Significance of Plaque Ulceration in Symptomatic Patients With High-Grade Carotid Stenosis

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Background and Purpose
The importance of carotid plaque ulceration as a cause of cerebral ischemic symptoms remains uncertain. Moreover, its prominence in symptomatic patients with severe carotid stenosis is unknown.

Methods
The association between angiographically defined plaque ulceration and risk of subsequent stroke was assessed using Cox proportional hazards regression in 659 patients with severe (70% to 99%) carotid stenosis from the North American Symptomatic Carotid Endarterectomy Trial.

Results
Treatment assignment (medical versus surgical) and degree of ipsilateral stenosis were identified as having a significant influence on the results. The risk of ipsilateral stroke at 24 months for medically treated patients with ulcerated plaques increased incrementally from 26.3% to 73.2% as the degree of stenosis increased from 75% to 95%. For patients with no ulcer, the risk of stroke remained constant at 21.3% for all degrees of stenosis. The net result yielded relative risks of stroke (ulcer versus no ulcer) ranging from 1.24 (95% confidence interval, 0.61 to 2.52) to 3.43 (95% confidence interval, 1.49 to 7.88). Conversely, for surgically treated patients with antecedent presence of an ulcerated plaque, the risk of stroke increased slightly at the highest degrees of stenosis. Overall, carotid endarterectomy reduced the risk of ipsilateral stroke at 24 months by at least 50%. Similar results were obtained for risk of major ipsilateral stroke and risk of all strokes and death.

Conclusions
The presence of angiographically defined ulceration for medically treated symptomatic patients is associated with an increased risk of stroke. The risk of stroke more than doubles at higher degrees of stenosis. Carotid endarterectomy is beneficial in substantially reducing the risk of stroke, regardless of plaque ulceration and degree of severe carotid stenosis. (Stroke. 1994;25:304-308.)

Key Words • carotid endarterectomy • clinical trials • prognosis • stenosis

Atherosclerotic disease at the bifurcation of the common carotid artery is a well established factor in the etiology of strokes and transient ischemic attacks. Nevertheless, the importance of plaque morphology, in addition to the degree of stenosis, is still a subject of dispute.1-4 The presence of plaque ulceration is thought to be of major importance when considering carotid endarterectomy (CE),5 yet no compelling evidence has been documented. Early reports described the benefit of CE for symptomatic patients with ulcerated nonstenotic carotid lesions.6,7 Subsequent studies were primarily retrospective and related the presence of ulcerated plaques to ischemic symptoms in patients who underwent CE.8-9 Ulceration was found frequently in plaques ipsilateral to the symptoms. Other studies compared the prevalence of ulceration in asymptomatic and symptomatic patients, but the coexistence of stenosis made the comparisons difficult and thus yielded conflicting results.2,10 Studies of prognosis regarding asymptomatic and symptomatic patients with ulcerated plaques also provided contradictory reports.11-15 A recent review concluded that the importance of plaque ulceration as a cause of cerebral ischemic symptoms remains controversial.1 Previous studies combining symptomatic and asymptomatic patients, concomitant carotid stenosis, and different methods to measure the degree of stenosis and to identify ulceration have all contributed to this quandary.

The aim of this study is to assess the prognostic implication of plaque ulceration as measured by strict angiographic criteria in symptomatic patients with high-grade (70% to 99%) carotid stenosis. All the patients were recruited by the North American Symptomatic Carotid Endarterectomy Trial (NASCET); for this group of patients, the study had been terminated when it became apparent that CE was beneficial.16

Subjects and Methods
NASCET, a multicenter study, was designed to find the role of CE in symptomatic patients with moderate (30% to 69%) and severe (70% to 99%) stenosis at the carotid bifurcation. Biplane (anteroposterior, lateral, or oblique) selective carotid angiography was used for the initial (preoperative) assessment of the degree of stenosis and of plaque appearance in all patients. After randomization, half of the patients underwent surgery to remove their plaques regardless of ulceration.

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Presented in part at the 17th International Joint Conference on Stroke and Cerebral Circulation, Phoenix, Ariz, January 30 to February 1, 1992.
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TABLE 1. Relation of Angiographic Plaque Appearance to Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Factor</th>
<th>Nonulcerated (n=429)</th>
<th>Ulcerated (n=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>63.9</td>
<td>64.8</td>
</tr>
<tr>
<td>Surgical treatment, %</td>
<td>49.2</td>
<td>50.9</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>63.9</td>
<td>77.4*</td>
</tr>
<tr>
<td>TIA at entry, %</td>
<td>63.4</td>
<td>76.5*</td>
</tr>
<tr>
<td>History, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>19.6</td>
<td>24.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>62.2</td>
<td>59.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20.1</td>
<td>18.3</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>17.0</td>
<td>19.1</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>25.6</td>
<td>30.0</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>12.8</td>
<td>20.9*</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>31.7</td>
<td>32.2</td>
</tr>
<tr>
<td>Smoking within 5 years of randomization, %</td>
<td>56.8</td>
<td>57.0</td>
</tr>
<tr>
<td>Antithrombotic medications, %</td>
<td>83.9</td>
<td>87.4</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack.

*P<.01.

categories were combined to constitute a "nonulcerated" group.

Statistical Analysis

The association of plaque appearance with patient characteristics (risk factors) was analyzed using either the Pearson \( x^2 \) test for categorical variables or the Student's \( t \) test when the variable was continuous. Cox proportional hazards regression modeling was used to assess the relation between plaque appearance (ulcer present or absent) and the subsequent risk of outcome events, to allow for the varying lengths of patient follow-up. Analysis was performed using program 2L of the BMDP statistical package. Hazard rates and adjusted hazard ratios with corresponding 95% confidence intervals (CI) were used in reporting the results.

The estimated hazard rates and hazard ratios (or relative hazard) are measures that can be interpreted as approximate risks and relative risks, respectively.

Although stratified analysis could have been used, the number of subcategories over which the data would have been dispersed would have yielded imprecise estimates of risk. Regression modeling is desirable because it preserves precision while simultaneously controlling for many potentially confounding factors, as well as checking for statistical interactions in an efficient manner.

TABLE 2. Relation of Angiographic Plaque Appearance to Angiographic Features

<table>
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<th>Nonulcerated (n=429)</th>
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<tr>
<td>Mean ipsilateral stenosis, %</td>
<td>82.8</td>
<td>81.7</td>
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<tr>
<td>70% to 100% contralateral stenosis, % of group</td>
<td>16.6</td>
<td>23.9*</td>
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*P<.05.

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Fig 1. Cervical angiogram showing a definite ulcer niche (arrow) in a stenotic plaque at the carotid bifurcation.

The present study is based on data obtained from 659 recruited patients with severe stenosis. All patients had ischemic symptoms (transient ischemic attack [TIA] or nondisabling stroke relating to their carotid lesion) within 4 months before randomization and were without cardiac pathology likely to result in cerebral embolism. Details of the study protocol have been published.

Hard copies of all angiograms were sent to the Central Office and reviewed by the principal neuroradiologist (A.J.F.), who was blinded to the protocol. In each case, a jeweller's eyepiece with a submillimeter scale was used to measure the diameter of the artery at the region of maximal stenosis and to measure the diameter of the normal artery well beyond the bulb. The degree of stenosis then was calculated using the ratio of these two measurements. In addition, the appearance of the plaque was classified into one of three categories: ulcerated, irregular/uncertain ulceration, or smooth/no ulceration. A plaque was classified as "ulcerated" if it fulfilled radiographic criteria of ulcer niche, seen in profile as a crater from the lumen into a stenotic plaque (Fig 1) and (when visible) double density on en face view. The "irregular plaque" or "uncertain ulceration" category was used for wall irregularity or multiple small possible craters or when there was difficulty distinguishing a real crater from normal wall between two plaques. The "smooth" or "no ulceration" category was used for patients with smooth stenosis or when a relatively smooth outpouching between two smooth narrowings was most consistent with the expected position of the carotid bulb wall. The intraobserver reliability of classifying plaque appearance was estimated on the basis of blind repeated review of 42 randomly selected angiograms. Overall accuracy was 88%, with \( k=0.73 \). For the purpose of this study, the irregular/uncertain ulceration and smooth/no ulceration categories were combined to constitute a "nonulcerated" group.

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<td>23.9*</td>
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*P<.05.
Outcome events included all strokes (defined as an acute ischemic event where symptoms or signs persisted for more than 24 hours) and all deaths. Strokes were then divided by territory and severity: We analyzed separately carotid ipsilateral (to the symptomatic side) strokes and major ipsilateral strokes (disabling functional deficits persisting beyond 90 days), as well as all strokes and any deaths. In a further analysis, the combined risk of ipsilateral strokes and TIAs was also assessed.

The modeling strategy consisted of fitting an initial model with the two primary factors: plaque appearance and treatment group. Subsequent variables were added into the model one at a time. Interaction terms between plaque appearance and each variable remaining in the model from the previous step were added and tested for significance. Use of interaction terms determined whether the relation between plaque appearance and risk of outcome events was modified by the impact of significant risk factors. Next, nonconfounders were eliminated from the fitted model using a backward selection approach. Finally, the estimated regression coefficients from the remaining "parsimonious" model were compared with the coefficients from a "saturated" model to assure that any groups of confounders, working collectively, were not overlooked.

Results

Of the 659 patients, 230 (34.9%) were identified from the angiograms as having ulcerated plaques on the stenotic side, ipsilateral to the symptoms (113 and 117 patients in the medical and surgical arms, respectively). Baseline patient characteristics are shown in Tables 1 and 2. Univariate analyses indicated that male sex, TIA at entry, presence of intermittent claudication, and higher degrees of contralateral stenosis were positively associated with plaque ulceration.

The average duration of follow-up was 18 months. Using proportional hazards regression analysis to relate the risk of outcome events with plaque appearance, the final model retained only the variables corresponding to treatment assignment and degree of ipsilateral stenosis. Inclusion of the other risk factors in the model did not meaningfully change the results. Thus, no baseline patient characteristics were identified as confounders. Multivariate modeling did reveal, however, statistical interaction with treatment assignment and with degree of ipsilateral stenosis; ie, treatment and stenosis were identified as having a significant influence on the association between plaque appearance and risk of stroke. Results from four proportional hazards models appear in Tables 3 through 6, corresponding to risk of ipsilateral strokes, risk of major ipsilateral strokes, risk of any stroke or death, and risk of ipsilateral stroke or ipsilateral TIA, respectively. Each table shows the fitted risk

Table 4. Estimates of Hazard Rates and Ratios at 24 Months for Major Ipsilateral Strokes From Proportional Hazards Regression Analysis

<table>
<thead>
<tr>
<th>% Stenosis</th>
<th>Medical</th>
<th>Surgical</th>
<th>Hazard Ratios* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non</td>
<td>Ulcer</td>
<td>Non</td>
</tr>
<tr>
<td>75</td>
<td>8.9</td>
<td>7.1</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.26-2.42)</td>
</tr>
<tr>
<td>85</td>
<td>9.3</td>
<td>21.4</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1.22-4.34)</td>
</tr>
<tr>
<td>95</td>
<td>9.8</td>
<td>64.4</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2.40-18.03)</td>
</tr>
</tbody>
</table>

Non indicates nonulcerated; Ulcer, ulcerated; and CI, confidence interval.
of outcome events at 24 months (estimated by a hazard rate) and also provides a measure of the increased risk associated with the presence of plaque ulceration under different circumstances. For illustrative purposes, Table 3 indicates that medically treated patients with ulcerated 85% ipsilateral carotid stenosis have a stroke risk of 43.9% at 2 years compared with 21.3% for patients with the same degree of stenosis but with no plaque ulcer. Thus, medically treated patients with ulcerated plaques and 85% stenosis are 2.06 times (95% Cl, 1.18 to 3.62) more likely to suffer an ipsilateral stroke than patients with no ulcer. For patients that underwent CE, the risk of stroke at 2 years is reduced to approximately 11% (ie, 11.5% and 10.6%) in both situations.

In general, it is observed from the tables that the presence of angiographically defined ulceration for medically treated patients is associated with an increased risk of stroke. The risk of stroke more than doubles at higher degrees of stenosis. For surgically treated patients with antecedent presence of an ulcerated plaque, the risk of stroke increases slightly at the highest degrees of stenosis. Overall, CE reduces the risk of stroke by at least 50% at 24 months of follow-up, regardless of plaque ulceration and degree of severe carotid stenosis. A similar but less pronounced association is noted in the case of the combined risks of ipsilateral stroke and TLA (Table 6). The hazard ratios, all being proximate to 1.0, indicate that the risk of TIAs is virtually unrelated to the presence of ulceration (Table 6 compared with Table 3).

The risk of stroke also can be interpreted in terms of cumulative hazard curves, which graphically display the risk experience over the entire follow-up period. For example, the risk of any ipsilateral stroke is shown in Fig 2. Visual inspection of the curves reveals additional points of interest. Specifically, the risk of stroke steadily increases over time, and there is no sign of convergence among the curves. Hazard curves for the risk of any major stroke and for the risk of all strokes and death yielded similar patterns.

**Discussion**

The present study demonstrates that plaque ulceration in patients with symptomatic high-grade carotid stenosis, when identified using very strict angiographic criteria, is a marker for poor prognosis that is affected by the degree of stenosis and subsequent patient management. Patients who did not undergo carotid endarterectomy realized an absolute risk of ipsilateral stroke between 26.3% and 73.2% at 24 months, depending on their degree of carotid stenosis. When such patients are subjected to CE, the risk is substantially reduced.

Previous reports were retrospective and dealt mainly with nonstenotic carotid lesions or asymptomatic patients.11-14 This may reflect previous enthusiasm for operation for most symptomatic patients as well as for many asymptomatic patients with some degree of carotid stenosis or even nonstenotic lesions but with angiographic evidence of large ulcers.11,12 Another explanation for the paucity of previous and comparable
reports is the need to include a large number of patients to account for the concomitant carotid stenosis when evaluating the role of plaque ulceration.

Only one previous report dealing with prognosis considered both factors in the analysis. Plaque ulceration was found to be important in symptomatic patients with nonstenotic lesions but not in patients with hemodynamically significant (>50%) carotid stenosis. Our results dispute this finding. Possible explanations for this discrepancy include different definitions of stenosis severity (we used very strict angiographic criteria), different definitions of ulceration (not stated in the former study), and an exceptionally small sample size in the other study. A mere 17 arteries were available for analysis in the >50% stenosis group.

The inability of angiography to detect all ulcers seen on surgical specimens has been well publicized. Nevertheless, the clear prognostic significance of ulcerated plaques, coupled with severe carotid stenosis, observed in our study leads to the conclusion that it is perhaps the distinct angiographic appearance that is important, and only such ulcers carry potential mechanisms leading to the formation of thrombi large enough to cause clinically important infarcts when dislodged as a consequence of appropriate turbulent flow.

Acknowledgments

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