Interrelation Between Plaque Surface Morphology and Degree of Stenosis on Carotid Angiograms and the Risk of Ischemic Stroke in Patients With Symptomatic Carotid Stenosis

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Background and Purpose—The risk of ischemic stroke distal to an atherothrombotic carotid stenosis increases with the degree of stenosis. The main mechanism of stroke is thought to be embolism from fissured or ruptured plaque, but there are few published data on the relationship between plaque morphology and severity of stenosis and their independent effects on the risk of ischemic stroke. We sought to determine the interrelation between plaque surface morphology, degree of carotid stenosis, and the risk of ipsilateral ischemic stroke.

Methods—Severity of stenosis and plaque surface morphology were assessed on angiograms of the symptomatic carotid artery in 3007 patients in the European Carotid Surgery Trial and were related to baseline clinical characteristics, pathological characteristics of plaques examined at endarterectomy, and the risks of carotid territory ipsilateral ischemic stroke and other vascular events on follow-up.

Results—The early risk of ipsilateral ischemic stroke on medical treatment was closely related to the degree of carotid stenosis. However, the initial degree of carotid stenosis was not predictive of strokes occurring more than 2 years after randomization. Angiographic plaque surface irregularity and plaque surface thrombus at endarterectomy increased in frequency as the degree of stenosis increased (both \( P < 0.0001 \)). However, the degree of stenosis was still predictive of the 2-year risk of stroke on medical treatment after correction for plaque surface irregularity. Angiographic plaque surface irregularity was an independent predictor of ipsilateral ischemic stroke on medical treatment at all degrees of stenosis (hazard ratio = 1.80; 95% CI, 1.14 to 2.83; \( P = 0.01 \)). This relationship was maintained when the analysis was confined to strokes occurring more than 2 years after randomization (hazard ratio = 2.75; 95% CI, 1.30 to 5.80; \( P = 0.01 \)). Neither the degree of stenosis nor plaque surface irregularity was predictive of the “background” stroke risk after endarterectomy or the risk of nonstroke vascular events.

Conclusions—Angiographic plaque surface irregularity is associated with an increased risk of ipsilateral ischemic stroke on medical treatment at all degrees of stenosis. The increase in stroke risk with degree of stenosis is partly accounted for by the parallel increase in plaque surface irregularity and thrombus formation, but the degree of narrowing of the vessel lumen is still an independent predictor of ischemic stroke within 2 years of presentation. (Stroke. 2000;31:615-621.)

Key Words: carotid arteries ■ carotid stenosis ■ risk factors ■ stroke, ischemic

Cerebral infarction in the territory of the carotid arteries accounts for most strokes in Western countries.1,2 Significant atherosclerotic narrowing of the origin of the internal carotid artery ipsilateral to the infarct is found in 20% to 30% of those who are investigated3–5 compared with 5% to 10% of the general population.6,7 That carotid atheroma may cause stroke was suggested at the beginning of the century8 and was finally proven by the observation that endarterectomy of severe carotid stenosis reduces the risks of both asymptomatic cerebral microemboli9 and, most importantly, ipsilateral carotid territory ischemic stroke.10,11 However, although the risk of stroke increases with the severity of stenosis,10,12 the relative importance of the degree of vessel narrowing and the plaque surface morphology is uncertain.13 Cerebral infarction may result from the reduction in cerebral perfusion pressure that occurs distal to a tight carotid stenosis or occlusion,14–17 but analogy with coronary atherosclerosis would suggest that plaque instability, rupture, local thrombus...
formation, and distal embolization are also likely to be important. Stable angina is associated with uncomplicated plaques with a smooth fibrous surface and little adherent thrombus, whereas unstable angina and myocardial infarction are almost invariably associated with an irregular, fissured, or ruptured plaque with local thrombus formation.\(^{18,19}\) The likely role of embolism in carotid ischemic stroke is suggested by the observation of embolic material in the retinal circulation of patients with transient ischemic attacks.\(^{20,21}\) The high frequency of cerebral microemboli distal to symptomatic carotid stenosis,\(^{22,23}\) and the fall in frequency of microemboli and the prevalence of plaque surface thrombus with time after a symptomatic ischemic event.\(^{9,24,25}\)

An understanding of the relative importance of plaque surface morphology and the degree of vessel narrowing in the pathogenesis of ischemic stroke associated with symptomatic carotid stenosis would influence treatment strategies and might also help to identify patients at particularly high risk of stroke. However, since most patients with severe symptomatic carotid stenosis now routinely undergo endarterectomy, the natural history of the condition is no longer amenable to study. Previous studies of the angiographic appearance of symptomatic carotid atherosclerosis have been small and have produced contradictory results.\(^{3-5,26-31}\) The North American Symptomatic Carotid Endarterectomy Trial (NASCET) trialists have shown, in patients with very severe stenosis (80% to 99% by the European Carotid Surgery Trial [ECST] method of measurement), that angiographically irregular plaques are associated with a high risk of stroke.\(^{26,27}\) However, they did not study patients with less severe stenosis or investigate the interrelation between plaque surface morphology and degree of stenosis, and they did not correct the relationship between plaque surface morphology and stroke risk for differences in baseline clinical characteristics. Moreover, no study has examined the relationship between plaque surface morphology and the background risk of ipsilateral carotid territory ischemic stroke after endarterectomy, ie, those strokes that occur >30 days after endarterectomy. To conclude that any relationship seen between plaque surface morphology and stroke risk on medical treatment is causal, it is necessary to show that it is abolished by removal of the plaque at surgery.

We therefore studied the angiographic characteristics of 3007 recently symptomatic carotid plaques, 1671 of which were subsequently examined at endarterectomy, in patients randomized in the ECST.\(^{32}\) This is the largest cohort of patients with carotid stenosis imaged and measured by angiography ever reported. The reproducibility of assessment of angiographic plaque surface morphology was determined, and plaque surface irregularity was related to baseline clinical characteristics and to the macroscopic appearance of the plaque at endarterectomy. Baseline severity of carotid stenosis and angiographic plaque surface morphology were related to the subsequent risk of ischemic stroke on medical treatment alone, the “background” risk of ipsilateral carotid territory ischemic stroke after carotid endarterectomy, and the risk of nonstroke vascular events on follow-up.

**Subjects and Methods**

We studied the carotid angiograms of patients randomized in the ECST, the methods and results of which have been published previously.\(^{32}\) Briefly, patients with recent ocular or carotid territory cerebral ischemia and who had evidence of carotid stenosis on angiography were randomized to carotid endarterectomy and best medical treatment versus best medical treatment alone in a ratio of 60:40. Baseline clinical data were recorded, and patients were followed up by a physician at 4 months, 12 months, and annually thereafter.

**Carotid Angiograms**

Carotid angiograms were performed on all patients before randomization and sent to the trial center. The degree of stenosis of both internal carotid arteries was measured by 2 independent observers (P.M.R. and C.P.W.) using the ECST method.\(^{33}\) Details of the reproducibility of this measurement and the equivalence with other methods have been published previously.\(^{33,34}\) The mean of the 2 measurements was used in all analyses. Details of the angiographic techniques used have been published previously.\(^{35}\) The present study was confined to 3007 (99.6%) of the 3018 ECST patients in whom a randomization angiogram was available in the trial center.

**Assessment of Plaque Surface Morphology on the Angiograms**

Carotid plaque surface morphology was simply classified as smooth or irregular (Figure 1). This was a subjective judgment and was not based on any standardized criteria. However, this categorization has been shown by others to have pathological validity and to be predictive of ischemic stroke distal to severe carotid stenosis.\(^{26,27}\) All...
angiograms were assessed blind to clinical details and outcome. In patients with bilateral symptoms, the designation of the symptomatic carotid artery in the ECST is explained elsewhere.32

Observer A (P.M.R.) assessed plaque surface morphology on the angiograms of all 3007 symptomatic carotid arteries. To determine the interobserver reproducibility of the assessment, observer B (R.G.) assessed the angiograms of the symptomatic carotid artery in a consecutive series of 1000 patients randomized to medical treatment. Observer B was blind to the previous assessments by observer A. Each observer reassessed, at least 1 month after the initial assessment, a random selection of 50 angiograms to determine intraobserver reproducibility.

Pathological Correlation
In patients randomized to carotid endarterectomy, the study surgeon was asked to record whether or not the lumen surface of the plaque had macroscopic ulceration and whether or not there was any adherent thrombus. These assessments were not based on any standardized criteria, and the surgeon was not blind to the angiogram.

Outcome Events
Follow-up was performed at a hospital clinic by the randomizing physician at 4 and 12 months after randomization and annually thereafter. Clinical details of all strokes and deaths, results of any investigations, and any postmortem information were sent to the main trial center for classification by a trial neurologist (C.P.W. or P.M.R.). Classification of all strokes and deaths was then reviewed by an independent blinded audit committee. For the purpose of this study, the analysis of the risk of ischemic stroke is restricted to first strokes lasting >7 days, ie, “major” ischemic strokes. When no CT brain scan was available or when the scan was performed >30 days after the stroke, the stroke was categorized as ischemic.

Background strokes occurring after endarterectomy were defined as ipsilateral carotid territory ischemic strokes that occurred >30 days after carotid endarterectomy. Myocardial infarction and non-stroke vascular death on follow-up were defined as described previously.32

Statistical Analysis
Reliability of assessment of plaque surface morphology was measured with the k statistic.36 All analyses of the risk of ischemic stroke ipsilateral to the symptomatic carotid artery were performed with Kaplan-Meier survival analysis and with censoring for nonstroke death. All analyses were performed on an intention-to-treat basis. Survival analyses, multiple logistic regression analyses, and Cox proportional hazards modeling were performed with SPSS for Windows version 7.0.

Results
Of the 3007 patients studied, 1208 patients were randomized to medical treatment alone and 1799 patients were randomized to surgery. Of the patients randomized to surgery, 1739 (97%) underwent carotid endarterectomy. The median time from last ischemic symptoms referable to the symptomatic artery and randomization was 47 days (interquartile range, 21 to 91 days). In patients randomized to surgery, the median time to endarterectomy was 14 days (interquartile range, 6 to 30 days). Mean follow-up was 6.4 years (range, 1 to 13 years). Patient characteristics, trial results, and morbidity and mortality of surgery are reported elsewhere.32

Carotid Stenosis and Stroke Risk
The Kaplan-Meier risks of carotid territory ischemic stroke ipsilateral to the symptomatic carotid artery averaged across all degrees of severity of stenosis in patients randomized to medical treatment alone were 7.9% (95% CI, 6.4% to 9.4%) at 2 years and 12.4% (95% CI, 10.4% to 14.4%) at 5 years. The background risks of carotid territory ischemic stroke ipsilateral to the symptomatic carotid artery in patients who underwent carotid endarterectomy (excluding strokes occurring within 30 days of the operation) were 2.3% (95% CI, 1.6% to 3.0%) and 4.2% (95% CI, 3.1% to 5.3%), respectively.

The risk of ipsilateral carotid territory ischemic stroke in the no-surgery group was closely related to the degree of carotid stenosis for the first 2 years after trial entry (Figure 2). During the first 2 years, the risk increased sharply with the degree of stenosis, whereas the background stroke risk after endarterectomy in the surgery group (ie, excluding operative strokes) was unrelated to the degree of stenosis. However, the annual risk of ipsilateral carotid territory ischemic stroke on medical treatment fell rapidly with time from randomization (Figure 3), whereas the background risk of stroke after
endarterectomy, as well as the annual risks of acute myocardial infarction and nonstroke vascular death, remained relatively constant (Figure 4). By 3 years after randomization, the annual risk of carotid territory ischemic stroke in the medical treatment group was very low and did not appear to be related to the baseline measurement of carotid stenosis. However, because 65% (89/136) of ipsilateral carotid territory ischemic strokes in the medical treatment group occurred within the first 2 years after randomization, the degree of stenosis of the symptomatic artery was highly predictive of the overall risk (ie, at any time during follow-up) of stroke in the medical treatment group after correction for age, sex, and the other baseline clinical and angiographic characteristics listed in Table 1. However, when the analysis was confined just to strokes occurring ≥2 years after randomization, the risk of stroke was unrelated to the initial degree of stenosis (linear model: hazard ratio=1.01 per 10% increase in degree of stenosis; 95% CI, 0.9 to 1.30; P=0.8).

Plaque Surface Morphology

Reproducibility

Two independent observers agreed on the categorization of 1000 consecutive stenoses as smooth or irregular in 81% of cases (κ=0.56; 95% CI, 0.53 to 0.59). Intraobserver agreement on a random sample of 50 angiograms was good: observer A, κ=0.67 (95% CI, 0.3 to 0.9); observer B, κ=0.56 (95% CI, 0.2 to 0.9).

Clinical Characteristics

A total of 1897 symptomatic stenoses (63.1%) had surface irregularity on the angiogram. There were small but statistically significant differences in mean age and mean cholesterol concentration between patients with smooth and irregular plaques but no difference in sex, blood pressure, or the prevalence of diabetes or smoking. Patients with irregular plaques were more likely than those with smooth plaques to have had a previous myocardial infarction but not a history of angina (Table 2). There was a small excess of patients with irregular plaques taking aspirin at baseline, but there was no significant relation between the risk of stroke and the linear stenosis term.

Pathological Correlation

Data on the macroscopic appearance of the carotid plaque from the symptomatic carotid artery at endarterectomy were available in 1671 patients (96% of the 1739 who were randomized to surgery and underwent endarterectomy). Macroscopic ulceration was reported in 1132 cases (68%), and thrombus adherent to the plaque surface was reported in 493 cases (26%). Macroscopic ulceration was more frequent in those cases in which the plaque surface morphology was classified as irregular at angiography compared with those classified as smooth (779/1066 [73%] versus 353/605 [58%]; odds ratio=1.94; 95% CI, 1.57 to 2.39; P<0.0001). Surface thrombus was also more frequent in those cases in which the plaque surface morphology was classified as irregular at angiography compared with those classified as smooth (345/1066 [33%] versus 148/605 [24%]; odds ratio=1.74; 95% CI, 1.39 to 2.17; P<0.0001). Plaque ulceration and macroscopic plaque surface thrombus formation visible at endarterectomy were themselves closely related. Thrombus formation was reported much more frequently when macroscopic plaque surface ulceration was present than when it was not (449/1132 [40%] versus 44/539 [8%]; odds ratio=7.4; 95% CI, 5.3 to 10.3; P<0.0001).

Table 1. Predictive Value of Degree of Symptomatic Carotid Stenosis and Surface Morphology of Symptomatic Plaque for First Carotid Territory Ischemic Stroke Ipsilateral to Symptomatic Stenosis

<table>
<thead>
<tr>
<th>Patients randomized to medical treatment only</th>
<th>Wald Statistic*</th>
<th>P</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque surface irregularity</td>
<td>6.5</td>
<td>0.01</td>
<td>1.80 (1.14–2.83)</td>
</tr>
<tr>
<td>Degree of carotid stenosis†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cubic term</td>
<td>28.9</td>
<td>0.0000</td>
<td>1.34 (1.22–1.52)</td>
</tr>
<tr>
<td>Square term</td>
<td>28.4</td>
<td>0.0000</td>
<td>1.30 (1.18–1.40)</td>
</tr>
<tr>
<td>Linear term</td>
<td>26.4</td>
<td>0.0000</td>
<td>1.25 (1.15–1.34)</td>
</tr>
<tr>
<td>Patients randomized to surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque surface irregularity</td>
<td>2.27</td>
<td>0.13</td>
<td>1.39 (0.91–2.12)</td>
</tr>
<tr>
<td>Degree of carotid stenosis (linear term)‡</td>
<td>1.1</td>
<td>0.29</td>
<td>1.06 (0.95–1.17)</td>
</tr>
</tbody>
</table>

The terms are derived from a Cox proportional hazards model which included all the baseline clinical and angiographic variables listed below. Additional variables included in model were age, sex, cerebral events vs ocular events, residual neurological signs after 7 days, diabetes, any ischemic event within last 2 months, number of events within last 3 months, previous myocardial infarction, systolic blood pressure, diastolic blood pressure, peripheral vascular disease, angina without previous myocardial infarction, ECG signs of left ventricular hypertrophy, cerebral infarction on symptomatic side on CT brain scan, occlusion of the contralateral internal carotid artery, and postoperative collapse of the internal carotid artery.

*Degrees of freedom for all variables=1.
†Cubic term used in the model shown. Parameters given for squared and linear terms are those obtained when the term was substituted for the cubic term. For the purpose of illustration, the hazard ratios and CIs given in the table refer to the increase in risk for 80% stenosis vs 70% stenosis.
‡Squared and cubic stenosis terms were not used because there was no significant relation between the risk of stroke and the linear stenosis term.

Figure 4. Annual risk of background ipsilateral carotid territory ischemic stroke after endarterectomy (excluding strokes occurring within 30 days of endarterectomy) in the surgery group, and annual risks of nonstroke vascular death and acute myocardial infarction in both treatment groups combined, in each of the first 6 years after trial entry.
Relationship to Severity of Stenosis

Both the proportion of stenoses with surface irregularity at angiography ($\chi^2$ for trend = 123; $P<0.0001$) and the proportion reported to have adherent surface thrombus at operation ($\chi^2$ for trend = 57; $P<0.0001$) increased with the degree of stenosis of the symptomatic artery (Figure 5). However, angiographic irregularity remained a significant predictor of surface thrombus formation after correction for the degree of stenosis of the symptomatic artery in a multiple logistic regression analysis (hazard ratio $= 1.32; 95\%$ CI, 1.16 to 1.44; $P = 0.0006$).

Risk of Stroke

In the medical treatment group, the 2-year risk of ischemic stroke in the territory of arteries with stenoses that appeared irregular at angiography was greater than that distal to those that appeared smooth at all degrees of stenosis (Figure 6). This difference remained after formal correction for the degree of stenosis of the symptomatic artery and the other baseline clinical and angiographic characteristics listed in Table 1, in a Cox proportional hazards model (hazard ratio $= 1.80; 95\%$ CI, 1.14 to 2.83; $P = 0.01$). Plaque surface irregularity was also predictive of strokes occurring $>2$ years after randomization (hazard ratio = 2.75; 1.30 to 5.80; $P = 0.01$). By contrast, in patients treated surgically, angiographic plaque surface irregularity was unrelated to the risk of ipsilateral carotid territory ischemic stroke on follow-up (Table 1). In particular, there was no association with the background risk of ipsilateral carotid territory ischemic stroke occurring $>30$ days after surgery (hazard ratio = 1.04; 0.82 to 1.30; $P = 0.77$).

Discussion

This is the largest cohort of patients with symptomatic carotid stenosis imaged and measured by angiography ever reported. Moreover, since carotid endarterectomy was allocated at random, and the surgery and no-surgery groups were therefore likely to be identical in all respects other than initial surgical treatment, it was possible to compare the effect of severity of carotid stenosis and plaque surface morphology on the risk of ipsilateral ischemic stroke on medical treatment alone with that

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### TABLE 2. Characteristics at Randomization of Patients With Irregular Carotid Plaques vs Smooth Plaques on Angiograms of the 3007 Symptomatic Carotid Arteries

<table>
<thead>
<tr>
<th>Plaque Surface Morphology</th>
<th>Irregular</th>
<th>Smooth</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>1897</td>
<td>1110</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>1383 (73%)</td>
<td>778 (70%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD) age, y</td>
<td>62.9 (8.0)</td>
<td>61.6 (8.4)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Mean (SD) ICA stenosis, %</td>
<td>61.8 (19.3)</td>
<td>52.7 (21.9)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Mean (SD) systolic BP, mm Hg</td>
<td>150.9 (23.6)</td>
<td>149.6 (22.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD) diastolic BP, mm Hg</td>
<td>86.2 (11.6)</td>
<td>85.8 (12.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD) cholesterol, mmol/L*</td>
<td>6.4 (1.4)</td>
<td>6.3 (1.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>Diabetes</td>
<td>226 (12%)</td>
<td>123 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Current cigarette smoking†</td>
<td>877 (46%)</td>
<td>522 (47%)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous angina‡</td>
<td>217 (11%)</td>
<td>121 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>251 (13%)</td>
<td>111 (10%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>1107 (58%)</td>
<td>586 (53%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Other antiplatelet</td>
<td>189 (10%)</td>
<td>105 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>Warfarin</td>
<td>133 (7%)</td>
<td>87 (8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Lipid-lowering drug</td>
<td>55 (3%)</td>
<td>45 (4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Presenting events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>941 (50%)</td>
<td>544 (49%)</td>
<td>NS</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>406 (21%)</td>
<td>251 (23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Nondisabling major stroke</td>
<td>507 (27%)</td>
<td>319 (29%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ipsilateral cerebral infarct on CT brain scan</td>
<td>458 (24%)</td>
<td>291 (26%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

ICA indicates internal carotid artery; BP, blood pressure.
*Data available in 2631 (88%) cases.
†Data available in 2688 (89%) cases.
‡Angina without previous myocardial infarction.

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Figure 5. Prevalence of plaque surface irregularity on angiograms of 3007 symptomatic carotid stenoses and the prevalence of macroscopic thrombus adherent to the plaque surface at operation on 1671 symptomatic carotid stenoses at endarterectomy by degree of stenosis.

Figure 6. Two-year Kaplan-Meier (KM) risk of ischemic stroke in the territory of the symptomatic carotid artery according to degree of carotid stenosis and angiographic appearance of the plaque surface in patients randomized to medical treatment only.
following endarterectomy and to therefore draw conclusions about causality without bias or confounding.

**Carotid Stenosis and Stroke Risk**

The reproducibility of the measurement of carotid stenosis using the ECST method and its equivalence with other methods have been reported previously. To reduce the imprecision in measurement of stenosis in this study, we used the mean of 2 measurements by independent observers. The 2-year risk of carotid territory ischemic stroke increased sharply with the degree of stenosis (Figure 2). Stroke risk for >80% stenosis was nearly 10 times higher than the risk for <40% stenosis. However, stroke risk fell very rapidly with time. By 3 years, the risk was low and no longer clearly related to the initial measurement of stenosis (Figure 3). Thus, in patients presenting with transient ischemic attack or nondisabling ischemic stroke, the majority of carotid territory ischemic strokes attributable to symptomatic carotid stenoses occur in the first 2 years after the occurrence of symptoms. Why the risk of stroke should decline so quickly is uncertain. There are at least 3 possible explanations. First, if the onset of symptoms is related to instability and rupture of carotid plaque, then the risk of stroke should fall with time as the plaque heals. Second, collateral circulation, via the external carotid circulation or the circle of Willis, may improve with time and might be expected to reduce the risk of stroke. Third, if only a proportion of patients are actually susceptible to ischemic stroke distal to a carotid stenosis, for reasons possibly relating to their cerebral circulation or metabolism, then the risk of stroke would be expected to fall with time as these patients had strokes and the patients remaining were less susceptible. Which, if any, of these explanations accounts for our findings is unclear.

To estimate the proportion of ipsilateral carotid territory ischemic strokes that occurred as a direct consequence of the stenosis, the stroke risk in patients on medical treatment alone was compared with the background risk of stroke after carotid endarterectomy (excluding strokes that occurred within 30 days of endarterectomy), ie, the risk presumably attributable to ulceration and thrombus formation at operation. Operative assessment of surface irregularity was not blind to the angiogram, but these results do accord with previous studies. The ECST data now show that the association between surface irregularity and an increased risk of ipsilateral carotid territory ischemic stroke holds for all degrees of stenosis and that the effect is independent of other clinical and angiographic factors. The data also show that plaque surface morphology does not predict background stroke risk after carotid endarterectomy, indicating that the association with ipsilateral carotid territory ischemic stroke in the medical treatment group is likely to be causal. Indeed, given that assessment of surface irregularity on angiograms is relatively crude, the true association between plaque surface morphology and ischemic stroke risk may well be much stronger. If so, the close association between the prevalence of surface irregularity and the degree of stenosis would tend to result in an overestimation of the importance of stenosis because it can be measured more accurately in any analyses predicting the risk of stroke on medical treatment.

The analyses of the macroscopic appearance of endarterectomy specimens suggest that the effect of plaque irregularity on stroke risk may be mediated by ulceration and surface thrombus formation, presumably resulting in local thrombotic occlusion or distal embolism. This is supported by the observation that cerebral microemboli are more frequent distal to carotid plaques that are subsequently found to have surface thrombus at endarterectomy. Moreover, the presence of thrombus at endarterectomy and the number of cerebral emboli detected by transcranial Doppler scanning fall with time from last clinical symptoms. Temporary plaque instability, thrombus formation, and embolism could therefore account for the rapid fall in risk of carotid territory ischemic stroke with time from trial entry in the medical treatment group. The absence of a similar trend in the background risk of stroke in the surgery group and the risks of acute myocardial infarction and nonstroke vascular death are consistent with the high early stroke risk being due to local rather than systemic factors. The fact that plaque surface irregularity is still predictive of ipsilateral carotid territory ischemic stroke occurring >2 years after randomization in the medical treatment group could be explained by a tendency of plaque instability to recur in the same patients.

**Conclusions**

We have shown that the vast majority of ischemic strokes in the territory of a recently symptomatic severe carotid stenosis occur as a consequence of the stenosing plaque. The degree of stenosis is an independent predictor of the risk of stroke on medical treatment within 2 years of presenting symptoms but is unrelated to the risk of stroke thereafter. Plaque surface
irregularity is highly predictive of ipsilateral ischemic stroke on medical treatment. This association is independent of the degree of stenosis, is maintained after 2 years, and is abolished by endarterectomy. The increase in the 2-year risk of stroke with the degree of carotid stenosis is partly, although not completely, accounted for by the parallel increase in plaque surface irregularity and thrombus formation. We conclude that, in common with the pathogenesis of acute coronary syndromes, local thrombus formation due to an unstable carotid atherosclerotic plaque is likely to be an important mechanism of ischemic stroke distal to a recently symptomatic carotid stenosis. Angiographic plaque surface morphology should be used along with the degree of carotid stenosis to identify patients most likely to benefit from carotid endarterectomy and other preventative treatments.38 The ability of noninvasive techniques of carotid imaging to identify irregular plaques should therefore be validated against angiography.

Acknowledgment

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References


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