ORIGINAL RESEARCH

Optimal Carotid Plaque Features on Computed Tomography Angiography Associated With Ischemic Stroke

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BACKGROUND: Stenosis has historically been the major factor used to determine carotid stroke sources. Recent evidence suggests that specific plaque features detected on imaging may be more highly associated with ischemic stroke than stenosis. We sought to determine computed tomography angiography (CTA) imaging features of carotid plaque that optimally discriminate ipsilateral stroke sources.

METHODS AND RESULTS: In this institutional review board–approved retrospective cross-sectional study, 494 ipsilateral carotid CTA-brain magnetic resonance imaging pairs were available for analysis after excluding patients with alternative stroke sources. Carotid CTA and clinical markers were recorded, a multivariable Poisson regression model was fitted, and backward elimination was performed with a 2-sided threshold of \( P < 0.10 \). Discriminatory value was determined using receiver operating characteristic analysis, area under the curve, and bootstrap validation. The final CTA carotid-source stroke prediction model included intraluminal thrombus (prevalence ratio, 2.8 \[ P < 0.001 \]; 95% CI, 1.6–4.9), maximum soft plaque thickness (prevalence ratio, 1.2 \[ P < 0.001 \]; 95% CI, 1.1–1.4), and the rim sign (prevalence ratio, 2.0 \[ P = 0.007 \]; 95% CI, 1.2–3.3). The final discriminatory value (area under the curve=78.3%) was higher than intraluminal thrombus (56.4%, \( P < 0.001 \)), maximum soft plaque thickness (76.4%, \( P = 0.007 \), or rim sign alone (69.9%, \( P = 0.001 \)). Furthermore, NASCET (North American Symptomatic Carotid Endarterectomy Trial) stenosis categories (cutoffs of 50% and 70%) had lower stroke discrimination (area under the curve=67.4%, \( P < 0.001 \)).

CONCLUSIONS: Optimal discrimination of ipsilateral carotid sources of stroke requires information on intraluminal thrombus, maximum soft plaque thickness, and the rim sign. These results argue against the sole use of carotid stenosis to determine stroke sources on CTA, and instead suggest these alternative markers may better diagnose vulnerable carotid plaque and guide treatment decisions.

Key Words: atherosclerosis ■ carotid artery ■ computed tomography angiography ■ stroke
IPH has long been known to be important in stroke risk, but MRI detection only became possible 10 years ago. Newer heavily T1-weighted sequences including the magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence can be used to accurately detect IPH separate from lipid and necrosis, and outperforms other T1-weighted sequences and 3-dimensional time-of-flight. Three separate meta-analyses have found that patients with symptomatic carotid IPH have a high annual stroke risk of 15% to 45% despite medical therapy.9-11

Because carotid MRI has inherent limitations of lengthy acquisition times and patient contraindications, there is a critical need to optimize CTA prediction models of carotid plaque features associated with ipsilateral stroke. Initial attempts at linking plaque density with IPH were limited by overlapping Hounsfield units for IPH with other plaque components, including lipid-rich and necrotic elements.12 CTA markers linked to IPH using univariable analysis include stenosis, maximum plaque thickness (specifically soft plaque),13 ulceration12 and calcification.14 These are in addition to clinical factors including age, male sex, and hypertension.15-18 Of these, IPH is most highly linked to maximum soft plaque thickness. Along with soft plaque, the addition of thin adventitial calcification (a “rim sign”) on CTA is highly predictive of IPH.17

Given that CTA can predict IPH with some likelihood, our goal was to determine the optimal combination of CTA markers associated with ipsilateral stroke. Our hypothesis was that CTA markers of carotid IPH, specifically soft plaque thickness and a rim sign, would be required for optimal discrimination. In this retrospective study, we evaluated patients undergoing potential stroke workup with CTA neck and MRI brain within 1 month of each other from 2009 to 2016 and used multivariable Poisson regression to determine essential CTA markers of carotid-source stroke, and compared these methods with traditional lumen stenosis.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Clinical Study Design

Institutional review board approval was obtained before this retrospective cohort study from 2009 to 2016 in patients undergoing acute stroke workup at 2 facilities, the University Medical Center and the VA Medical Center. Informed consent was waived by the institutional review board. The only inclusion criteria were patients undergoing stroke workup who had both carotid CTA and brain MRI within a 1-month period of each other. A total of 950 patients met inclusion criteria.

Exclusions were made to eliminate alternate stroke sources after review of electronic medical records. A total of 696 patients were excluded for the following reasons: cardioembolic sources (235; eg, atrial fibrillation), vasculopathy (98; eg, dissection and fibromuscular dysplasia), posterior circulation strokes (88), intracranial large and small vessel disease (96; eg, intracranial atherosclerosis with >50% stenosis, isolated perforator distribution stroke, and vasculitis), hypercoagulable states (76; eg, antiphospholipid syndrome), ischemic stroke mimics (41; eg, multiple sclerosis and complex migraine headache), proximal vascular disease (3; eg, aortic arch thrombus), iatrogenic stroke (17; eg, postcardiothoracic surgery), drugs of abuse (10; eg, methamphetamine use), head/neck tumor (21), and intracranial hemorrhage (11). A total of 254 patients remained in the analysis, contributing 508 carotid arteries (Figure 1). Unilateral carotid occlusions (11), near-occlusions

Nonstandard Abbreviations and Acronyms

| Abbreviation | Description |
|--------------|-------------|
| CTA          | computed tomography angiography |
| DWI          | diffusion-weighted imaging |
| IPH          | intraplaque hemorrhage |
| MPRAGE       | magnetization-prepared rapid acquisition gradient echo |
| NASCET       | North American Symptomatic Carotid Endarterectomy Trial |
| TOAST        | Trial of Org 10172 in Acute Stroke Treatment |
(2), and previously stented carotid arteries (1) were excluded because CTA markers could not easily be assessed. In addition, no patients with recent carotid endarterectomy were included in this study. A total of 494 carotid artery and ipsilateral brain pairs (508–14=494) remained for final analysis.

**CTA Imaging, Markers, and Reviewers**

CTA was performed per institutional protocol as previously described. CTA markers included the time between MRI and CTA, rim sign present or absent, NASCET percent diameter stenosis, mm-stenosis, maximum plaque thickness (soft and hard), ulceration,
and intraluminal thrombus as previously defined.\textsuperscript{17} CTA markers were determined by reviewers blinded to stroke presence and distribution, as well as stroke status and clinical covariates. These reviewers had experience with neurovascular imaging interpretation and included 2 radiology residents (L.B.E. and P.J.H.) and a board-certified neuroradiology attending physician (J.S.M.). Carotid measurements were obtained using a picture archiving and communication system workstation, multiplanar reformats, and a sub-mm measurement tool. Briefly, both resident reviewers underwent specific training in detecting CTA features and had experience with neurovascular imaging interpretation. On study initiation, the carotid imaging markers were determined by the 2 residents. In cases of disagreement, consensus was obtained with the neuroradiology attending. Kappa analysis was previously performed to determine the rim sign interrater reliability (0.85) and intrarater reliability (0.86).\textsuperscript{17}

**Ipsilateral Ischemic Stroke Determination**

Ischemic stroke was determined using the American Heart Association definition of infarction as previously described.\textsuperscript{19} Briefly, ipsilateral ischemic stroke was defined by brain infarction or retinal cell death based on: (1) imaging evidence of cerebral or retinal ischemia in the carotid distribution; or (2) clinical symptoms persisting $\geq24$ hours, with other causes excluded.\textsuperscript{20} Stroke imaging used the diffusion-weighted imaging (DWI) technique derived from diffusion tensor imaging trace images from our standard clinical imaging protocol, as previously described.\textsuperscript{21} Diffusion tensor imaging trace images have been shown to be superior to conventional diffusion-weighted sequences in detecting recent infarcts.\textsuperscript{22} Briefly, diffusion tensor imaging trace images were shown to be superior to conventional diffusion-weighted sequences in detecting recent infarcts.\textsuperscript{22} Briefly, diffusion tensor imaging trace images correspond to a recent infarct at the time of the scan.\textsuperscript{23,24} Only DWI-positive embolic infarcts in the ipsilateral internal carotid artery territory were placed in the DWI-positive category for carotid-source strokes after excluding other stroke sources under our clinical study design. Embolic infarcts were defined as those involving the cortex or subcortical white matter, whereas microvascular infarcts were defined as those involving only the basal ganglia or adjacent white matter. DWI images were interpreted by a subspecialty-trained, certificate of added qualification–certified neuroradiologist blinded to carotid imaging.

**Clinical Demographics**

Clinical demographics and carotid atherosclerosis risk factors were determined by chart review. These included age, male sex, diabetes mellitus, hypertension, hyperlipidemia, and smoking status, and were determined by standard clinical definitions as previously described.\textsuperscript{17} For hypertension, the diagnosis was made when the average of $\geq2$ diastolic blood pressure measurements on at least 2 subsequent visits was $\geq90$ mm Hg or when the average of multiple systolic blood pressure readings on $\geq2$ subsequent visits was $\geq140$ mm Hg. For hyperlipidemia, the diagnosis was made when low-density lipoprotein was $>100$ mg/dL. Cerebrovascular medications were also recorded, including antiplatelet, anticoagulant, statin, and antihypertensive medications.

**Statistical Analysis**

To account for up to 2 carotid arteries per patient, generalized estimating equations were used. Carotid arteries were treated as separate units grouped within each patient. This is because stroke may be associated with local markers of carotid plaque vulnerability (eg, stenosis), as well as systemic clinical factors affecting both carotid arteries (eg, age). Given that $>1$ marker for stroke was being studied, confounding was investigated on the outcome variable (ipsilateral stroke), therefore only 1 data table was required, with $P$ values from univariable generalized estimating equation Poisson regression models. The Poisson regression approach directly estimates the prevalence ratio, which is more intuitive than the odds ratio obtained from logistic regression.\textsuperscript{25} Next, all potential confounding variables with $P<0.20$ from the univariable model were placed in the initial multivariable generalized estimating equation Poisson regression model for stroke. This was followed by backwards elimination until all remaining variables met the threshold $P<0.10$. The significance criteria of $P<0.10$ was used to protect against residual confounding.\textsuperscript{26}

For hypothesis testing of markers predictive of ipsilateral ischemic stroke, we used the traditional $P<0.05$. It is widely accepted that in binary models, 10 outcome events for every predictor variable are sufficient to avoid overfitting. With 108 ipsilateral stroke events and 384 nonstroke events, 108/10 or up to 11 predictor variables could be included in the model without overfitting, which is more than remaining variables in our final model. To assess the discriminatory potential of the final model and each marker, we reported clustered data area under the receiver operating characteristic curve (AUC), with bootstrapped 95% CIs.\textsuperscript{26} To guard against overfitting and optimism of the AUCs, in which an AUC could be higher in the present sample of patients than it would in future patients, we performed a bootstrap validation for each clustered data AUC calculation on the fixed list of predictors in the model.\textsuperscript{27} In all cases, the optimism was $<0.2\%$, and the original
RESULTS

Clinical Characteristics

Two-hundred fifty-four patients were included in the final analysis. Patients were predominantly older men (mean age, 63.5 years; 61.8% men) with carotid atherosclerosis risk factors (47.7% were current or prior smokers, 61.0% had hypertension, 48.4% had hyperlipidemia, and 26.8% had diabetes mellitus), and many were on medical treatment (50.0% taking antihypertensives, 41.7% taking statins, and 42.5% taking antiplatelets) (Table 1).

Imaging and Clinical Characteristics by Vessel

We evaluated imaging and clinical characteristics by vessel, in groups positive and negative for stroke in Table 2. There were 108 ipsilateral strokes. An example of a patient with a positive rim sign and measurements of stenosis and plaque thickness is shown in Figure 2. Each patient contributed up to 2 ipsilateral carotid-brain pairs (494 total). The degree of luminal stenosis was higher in the stroke versus nonstroke group (mean NASCET stenosis of 38.0% versus 11.6% and mm-stenosis of 2.94 versus 4.08 mm, P<0.001). A slight majority of strokes occurred in the mild stenosis group, with 57.4% of strokes in the <50% group compared with 42.6% of strokes in the ≥50% stenosis group. Maximum total plaque thickness was higher in the stroke versus the nonstroke group (4.37 versus 2.32 mm, P<0.001), as was maximum soft-plaque thickness (3.94 versus 2.06 mm, P<0.001) and maximum hard-plaque thickness (2.28 versus 1.47 mm, P<0.001). There was a higher prevalence of plaque ulceration (47.2% versus 17.9%, P<0.001) and intraluminal thrombus (13.0% versus 0.3%, P<0.001), although intraluminal thrombus was rare. The carotid rim sign was also highly prevalent in the stroke versus the nonstroke groups (50.9% versus 11.1%, P<0.001). Many clinical confounders were also more prevalent in stroke, including male sex, age, hypertension, hyperlipidemia, diabetes mellitus, and cardiovascular medications. Factors with P<0.20 were considered potential confounders between groups positive and negative for stroke, requiring multivariable regression.

Multivariable Generalized Estimating Equation Poisson Regression Analysis

Multivariable regression analysis was performed with the outcome of ipsilateral stroke. Potential confounders were eliminated in a backward fashion with a threshold of P<0.10. The final model for ipsilateral stroke prediction included the following CTA markers: the presence of intraluminal thrombus (prevalence ratio=2.8, P<0.001; 95% CI, 1.6–4.9), maximum soft plaque thickness (for each mm increase in thickness, prevalence ratio=1.2, P<0.001; 95% CI, 1.1–1.4), and rim sign (prevalence ratio=2.0, P=0.007; 95% CI, 1.2–3.3) (Table 3). NASCET stenosis, ulceration, and all other markers were eliminated with P>0.10. In addition, each measurement of stenosis (mm-stenosis, NASCET categories, NASCET continuous) was eliminated from the final multivariable model after backwards elimination to the P<0.10 level, if either placed together or separately in the initial model.

Ipsilateral Stroke Receiver Operating Characteristic Comparison Analysis

Receiver operating characteristic comparison analysis for ipsilateral stroke is shown in Figure 3. The discriminatory value of our final model for stroke was an AUC of 78.3%. This was significantly higher than each marker alone, including intraluminal thrombus (56.4%, P<0.001), maximum soft plaque thickness (76.4%, P=0.007), and rim sign alone (69.9%, P=0.001). NASCET stenosis categories (cutoffs of 50% and 70%) had significantly lower discrimination for stroke (AUC=67.4%, P<0.001) compared with our final model, and the rim sign added significant discrimination to these categories (AUC=74.3%, P=0.003). Furthermore, the continuous NASCET measurement had significantly lower discrimination for stroke (AUC=73.8%, P=0.03) compared with our final model.
DISCUSSION

Carotid plaque features are critical determinants of stroke. For more than 30 years, stenosis has been the primary determinant of carotid stroke potential based on data from NASCET and other trials and stratification criteria including TOAST. Increasing evidence suggests that plaque features, many of which can be detected on MRI, ultrasonography, and CTA are more strongly associated with stroke than luminal stenosis. In our cross-sectional evaluation of patients undergoing stroke workup, we found that specific imaging markers on CTA, including soft plaque thickness, an adventitial rim sign, and intraluminal thrombus, were significantly associated with downstream acute infarction and that considering these imaging markers were more predictive of stroke than degree of stenosis.

The inclusion of soft plaque thickness in the prediction of carotid sources of stroke corroborates prior research. Studies have shown that plaque thickness indicates a more vulnerable plaque phenotype, with increased plaque thickness associated with MPRAGE-detected IPH. Importantly, plaque thickness and plaque area have been associated with IPH, and this association is enhanced in the setting of low vitamin D. This may be related to a larger lipid core, higher microvessel density, and higher potential for intraplaque hemorrhage. Alternatively, increased plaque thickness may be secondary to bouts of microvessel leakage, since IPH accelerates plaque growth and stenosis.

The importance of the rim sign in our final stroke-prediction model fits with its high association with carotid IPH. Thin peripheral calcification may be a marker of chronic adventitial inflammation, and adventitial microvessel leakage has been implicated in carotid IPH. Adventitial inflammation has also been linked to endothelial bone morphogenetic protein-4 production, which may stimulate calcification.

In addition, activation of the angiotensin system in
animal models results in IPH, and low vitamin D levels correspond to increased IPH in humans. Both the angiotensin system and vitamin D play a central role in calcium homeostasis, and aberrations in these pathways may lead to carotid IPH and adventitial calcification.

Intraluminal thrombus, although rare, was highly associated with acute ipsilateral stroke in the current study, affirming previous data. The rarity of intraluminal thrombus in the setting of carotid-source stroke is somewhat puzzling. Intraluminal thrombi may still exist below CTA detection limits or the entire clot may have embolized during the stroke. Catheter-directed optical coherence tomography has detected small adherent thrombi in patients with stroke, and similar higher-resolution techniques may increase sensitivity for culprit plaques.

Overall, these findings highlight the ability of CTA to identify plaque features that are strongly associated with cerebrovascular ischemia. Although the AUC of the CTA final model (78.3%) is slightly lower than that obtained with MRI-IPH (86.2%), our findings suggest that routine CTA can still provide robust carotid plaque assessment, which is highly correlated with cerebrovascular ischemia.

**Figure 2.** Computed tomography (CT) angiography carotid imaging markers and stroke workup.

This 83-year-old man presented with abrupt onset left-sided weakness and numbness with an acute infarct in the right middle cerebral artery distribution on diffusion-weighted imaging (A). CT angiography (CTA) of the carotid arteries demonstrated a thick right carotid bifurcation/proximal internal carotid artery plaque with a positive rim sign (B), consisting of thin peripheral adventitial calcification (<2 mm) and internal soft plaque (≥2 mm). Maximum soft plaque thickness measured 5.1 mm (M1) and maximum hard plaque thickness measured 1.9 mm (M2) using the picture archiving and communication system sub-mm measurement tool (C). NASCET (North American Symptomatic Carotid Endarterectomy Trial) percent diameter stenosis measured \([\frac{(6.6 - 2.6)}{6.6}] \times 100\% = 61\%\), and mm-stenosis measured 2.6 mm on multiplanar reformats (D). No other CTA markers were present (eg, no ulceration or intraluminal thrombus).
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cerebrovascular ischemia. Although much attention is focused on MRI-based plaque assessment, CTA appears to be a powerful tool in evaluating carotid stroke sources.41 Furthermore, these data question the sole use of stenosis to identify stroke sources and suggest that stroke causes criteria should be revised. A threshold of ≥50% stenosis has been used for years as part of the TOAST criteria in identifying potential large artery stroke sources.1 Our current data suggest that a slight majority (57.4%) of carotid stroke sources have <50% stenosis by NASCET criteria. Furthermore, the AUC using NASCET stenosis cutoffs was significantly lower (67.4%) than our final model (78.3%), suggesting that CTA-identified plaque characteristics have improved discrimination compared with stenosis alone. This highlights the importance of detailed carotid plaque evaluation, even in cases of nonstenosing plaque.

While this study lacks information on future stroke risk, the cross-sectional nature has the important advantage of evaluating plaque features in close proximity to stroke onset when determination of stroke sources is paramount. A key next step is to prospectively examine these CTA markers and their associated recurrent stroke risk and determine which markers better stratify patients for endarterectomy versus specific medical treatment regimens. Another potential limitation is that recruitment was limited to patients undergoing stroke workup at 1 of 2 local centers. Further confirmation of these results is warranted by other centers with regional differences.

Determining stroke cause is critically important in future stroke prevention by directing appropriate treatment. In the setting of ipsilateral embolic stroke, CTA identification of carotid intraluminal thrombus, high soft plaque thickness, or a rim sign suggests a carotid plaque stroke source is likely and further imaging tests may not add further information. The majority of carotid-source strokes occur in patients with <50% carotid stenosis, arguing against stroke source identification using stenosis alone. Instead, these alternative markers may allow clinicians to better diagnose vulnerable carotid plaque and guide treatment decisions, including stratification to medical therapy or surgery.

### Table 3. Final Stroke Prediction Model

| Vulnerable Carotid Plaque (ipsilateral Stroke) Predictors | PR | P Value | 95% CI |
|----------------------------------------------------------|----|---------|--------|
| Intraluminal thrombus                                    | 2.8| <0.001  | 1.6    | 4.9   |
| Maximal soft plaque thickness (per each mm)              | 1.2| <0.001  | 1.1    | 1.4   |
| Positive rim sign                                        | 2.0| 0.007   | 1.2    | 3.3   |

The final stroke prediction model depended on 3 factors with P<0.10: intraluminal thrombus, maximum soft plaque thickness and a positive rim sign. PR indicates prevalence ratio.

![Figure 3](image-url) Receiver operating characteristic comparison analysis demonstrates the superiority of the final model and the rim sign in predicting ipsilateral stroke.

**A**, Final model versus singular components: the discriminatory value of our final model for stroke was an area under the receiver operating characteristic curve (AUC) of 78.3%, significantly higher than each plaque component alone: intraluminal thrombus (56.4%, P<0.001), maximum soft plaque thickness (76.4%, P=0.007), and rim sign alone (69.9%, P=0.001). Final model: solid circles, solid line; intraluminal thrombus: black triangle, dashed line; maximum soft plaque thickness: light gray diamonds, dashed line; rim sign: gray circle, dotted line.

**B**, Final model, rim sign, NASCET (North American Symptomatic Carotid Endarterectomy Trial) categories, and continuous measurement: our final model (AUC=78.3%) has significantly higher stroke source discrimination compared with traditional NASCET stenosis cutoffs of 50% and 70% (AUC=67.4%, P<0.001), and the rim sign added significant discrimination to these categories (AUC=74.3%, P=0.003). Furthermore, the continuous NASCET measurement had significantly lower discrimination for stroke (AUC=73.8%, P=0.03) compared with our final model. Final model: solid circles, solid line; rim sign + NASCET categories: light gray diamonds, dashed line; NASCET categories: dark gray square, dotted line. Continuous NASCET: dark gray triangles, dashed line.
CONCLUSIONS

Vulnerable carotid plaque stroke sources can be identified with CTA features including intraluminal thrombus, maximum soft plaque thickness, and a rim of adventitial calcification. These markers can identify vulnerable plaque and potential stroke sources otherwise ignored by stenosis.

ARTICLE INFORMATION

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Disclosures

None.

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