Published in final edited form as:

Ann Neurol. 2008 August ; 64(2): 149–157. doi:10.1002/ana.21424.

Carotid Plaque CT Imaging in Stroke and Non-Stroke Patients

Max Wintermark, M.D.¹, Sandeep Arora, M.B.B.S.¹, Elizabeth Tong, Ph.D.¹, Eric Vittinghoff, Ph.D.², Benison C. Lau¹, Jeffrey D. Chien, B.A.¹, William P. Dillon, M.D.¹, and David Saloner, Ph.D.¹

¹University of California, San Francisco, Department of Radiology, Neuroradiology Section

²University of California, San Francisco, Department of Epidemiology and Biostatistics

Abstract

OBJECTIVE—To identify a set of computed tomography (CT) features of carotid atherosclerotic plaques that is significantly associated with ischemic stroke.

METHODS—In a cross-sectional study, we retrospectively identified 136 consecutive patients admitted to our emergency department with suspected stroke who underwent a CT-angiogram (CTA) of the cervical and intracranial carotid arteries. CTA studies of the carotid arteries were processed automatically using a custom, CT-based automated computer classifier algorithm that quantitatively assesses a battery of carotid CT features. Acute stroke patients were categorized into "acute carotid stroke patients" and "non-acute carotid stroke patients" independent of carotid wall CT features, using the Causative Classification System for Ischemic Stroke, which includes the neuroradiologist's review of the imaging studies of the brain parenchyma and of the degree of carotid stenosis, and charted test results (such as EKG and Holter). Univariate followed by multivariate analyses were used to build models to differentiate between these patient groups and to differentiate between the infarct and unaffected sides in the "acute carotid stroke patients". A receiver operating characteristic curve analysis determined which model was most accurate.

RESULTS—Forty "acute carotid stroke" patients and 50 "non-acute carotid stroke" patients were identified. Multivariate modeling identified a small number of the carotid wall CT features that were significantly associated with acute carotid stroke, including: wall volume, fibrous cap thickness, number and location of lipid clusters, and number of calcium clusters.

INTERPRETATION—Patients with acute carotid stroke demonstrate significant differences in the appearance of their carotid wall ipsilateral to the side of their infarct, when compared with either non-acute carotid stroke patients or the carotid wall contralateral to the infarct side.

Objective

Luminal narrowing is the standard parameter used to report the extent and severity of carotid artery stenosis due to atherosclerosis. The widespread use of this measure is based primarily on the results of several randomized clinical trials that demonstrated a reduction in the risk of ischemic stroke in patients with luminal stenosis of $\geq 50\%$ (assessed on conventional angiograms) after carotid endarterectomy compared with medical treatment alone.^{1–4} However, $\geq 50\%$ -carotid stenosis occurs in fewer than 5% of patients, whereas $< 50\%$ -carotid stenosis is extremely frequent in the general population (70% in men and 60% in women over 64 years of age).^{5,6} In patients with $< 50\%$ carotid stenosis, high-resolution lumenography provides limited insight into the associated risk of stroke because

Address for correspondence and reprint requests: Max Wintermark, MD, University of California, San Francisco, Department of Radiology, Neuroradiology Section, 505 Parnassus Avenue, Box 0628, San Francisco, CA 94143-0628, Phone: (415) 353-1668, Fax: (415) 353-8593, E-mail: Max.Wintermark@radiology.ucsf.edu.

angiography is able to detect atherosclerosis only when >40% of the area of the vessel wall is occupied by atherosclerotic plaque.⁷

Plaque morphology and composition have been suggested as a complement to measurements of luminal dimension for assessing carotid atherosclerotic disease, leading to the concept of imaging the "vulnerable plaque", susceptible to rupture and embolization despite luminal size.⁸⁻¹² A number of carotid morphological features have been associated with an increased risk of stroke, the most studied descriptor being the common carotid artery (CCA) intima-media thickness.^{5, 6, 13-17} Carotid plaques with thin fibrous caps and large lipid cores^{18, 19}, as well as ulcerated plaques^{8, 12, 20-22}, are also considered to increase the risk of stroke. In contrast, plaques with high calcium content, especially when located superficially, are thought to be associated with a lower risk of stroke.^{23-24, 25} These features of carotid plaques have been studied separately in different studies using either ultrasound^{5, 6, 13-17} or magnetic resonance imaging (MRI), but to date not with computed tomography (CT).^{3, 7, 26-30}

Recently, a three-dimensional, computerized interpretation of multidetector-row, isotropic resolution CT-angiography (CTA) studies was reported to assess, in a quantitatively accurate and standardized fashion, the histological composition (including non-calcified components) and characteristics of carotid artery atherosclerotic plaques.²¹ In this study, there was 72.6% agreement between CTA and histology for carotid plaque classification, perfect concordance for calcifications, and good correlation with histology for large lipid cores.²¹ CTA was also accurate in the detection of ulcerations and in the measurement of fibrous cap thickness.²¹

The goal of our retrospective study was to identify CT features of carotid atherosclerotic plaques that are significantly associated with the occurrence of ischemic stroke using this standardized, computerized assessment of CTA studies.

Material and Methods

Study Design

Clinical and imaging data, obtained as part of standard clinical stroke care at our institution, was retrospectively reviewed with the approval of the institutional review board. At our institution, patients with suspicion of acute stroke and no history of significant renal insufficiency or contrast allergy routinely undergo a stroke CT survey including the following imaging protocol: noncontrast CT, perfusion-CT at two cross-sectional positions, CTA of the cervical and intracranial vessels, and a post-contrast cerebral CT.

We retrospectively identified all consecutive patients admitted to our emergency department from August 2006 through January 2007 who had undergone a CTA to evaluate their carotid arteries.

CTA Imaging Protocol

The CTA studies of the carotid arteries were obtained on a 16-slice CT scanner (General Electric Medical Systems, Milwaukee, WI). The image acquisition protocol was as follows: spiral mode, 0.6-second gantry rotation, collimation: 16×0.625 mm, pitch: 1.375:1, slice thickness: 0.625 mm, reconstruction interval: 0.5 mm, acquisition parameters: 120 kVp/240 mA. A caudo-cranial scanning direction was selected, covering the mid-chest to the vertex of the brain. Seventy milliliters (mL) of Iohexol (Omnipaque, Amersham Health, Princeton, NJ; 300 mg/mL of iodine) was injected into an antecubital vein with a power injector at a rate of 4 mL per second. Optimal timing of the CTA acquisition was achieved using a test bolus technique.

Image Post-Processing

The CTA studies of the carotid arteries were processed automatically using a custom, CT-based, automated classifier computer algorithm that was validated using histology derived from carotid endarterectomy specimens as a gold standard.²¹ This algorithm automatically segments the inner and outer contours of the carotid artery wall and distinguishes between the histological components of the wall (lipids, calcium) using appropriate thresholds of CT density.²¹ The algorithm creates a color overlay affording a visual display of the composition of the carotid wall for each CTA image (Fig. 1). It then automatically analyzes several CT features of the carotid arteries (Table 1, left column) and quantifies them three-dimensionally (not in a plane, as with B-mode ultrasound), independent of any subjective, human interpretation.

The location of the largest lipid and calcium clusters was described as a percent of the carotid wall thickness, with 0% indicating the center of the cluster immediately adjacent to the inner contour, and 100%, the center of the cluster immediately adjacent to the outer contour.

Measurements were recorded separately for the 3 cm of the common carotid artery (CCA) immediately proximal to the carotid bifurcation, for the 3 cm of the internal carotid artery (ICA) immediately distal to the carotid bifurcation, and for both these segments considered together (BIF).

The physician processing the CTA datasets was blinded to the clinical findings of the imaged patients and to the group to which they belonged.

Image Review

The CT studies of the brain parenchyma obtained at baseline and the brain imaging studies obtained within the first week after the baseline CT were reviewed by a neuroradiologist for the presence or absence of an acute infarct and its distribution (unilateral or bilateral, single or multiple vascular territories, and location of vascular territory). The neuroradiologist also reviewed the intracranial portion of the baseline CTA of the carotid arteries for the degree of completeness of the Circle of Willis. Based on the brain CT or MRI findings, the anatomy of the Circle of Willis, and published criteria,^{31, 32} the neuroradiologist decided whether the distribution of an acute infarct was consistent with a carotid origin.

The neuroradiologist reviewed the same studies of the brain parenchyma for remote infarcts and determined whether their distribution was consistent with a carotid origin. Patients with remote infarcts in a carotid distribution were excluded from our analysis because carotid atherosclerotic disease is an evolving process, and the carotid artery condition may have evolved in the time interval between when the remote infarct occurred and the time of our CTA study. This could have interfered with our identification of the carotid wall features associated with stroke.

Finally, the neuroradiologist assessed the degree of carotid stenosis on the cervical portion of the baseline CTA, but did not record any information regarding the carotid wall. During the review, the neuroradiologist was blinded to the results of the automatic analysis of the carotid wall produced by the computer algorithm.

Patient Classification

The medical records of the patients were reviewed to determine the likely etiologic origin of the stroke, using the Causative Classification System for Ischemic Stroke³³ and its electronic implementation available online (<http://www.strokedatabase.org/index.html>).³⁴

Based on the review of the imaging studies of the brain parenchyma by the neuroradiologist, degree of carotid stenosis, and test results available in patients' charts (such as EKG and Holter), but independently of carotid wall CT features, patients were categorized as "carotid stroke patients" (cases) if they had an acute infarct in a carotid distribution and the likely mechanism of stroke was large artery atherosclerosis. Patients with no acute stroke, and patients with an acute stroke in a distribution not consistent with a carotid origin were categorized as "non-carotid stroke patients" (controls) (Fig 2).

Statistical Analysis

Two similar analyses were performed. Analysis #1 compared the CT features from the carotid artery ipsilateral to the side of the infarct in "carotid stroke patients" (cases) to the more diseased carotid artery of the "non-carotid stroke patients" (controls). In Analysis #1, carotid CT features were compared for both case and control groups using unpaired T-tests for continuous variables and Mann-Whitney tests for categorical variables. Analysis #2 focused on "carotid stroke patients" and compared the carotid arteries ipsilateral to the infarct side (cases) to contralateral carotid arteries (controls) in stroke patients. Paired T-tests were used for continuous variables and McNemar tests for categorical variables. NASCET percentage of diameter narrowing, carotid lumen volume, minimal carotid lumen cross-sectional area, maximal carotid wall thickness, and fibrous cap thickness were considered as continuous variables. The number of lipid and calcium clusters were treated as continuous variables.

CT features from the same category (lumen, wall, lipids, calcium) were assessed for collinearity and interaction, and only non-collinear CT features associated with a p value < 0.3 in univariate analysis were considered for multivariate analysis. Multivariate analysis consisted of logistic regression for Analysis #1 and conditional, fixed-effects logistic regression for Analysis #2, using a p value of 0.05 as a threshold for statistical significance. Model selection was repeated using a stepwise forward and backward approach to assess whether the variables included in the final model were influenced by the approach for the multivariate analysis (sensitivity analysis). The models obtained for the CCA, ICA, and BIF were compared using a receiver operating characteristic curve (ROC) analysis to determine the most predictive model.

Analysis #1 was repeated separately for patients with $<50\%$ carotid luminal stenosis and for patients with $\geq 50\%$ stenosis. A similar approach was not possible for Analysis #2 because of the small sample size.

Results

Patients and Imaging Studies

The study population consisted of a consecutive series of 136 patients, admitted to the Emergency Department of our institution between August 2006 and January 2007, who underwent a CTA of their carotid arteries. Of the 136 patients studied, 77 (56.6%) were male and 59 (44.4%) were female. Their mean age was 66 ± 16 years old (range: 19–96). Classification of these 136 patients is summarized in Figure 2. Forty "carotid stroke patients" and fifty "non-carotid stroke" patients were considered for the remainder of the statistical analysis. As explained above, this classification was based on the review of the patients' charts, CT studies of the brain parenchyma obtained at baseline and imaging studies obtained within the first week after the baseline CT. All 90 patients (40 "carotid stroke patients" and 50 "non-carotid stroke patients") underwent perfusion-CT in addition to CTA.. Twenty-six of the 40 "carotid stroke patients" underwent MRI of their brain including diffusion-weighted imaging (DWI); 32 underwent a noncontrast CT of their brain prior to

discharge. Thirty-seven of the 50 "non-carotid stroke patients" underwent MRI with DWI. Degrees of carotid stenosis among the "carotid stroke patients" and "non-carotid stroke patients" are reported in Table 2. None of the 40 "carotid stroke patients" had a history of atrial fibrillation documented in their medical records.

Six out of 136 (4.41%) CTA studies were of poor quality, but none of them occurred among the 40 "carotid stroke patients" and 50 "non-carotid stroke patients".

Analysis #1—Comparison of the CT features between the carotid artery ipsilateral to the affected side in the 40 "carotid stroke patients" (cases) and the more diseased carotid artery in the 50 "non-carotid stroke patients" (controls)

Measurements of the carotid CT features for the 3 cm on each side of the carotid bifurcation are reported in Table 1. The differences between the 40 "carotid stroke patients" and 50 "non-carotid stroke patients", as well as the results of the statistical comparisons between the two groups are also summarized in Table 1. In this analysis, carotid CT features were compared using unpaired T-tests for continuous variables and Mann-Whitney tests for categorical variables.

Considering the results of the comparisons between cases and controls, and after checking for non-linearity and interactions between variables and excluding collinear variables, the following variables were statistically significant and retained for the multivariate analysis:

- *Carotid lumen*: lumen minimal cross-sectional area;
- *Wall*: wall volume, and fibrous cap thickness;
- *Lipids*: number of lipid clusters and location of the largest lipid cluster; and
- *Calcium*: number of calcium clusters and location of the largest calcium clusters.

Luminal minimal diameter, % of patients with >50% stenosis, wall maximal thickness, volume of lipids, percent of lipids, and lipid cluster maximal size were dropped because of collinearity. No interaction was found significant, and no interaction term was included in the multivariate analysis.

Analysis #2 in "carotid stroke patients"—Comparison of the carotid arteries ipsilateral to the infarct side (cases) to contralateral carotid arteries (controls) in "carotid stroke patients"

A similar approach to that described under Analysis #1 was applied to the comparison of the carotid CT features between the infarct side and the contralateral side. For the univariate analysis, paired T-tests were used for continuous variables and McNemar tests for categorical variables (Table 1). Considering the results of the comparisons between cases and controls, and after checking for non-linearity and interactions between variables and excluding collinear variables, the following variables were statistically significant and retained for the multivariate analysis:

- *Carotid lumen*: % of patients with >50% stenosis;
- *Wall*: wall volume, and fibrous cap thickness;
- *Lipids*: number of lipid clusters and location of the largest lipid cluster; and
- *Ulcerations*: presence or absence of ulcerations.

Wall maximal thickness, volume of lipids, percent of lipids, lipid cluster maximal size, and volume of calcium were dropped because of collinearity. No interaction was found significant, and no interaction term was included in the multivariate analysis.

The results of the multivariate analyses, comparing stroke patients with non-stroke patients, comparing infarct side with contralateral side, and comparison using an ROC approach are summarized in Table 3. All models (considering all "significant" variables from univariate analyses, stepwise forward and stepwise backward) converged towards similar results and showed the wall volume, and the number and location of lipid clusters to be significantly associated with the risk of carotid stroke. The fibrous cap thickness and the number of calcium clusters were significant only in one of the models.

Considering the 3 cm of the common carotid artery (CCA) immediately proximal to the carotid bifurcation and the 3 cm of the internal carotid artery (ICA) immediately distal to the carotid bifurcation together (reported in Table 1 and Table 3) was more accurate than considering either separately (not reported in this article) ($p < 0.05$).

In patients with $<50\%$ stenosis, the multivariate model showed the wall volume (odds ratio = 6.84), number of lipid clusters (odds ratio = 1.22, 95% confidence interval CI = 1.06 – 1.41), location of the largest lipid cluster (odds ratio = 0.73, 95% = 0.60 – 0.89), and number of calcium clusters (odds ratio = 0.32, 95% = 0.16 – 0.068) to be statistically significant (area under the ROC curve = 0.773).

In patients with $\geq 50\%$ stenosis, the multivariate model showed the number of lipid clusters (odds ratio = 1.18, 95% = 1.01 – 1.39) and location of the largest lipid cluster (odds ratio = 0.62, 95% = 0.46 – 0.84) to be statistically significant (area under the ROC curve = 0.863).

The precision of these multiple analyses was challenged by the small size of the different subgroups. Analysis #1 could be performed in patients with $<50\%$ stenosis (25 carotid stroke patients and 40 non-carotid stroke patients, Figure 2). Sample size was smaller but still allowed the statistical model to converge for patients with $\geq 50\%$ stenosis (15 carotid stroke patients and 10 non-carotid stroke patients). Analysis #2 could not be performed (25 carotid stroke patients with $<50\%$ stenosis; 15 carotid stroke patients with $\geq 50\%$ stenosis).

Interpretation

The goal of this study was to identify a set of carotid wall CT features that is significantly associated with the risk of carotid embolic stroke. We performed two similar analyses – one comparing carotid arteries of "carotid stroke patients" and "non-carotid stroke patients", and the other comparing the carotid arteries on the affected and unaffected sides in the "carotid stroke patients". These two analyses converged, revealing that a small number of carotid wall CT features are significantly associated with acute carotid stroke. Specifically, increased risk of acute carotid stroke was associated with an increased wall volume, a thinner fibrous cap, a higher number of lipid clusters, and lipid clusters closer to the lumen. The number of calcium clusters was a protective factor. The fibrous cap thickness was not significant in the multivariate model, despite being a consistent predictor of clinical events in prior work.^{18, 19}

These observations mirror the current understanding as to how a carotid plaque might rupture and cause an embolic stroke. Carotid wall features have been suggested by others^{8–12} as a complement to luminal narrowing measurements for predicting the risk of stroke. Embolic phenomena have been previously reported as associated with thinning^{18, 19} and subsequent ulceration^{8, 12, 20–22} of the fibrous cap on the surface of atherosclerotic plaque, resulting in release of necrotic lipid debris from the plaque substance into the parent

vessel, especially in the case of a high lipid content.^{18, 19, 35-40} In contrast, plaques with high calcium content, especially when located close to the lumen, are thought to be associated with a lower risk of stroke.^{23, 24, 25}

In symptomatic patients with severe ($\geq 50\%$) stenosis, for whom the risk of stroke approximates 15%¹⁻⁴, identification of carotid plaques containing numerous and large lipid cores could potentially help refine the selection of subjects most likely to benefit from endarterectomy or stenting (15%), while the remaining patients (85%) could be managed conservatively.

Further investigations are needed to determine if identification of thick carotid wall or carotid plaques containing numerous and large lipid cores and few calcium clusters in patients with $< 50\%$ stenosis, usually treated conservatively, could trigger a surgical/stenting decision even in the absence of significant stenosis.

The originality of our research lies in the use of an imaging modality, CT, that has been demonstrated as accurate compared to conventional angiography in characterizing the degree of carotid stenosis, but that has been poorly explored in terms of carotid wall characterization, except for its calcium content. In order to characterize carotid wall features other than calcium from CT data^{24, 25}, we used an automated classifier computer algorithm that was validated using histology derived from carotid endarterectomy specimens as a gold standard.²¹ Our study, showing differences in the features assessed by the algorithm between stroke and non-stroke patients and the infarct and contralateral side, provides yet another type of validation. It demonstrates that CT is able to characterize the carotid wall in a clinically meaningful way.

This study using CT is not intended to detract from other imaging techniques. Ultrasound is noninvasive, can be performed at bedside, and gives accurate assessment of the carotid intima-media thickness. MRI, with appropriate sequences, affords unmatched tissue contrast between the different plaque components. However, CT presents the advantage of being obtained as part of the standard-of-care for numerous patients with cerebrovascular disease, as a result of the wide availability of CT scanners and the short duration of the CT studies. Our work shows that the interpretation of CT studies of the carotid arteries should not be limited to the evaluation of the degree of luminal narrowing, but should also include assessment of the carotid wall. The automated classifier computer algorithm approach affords a standardized, three-dimensional, volumetric assessment of the carotid artery wall.

We acknowledge several limitations to our study. Our results come from a cross-sectional analysis involving relatively few patients and will need to be confirmed in a larger longitudinal study.

Our study population was derived from patients admitted in our emergency department who underwent a CTA of their carotid arteries. This is a selected sample with a risk of stroke that is likely greater than that of the general population, which limits our ability to generalize our results. The internal validity of our study should, however, not be affected by this.

Our classification of patients as "carotid stroke patients" and "non-carotid stroke patients" was based on published criteria^{31, 32} and the Causative Classification System for Ischemic Stroke.³³ This classification has a reported inter-examiner reliability of 0.90 in characterizing the probable cause of a stroke, presenting the advantage of a very low rate (4%) of indeterminate-unclassified results.³³

Finally, our study was cross-sectional in nature. Carotid plaque features are known to change after stroke as a result of plaque rupture, intramural accumulation of blood

components, and displacement of intramural contents. This study allows the assessment of differences between symptomatic and asymptomatic plaques but not the prospective, longitudinal risk or benefit associated with a particular plaque feature.

In conclusion, our newly developed CT-derived model identified carotid wall features significantly different in acute carotid stroke patients and on the infarct side vessel. This model has yet to be validated prospectively in a longitudinal, adequately powered study. Our automated classifier computer algorithm offers a standardized method for interpreting the carotid artery wall findings using a routine imaging technique (CT). The utility of our model to monitor carotid wall composition in future trials, both to select patients for treatment and to determine whether drug treatments are effective in altering the size and composition of the atheroma^{41–43}, will be the object of future investigation.

Acknowledgments

This work was supported by Grant KL2 RR024130 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) and the NIH Roadmap for Medical Research and by Grant NS045085 from the National Institute of Neurological Disorders and Stroke, at the NIH. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on NCRR is available at <<http://www.ncrr.nih.gov/>>. Information on Re-engineering the Clinical Research Enterprise can be obtained from <<http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp>>.

References

1. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med.* 1991; 325:445–453. [PubMed: 1852179]
2. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med.* 1998; 339:1415–1425. [PubMed: 9811916]
3. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet.* 1998; 351:1379–1387. [PubMed: 9593407]
4. Mayberg MR, Wilson SE, Yatsu F, et al. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. *Jama.* 1991; 266:3289–3294. [PubMed: 1960828]
5. Ebrahim S, Papacosta O, Whincup P, et al. Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study. *Stroke.* 1999; 30:841–850. [PubMed: 10187889]
6. O'Leary DH, Polak JF, Kronmal RA, et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. The CHS Collaborative Research Group. *Stroke.* 1992; 23:1752–1760. [PubMed: 1448826]
7. Worthley SG, Helft G, Fuster V, et al. Serial in vivo MRI documents arterial remodeling in experimental atherosclerosis. *Circulation.* 2000; 101:586–589. [PubMed: 10673247]
8. Ballotta E, Da Giau G, Renon L. Carotid plaque gross morphology and clinical presentation: a prospective study of 457 carotid artery specimens. *J Surg Res.* 2000; 89:78–84. [PubMed: 10720456]
9. Lovett JK, Gallagher PJ, Hands LJ, et al. Histological correlates of carotid plaque surface morphology on lumen contrast imaging. *Circulation.* 2004; 110:2190–2197. [PubMed: 15466633]
10. McCarthy MJ, Loftus IM, Thompson MM, et al. Angiogenesis and the atherosclerotic carotid plaque: an association between symptomatology and plaque morphology. *J Vasc Surg.* 1999; 30:261–268. [PubMed: 10436445]
11. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation.* 2003; 108:1664–1672. [PubMed: 14530185]

12. Rothwell PM, Gibson R, Warlow CP. Interrelation between plaque surface morphology and degree of stenosis on carotid angiograms and the risk of ischemic stroke in patients with symptomatic carotid stenosis. On behalf of the European Carotid Surgery Trialists' Collaborative Group. *Stroke*. 2000; 31:615–621. [PubMed: 10700494]
13. Bonithon-Kopp C, Scarabin PY, Taquet A, et al. Risk factors for early carotid atherosclerosis in middle-aged French women. *Arterioscler Thromb*. 1991; 11:966–972. [PubMed: 2065047]
14. Bonithon-Kopp C, Touboul PJ, Berr C, et al. Relation of intima-media thickness to atherosclerotic plaques in carotid arteries. The Vascular Aging (EVA) Study. *Arterioscler Thromb Vasc Biol*. 1996; 16:310–316. [PubMed: 8620348]
15. Lorenz MW, von Kegler S, Steinmetz H, et al. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). *Stroke*. 2006; 37:87–92. [PubMed: 16339465]
16. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med*. 1999; 340:14–22. [PubMed: 9878640]
17. Zureik M, Touboul PJ, Bonithon-Kopp C, et al. Cross-sectional and 4-year longitudinal associations between brachial pulse pressure and common carotid intima-media thickness in a general population. The EVA study. *Stroke*. 1999; 30:550–555. [PubMed: 10066851]
18. Bassiouny HS, Sakaguchi Y, Mikucki SA, et al. Juxtaluminal location of plaque necrosis and neoformation in symptomatic carotid stenosis. *J Vasc Surg*. 1997; 26:585–594. [PubMed: 9357458]
19. Biasi GM, Froio A, Diethrich EB, et al. Carotid plaque echolucency increases the risk of stroke in carotid stenting: the Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) study. *Circulation*. 2004; 110:756–762. [PubMed: 15277320]
20. Prabhakaran S, Rundek T, Ramas R, et al. Carotid plaque surface irregularity predicts ischemic stroke: the northern Manhattan study. *Stroke*. 2006; 37:2696–2701. [PubMed: 17008627]
21. Wintermark M, Jawadi SS, Rapp JH, et al. High-Resolution CT Imaging of Carotid Artery Atherosclerotic Plaques. (submitted for publication).
22. Troyer A, Saloner D, Pan XM, et al. Major carotid plaque surface irregularities correlate with neurologic symptoms. *J Vasc Surg*. 2002; 35:741–747. [PubMed: 11932673]
23. Miralles M, Merino J, Busto M, et al. Quantification and characterization of carotid calcium with multi-detector CT-angiography. *Eur J Vasc Endovasc Surg*. 2006; 32:561–567. [PubMed: 16979917]
24. McKinney AM, Casey SO, Teksam M, et al. Carotid bifurcation calcium and correlation with percent stenosis of the internal carotid artery on CT angiography. *Neuroradiology*. 2005; 47:1–9. [PubMed: 15650832]
25. Nandalar KR, Hardie AD, Raghavan P, et al. Composition of the stable carotid plaque: insights from a multidetector computed tomography study of plaque volume. *Stroke*. 2007; 38:935–940. [PubMed: 17272781]
26. Adame IM, van der Geest RJ, Wasserman BA, et al. Automatic segmentation and plaque characterization in atherosclerotic carotid artery MR images. *Magma*. 2004; 16:227–234. [PubMed: 15029508]
27. Clarke SE, Hammond RR, Mitchell JR, Rutt BK. Quantitative assessment of carotid plaque composition using multicontrast MRI and registered histology. *Magn Reson Med*. 2003; 50:1199–1208. [PubMed: 14648567]
28. Coombs BD, Rapp JH, Ursell PC, et al. Structure of plaque at carotid bifurcation: high-resolution MRI with histological correlation. *Stroke*. 2001; 32:2516–2521. [PubMed: 11692010]
29. Shinnar M, Fallon JT, Wehrli S, et al. The diagnostic accuracy of ex vivo MRI for human atherosclerotic plaque characterization. *Arterioscler Thromb Vasc Biol*. 1999; 19:2756–2761. [PubMed: 10559022]
30. Yuan C, Mitsumori LM, Ferguson MS, et al. In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. *Circulation*. 2001; 104:2051–2056. [PubMed: 11673345]

31. Kang DW, Chalela JA, Ezzeddine MA, Warach S. Association of ischemic lesion patterns on early diffusion-weighted imaging with TOAST stroke subtypes. *Arch Neurol*. 2003; 60:1730–1734. [PubMed: 14676047]
32. Rovira A, Grive E, Rovira A, Alvarez-Sabin J. Distribution territories and causative mechanisms of ischemic stroke. *Eur Radiol*. 2005; 15:416–426. [PubMed: 15657788]
33. Ay H, Furie KL, Singhal A, et al. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol*. 2005; 58:688–697. [PubMed: 16240340]
34. Ay H, Benner T, Arsava EM, et al. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. *Stroke*. 2007; 38:2979–2984. [PubMed: 17901381]
35. Carr S, Farb A, Pearce WH, et al. Atherosclerotic plaque rupture in symptomatic carotid artery stenosis. *J Vasc Surg*. 1996; 23:755–765. discussion 765–756. [PubMed: 8667496]
36. Eliasziw M, Streifler JY, Fox AJ, et al. Significance of plaque ulceration in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial. *Stroke*. 1994; 25:304–308. [PubMed: 8303736]
37. Gronholdt ML. Ultrasound and lipoproteins as predictors of lipid-rich, rupture-prone plaques in the carotid artery. *Arterioscler Thromb Vasc Biol*. 1999; 19:2–13. [PubMed: 9888860]
38. Cinat M, Lane CT, Pham H, et al. Helical CT angiography in the preoperative evaluation of carotid artery stenosis. *J Vasc Surg*. 1998; 28:290–300. [PubMed: 9719324]
39. el-Barghouty N, Nicolaides A, Bahal V, et al. The identification of the high risk carotid plaque. *Eur J Vasc Endovasc Surg*. 1996; 11:470–478. [PubMed: 8846185]
40. Golledge J, Greenhalgh RM, Davies AH. The symptomatic carotid plaque. *Stroke*. 2000; 31:774–781. [PubMed: 10700518]
41. Cunningham EJ, Bond R, Mehta Z, et al. Long-term durability of carotid endarterectomy for symptomatic stenosis and risk factors for late postoperative stroke. *Stroke*. 2002; 33:2658–2663. [PubMed: 12411657]
42. Qureshi AI, Hutson AD, Harbaugh RE, et al. Methods and design considerations for randomized clinical trials evaluating surgical or endovascular treatments for cerebrovascular diseases. *Neurosurgery*. 2004; 54:248–264. discussion 264–247. [PubMed: 14744272]
43. Schmidt C, Fagerberg BW, Wikstrand J, Hulthe J. Multiple risk factor intervention reduces cardiovascular risk in hypertensive patients with echolucent plaques in the carotid artery. *J Intern Med*. 2003; 253:430–438. [PubMed: 12653872]

Fig. 1.

In-vivo CTA image of the common carotid artery, and automated classification computer algorithm-derived overlay showing lipid-rich necrotic core in yellow, calcification in blue, blood products in red, and remaining connective tissue in green. An ulceration is also identified, with direct exposure of the lipid core to the lumen. However, there is no significant carotid stenosis.

Fig. 2.

Classification of the 136 patients based on the presence/absence of acute/remote infarct at baseline, distribution of the infarcts, degree of carotid stenosis, and test results available in patients' charts (such as EKG and Holter) – but independent of carotid wall CT features. Of note, none of the 40 "carotid stroke patients" had any history of atrial fibrillation documented in their medical records. Patients with 20% > carotid stenosis > 50% were classified as "carotid stroke" patients only in case of a prior history of two or more ischemic stroke, transient ischemic attack, or transient monocular blindness from the territory of index artery, at least one event within the last month, according to the Causative Classification System for Ischemic Stroke.^{33 34}

Table 1
Measurements of the carotid CT features (mean ± standard deviation) for the 3 cm on each side of the carotid bifurcation

For Analysis #1 comparing stroke patients to non-stroke patients, values for the carotid artery ipsilateral to the infarct in the 40 "carotid stroke patients" and values for the more diseased carotid artery in the 50 "non-carotid stroke patients" were compared using unpaired T-tests for continuous variables and Mann-Whitney tests for categorical variables. For Analysis #2 comparing stroke side with contralateral side, values for the carotid artery ipsilateral to the infarct and values for the contralateral side in the 40 "carotid stroke patients" were compared using paired T-tests for continuous variables and McNemar tests for categorical variables. The CT features associated with a p value < 0.3 in univariate analysis are outlined in gray.

Carotid Descriptor	Unit	Carotid stroke patients - infarct side	Carotid stroke patients - contralateral side	Non-carotid stroke patients - more diseased side	Analysis #1 (comparison between infarct side in carotid stroke patients and more diseased side in non-carotid stroke patients)			Analysis #2 (comparison between infarct side and contralateral side in carotid stroke patients)		
					95% Confidence Interval		p value	95% Confidence Interval		p value
					Difference	Interval		Difference	Interval	
<u>Lumen</u>										
Lumen Volume	[mm ³]	1154.2 ± 62.6	1241.4 ± 62.3	1245.6 ± 79.3	-91.4	-289.0 to +106.2	0.362	-87.2	-262.2 to +87.9	0.327
Lumen Minimal Cross-Sectional Area	[mm ²]	23.9 ± 1.7	25.4 ± 1.5	27.7 ± 0.3	-3.8	-9.0 to +1.4	0.147	-1.6	-6.0 to +2.8	0.482
Lumen Minimal Diameter	[mm]	4.9 ± 0.2	5.0 ± 0.2	5.1 ± 0.2	-0.3	-0.9 to +0.3	0.270	-0.2	-0.6 to +0.3	0.501
NASCET % Lumen stenosis	%	29.1% ± 4.9%	23.9% ± 4.3%	26.3% ± 4.1%	+2.7%	-9.3% to +14.9%	0.647	+5.2%	-17.0% to +6.6%	0.386
% patients with >50% stenosis	%	15/40	2/40	10/50	OR 2.4	0.8 to 6.3	0.065	OR 2.5	0.4 to 27.6	0.279
<u>Wall</u>										
Wall Volume	[mm ³]	1404.1 ± 34.2	1281.9 ± 38.9	1206.1 ± 46.3	+198.0	+85.8 to +310.2	0.001	+122.2	+19.5 to +224.9	0.020
Wall Maximal Thickness	[mm]	5.0 ± 0.2	4.4 ± 0.2	4.2 ± 0.2	+0.9	+0.2 to +1.5	0.007	+0.7	+0.0 to +1.3	0.046
Fibrous Cap Thickness	[mm]	0.4 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	-0.2	-0.3 to -0.1	0.000	-0.2	-0.3 to -0.1	<0.001
<u>Ulcerations</u> (concave irregularities in the contour of the carotid lumen)		17/40	11/40	34/80	OR 1.0	0.5 to 2.2	0.891	OR 1.9	0.7 to 5.5	0.159
<u>Lipid-Rich Necrotic Core</u>										
Volume of Lipids	[mm ³]	24.9 ± 3.1	16.4 ± 5.4	13.9 ± 3.5	+11.0	+3.7 to +11.6	0.280	8.3	-4.4 to +21.3	0.196

Carotid Descriptor	Unit	Carotid stroke patients - infarct side	Carotid stroke patients - contralateral side	Non-carotid stroke patients - more diseased side	Analysis #1 (comparison between infarct side in carotid stroke patients and more diseased side in non-carotid stroke patients)			Analysis #2 (comparison between infarct side and contralateral side in carotid stroke patients)		
					95% Confidence		p value	95% Confidence		p value
					Difference	Interval		Difference	Interval	
Percent of Lipids compared to the total number of voxels in the carotid wall	%	1.7% ± 0.2%	1.0% ± 0.4%	1.1% ± 0.3%	+0.5%	-0.2% to +1.2%	0.150	+0.7%	+0.1% to +1.3%	0.056
Number of Lipids Clusters (20 or more "lipid" voxels adjacent to each other)		10.5 ± 0.6	3.7 ± 0.5	4.3 ± 0.6	+6.2	+4.5 to +8.0	0.000	+6.7	+5.3 to +8.2	<0.001
Lipid Cluster Maximal Size	[mm3]	5.8 ± 0.8	3.1 ± 0.8	3.5 ± 0.9	+2.3	+0.1 to +4.6	0.046	+2.7	+0.4 to +4.9	0.019
Location of the Largest Lipid Cluster	% wall from lumen	3.9% ± 0.4%	11.2% ± 1.0%	12.5% ± 1.5%	-8.6%	-11.5% to -5.7%	0.000	-7.3%	-5.0 to -9.6%	<0.001
Calcium										
Volume of Calcium	[mm3]	20.4 ± 7.3	36.7 ± 8.1	21.0 ± 6.1	-0.6	-19.8 to +18.6	0.952	-16.3	-37.9 to +5.2	0.136
Percent of Calcium compared to the total number of Voxels in the carotid wall	%	1.8% ± 0.5%	2.4% ± 0.4%	1.5% ± 0.4%	0.4%	-0.9% to +1.6%	0.573	-0.6	1.9 to +0.8	0.442
Number of Calcium Clusters (20 or more "calcium" voxels adjacent to each other)		0.9 ± 0.1	1.1 ± 0.1	1.4 ± 0.2	-0.5	-0.9 to +0.0	0.060	-0.3	-0.6 to +0.2	0.266
Calcium Cluster Maximal Size	[mm3]	6.2 ± 1.4	8.3 ± 1.5	6.8 ± 1.6	-0.6	-4.8 to +3.5	0.770	-2.1	-6.2 to +2.1	0.327
Location of the Largest Calcium Cluster	% wall from lumen	8.5% ± 1.2%	10.0% ± 1.1%	10.7% ± 1.3%	-2.2%	-5.8% to +1.4%	0.220	-1.5%	-4.8% to +1.8%	0.269

Table 2
Degrees of carotid stenosis among the 40 "carotid stroke patients" and 50 "non-carotid stroke patients"

These were evaluated by the neuroradiologist blinded to the results of the automatic analysis of the carotid wall by the computer algorithm.

degree of carotid luminal stenosis	all patients (n=180 carotid arteries)	"carotid stroke patients" (N=40 patients)		"non-carotid stroke " patients (N=50 patients)	
		infarct side (n=40 carotid arteries)	non-infarct side (n=40 carotid arteries)	worst side (n=50 carotid arteries)	other side (n=50 carotid arteries)
0-50%	142 (78.9%)	25 (62.5%)	34 (85.0%)	40 (80.0%)	43 (86.0%)
50-70%	29 (16.1%)	9 (22.5%)	4 (10.0%)	9 (18.0%)	7 (14.0%)
70-99%	8 (4.4%)	5 (12.5%)	2 (5.0%)	1 (2.0%)	0 (0.0%)
100%	1 (0.6%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3

Results of the multivariate analyses considering all "significant" variables from univariate analyses, comparing stroke patients to non-stroke patients (Analysis #1), and infarct side with contralateral side (Analysis #2), and comparison using a ROC analysis

A ROC analysis allows to assess the "quality" of a model. More specifically, the area under the ROC curve is a measure of the accuracy of the model. A model with a area under the ROC curve equal to 1 is a perfect model, where the predicted values match exactly the observed values; if the area under to ROC curve decreases below 1, this corresponds to the accumulation of false positive and false negative predicted values; finally, if the area under the ROC curve is 0.5, the model is as good in its predictive ability as flipping a coin.

"Carotid Stroke Patients" versus "Non-Carotid Stroke Patients" (Analysis #1)			Infarct Side versus Contralateral Side (Analysis #2)		
CT features	Odds ratio (95% CI)	p value	CT features	Odds ratio (95% CI)	p value
Lumen area [mm2]	0.79 (0.71 – 0.88)	<0.001			
wall volume [100 mm3]	4.08 (2.24 – 7.43)	<0.001	wall volume [100 mm3]	1.58 (1.00 – 2.49)	0.017
number of calcium clusters	0.31 (0.15 – 0.63)	0.001	fibrous cap thickness	0.11 (0.06 – 0.16)	0.013
number of lipid clusters	1.22 (1.08 – 1.39)	0.002	number of lipid clusters	1.58 (1.15 – 2.18)	0.005
location of largest lipid cluster	0.74 (0.61 – 0.89)	0.002	location of largest lipid cluster	0.83 (0.67 – 1.02)	0.048
Area under ROC curve = 0.796			Area under ROC curve = 0.832		

CI stands for confidence interval