The degree of arterial stenosis remains the primary imaging determinant of stroke risk in carotid atherosclerotic disease and has been used to select those groups of patients most likely to benefit from surgical revascularization.1–3 However, in light of improvements in the effectiveness of nonsurgical therapy for carotid atherosclerotic disease in the past 2 decades,4,5 there has been renewed interest in evaluating imaging techniques for risk stratification beyond luminal stenosis severity. One such approach involves direct vessel wall imaging to determine features of vulnerable plaque.6 Much of the recent work with carotid plaque imaging has been MRI based.7,9 However, there are several challenges in the wide implementation of multisequence carotid MRI as a risk stratification tool in the clinical setting, including the need for specialized MRI coils, lengthy acquisitions times, and the complexity of image interpretation.

Computed tomography (CT) of the brain and CT angiography (CTA) of the head and neck are frequently used in the evaluation of suspected stroke10 and offer significant advantages compared with MRI in terms of speed and availability. Despite these advantages, to date, CTA of carotid plaque has had limited clinical usefulness in risk stratification because of the difficulty of relying on Hounsfield units (HU) to distinguish between specific plaque elements11,12 and the need for specialized postprocessing techniques.13,14 However, in a recent study,15 investigators demonstrated that a simple linear measurement of maximum soft plaque thickness on routinely acquired axial CTA images was strongly associated with American Heart Association type VI plaque as defined by MRI, in which plaque is characterized by fibrous cap rupture, attached thrombus, or hemorrhage.8 However, this recent study assessed a wide range of stenosis and correlated plaque thickness measurements with symptomatic disease status in carotid artery stenosis. Prospective validation of these results may translate into a widely accessible stroke risk stratification tool in high-grade carotid artery atherosclerotic disease.

**Evaluation of Computed Tomography Angiography Plaque Thickness Measurements in High-Grade Carotid Artery Stenosis**

Ajay Gupta, MD; Hediyeh Baradaran, MD; Hooman Kamel, MD; Ankur Pandya, PhD; Atul Mangla, MD; Allison Dunning, MS; Randolph S. Marshall, MD, MS; Pina C. Sanelli, MD, MPH

**Background and Purpose**—Increasing evidence suggests that carotid artery imaging can identify vulnerable plaque elements that increase stroke risk. We correlated recently proposed markers, soft and hard plaque thickness measurements on axial computed tomography angiography source images, with symptomatic disease status (ipsilateral stroke or transient ischemic attack) in high-grade carotid disease.

**Methods**—Soft plaque and hard plaque thickness were measured with a recently validated technique using computed tomography angiography source images in subjects with ≥70% extracranial carotid artery stenosis. Logistic regression analyses were used to assess the strength of association between soft and hard plaque thickness measurements and previous stroke or transient ischemic attack. Receiver operating characteristic analysis was also performed.

**Results**—Compared with asymptomatic subjects, those with symptomatic carotid disease had significantly larger soft plaque and total plaque thickness measurements and smaller hard plaque thickness measurements. Each 1-mm increase in soft plaque resulted in a 2.7 times greater odds of previous stroke or transient ischemic attack. Soft plaque thickness measurements provided excellent discrimination between symptomatic and asymptomatic disease, with receiver operating characteristic analysis showing an area under the curve of 0.90. A cutoff of 3.5-mm maximum soft plaque thickness provided a sensitivity of 81%, specificity of 83%, positive predictive value of 85%, and a negative predictive value of 78%.

**Conclusions**—Increasing maximum soft plaque thickness measurements are strongly associated with symptomatic disease status in carotid artery stenosis. Prospective validation of these results may translate into a widely accessible stroke risk stratification tool in high-grade carotid artery atherosclerotic disease. *(Stroke. 2014;45:740-745.)*

**Key Words:** carotid arteries ■ ischemic attack, transient ■ stroke

*Stroke* is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.113.003882
thickness measurements with an imaging reference standard without assessment of clinical ischemic events. The purpose of our cross-sectional study was to assess the association of plaque thickness measurements obtained from neck CTA with stroke or transient ischemic attack (TIA) history in patients with high-grade carotid artery stenosis.

Methods

Subjects
Subject records were screened for this retrospective study via review of consecutive CTA neck examinations performed from August 2009 through August 2012. Subject inclusion criteria included the following: (1) unilateral high-grade extracranial internal carotid artery stenosis (70%–99%) identified on CTA neck examination; (2) documentation available in the electronic medical records to determine whether stroke or TIA had occurred before the CTA; and (3) detailed medical record documentation of pre-existing vascular risk factors. We excluded patients with complete extracranial carotid occlusions. The study was approved by the Human Subjects Institutional Review Board of our institution.

Imaging Technique
CTA neck studies were performed using a standardized protocol on one of several CT scanners at our clinical sites, including Lightspeed, Pro-16, or HD-750 (GE Healthcare; Milwaukee, WI). All CTA studies were performed in helical scanning mode, with coverage extending from the aortic arch to the C1 ring. Studies were collimated at 0.625 mm, with a peak kilovoltage of 120 and auto milliampere, with a rotation time of 0.5 s. Approximately 90 mL of nonionic iodinated contrast was administered via an 18-gauge peripheral intravenous catheter at 4 to 5 mL/s using a power injector and a SmartPrep region-of-interest on the aortic arch. Maximum intensity projection reconstructions (8-mm thickness with 2-mm intervals) in sagittal and coronal images were constructed. To assess the generalizability of this technique to clinical practice, only studies with image quality sufficient to provide clinical interpretation at the time of original image acquisition were included in our analysis.

Imaging Data Assessment
Carotid CTA plaque thickness measurements were performed by a board-certified neuroradiologist blinded to clinical data and in accordance with a previously described protocol.25 Briefly, axial sections of CTA were evaluated, and 3 separate measurements were obtained in each carotid plaque: (1) maximum thickness of the noncalcified, soft plaque component; (2) maximum thickness of the calcified, hard plaque component; and (3) maximum total plaque thickness (Figures 1 and 2). Measurements were obtained using single linear measurements taken on the axial slice(s) with the greatest luminal narrowing using the electronic caliper function of Centricity PACS (GE Healthcare; Milwaukee, WI), which allows measurements with a spatial resolution to 0.1 mm. All maximum thickness measurements were obtained on standard axial slices without additional postprocessing. Such routinely obtained standard axial images were used instead of orthogonal reconstructions both to simulate routinely used clinical imaging protocols and because excellent agreement between axial and orthogonal plaque element thickness measurements was previously found using this technique.25 Furthermore, when the soft plaque component thickness was >2 mm, a circular region-of-interest ≥2 mm² was drawn, avoiding areas of calcification or enhanced lumen, and HU mean, minimum, and maximum values were collected. Region-of-interest analysis was not performed for soft plaques measuring <2 mm given the difficulty of manually delineating region-of-interests in such small regions. For all image analysis, window/level settings were 800/200, with small adjustments made manually to optimize discrimination between soft and hard plaque. Percent degree of stenosis was determined using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method by the same neuroradiologist blinded to clinical data.25 Because measurements using the distal internal carotid artery as the denominator for stenosis measurements might underestimate the degree of stenosis in near occlusion, as per NASCET trial guidelines,16 in cases of near occlusion (string sign), a stenosis value of 95% was assigned. Finally, to test for reliability of measurements, a second board-certified neuroradiologist blinded to the initial measurements repeated linear axial dimension measurements on a subset of 20 subjects.

Clinical Data Assessment
History of ipsilateral TIA or stroke and pre-existing vascular risk factors were determined by the consensus of 2 stroke neurologists after a detailed examination of the electronic medical record. The neurologists were blinded to CTA image analysis. Stroke and TIA were defined in terms of the American Heart Association definitions,17 with stroke and TIA defined as a permanent or transient episode, respectively, of neurological dysfunction caused by focal brain or retinal ischemia. Ischemic events were only considered as symptomatic disease when referable to the stenotic internal carotid artery (ipsilateral stroke or TIA). Days between qualifying ipsilateral ischemic events and CTA imaging were calculated. The specific vascular risk factors collected in our study included the presence or absence of a history of smoking, diabetes mellitus (defined as a hemoglobin A1C of >6.5% or on diabetic medication), hypertension (blood pressure ≥140/90 mm Hg or on antihypertensive medication), atrial fibrillation, hyperlipidemia (low-density lipoprotein >100 or on statin), and presence of coronary artery disease.

Statistical Analysis
We used multiple logistic regression analysis to measure the strength of association between each 1-mm increase of soft plaque thickness and symptomatic disease status while controlling for the percent...
degree of NASCET stenosis and any additional covariate risk factors found to be statistically significant in univariate analyses at a threshold of \( P < 0.05 \). In addition, receiver operating characteristic curve analysis was performed to determine which imaging feature (maximum total plaque thickness, maximum soft plaque thickness, or maximum hard plaque thickness) had the best discrimination for symptomatic carotid disease status. An optimum cutoff was calculated for the plaque measurement shown to have the highest area under the curve, with sensitivity, specificity, positive predictive value, and negative predictive value calculated for this threshold value. All \( P \) values \(<0.05\) were considered statistically significant. All statistical analyses were performed using SAS 9.3 (Cary, NC).

**Results**

**Subject Characteristics**

We screened 1224 patients who had undergone CTA. We excluded 1103 patients because these subjects did not have \( \geq 70\% \) unilateral extracranial internal carotid artery stenosis and 45 because of complete carotid occlusion, leaving 76 of the original 1224 (6.2\%) in the final cohort. Clinical indications for CTA included clinical suspicion for acute stroke or TIA referable to any vascular territory in 45 subjects (59.2\%), routine imaging surveillance for known carotid stenosis in 25 subjects (32.9\%), altered mental status in 2 subjects (2.6\%), syncope in 2 subjects (2.6\%), intracranial aneurysm surveillance in 1 subject (1.3\%), and known cancer surveillance in 1 subject (1.3\%).

Patient demographics and study characteristics are shown in Table 1. A total of 42 of 76 subjects (55\%) had ischemic symptoms ipsilateral to the side of high-grade carotid stenosis. Among the symptomatic patients, 33 had ipsilateral strokes, which occurred a mean of 18.5 days before CTA imaging (range, 0–180 days), and 9 had ipsilateral TIsAs, which occurred a mean of 15.4 days before CTA imaging (range, 0–60 days). Vascular risk factors were not significantly different between groups except for age and prevalence of coronary artery disease, which were both higher in the asymptomatic group (Table 1).

**CTA Plaque Imaging**

Mean values for the maximum total plaque thickness and maximum soft plaque thickness (Figures 1 and 2) were significantly higher in subjects with symptomatic carotid disease, whereas maximum hard plaque thickness was found to be significantly higher in asymptomatic subjects (Table 2). The degree of NASCET stenosis was not different between groups. In the subset of 52 subjects with soft plaque thickness measurements >2 mm, no significant differences in HU were found when comparing between asymptomatic and symptomatic subjects. After adjusting for age, coronary artery disease status, and percent stenosis, multivariate logistic regression analysis (Table 3) demonstrated that for every 1-mm increase in maximum soft plaque thickness, there was an \( \approx 2.7 \) times greater likelihood (odds ratio=2.7) of previous ipsilateral stroke or TIA \( (P<0.0001) \). Conversely, for each 1-mm increase in hard plaque thickness, there was 45\% (odds ratio=0.55) decreased likelihood of previous ipsilateral stroke or TIA \( (P=0.007) \).

**Receiver Operating Characteristic Analysis**

Receiver operating characteristic curves are shown in Figure 3, with the largest area under the curve of 0.90 calculated for maximum soft plaque thickness (Table 3). Maximum plaque wall thickness and maximum hard plaque thickness had a slightly lower area under the curve of 0.82 each. After adjustments were made for coronary artery disease status, age, and percent degree of stenosis, there were no significant differences between groups. In the subset of 52 subjects with soft plaque thickness measurements >2 mm, no significant differences in HU were found when comparing between asymptomatic and symptomatic subjects. After adjusting for age, coronary artery disease status, and percent stenosis, multivariate logistic regression analysis (Table 3) demonstrated that for every 1-mm increase in maximum soft plaque thickness, there was an \( \approx 2.7 \) times greater likelihood (odds ratio=2.7) of previous ipsilateral stroke or TIA \( (P<0.0001) \). Conversely, for each 1-mm increase in hard plaque thickness, there was 45\% (odds ratio=0.55) decreased likelihood of previous ipsilateral stroke or TIA \( (P=0.007) \).

**Table 1. Baseline Demographics, Including Vascular Risk Factor Differences Between Main Study Groups**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Asymptomatic ( (n=54) )</th>
<th>Symptomatic ( (n=42) )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>77.6±8.3</td>
<td>73.1±9.8</td>
<td>0.0369</td>
</tr>
<tr>
<td>Male sex</td>
<td>62% (21)</td>
<td>64% (27)</td>
<td>0.8208</td>
</tr>
<tr>
<td>CT imaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis, %</td>
<td>80.3±7.8</td>
<td>83.3±9.0</td>
<td>0.1402</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td>62% (21)</td>
<td>74% (31)</td>
<td>0.2613</td>
</tr>
<tr>
<td>Hypertension</td>
<td>85% (29)</td>
<td>98% (41)</td>
<td>0.0836</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>85% (29)</td>
<td>86% (36)</td>
<td>0.9587</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15% (5)</td>
<td>19% (8)</td>
<td>0.6172</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>59% (20)</td>
<td>24% (10)</td>
<td>0.0019</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>21% (7)</td>
<td>7% (3)</td>
<td>0.0847</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3% (1)</td>
<td>5% (2)</td>
<td>0.6852</td>
</tr>
</tbody>
</table>

Mean percent values are shown with number of subjects in parentheses. CT indicates computed tomography.
differences in area under the curve. Sensitivity and specificity were optimized using a maximum soft plaque thickness of 3.5 mm, a cutoff that provided a sensitivity of 81%, specificity of 83%, positive predictive value of 85%, and negative predictive value of 78%.

### Measures of Diagnostic Test Reproducibility

Inter-reader correlation coefficients for measurements of maximum total wall thickness, maximum soft plaque thickness, and maximum hard plaque thickness were 0.93, 0.91, and 0.88, respectively, indicating excellent interobserver reliability.

### Discussion

Our current study demonstrates a strong association between increasing soft plaque thickness measurements and ipsilateral ischemic events. We found that with each 1-mm increase in plaque thickness, patients with high-grade extracranial internal carotid artery disease had 2.7 times greater likelihood to have had ipsilateral ischemic disease. On the contrary, densely calcified plaque was associated with a lower risk of symptomatic disease, with maximum hard plaque thickness substantially higher in asymptomatic patients. Of the plaque imaging characteristics we studied, maximum soft plaque thickness had the best ability to discriminate between symptomatic and asymptomatic subjects, with an optimal cutoff of 3.5 mm.

Several studies have used CTA plaque characteristics in defining carotid disease. However, the clinical relevance to patients with carotid disease has been limited because these studies have often studied a wide range of stenosis severity and have used advanced imaging post-processing techniques that could be a barrier to adoption in routine clinical practice. However, a recent study by Trelles et al suggests that soft and hard plaque thickness measurements made on routine axial CTA neck source images can predict complicated MRI-defined American Heart Association type VI plaque across a wide range of stenosis severity. Our results are consistent with this previous work because our optimal cutoff of 3.5-mm maximum soft plaque thickness is within 1 mm of the optimal cutoff threshold of 4.4 mm for prediction of American Heart Association type VI MRI plaque phenotype.

Unlike previous work using this CTA source image technique, our cohort had a tightly controlled range of NASCET-defined stenosis as well as a known history of stroke/TIA. We found increased soft plaque thickness measurements even in cases in which imaging was performed outside of the immediate 24 hours after stroke/TIA. Because of the cross-sectional design of our study and the dynamic nature of atherosclerosis, it is unclear to what extent plaque thickness measurements can function as predictors of future events. However, given the mounting MRI evidence demonstrating that plaque elements

### Table 2. CTA Plaque Characteristics Stratified by Symptomatic Carotid Disease Status

<table>
<thead>
<tr>
<th>Predictors of interest</th>
<th>Asymptomatic (n=34)</th>
<th>Symptomatic (n=42)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Stenosis</td>
<td>80.3±7.8</td>
<td>83.3±9.0</td>
<td>0.1402</td>
</tr>
<tr>
<td>Maximum plaque wall thickness, mm</td>
<td>4.19±1.33</td>
<td>5.05±1.08</td>
<td>0.0027</td>
</tr>
<tr>
<td>Maximum hard plaque thickness, mm</td>
<td>3.25±1.51</td>
<td>2.10±1.22</td>
<td>0.0004</td>
</tr>
<tr>
<td>Maximum soft plaque thickness, mm</td>
<td>2.01±1.65</td>
<td>4.51±1.46</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

If maximum soft plaque thickness >2 mm (n=52)

<table>
<thead>
<tr>
<th>n</th>
<th>Mean HU</th>
<th>SD HU</th>
<th>Minimum HU</th>
<th>Maximum HU</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>47.4±24.7</td>
<td>13.9±8.1</td>
<td>23.9±31.1</td>
<td>70.0±25.5</td>
</tr>
<tr>
<td>39</td>
<td>48.6±33.5</td>
<td>13.4±12.7</td>
<td>28.8±37.1</td>
<td>72.4±41.0</td>
</tr>
</tbody>
</table>

Mean values±range are shown. CTA indicates computed tomography angiography; and HU, Hounsfield units.

### Table 3. Univariate and Multivariate OR Associating Plaque Characteristics With Symptomatic Carotid Disease

<table>
<thead>
<tr>
<th>Predictors of Interest</th>
<th>Univariate Logistic Regression</th>
<th>Adjusted Logistic Regression*</th>
<th>Difference in Univariate and Adjusted AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI AUC P Value</td>
<td>OR 95% CI AUC P Value</td>
<td>P Value</td>
</tr>
<tr>
<td>Maximum plaque wall thickness, mm</td>
<td>1.82 1.20–2.76 0.71 0.0048</td>
<td>2.14 1.27–3.60 0.82 0.0042</td>
<td>0.0852</td>
</tr>
<tr>
<td>Maximum hard plaque thickness, mm</td>
<td>0.53 0.36–0.79 0.74 0.0015</td>
<td>0.55 0.35–0.85 0.82 0.0073</td>
<td>0.0823</td>
</tr>
<tr>
<td>Maximum soft plaque thickness, mm</td>
<td>2.52 1.70–3.73 0.87 &lt;0.0001</td>
<td>2.66 1.70–4.16 0.9 &lt;0.0001</td>
<td>0.2763</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; CI, confidence interval; and OR, odds ratio.

*Adjusted for age, stenosis percentage, and coronary artery disease.
such as hemorrhage, lipid-rich necrotic core, or fibrous cap rupture are powerful predictors of future events, it is reasonable to hypothesize that because these plaque elements are likely key components of soft plaque, a similarly strong predictive capability for CTA plaque measurements might also exist. Furthermore, although changes in vulnerable plaque elements are known to occur, in a recent MRI study of intraplaque hemorrhage in symptomatic carotid disease, Hosseini et al. found that stroke risk with plaque hemorrhage was preserved for ≥5 years. Similarly, in a longitudinal MRI study of the natural history of carotid artery plaques, Kwee et al. found that specific plaque elements that are likely components of soft plaque on CTA, such as lipid-rich necrotic core, fibrous cap abnormalities, and intraplaque hemorrhage, are largely unchanged in symptomatic patients for a 1-year period. Our results suggest that soft plaque thickness measurements could represent a similarly robust biomarker of plaque vulnerability in carotid atherosclerotic disease, although this requires further confirmation.

There are several strengths to the technique of plaque characterization used in our study. First, this technique allows a relatively simple distinction between 2 broad categories of plaque defined easily on CTA: calcified and noncalcified plaque. Although quantitative HU measurements do offer the potential for greater soft tissue element discrimination, such measurements have been shown by several investigators as poor discriminators of specific plaque components such as lipid, fibrosis, and hemorrhage compared with histopathologic analysis or MRI. In our study, HU values also performed poorly in discriminating between asymptomatic and symptomatic carotid plaques. Because low-density regions likely represent a combination of elements such as intraplaque hemorrhage and lipid-rich necrotic cores, our data suggest that differentiation between these specific elements may not be necessary because both elements are predictors of future ischemic events. Similarly, our work supports data from previous CTA studies of carotid plaque, suggesting that extensive calcification may afford a protective effect, possibly by preventing adhesion and subsequent aggregation of platelet-rich thrombi, although this claim requires further histopathologic confirmation.

An additional strength of maximum soft plaque thickness measurements is that such data are readily acquired from standard axial source images in CTA, with a highly reproducible simple linear measurement. Wintermark et al., for example, demonstrated in a cross-sectional analysis from CTA data that certain carotid wall characteristics were significantly associated with stroke, including wall volume, fibrous cap thickness, and number and location of lipid clusters on source images. However, this analysis was performed using customized postprocessing, a CT-based automated classifier algorithm not routinely used in clinical settings. A related strength of our approach is that this protocol does not require the acquisition of precontrast neck CT images. For example, although Romero et al. demonstrated a correlation between arterial wall enhancement and symptomatic disease status on CTA, their technique requires comparison of CTA images with precontrast CT images through the carotid arteries. Finally, although qualitative plaque morphological features on sonography and CTA, such as lumen shape, ulceration, or plaque heterogeneity, have been proposed as markers of higher-risk plaque, the technique used in our study may be less prone...
to reader subjectivity and operator dependence, as demonstrated by high inter-rater reliability by us and others.15

Our study has limitations that should be considered. First, this was a cross-sectional study and retrospective in design. As such, as previously discussed, because plaque and clinical stroke/TIA data were collected at a single time point, it remains unclear to what extent future events can be predicted by the use of this technique. Second, the histopathologic basis for this technique has not specifically been studied, and it remains unclear exactly what plaque components may be conferring greater stroke/TIA risk. Confirmatory correlations with pathology and MRI are needed.

Conclusions

In summary, our study demonstrates that routinely acquired, axial CTA source images, already commonly used to measure stenosis degree, can be used to measure linear maximum soft plaque thickness, which is strongly associated with previous ischemic events in patients with high-grade carotid artery stenosis. A prospective validation of this study could provide the basis for a complementary risk stratification tool that could be obtained at the time of stenosis assessment and provide guidance for clinical management.

Sources of Funding

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Disclosures

None.

References

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