateral to stroke side, an association not seen in women with ESUS. These results support prior observations that nonstenotic carotid plaque contributes to anterior circulation stroke in patients with ESUS^{1,2} and additionally suggest a differential contribution of atheroembolism from carotid plaque in men and women with ESUS.

How sex differences in vascular biology affect atherogenesis is not well understood and has not been addressed mechanistically in the ESUS population. Studies suggest estrogen in women has a protective effect in early-midlife in cardiovascular health.⁷ Considering these protective effects during early-midlife, women have a shorter period of time for high-risk plaque features to develop compared with men. This reasoning may in part explain why despite the same median age of 65 years in men and women with ESUS in our cohort, plaque ipsilateral to stroke side in women showed fewer high-risk features.

Also interesting is the significant association of BMI with LRNC_{ipsi} plaque volumes in the overall ESUS cohort in the multivariate analysis. This positive

association was not seen in women with ESUS. In fact, women with ESUS had significantly higher BMI than men but lower LRNC_{ipsi} plaque volumes. Studies indicate that despite higher body fat in women throughout life, men with typical central obesity are at risk of deleterious metabolic consequences, which contrasts with women who distribute fat peripherally (eg, gluteal-femoral adipose tissue distribution) and have lower cardiovascular risks.⁸ Thus the higher BMI in women in our results further supports that women's metabolic profiles are different from men, which could lead to different stroke mechanisms.

IPH is considered a strong imaging biomarker of plaque instability.³ Incidence of IPH comprising 50% or more of total plaque thickness was found to be 4 times more common in symptomatic plaques compared with asymptomatic plaques by histology.⁴ Our results of higher volumes of carotid IPH in men with ESUS and the absence of this finding in the control AF cohort increases diagnostic confidence in suggesting a carotid source of embolism. Although carotid LRNC volumes were not significantly different by sex in the ESUS cohort, the ratio of IPH/LRNC volumes was significantly higher in men. LRNCs do not always progress to plaque rupture if the fibrous cap remains intact and can also develop into fibrosis or even calcify.⁹ Rather, increased neovascularity and IPH within LRNCs create a proinflammatory milieu, expand the necrotic core, and may lead to greater rupture risk.⁹ Hence, the ratio of IPH/LRNC may be a stronger predictor of rupture risk and be suggestive of an embolic source.¹⁰

Calcified plaque volume was also significantly higher and associated with the male sex in carotid arteries ipsilateral to the ischemic stroke in patients with ESUS. Although calcified plaque is commonly regarded as a marker of plaque stability, an increasing number of studies suggest different types of calcifications may play a differential role in atherogenesis.

The number of spotty calcifications or superficial calcifications (eg, closer to the intimal-luminal interface) has been associated with IPH and plaque rupture in coronary and carotid arteries possibly because of altered biomechanical stress predisposing plaque to rupture.¹¹

The role of calcified plaque in association with IPH in nonstenotic carotid plaque is a relatively unexplored area in carotid plaque research. As detection of calcification is far more sensitive by CT, using CT to characterize types of calcifications might provide important insights not captured by MRI. For example, coronary calcium scoring on CT is a well-established test for risk stratification of coronary artery disease. Data from CT imaging of carotid atherosclerosis might be similarly useful, though this has not been as extensively studied. Although currently, MR is the dominant imaging modality to study vulnerable carotid plaque features given its sensitivity for detecting IPH,³ newer CT techniques such as photon-counting spectral CT show promise for distinguishing noncalcified plaque components.¹² Given that CTA has now become the dominant form of vascular imaging for acute stroke patients at most centers, there may be a wealth of additional diagnostic information available by newer emerging CT technologies.

There are several limitations to this study. Although the small sample size may limit the power to identify differences in plaque subcomponent volumes, the sample size is comparable to¹ and larger¹³ than prior ESUS studies evaluating plaque features. Second, despite a retrospective study design, the study cohort was systematically derived from a prospectively collected stroke database and included a consecutive series of patients from a single integrated health system in which acute CTA on initial presentation is the standard imaging modality. Additionally, image analysis was performed with blinding of the neuroradiologist to clinical history, sex, and stroke laterality. It is therefore unlikely that this introduced a significant bias in either the patients included or the radiologic interpretation. The ipsilateral/contralateral comparison, with each patient serving as their own control, would also serve to minimize bias. Further, we included a cohort of patients with AF, identified and analyzed in the same way as the ESUS cohort, as a negative control. Third, quantitative plaque analysis was limited to 4 cm of the carotid bifurcation potentially missing aortic arch or distal carotid artery plaque. Plaques most commonly develop at branch points because of hemodynamic alterations,¹⁴ and this anatomic predilection is not expected to be biased by sex. Fourth, plaque components were not validated histologically nor by MRI. Owing to overlapping Hounsfield units, distinguishing IPH and LRNC by conventional CT may not be accurate and may be further limited by

a blooming effect of calcified plaque.¹⁵ However, the software algorithm is designed to mitigate blurring and partial volume effects and showed high correlation and low bias with ex vivo histopathologic quantitative measures of LRNC and calcium.⁶ Other studies have also used this software to analyze carotid plaque composition on CTA imaging.¹⁰ Although current conventional CT technology is limited in plaque compositional analysis without sophisticated segmentation software, a future direction is to investigate the utility of advanced photon-counting spectral CT technology to distinguish plaque components with histologic and MR validation.

CONCLUSIONS

In this cohort of anterior circulation ESUS, men had higher IPH and calcified plaque volumes and a higher IPH/LRNC ratio ipsilateral to stroke side compared with women. Nonstenosing carotid plaque may more often be the operative stroke mechanism in ESUS in men compared with women.

ARTICLE INFORMATION

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Supplementary Material

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SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

Available technical methods for the segmentation software are further referenced in detail in Sheahan et al.⁶ Measurements are calculated by the software based on the user's target initializations, outer wall and lumen contour segmentations, and user-defined inputs for carotid anatomic structure selection and software-defined tissue characteristics for lipid rich necrotic core (LRNC), calcium, and intraplaque hemorrhage (IPH). The software's default lower and upper limit Hounsfield units on enhanced computed tomographic angiography images for calcium (250 to 3000 HU), LRNC (-300 to 45 HU), and IPH (120-170 HU) for the software were used for segmentation. The software uses HU as a proxy for lipid, fibrous, and calcifications, and acknowledges the use of HU may overlap with tissue components.

Table S1: Multivariate analyses for intraplaque hemorrhage and calcium with exponentiated beta coefficients of carotid arteries ipsilateral to stroke side

	β (95% Confidence Intervals)	Exp(β) (95% Confidence Intervals)	p
Intraplaque Hemorrhage (IPH)_{ipsi}			
Male sex	0.49 (0.11, 0.87)	1.63 (2.03, 4.50)	0.01
Coronary Artery Disease	-0.38 (-0.82, 0.06)	0.68 (0.44, 1.06)	0.09
IPH _{contra} volume	0.32 (0.13, 0.50)	1.37 (1.14, 1.66)	0.001
Calcium_{ipsi}			
Age	0.02 (0, 0.04)	1.02 (1.00, 1.04)	0.03
Male Sex	0.78 (0.33, 1.23)	2.19 (1.40, 3.43)	0.0008
Hypertension	0.57 (0.09, 1.05)	1.77 (1.09, 2.86)	0.02
Transient ischemic attack	-0.67 (-1.38, 0.04)	0.51 (0.25, 1.04)	0.06
Calcium _{contra} volume	0.39 (0.23, 0.55)	1.48 (1.26, 1.74)	<0.0001
Lipid Rich Necrotic Core (LRNC)_{ipsi}			
	β (95% Confidence Intervals)		p
Age	1.65 (0.40, 2.9)		0.01
Body Mass Index	5.56 (3.04, 8.1)		<0.0001
Hypertension	-31.9 (-65.1, 1.21)		0.06
Diabetes	25.3 (-8.4, 59.1)		0.14
LRNC _{contra} volume	0.45 (0.26, 0.64)		<0.0001

Table S2: Comparisons of Plaque Volumes of the Ipsilateral and Contralateral Carotids in ESUS

Plaque subcomponent volumes (mm ³)	Men with ESUS (n=42)			Women with ESUS (n=52)		
	Ipsilateral	Contralateral	p	Ipsilateral	Contralateral	p
Calcium Volume	63.9 (27.9, 116.3)	34.1 (12.6, 99.2)	0.03	19.6 (8.1, 64.0)	14.7 (2.5, 63.7)	0.67
IPH Volume	9.4 (2.5, 15.3)	7.5 (3.7, 17.4)	0.73	3.31 (1.76, 8.32)	4.3 (1.4, 12.5)	0.23
LRNC Volume	59.0 (23.3, 117.9)	48.4 (16.0, 117.5)	0.94	51.1 (19.3, 111.6)	63.3 (14.7, 105.5)	0.69
IPH/LRNC	0.17 (0.05, 0.38)	0.15 (0.05, 0.43)	0.45	0.07 (0.03, 0.16)	0.09 (0.03, 0.21)	0.35

Abbreviations: ESUS, embolic stroke of undetermined source; IPH, Intraplaque hemorrhage; LRNC, lipid rich necrotic core

Table S3: Serum levels of Low-density lipoprotein, A1C, and erythrocyte sedimentation rate in the ESUS cohort

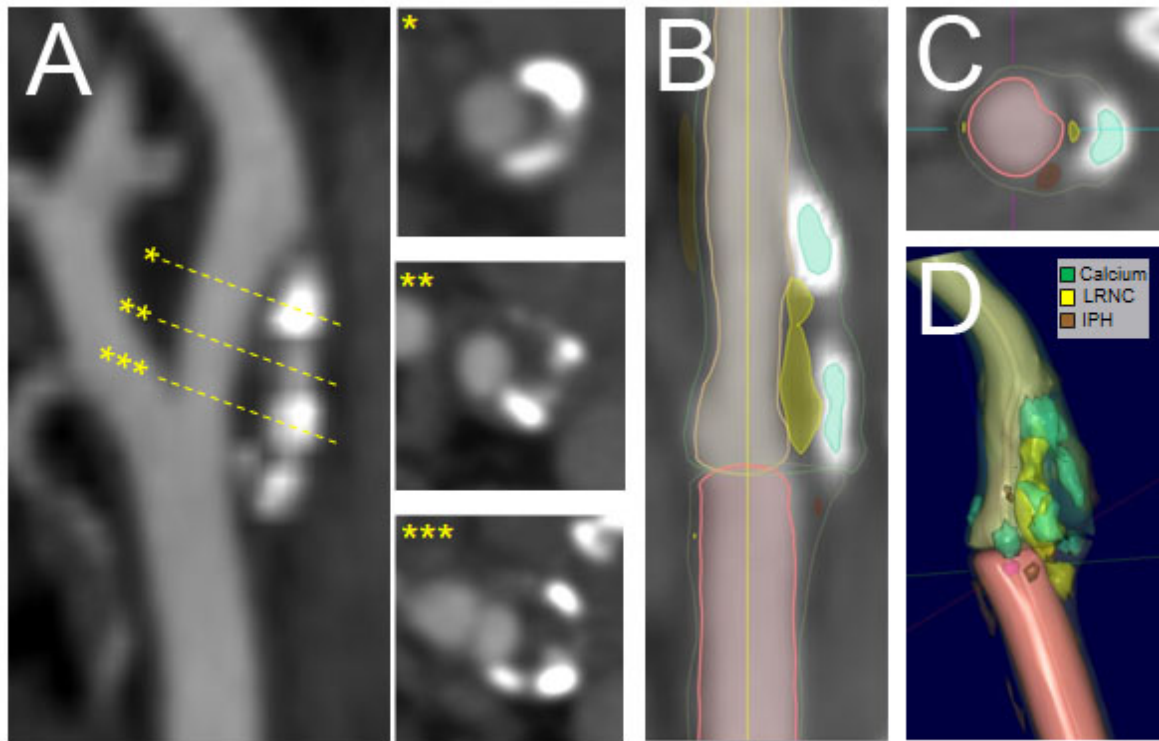
	Men	Women	p
Low-density lipoprotein (mg/dL)	107.0 (IQR 80.0, 135.0)	101.5 (IQR 79.3, 126.3)	0.82
Hemoglobin A1C	5.9 (IQR 5.5, 6.4)	5.6 (IQR 5.4, 6.4)	0.30
Erythrocyte sedimentation rate (mm/hr)	10.0 (IQR 5.0, 24.0)	20.0 (IQR 8.0, 33.0)	0.15

Table S4: Correlation of serum markers and plaque components by sex in the ESUS cohort

	Low-density lipoprotein (mg/dL)	Hemoglobin A1C	Erythrocyte sedimentation rate (mm/hr)
Calcium_{ipsi} Volume			
Men with ESUS	0.004 p=0.98	0.45 p=0.45	0.13 p=0.41
Women with ESUS	0.16 p=0.28	-0.001 p=0.99	0.17 p=0.25
IPH_{ipsi} Volume			
Men with ESUS	-0.18 p=0.29	0.37 p=0.37	-0.23 p=0.14
Women with ESUS	-0.07 p=0.64	-0.17 p=0.26	-0.09 p=0.55
LRNC_{ipsi} Volume			
Men with ESUS	-0.25 p=0.13	0.43 p=0.43	-0.22 p=0.17
Women with ESUS	-0.26 p=0.08	0.08 p=0.59	-0.008 p=0.96

Values represent Spearman rank's correlation coefficient (ρ).

Figure S1: Carotid plaque segmentation



A) Coronal CTA maximum image projection of the right carotid bifurcation of a patient with ESUS is shown. Three orthogonal planes through the carotid plaque, denoted by asterisks for each respective level, illustrate the presence of calcified and non-calcified plaque.

B-C) Segmentation of the same carotid artery subcomponents are shown.

D) A 3D-surface rendering of the carotid segmentation is shown.

Abbreviations: LRNC, lipid rich necrotic core; IPH, intraplaque hemorrhage