Atherosclerotic Plaque Surface Morphology in the Carotid Bifurcation Assessed With Multidetector Computed Tomography Angiography

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Background and Purpose—Complicated (irregular or ulcerated) carotid plaques have proven to be independent predictors of stroke. We analyzed the frequency and location of plaque irregularities in a large cohort of patients with ischemic cerebrovascular disease and the relation with severity of stenosis, cardiovascular risk factors, and symptomatology.

Methods—Multidetector CT angiography images from 406 patients were evaluated. Plaque surface morphology was classified as smooth, irregular, or ulcerated. The location of the ulceration was defined as proximal or distal to the point of maximum stenosis.

Results—Atherosclerotic plaques with an open lumen were present in 448 carotid arteries; these plaques were classified as: smooth, 276 (62%); irregular, 99 (22%); and ulcerated, 73 (16%). Sixty-two (69%) of the ulcerations were located proximal to the point of maximum luminal stenosis. Complicated plaques were significantly ($P<0.001$) more common in carotid arteries with stenosis $>30\%$ than in those with stenosis $<30\%$. There is an association between complicated plaques and hypercholesterolemia (OR, 3.0) and a trend toward an association with smoking (OR, 1.9). Complicated plaques are more often present in the symptomatic carotid artery than in the contralateral asymptomatic carotid artery; however, this is fully attributed to a significantly higher degree of stenosis in the symptomatic arteries.

Conclusions—Multidetector CT angiography allows the classification of atherosclerotic carotid plaque surface. Complicated plaques are frequent in atherosclerotic carotid disease, especially with higher stenosis degree. Ulcerations are mostly located in the proximal part of the atherosclerotic plaque. Hypercholesterolemia and smoking are related with the presence of complicated plaques. (Stroke. 2009;40:1334-1340.)

Key Words: atherosclerosis ■ carotid stenosis ■ CT ■ risk factors ■ ulceration
DSA in the detection of plaque irregularities and ulcerations.13 Walker and colleagues evaluated 165 CTA studies, compared them with endarterectomy specimens, and reported a sensitivity of 60% and a specificity of 74%.14 A recent multidetector CTA (MDCTA) study reported an even higher sensitivity and specificity for the detection of ulcerations (94% and 99%, respectively).15

The purpose of this study was to assess atherosclerotic plaque surface morphology in the carotid arteries with MDCTA in a large consecutive cohort of patients with ischemic cerebrovascular disease. Plaque surface morphology was related to severity of stenosis, cardiovascular risk factors, and type of ischemic cerebrovascular symptoms.

Methods

Study Population

Consecutive patients (n=406) with ischemic cerebrovascular disease, including amaurosis fugax or focal cerebral ischemia (TIA and minor ischemic stroke), were prospectively studied. Patients were enrolled from the neurology department’s specialized TIA/stroke outpatient clinic or neurology ward. Patients underwent neurological examination on admission. Medical history was recorded from all patients. All patients underwent multidetector CT of the brain and MDCTA of the carotid arteries. In all patients, MDCTA has been performed as part of a research protocol that was approved by the Institutional Review Board and all patients had given written informed consent. The inclusion period ranged from November 2002 to January 2005.

Scanning and Image Reconstruction

Scanning was performed on a 16-slice multidetector CT scanner (Sensation 16; Siemens, Erlangen, Germany) with a standardized optimized contrast-enhanced protocol (120 kVp, 180 mAs, collimation 16×0.75 mm, pitch 1).16,17 The MDCTA scan range reached from the ascending aorta to the intracranial circulation (2 cm above the sella turcica). All patients received 80 mL contrast material (320 mg/mL iodixanol, Visipaque; Amersham Health, Little Chalfont, UK) followed by 40 mL saline bolus chaser, both with an injection rate of 4 mL/s. Synchronization between the passage of contrast material and data acquisition was achieved by real-time bolus tracking at the level of the ascending aorta. The trigger threshold was set at an increase in attenuation of 75 Hounsfield units above baseline attenuation (approximately 150 Hounsfield units in absolute Hounsfield units value).

Image reconstructions were made with field of view 100 mm, matrix size 512×512 (real in-plane resolution 0.6×0.6 mm), slice thickness 1.0 mm, increment 0.6 mm, and with an intermediate reconstruction algorithm.18

Analysis of the Atherosclerotic Plaque

The MDCTA images were sent to a standalone workstation (Leonardo-Siemens Medical Solutions, Forchheim, Germany) with dedicated 3-dimensional analysis software. On the workstation, both carotid bifurcations were evaluated with multiplanar reformattting software. With this software, oblique planes can be adjusted to evaluate the carotid bifurcation in multiple reformations in the short axis and long axes with respect to the carotid artery.

First, the presence of an atherosclerotic plaque was evaluated. The criterion used for the presence of an atherosclerotic lesion was the presence of a calcification and/or thickening of the vessel wall. If a plaque was visible, the surface of the plaque was evaluated and classified as ulcerated, irregular, or smooth (Figures 1 and 2). Plaques were classified as ulcerated if extension of contrast material was present beyond the vascular lumen into the surrounding plaque. Ulcerated plaques were categorized according to the shape of the ulcer as Type 1 to 4 (Figure 2) as previously described by Lovett et al.8 Type 1 is an ulcer that points out perpendicular to the lumen; Type 2 has a narrow neck and points out proximally and distally; Type 3 has an ulcer neck proximally and points out distally, and Type 4 has an ulcer neck distally and points out proximally. The location of the ulcer was defined as proximal or distal to the point of maximum luminal stenosis. Plaques were classified as irregular if pre- or poststenotic dilatation was present and/or if the plaque surface morphology showed irregularities without any sign of ulceration. If the plaque was not ulcerated or irregular, it was classified as smooth. To calculate interobserver reproducibility, a second observer reassessed 100 consecutive MDCTA scans.

Severity of Stenosis

The severity of stenosis on CTA was measured according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET)19 criteria. Oblique multiplanar reformattting images, parallel to the central lumen line, were used for measurements. The severity of stenosis was defined as the remaining lumen at the site of stenosis as percentage of the normal lumen distal to the stenosis and categorized into 0% to 29%, 30% to 49%, 50% to 69%, 70% to 99%, and 100%.

Cardiovascular Risk Factors

Clinical measures and information on risk factors and medication were obtained at admission to the hospital. Subjects were categorized...
as current, past, and never smokers. Hypertension was defined as systolic blood pressure over 140 mm Hg and/or diastolic blood pressure over 90 mm Hg during 2 episodes of at least 15 minutes of continuous noninvasive blood pressure measurement or treatment with antihypertensive medication. Blood pressure-lowering drugs comprised angiotensin-converting enzyme inhibitors, calcium antagonists, β-blockers, and diuretics.

Hypercholesterolemia was defined as fasting cholesterol >5.0 mmol/L or on treatment with cholesterol-lowering drugs. Diabetes was defined as fasting serum glucose levels >7.9 mmol/L, nonfasting serum glucose levels >11.0 mmol/L, or use of antidiabetic medication.

Information on previous cardiovascular disease (myocardial infarction, atrial fibrillation, angina pectoris, chronic heart failure, coronary artery bypass grafting) and previous ischemic cerebrovascular disease (TIA or ischemic stroke other than the event for which the patient was currently evaluated) was collected.

Symptoms
Amaurosis fugax was defined as a sudden, focal neurological deficit that was presumed to be of vascular origin and confined to the eye. TIA was defined as a sudden, focal neurological deficit that was presumed to be of vascular origin and was confined to an area of the brain perfused by a specific artery and that lasted <24 hours. In addition, no relevant infarct (one that explains the deficit) should be seen on the CT scan. An ischemic stroke was defined as a sudden focal neurological deficit that lasted ≥24 hours or which was accompanied by a relevant infarct on the CT scan.

Statistics
Data are presented as mean±SD. Analysis was performed for complicated (irregular or ulcerated) plaques. Reliability of assessment of plaque surface morphology was measured using the kappa statistics. Differences between categorical data and continuous data were analyzed with a χ² test and a Mann-Whitney test or Student t test, respectively. In exploratory analysis, we evaluated the association between the presence of complicated plaque and possible determinants: severity of stenosis and cardiovascular risk factors (smoking, hypertension, hypercholesterolemia, diabetes, previous cardiovascular disease, previous ischemic cerebrovascular disease). All determinants were included in a multiple logistic regression model to assess their association with complicated plaque independently from other determinants. No stepwise procedures were used. The associations were expressed as ORs with 95% CIs, which implies we used P<0.05 as the value for statistical significance. The same analysis was repeated for ulcerated plaques only. Finally, in the patients with symptoms in the territory of the carotid arteries, the association between the presence of complicated plaque and symptomatic side was evaluated with a logistic regression model after adjustment for severity of stenosis. All calculations were made with SPSS 14.0 for Windows.

Results
The MDCTA images and medical histories of 406 patients were evaluated. Two patients were excluded because of poor image quality due to dental artifacts. General patient characteristics are shown in Table 1. With respect to age, the symptomatic artery, and ischemic cerebrovascular disease, there were no significant differences between men and women. However, men were more frequently smokers and had more frequently experienced previous cardiac disease, whereas women had more frequently hypercholesterolemia.

In 142 patients (35%), both carotid arteries were free of atherosclerosis; in 68 patients (17%), presence of atherosclerosis was determined in one of the carotid arteries; in 190 patients (47%), both carotid arteries showed atherosclerosis and in 21 patients, at least one of the carotid arteries was occluded. Overall, from the 808 studied arteries, 337 (42%) were normal without atherosclerotic plaque, 448 (55%) were diseased, and 23 (3%) were occluded. Table 2 shows the plaque surface morphology characteristics of the 448 carotid arteries with atherosclerotic plaque. We found 90 ulcers in 73 carotid arteries of 61 patients. Both carotid arteries were ulcerated in 12 patients, and some patients had multiple (up to 4) ulcerations in the same carotid artery. The prevalence of ulceration among the patients with at least one atherosclerotic carotid artery (n=258) was 24%. Most of the ulcerations (69%) were located proximal to the point of maximum stenosis, and ulcer Type 1 and ulcer Type 3 were most frequently observed. An irregular plaque was demonstrated in 22% of the carotid arteries with atherosclerotic disease. The 2 observers agreed on the presence of complicated plaque in 93% of the cases (kappa=0.84; 95% CI, 0.70 to 0.97), on the presence of ulcerated plaque in all cases (kappa=1; 95% CI, 0.86 to 1.00), on the location of plaque ulceration in 96% of the cases (kappa=0.91; 95% CI, 0.54 to 1.00), and on the types of plaque ulceration in all cases (kappa=1; 95% CI, 0.95 to 1.00). Table 3 shows a crosstable with the degree of stenosis compared with the plaque surface morphology. It can be observed that ulcerated and irregular plaques are significantly (P<0.001) more common and smooth plaques less common among carotid arteries with a higher degree of stenosis (30% to 99%). There were not enough ulcerated plaques to determine significant differences in the distribution of ulcer type among the different degrees of stenosis.
The OR for the association between complicated plaques and severity of stenosis (per 10% increase) adjusted for age and gender is 2.3 (95% CI, 1.9 to 2.9). The OR for the association between ulcerated plaques and severity of stenosis (per 10% increase) adjusted for age and gender is 1.5 (95% CI, 1.3 to 1.7).

The multivariable adjusted ORs for the association between cardiovascular risk factors and complicated plaque in one of the carotid arteries with at least atherosclerotic disease in one of the carotid arteries (n/H11005/H11021/258) are shown in Table 4. A significant association was found with hypercholesterolemia (OR, 3.0; 95% CI, 1.0 to 8.9) and a trend toward an association with smoking (OR, 1.9; 95% CI, 0.9 to 4.1).

The multivariable analysis for the association between cardiovascular risk factors and plaque ulceration in one of the carotid arteries showed no significant association between cardiovascular risk factors and plaque ulceration.

Table 5 shows that atherosclerotic plaques were present in both symptomatic and asymptomatic carotid arteries (55% versus 56%). Symptomatic carotid arteries more often harbored complicated plaques than asymptomatic carotid arteries (25% versus 18%, P=0.01, respectively). However, multivariable analysis showed that this can be attributed to the significantly higher degree of stenosis present in symptomatic arteries compared with asymptomatic arteries (P<0.01).

Complicated plaques were less often observed among patients with amaurosis fugax (17%) compared with patients with focal cerebral ischemia (28%); moreover, in the patients with amaurosis fugax, symptomatic arteries were not more often complicated than asymptomatic arteries (17% versus 17%) as opposed to patients with focal cerebral ischemia (28% versus 20%; P=0.03). Nonetheless, also in patients with focal cerebral ischemia, the difference in incidence of complicated plaques was attributable to the significantly higher stenosis degree present in symptomatic arteries.

Discussion

This study demonstrates that MDCTA can assess atherosclerotic carotid plaque surface morphology with differentiation...
between smooth, irregular, and ulcerated surfaces. It shows that the majority of ulcerations are located proximally to the maximum stenosis and that ulcerated and irregular plaques are more frequently encountered with a higher degree of stenosis. Of all cardiovascular risk factors, hypercholesterolemia was associated with complicated plaque, whereas smoking showed a trend toward an association with complicated plaque. Finally, it was shown that complicated plaque is more common in the symptomatic artery of patients with cerebrovascular symptomatology than in the asymptomatic artery; however, this can be ascribed to the significantly higher stenosis degree present in symptomatic arteries compared with asymptomatic arteries.

The present study found ulceration in 11% of the symptomatic carotid artery and in 40% of the carotid arteries with a moderate to severe degree of stenosis (30% to 99%). The proportion of ulcerated plaques is lower in high-grade stenosis (70% to 90%) compared with 50% to 69% stenosis. The difference is not statistically significant but it might indicate a real difference for which we have 2 possible explanations: (1) with severe stenosis, calcifications are larger, which hampers identification of ulcerations with MDCTA; and (2) the risk of rupture might differ with plaque composition, which may change with increasing severity of stenosis. Plaques with a moderate stenosis degree have a larger proportion of lipid, whereas plaques with severe stenosis are more calcified.

Table 4. The Multivariable Adjusted ORs for Associations Between the Complicated Carotid Plaques and Cardiovascular Risk Factors for All Patients With Atherosclerosis (n=258) and the Multivariable Adjusted ORs for Associations Between the Ulcerated Carotid Plaques and Cardiovascular Risk Factors for All Patients With Atherosclerosis (n=258)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable</th>
<th>Complicated plaque</th>
<th>Age per increasing decade</th>
<th>Gender</th>
<th>Previous cerebrovascular disease</th>
<th>Previous cardiac disease</th>
<th>Hypertension</th>
<th>Hypercholesterolemia</th>
<th>Diabetes</th>
<th>Smoking</th>
<th>Degree of stenosis per 10% increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td>Complicated plaque</td>
<td></td>
<td>1.1 (0.8–1.5)</td>
<td>0.50</td>
<td></td>
<td>1.1 (0.5–2.3)</td>
<td>1.8 (0.9–3.7)</td>
<td>0.12</td>
<td>0.9 (0.4–2.3)</td>
<td>3.0 (1.0–8.9)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>1.0 (0.7–1.4)</td>
<td>0.92</td>
<td></td>
<td>1.2 (0.6–2.6)</td>
<td>1.0 (0.5–2.0)</td>
<td>0.94</td>
<td>0.9 (0.4–2.2)</td>
<td>0.9 (0.4–2.2)</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Previous cerebrovascular disease</td>
<td></td>
<td>1.5 (1.4–1.8)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
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</table>

Table 5. Plaque Surface Morphology in Symptomatic and Asymptomatic Carotid Arteries Stratified for Cerebrovascular Symptoms*

<table>
<thead>
<tr>
<th>Cerebrovascular Symptoms</th>
<th>Total</th>
<th>Amaurosis</th>
<th>Fugax</th>
<th>TIA/Minor Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic carotid artery (ipsilateral)</td>
<td>350</td>
<td>83</td>
<td>267</td>
<td></td>
</tr>
<tr>
<td>Atherosclerotic plaque (%)</td>
<td>193 (55%)</td>
<td>39 (47%)</td>
<td>154 (58%)</td>
<td></td>
</tr>
<tr>
<td>Complicated plaque (%)</td>
<td>89 (25%)</td>
<td>14 (17%)</td>
<td>75 (28%)</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic carotid artery (contralateral)</td>
<td>458</td>
<td>83</td>
<td>267</td>
<td></td>
</tr>
<tr>
<td>Atherosclerotic plaque (%)</td>
<td>255 (56%)</td>
<td>41 (49%)</td>
<td>155 (58%)</td>
<td></td>
</tr>
<tr>
<td>Complicated plaque (%)</td>
<td>83 (18%)</td>
<td>14 (17%)</td>
<td>54 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

Based on the DSA data of the European Carotid Surgery Trialists (ECST) study, Lovett et al reported a prevalence of ulceration of 14% in 3007 symptomatic carotid arteries in patients with TIA or minor stroke, and a prevalence of 18% for symptomatic carotid arteries with a stenosis >30%. In the NASCET study, ulcerations were found in 35% of symptomatic carotid arteries with a stenosis >70%. In the present study, complicated plaque was present in 89% of the carotid arteries with stenosis >30%, which exceeds the reported frequency (63%) of carotid plaque surface abnormality detected with DSA. The discrepancy in the frequencies of ulceration with MDCTA and DSA can be explained by the lower sensitivity for DSA might be a result of the limited viewing directions (usually 2). Besides MDCTA and DSA, MR angiography has been used for the assessment of atherosclerotic carotid plaque surface morphology. One study made a comparison between these techniques and concluded that luminal surface irregularities were most frequently seen at CTA and that with CTA and MR angiography, more ulcerations were detected than with DSA. Saba et al have recently showed that ultrasound has a high specificity (93%) but a low sensitivity (38%) for the detection of carotid ulceration, which is in concordance with previous studies. The low sensitivity can be ascribed, in part, to the fact that acoustic shadowing from calcifications obscures the presence of ulcerations.

A recent histological study of symptomatic carotid endarterectomy specimens from 526 consecutive patients with a stenosis degree of 75% to 90% found ulceration in 58% of the specimens. The discrepancy in the frequencies of ulceration between MDCTA and histology in patients with a severe degree of stenosis can be explained by the higher resolution of histology, which enables the detection of small ulcerations, and the higher volume of calcifications in severe stenosis, which hampers accurate detection of small ulcerations by MDCTA. In addition, thrombus formation on the location of...
a rupture may fill the ruptured site, which will lead to nonvisualization with MDCTA.

Lovett et al\textsuperscript{9} characterized ulcerations as Type 1 to 4 and determined that Type 1 and Type 3 are the most frequent type of rupture; the present study confirms these findings. However, the categorization of ulcers is only important when their occurrence can be related to different clinical behavior; this has not yet been demonstrated.

Ulcerations were most frequently seen at the proximal site of the maximum stenosis. The ECST data revealed the same distribution of ulcer location in the carotid artery (71% at the proximal site) as in the present study.\textsuperscript{9} An intracoronary ultrasound study found that 69\% of the ulcerated ruptured plaques (80\%) were proximal to the minimal lumen site.\textsuperscript{23} The proximal site as a predilection site for ulceration is in concordance with shear stress theories. It is thought that high shear stress on the plaque surface (due to the lumen narrowing) weakens the cap through numerous signaling pathways.\textsuperscript{10} Indeed, in a recent case report, Groen et al\textsuperscript{24} showed in a serial MRI study that the ulceration was located at the high shear stress region. Shear stress may therefore play an important role in the rupture of plaques.

The present study showed that plaque ulceration is not only present in high-grade stenosis, but can also occur in hemodynamically insignificant stenosis. A similar observation was made on the ECST data.\textsuperscript{4} Most of the patients with an ischemic stroke did not have severe stenosis despite the accumulation of a substantial amount of atherosclerotic plaque in the carotid bifurcation. Detection of plaque ulceration thereby provides a clue to the underlying pathophysiology of the previously occurring ischemic stroke; rupture of the plaque may have been accompanied by thrombus formation and embolization of plaque material or thrombus into the intracranial circulation. In addition, detection of plaque ulceration indicates that a patient has an increased risk of a new ipsilateral ischemic stroke.\textsuperscript{4} Whether surgical or endovascular intervention in symptomatic patients without significant stenosis but with plaque ulceration is justified remains to be demonstrated in larger prospective studies. Ideally, these studies should use the noninvasive imaging tools that are currently available.

In the present study, hypercholesterolemia is positively and significantly associated with the presence of complicated plaques, whereas smoking had a positive (but not significant) association with the presence of complicated plaques. Previous studies with univariate analysis revealed associations between irregular plaques and gender,\textsuperscript{3} age,\textsuperscript{4} carotid stenosis,\textsuperscript{4} hypercholesterolemia,\textsuperscript{4} and previous myocardial infarction.\textsuperscript{4} Because irregular plaques are related to the severity of stenosis, multivariable analysis with adjustment for the severity of stenosis is necessary to demonstrate whether certain cardiovascular risk factors are independently related to the presence of irregular plaques.

The association with hypercholesterolemia might be explained by the atherogenic effect of lipoprotein(a) in the presence of high plasma low-density lipoprotein cholesterol levels, which increases lipid deposition in atherosclerotic plaque,\textsuperscript{25,26} making the plaque probably more vulnerable for rupture. Cigarette smoking is considered to influence inflammation and hemostasis in such a way that plaque inflammation and thrombogenicity increases with cap degradation, plaque rupture, and subsequent thrombus formation as a possible result.\textsuperscript{27}

In the present study, ulcerated and irregular plaques are significantly more common in the ipsilateral symptomatic carotid artery than in the asymptomatic carotid artery, which is in line with the findings of Sitzer et al,\textsuperscript{28} who concluded that plaque ulceration is more common in carotid endarterectomy specimens from symptomatic arteries than from asymptomatic arteries. However, multivariate analysis showed that this difference does not remain significant when severity of stenosis was added to the model. This indicates that besides local factors like plaque composition or shear stress, also systemic factors are important in the occurrence of plaque rupture. A reasoning that is supported by the findings of Rothwell et al,\textsuperscript{29} who reported that patients with irregular plaque in the symptomatic carotid artery were more likely to have irregular plaques in the contralateral artery, and by a study from Fisher et al,\textsuperscript{30} which concluded that plaque ulceration was more common in symptomatic patients than in asymptomatic patients but that the prevalence of ulceration in the ipsilateral and contralateral carotid artery in symptomatic patients was the same.

Although the recent paper by Saba et al\textsuperscript{15} showed that MDCTA is an excellent technique to evaluate carotid ulceration, we realize that it is a limitation of our study that we do not have a gold standard (eg, histological specimens). Unfortunately, correlation with histological results is troublesome, because only patients with severe stenosis (NASCET >70\% stenosis) are eligible for intervention, which in our hospital includes stenting in approximately 50\% of the cases. Therefore, it is not possible to obtain histology from a vast majority of patients.

A second limitation of our study is its cross-sectional design. The evaluation of the causal association between severity of stenosis and complicated plaques, between cardiovascular risk factors and complicated plaques, and between complicated plaques and ischemic cerebrovascular disease requires a prospective design in which the atherosclerotic plaque is evaluated serially to detect changes in plaque surface morphology.

**Conclusion**

This study shows that MDCTA can classify atherosclerotic carotid plaque surface morphology. Furthermore, it shows that the presence of a complicated plaque surface in an atherosclerotic plaque is strongly related with the severity of stenosis and that the site of ulceration is mostly proximal to the most stenotic site. In addition, it is shown that hypercholesterolemia and probably smoking are related to the presence of complicated plaques.

**Disclosures**

A.v.d.L. is recipient of a fellowship from the Netherlands Organisation for Health Research and Development (NWO-KF grant 907-00-122).
References


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*Stroke*. 2009;40:1334-1340; originally published online March 5, 2009;
doi: 10.1161/STROKEAHA.108.538439
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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