Low Risk of Ischemic Stroke in Patients With Reduced Internal Carotid Artery Lumen Diameter Distal to Severe Symptomatic Carotid Stenosis

Cerebral Protection Due to Low Poststenotic Flow?

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Background and Purpose—Patients with recently symptomatic severe carotid stenosis have a high risk of ischemic stroke on medical treatment. The main mechanism of stroke appears to be plaque surface thrombus formation and distal embolism. It is unclear to what extent reduction in blood flow across the stenosis, and the consequent reduction in cerebral perfusion pressure, is also important. Angiographic indices of reduced cerebral perfusion may identify patients at a particularly high risk of stroke who require urgent endarterectomy. The most direct angiographic correlate of poststenotic perfusion pressure is the degree of narrowing of the distal internal carotid artery (ICA) lumen. We sought to develop criteria for the definition of poststenotic narrowing of the ICA and to determine the effect of this and other angiographic characteristics likely to be associated with reduced cerebral perfusion on the risk of ipsilateral ischemic stroke in patients with recently symptomatic carotid stenosis.

Methods—We studied the carotid angiograms of 3007 patients in the European Carotid Surgery Trial. Poststenotic narrowing of the ICA was defined with use of the ratio of the lumen diameter of the ICA to that of the common carotid artery (CCA). The normal range of the ICA/CCA ratio was defined in 2966 symptomatic or contralateral carotid arteries with 0% to 49% stenosis. Arteries with 70% to 99% symptomatic stenosis and an ICA/CCA ratio below this range were categorized as narrowed. We related the presence of narrowing and other angiographic characteristics to the risk of ipsilateral ischemic stroke on medical treatment.

Results—An assessment of the ICA/CCA ratio had good interobserver reproducibility. Poststenotic narrowing of the ICA was defined as an ICA/CCA ratio of <0.42. The 5-year risk of ipsilateral carotid territory ischemic stroke on medical treatment was 8% in patients with 70% to 99% stenosis and narrowing of the ICA versus 25% in patients without narrowing (log rank test, P=0.02). This difference remained after correction for other clinical and angiographic variables (hazard ratio 0.40, 95% CI 0.17 to 0.94, P=0.03). The other angiographic characteristics did not predict stroke.

Conclusions—Poststenotic narrowing of the ICA was associated with a low risk of stroke on medical treatment. This suggests that low flow alone is not usually sufficient to cause ischemic stroke distal to symptomatic carotid stenosis. Poststenotic narrowing may be protective because blood flow distal to the stenosis is insufficient to carry emboli to the brain. (Stroke. 2000;31:622-630.)

Key Words: carotid arteries ■ carotid endarterectomy ■ risk factors ■ stroke ■ ischemia

Atherothrombotic stenosis of the origin of the internal carotid artery (ICA) is a common cause of carotid territory ischemic stroke.1,2 The risk of stroke increases with the severity of carotid stenosis and is reduced after carotid endarterectomy.3,4 However, because even with severe recently symptomatic carotid stenosis, only about one third of patients have a stroke on medical treatment alone, endarterectomy can be helpful in only a minority of patients. To maximize the effectiveness of endarterectomy, it is necessary to identify and operate on patients with a high risk of stroke without surgery. Plaque surface thrombus formation and distal embolism are important mechanisms of stroke in patients with carotid stenosis,5–7 and angiographic plaque surface irregularity is associated with an increased risk of ischemic stroke at all degrees of stenosis,8,9 but there also is evidence that hemodynamic factors may be important. A proportion of patients with a recently symptomatic severe carotid stenosis or occlusion have diminished perfusion of the...
ipsilateral cerebral hemisphere and cannot increase perfusion in response to raised levels of carbon dioxide.\(^{10–24}\) Consistent results have been obtained from studies with transcranial Doppler ultrasound,\(^{10–13}\) single-photon emission computed tomography,\(^{14–16}\) positron emission tomography,\(^{15,22–24}\) and other imaging techniques.\(^{17–21}\) Such patients also have metabolic changes in the affected hemisphere that are consistent with ischemia in the absence of any evidence of cerebral infarction.\(^{25–28}\) Both the perfusion deficit and the metabolic changes can be reversed after carotid endarterectomy and extracranial/intracranial bypass graft surgery.\(^{19,22,29–31}\)

It is conceivable that indexes of reduced cerebral perfusion might be useful in the identification of patients with carotid stenosis who are at a particularly high risk of ischemic stroke. For example, 2 small studies have recently shown that reduced cerebral perfusion is associated with an increased risk of stroke on medical treatment in patients with unilateral carotid occlusion,\(^{13,24}\) but no such link has yet been demonstrated in patients with carotid stenosis. Using carotid angiograms of patients with recently symptomatic carotid stenosis who were randomized in the European Carotid Surgery Trial (ECST), we studied the effect of a number of angiographic indices that would be expected to reduce cerebral perfusion pressure on the risk of ipsilateral carotid territory ischemic stroke on medical treatment.

The most direct angiographic correlate of ipsilateral poststenotic perfusion pressure is likely to be the degree of narrowing of the distal ICA. In some patients with a tight carotid stenosis, the normal ICA distal to the stenosis is narrowed or collapsed on the angiogram,\(^ {32–34}\) indicating particular low poststenotic intraluminal pressure. Low flow is frequently manifest at angiography as delayed filling of the distal ICA with contrast medium. Such patients are often assumed to have a high risk of stroke and to require urgent endarterectomy. To test this assumption, we identified narrowing of the ICA with use of the ratio of the ICA lumen diameter to that of a disease-free portion of the CCA. These measurements were made by a single observer on all available angiograms of the symptomatic and contralateral carotid arteries in the main trial office. To determine the reproducibility of measurement of the ICA/CCA ratio, a second independent observer made the same measurements on a consecutive series of 976 angiograms of the symptomatic carotid artery with a full range of stenoses. The second observer was blind to the measurements of the first observer, and no marks had been placed on the angiograms.

We have shown previously, in a subset of 1001 ECST patients, that the mean ratio was relatively constant in patients with \(\leq 69\%\) ECST stenosis but then fell significantly as stenosis increased further.\(^ {36}\) It has also been shown that arterial stenoses of \(< 50\%\) do not cause any reduction in flow or pressure distal to the lesion.\(^ {32,38,39}\) To define the normal range of the ICA/CCA ratio, we therefore studied patients with 0% to 49% stenosis. We determined the ICA/CCA ratio on angiograms of patients with 0% to 49% symptomatic stenosis and in patients with 0% to 49% stenosis of the contralateral carotid artery.

**Poststenotic Narrowing of the ICA**

We proposed to define poststenotic narrowing using the ratio of the diameter of a representative section of the normal disease-free distal ICA to that of a disease-free portion of the CCA. These measurements were made by 2 independent observers (P.M.R. and C.P.W.) using the ECST method.\(^ {36}\) Details of the reproducibility of this measurement and the equivalence with other methods have been published previously.\(^ {36,37}\) The mean of the 2 measurements was used in all analyses.

**Normal ICA/CCA Lumen Ratio**

We proposed to identify poststenotic narrowing using the ratio of the diameter of a representative section of the normal disease-free distal ICA to that of a disease-free portion of the CCA. These measurements were made by 2 independent observers (P.M.R. and C.P.W.) using the ECST method.\(^ {36}\) Details of the reproducibility of this measurement and the equivalence with other methods have been published previously.\(^ {36,37}\) The mean of the 2 measurements was used in all analyses.

**Carotid Angiography**

Carotid angiograms were performed on all patients before randomization and sent to the trial center. Details of the angiographic techniques have been published previously.\(^ {34}\) The present study was confined to the 3007 (99.6%) of the 3018 ECST patients in whom a randomization angiogram was available in the trial center. In patients with bilateral symptomatic, the designation of the symptomatic carotid artery in the ECST is explained elsewhere.\(^ {3}\) The following assessments were made on all angiograms for the purpose of the present study:

**Degree of Carotid Stenosis**

The degree of stenosis of both ICAs was measured by 2 independent observers (P.M.R. and C.P.W.) using the ECST method.\(^ {36}\) Details of the reproducibility of this measurement and the equivalence with other methods have been published previously.\(^ {36,37}\) The mean of the 2 measurements was used in all analyses.

**Stenosis or Occlusion of the Ipsilateral External Carotid Artery**

The degree of stenosis of the external carotid artery ipsilateral to the symptomatic carotid stenosis was measured by 1 observer using a method similar to the ECST method of measuring the degree of stenosis of the ICA (ie, the denominator was the estimated normal lumen diameter at the site of maximum stenosis).

**Stenosis or Occlusion of the Contralateral Carotid Artery**

The degree of stenosis of the contralateral carotid artery ipsilateral to the symptomatic stenosis was measured by 1 observer using the ECST method.

**Length of the Hemodynamically Significant Portion of the Stenosis**

The length of an arterial stenosis has been shown to have a measurable hemodynamic effect.\(^ {32,38,39}\) The effect is greatest when the degree of stenosis of the vessel is severe.\(^ {38}\) We defined the hemodynamically significant portion of the stenosis as the length of that portion of the stenosis where the lumen was narrowed by \(> 50\%\). This was recorded as a ratio with the diameter of a disease-free portion of the CCA.
Plaque Surface Morphology

Carotid plaque surface morphology was classified by 1 observer as smooth or irregular, as we previously defined.9

Outcome Events

Details of any strokes or deaths occurring during follow-up were obtained at clinical review. Clinical details, 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.). Classifications of all strokes and deaths were then reviewed by an independent blinded audit committee. For the purpose of the present study, the analysis of the risk of ipsilateral carotid territory ischemic stroke is restricted to first strokes lasting >7 days (ie, “major” ischemic strokes). Where CT brain scan was not available or where the scan was performed >30 days after the stroke, the stroke was categorized as ischemic. A disabling stroke was defined as one in which the Rankin scale score at 6 months after the stroke was ≥3.3

Transient ischemic attacks that occurred during follow-up were recorded but were not submitted for blinded audit.

Statistical Analysis

All actuarial risks of ischemic stroke were performed with Kaplan-Meier survival analysis and censoring for nonstroke death. Survival analyses, multiple logistic regression analyses, and Cox’s proportional hazards modeling were performed with SPSS for Windows version 7.0.

Results

Of the 3007 patients studied, 1208 patients were randomized to receive medical treatment alone and 1799 patients were randomized to undergo surgery. Of the patients randomized to undergo surgery, 1739 (97%) underwent carotid endarterectomy. The median time from the last ischemic symptoms referable to the symptomatic artery and randomization was 47 days (interquartile range 21 to 91 days). Mean follow-up was 6.4 years (range 1 to 13). Patient characteristics, the trial results, and the morbidity and mortality rates for surgery are reported elsewhere.3

Normal ICA/CCA Ratio

Measurements of the ICA and CCA lumen diameters were made on angiograms of 2901 (96.5%) symptomatic carotid arteries and 2211 nonoccluded contralateral carotid arteries. A comparison of measurements made by 2 independent observers on a consecutive sample of 976 symptomatic arteries of all degrees of stenosis is shown in Figure 1. Overall agreement was good, particularly at low ICA/CCA ratios. To assess whether the normal premorbid ICA/CCA ratio on the symptomatic side could be estimated from the ratio on the contralateral side, the ratios on the symptomatic and contralateral sides were compared in the 653 patients with stenosis of <50% on both sides. The correlation between the ICA/CCA ratio of the symptomatic artery and that of the contralateral artery was very poor (r=0.07, P=0.08). Whether one ICA is narrowed therefore could not be determined relative to the contralateral ICA, and it was necessary to define an absolute value of the ICA/CCA ratio below which an ICA could be said to be narrowed.

The degree of stenosis was in the range of 0% to 49% in 1034 symptomatic arteries and 1932 contralateral arteries. The measurement characteristics of the ICA/CCA ratio in these samples are given in Table 1. The distributions of the measurements in the 2 samples were virtually identical. In both samples, the ICA/CCA ratio was normally distributed with a fairly narrow range. The mean (SD) ratios in the symptomatic and contralateral arteries were 0.62 (0.1) and 0.63 (0.1), respectively. The lower limit of the 95% range was 0.42 in both samples. The lower limit of normal of the ICA/CCA ratio was therefore defined as 0.42. The distribution of ICA/CCA ratios in both samples combined is shown in Figure 2. There were 316 angiograms of the contralateral ICA in which there was no discernible stenosis. In this group, the mean ratio was 0.63 (SD 0.1, median 0.62, 95% range 0.44 to 0.80). Given the relatively small number of cases in this group, the results were consistent with a lower limit of normal for the ICA/CCA ratio of ∼0.42.

Poststenotic Narrowing of the Symptomatic ICA

The mean ICA/CCA ratio on the symptomatic side remained constant until the degree of stenosis exceeded 70% (Figure 3). Thereafter, the mean ratio in each decile fell as stenosis increased (ANOVA, P<0.0001). The mean (SE) ratios were 0.70% to 79%, n=383, 0.60 (0.06); 80% to 89%, n=399, 0.55 (0.05); and 90% to 99%, n=166, 0.46 (0.015). As a result, the proportion of patients with an ICA/CCA ratio of <0.42 increased with the severity of stenosis (Figure 4). The ratio was <0.42 in 149 (8%) patients with 50% to 99% stenosis

![Figure 1. Relationship between measurements of the ICA/CCA ratio by 2 independent observers on angiograms of 967 symptomatic arteries with stenosis ranging from 0% to 99%.](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symptomatic Artery (n=1034)</th>
<th>Contralateral Artery (n=1932)</th>
<th>All Arteries (n=2966)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.62</td>
<td>0.63</td>
<td>0.63</td>
</tr>
<tr>
<td>SEM</td>
<td>0.003</td>
<td>0.003</td>
<td>0.002</td>
</tr>
<tr>
<td>SD</td>
<td>0.10</td>
<td>0.11</td>
<td>0.11</td>
</tr>
<tr>
<td>Median</td>
<td>0.62</td>
<td>0.625</td>
<td>0.625</td>
</tr>
<tr>
<td>Range</td>
<td>0.25–1.5</td>
<td>0.32–1.6</td>
<td>0.25–1.6</td>
</tr>
<tr>
<td>95% Range</td>
<td>0.42–0.88</td>
<td>0.42–0.87</td>
<td>0.42–0.87</td>
</tr>
</tbody>
</table>
and in 102 (18%) patients with 80% to 99% stenosis. The number of patients with significant stenosis of the contralateral carotid artery was much lower, but poststenotic narrowing of the ICA also increased with the severity of stenosis: 20 of 1928 (1%) patients with 0% to 69% stenosis and 19 of 283 (7%) patients with 70% to 99% stenosis (Fisher’s exact test, \( P < 0.0001 \)). The interobserver agreement for the assessment of poststenotic narrowing (ie, an ICA/CCA ratio of \(<0.42\)) was good: both observers agreed in 937 of 976 cases (96%; \( \kappa = 0.61, 95\% \) CI 0.5 to 0.72, \( P < 0.00001 \)).

The baseline clinical and imaging characteristics of patients with an ICA/CCA ratio of \(<0.42\) and those with a ratio of \(>0.42\) are given in Table 2. An ICA/CCA ratio of \(<0.42\) was associated with presentation with an ipsilateral major nondisabling ischemic stroke and the presence of infarction in the territory of the symptomatic artery on the randomization CT brain scan. The association with infarction on CT brain scan remained significant after correction for confounding by the degree of carotid stenosis in a multiple regression analysis.

**Stroke Risk**

The risk of ischemic stroke on medical treatment distal to the symptomatic carotid stenosis increased as the severity of stenosis increased and then fell in those patients with poststenotic narrowing of the ICA (Figure 5). In patients with 70% to 99% symptomatic stenosis randomized to medical treatment, the 5-year actuarial risk of ipsilateral carotid territory
ischemic stroke was 8% in the 45 patients with narrowing and 25% in patients without narrowing (log rank test, \( P = 0.02 \)).
The 5-year risk of disabling or fatal ipsilateral carotid territory ischemic stroke was also lower in patients with poststenotic narrowing, but this did not reach statistical significance (log rank test, \( P = 0.1 \); 9% versus 16%).
The risk of stroke in patients without narrowing was 22% distal to 80% to 89% stenosis and 32% distal to 90% to 99% stenosis (Figure 5). In a Cox proportional hazards analysis, with all of the baseline clinical and angiographic characteristics listed in Table 2 taken into account, including the degree of symptomatic carotid stenosis, poststenotic narrowing was a significant predictor of a reduced risk of stroke in the medical group as a whole (hazard ratio 0.40, 95% CI 0.17 to 0.94, \( P = 0.03 \)). In contrast, there was no difference in the 5-year actuarial risk of ischemic stroke in other territories (contralateral carotid and vertebrobasilar) between patients with and those without narrowing of the symptomatic ICA: 10% versus 10% (log rank test, \( P = 0.8 \)).

The prevalence of 50% to 99% stenosis or occlusion of the ipsilateral external carotid artery and the contralateral carotid artery both increased with the degree of stenosis of the symptomatic ICA. It was necessary, therefore, to correct for this in the analysis of the relationship between these factors and the risk of carotid territory ischemic stroke on medical treatment. After correction for severity of symptomatic carotid stenosis, none of these other angiographic indices thought to possibly be associated with reduced cerebral perfusion were independently associated with stroke risk (Table 3).

**Discussion**

**Definition of Poststenotic Narrowing of the ICA**

Williams and Nicoliades\(^40\) showed that the ICA/CCA ratio ranged from 0.5 to 1.0 in angiograms of 61 normal carotid bifurcations. We found similar results in 316 ECST patients with normal contralateral carotid arteries and defined the properties of the ratio with precision in nearly 3000 symptomatic and contralateral carotid arteries with 0% to 49% stenosis. Measurement of the ICA/CCA ratio had good interobserver reproducibility. We have shown that the ICA begins to narrow when the degree of stenosis reaches 70% with the ECST method (50% stenosis with the North American Symptomatic Carotid Endarterectomy Trialists [NASCET] method). It is difficult to identify minor degrees of narrowing in individual patients because of the variation in the normal ICA/CCA ratio. Minor narrowing is only apparent when considering the mean ICA/CCA ratio in a population of patients (Figure 3). Moreover, it was not possible to use the ICA/CCA ratio of the contralateral ICA as a standard with which to compare the ratio on the symptomatic side. The correlation between the ICA/CCA ratio on the symptomatic and contralateral sides was very poor even when the degree of stenosis was <50% on both sides. To define narrowing of the ICA with a degree of certainty, we therefore had to use a cutoff point below which we could confidently say that the majority of cases had definite narrowing. We defined the cutoff point as 2 SDs below the mean ICA/CCA ratio in patients with 0% to 49% stenosis (ie, a level at which only 2.5% of the normal population would be expected to lie). Although 2 SDs about the mean is the most frequently used standard by which to define the normal range for a variable, it is a compromise. On the one hand, it limits the proportion of normal arteries that would be misdiagnosed as narrowed to 2.5%, but on the other hand, it means that a patient in whom the original ICA/CCA ratio was 0.8 will have to develop a major degree of narrowing before being included. More detailed analysis of the relationship between narrowing of the ICA and the risk of stroke, with the ICA/CCA ratio used as a continuous variable, may be possible if studies such as ECST and NASCET are combined to produce a dataset with a sufficiently large number of patients.
Despite the limitations of defining narrowing of the ICA using a single cutoff point, the classification does appear to be clinically useful. Patients with a 70% to 99% symptomatic carotid stenosis and an ICA/CCA ratio $<$0.42 had a significantly lower risk of ipsilateral carotid territory ischemic stroke on medical treatment than did patients with the same range of stenosis and no narrowing. Contrary to the current clinical impression, patients with recently symptomatic tight carotid stenosis and narrowing of the distal ICA are not at a high risk of stroke. This is consistent with the finding of a low risk of stroke on medical treatment in patients with severe stenosis and almost complete collapse of the distal ICA (the “carotid string sign”) in NASCET. Our data suggest that the low risk extends to patients with less marked degrees of poststenotic narrowing of the ICA. It is interesting to note that Norris and Zhu reported a fall in the risk of cerebral ischemic events in patients with very severe, or “critical,” carotid stenosis in their ultrasound-based study of

### TABLE 2. Baseline Clinical and Angiographic Characteristics of Patients With 70% to 99% Symptomatic Carotid Stenosis and Narrowing of Poststenotic Internal Carotid Artery (ICA/CCA ratio $<$0.42) Compared With Those of Patients With 70% to 99% Stenosis and No Narrowing (Medical and Surgical Groups Combined)

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>ICA/CCA Ratio</th>
<th>$&lt;$0.42</th>
<th>$&gt;$0.42</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td></td>
<td>124</td>
<td>829</td>
<td></td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
<td></td>
<td>61.8 (8)</td>
<td>63.0 (8)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td></td>
<td>10 (8)</td>
<td>92 (11)</td>
<td>0.3</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td></td>
<td>23 (19)</td>
<td>158 (19)</td>
<td>0.9</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td></td>
<td>10 (8)</td>
<td>113 (14)</td>
<td>0.1</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td></td>
<td>22 (18)</td>
<td>156 (19)</td>
<td>0.8</td>
</tr>
<tr>
<td>Residual neurological signs, n (%)</td>
<td></td>
<td>39 (31)</td>
<td>209 (25)</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean diastolic blood pressure, mm Hg (SD)</td>
<td></td>
<td>86.8 (12)</td>
<td>85.2 (12)</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean systolic blood pressure, mm Hg (SD)</td>
<td></td>
<td>151.9 (22)</td>
<td>151.0 (24)</td>
<td>0.7</td>
</tr>
<tr>
<td>Events before randomization, n (%)</td>
<td></td>
<td>59 (48)</td>
<td>381 (46)</td>
<td>0.9</td>
</tr>
<tr>
<td>Cerebral transient ischemic attack</td>
<td></td>
<td>53 (43)</td>
<td>382 (46)</td>
<td>0.3</td>
</tr>
<tr>
<td>Ocular transient ischemic attack</td>
<td></td>
<td>27 (22)</td>
<td>158 (19)</td>
<td>0.4</td>
</tr>
<tr>
<td>Minor ischemic stroke</td>
<td></td>
<td>38 (30)</td>
<td>186 (22)</td>
<td>0.05</td>
</tr>
<tr>
<td>Major nondisabling stroke</td>
<td></td>
<td>82 (66)</td>
<td>514 (62)</td>
<td>0.4</td>
</tr>
<tr>
<td>Imaging before randomization</td>
<td></td>
<td>42 (34)</td>
<td>172 (21)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cerebral infarction in the symptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>carotid territory on CT brain scan, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque surface irregularity on symptomatic side, n (%)</td>
<td></td>
<td>92 (74)</td>
<td>614 (74)</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean stenosis of ipsilateral external</td>
<td></td>
<td>16 (27)</td>
<td>18 (25)</td>
<td>0.6†</td>
</tr>
<tr>
<td>carotid artery, % (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean stenosis of contralateral carotid</td>
<td></td>
<td>33 (26)</td>
<td>37 (27)</td>
<td>0.2†</td>
</tr>
<tr>
<td>artery, % (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occlusion of the contralateral carotid</td>
<td></td>
<td>10 (8)</td>
<td>54 (7)</td>
<td>0.6</td>
</tr>
<tr>
<td>artery, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Categorical variables were compared with use of the Fisher exact test, and mean values were compared with use of Student’s t test unless otherwise specified.
†Nonparametric data; Mann-Whitney test was used to compare groups.

### TABLE 3. Cox Proportional Hazards Model Predicting First Carotid Territory Ischemic Stroke Ipsilateral to Symptomatic Stenosis on Medical Treatment With Correction for Age, Gender, and Degree of Ipsilateral Carotid Stenosis

<table>
<thead>
<tr>
<th>Angiographic Characteristic</th>
<th>Patients, %</th>
<th>Hazard Ratio (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of symptomatic stenosis*</td>
<td>NA</td>
<td>0.90 (0.74–1.08)</td>
<td>NS</td>
</tr>
<tr>
<td>50–99% stenosis of ipsilateral external</td>
<td>111 (4)</td>
<td>0.98 (0.50–1.44)</td>
<td>NS</td>
</tr>
<tr>
<td>carotid artery, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occlusion of the ipsilateral external</td>
<td>28 (1)</td>
<td>0.40 (0.05–3.0)</td>
<td>NS</td>
</tr>
<tr>
<td>carotid artery, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–99% stenosis of contralateral carotid</td>
<td>262 (9)</td>
<td>1.11 (0.73–1.68)</td>
<td>NS</td>
</tr>
<tr>
<td>artery, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occlusion of the contralateral carotid</td>
<td>90 (3)</td>
<td>0.80 (0.33–1.97)</td>
<td>NS</td>
</tr>
<tr>
<td>artery, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Length of hemodynamically significant portion of the symptomatic carotid stenosis (see text for definition).
asymptomatic carotid stenosis. More work is required to define the Doppler ultrasound characteristics of patients with poststenotic narrowing on angiography.

**Low-Flow Cerebral Protection Hypothesis**

It is interesting to speculate as to why patients with poststenotic narrowing should be at a lower risk of ipsilateral ischemic stroke than patients with the same degree of stenosis but no narrowing, despite having similar clinical characteristics and similar plaque surface morphology. Poststenotic narrowing must indicate low intraluminal pressure due to reduced flow across the stenosis. This is seen as delayed filling of the distal ICA on injection of contrast during conventional angiography. One possible explanation for the low risk of stroke in patients with poststenotic narrowing is that blood flow across the stenosis is now too low to dislodge emboli from the surface of the plaque or to carry large emboli to the brain. It has been suggested that both cerebral microemboli and cerebral hypoperfusion are usually required to cause major cerebral infarction. Patients with poststenotic narrowing of the ICA are likely to have poor perfusion of the ipsilateral cerebral hemisphere, but they are less likely to have cerebral emboli. The number of microemboli detected with transcranial Doppler scanning of the middle cerebral artery distal to symptomatic carotid stenoses falls significantly as the degree of stenosis exceeds 90% and is particularly low in patients with poststenotic narrowing (Prof Hugh Markus, personal communication). Our data are consistent with the hypothesis that in the absence of cerebral emboli, hypoperfusion alone is usually insufficient to cause major cerebral infarction.

It is paradoxical that patients with poststenotic narrowing of the ICA have a low risk of stroke on follow-up but a high frequency of major stroke in the past and a high frequency of infarction in the ipsilateral cerebral hemisphere compared with patients without poststenotic narrowing. However, this is not inconsistent with our hypothesis. The high risk of ipsilateral cerebral infarction in the past suggests that these patients may well have relatively poor cerebral perfusion reserve. In combination with cerebral embolism, this would lead to a high risk of stroke. However, poor perfusion reserve would be a risk factor only for cerebral infarction in the presence of cerebral emboli. When the stenosis becomes very severe and leads to poststenotic narrowing, the emboli rate and the stroke risk fall. In this respect, it may be relevant that the risk of stroke in patients with poststenotic narrowing is similar to that distal to symptomatic carotid occlusion. Moreover, recent results from the NASCET study directly support this hypothesis. An absence of angiographic collateral vessels feeding the cerebral hemisphere distal to the symptomatic carotid stenosis was associated with a high risk of stroke in patients who did not have poststenotic narrowing of the ICA but had no effect on stroke risk in patients with poststenotic narrowing. In other words, low poststenotic flow protected patients from the high stroke risk normally associated with absent collateral circulation.

**Implications for Carotid Imaging, Carotid Endarterectomy, and Measurement of Carotid Stenosis**

First, patients with very severe stenosis and narrowing of the distal ICA may be misdiagnosed as having a complete occlusion with noninvasive methods of imaging such as Doppler ultrasound and magnetic resonance angiography. This has been regarded as one of the main advantages of conventional arterial angiography. However, although further work is required to determine whether these patients derive any benefit from endarterectomy, the low risk of stroke on medical treatment in patients with poststenotic narrowing potentially reduces the importance of misdiagnosis.

Second, contrary to the current clinical impression, patients with recently symptomatic severe carotid stenosis and nar-
rowing of the distal ICA are at a relatively low risk of stroke and do not necessarily require urgent endarterectomy. However, there were too few patients with poststenotic narrowing in the ECST to allow us to sensibly consider the effectiveness of endarterectomy in this subgroup. We intend, therefore, in collaboration with Prof H.J.M. Barnett, to apply the same definition of poststenotic narrowing to patients with symptomatic carotid stenosis in the NASCET trial. The combination of data from the 2 trials should produce a subgroup of sufficient size to allow us to consider the effect of surgery.

Third, the gradual narrowing of the distal ICA as the severity of stenosis exceeds 70% with the ECST method (50% with the NASCET method) has implications for the measurement of carotid stenosis. Patients with and without poststenotic narrowing of the ICA who have the same degree of stenosis with the ECST method (or the common carotid method) will have different degrees of stenosis when measured with the NASCET method. Narrowing of the distal ICA will lead to underestimation of stenosis with use of the NASCET method. In NASCET, this problem was circumvented by the use of the near-occlusion category of stenosis.

The assessment of near occlusion was based primarily on the presence on the randomization angiogram of collateral flow to the symptomatic hemisphere via the circle of Willis or the external carotid artery. Some of these patients had narrowing of the distal ICA, and some did not.

Other Potential Angiographic-Hemodynamic Correlates

Blood flow through an artery begins to fall when linear stenosis exceeds 50%. However, although patients with severe carotid stenosis often have reduced perfusion reserve in the ipsilateral cerebral hemisphere and >50% stenosis is necessary for this to occur, it is rarely sufficient on its own. Patients with hemodynamic insufficiency often also have evidence of reduced collateral flow, usually with ≥50% stenosis of the contralateral ICA and evidence of collateral flow through the ipsilateral external carotid artery. Severe stenosis or occlusion of the contralateral ICA, or possibly even the ipsilateral external carotid artery, might therefore exacerbate any hemodynamic insufficiency by reducing collateral flow. However, we found no association between these characteristics and the risk of ipsilateral ischemic stroke on medical treatment in ECST patients with 50% to 99% symptomatic stenosis. Similarly, the length of an arterial stenosis has been shown to have a measurable hemodynamic effect. The effect is greatest when the degree of stenosis of the vessel is >50%. However, the length of the hemodynamically significant portion of the symptomatic carotid stenosis was unrelated to the risk of stroke on medical treatment. It is possible that these angiographic characteristics are too poorly correlated with cerebral perfusion to have any effect on the risk of stroke on medical treatment, particularly as we were unable to assess the presence or absence of collateral flow via the external carotid circulation and the circle of Willis. It is also possible that an effect was missed because of an insufficient numbers of patients and strokes. However, despite these limitations, occlusion of the contralateral carotid artery has been shown consistently to be associated with an increased risk of stroke due to carotid endarterectomy. It is at least possible to conclude that there was no evidence to suggest that these angiographic characteristics are of major value in the identification of patients at an especially high risk of stroke on medical treatment.

Conclusions

Poststenotic narrowing of the ICA can be defined in a reproducible and clinically useful way with the ICA/CCA ratio. Patients with recently symptomatic severe carotid stenosis who have a ratio that is below the lower limit of normal in patients with 0% to 49% stenosis (=0.4) have a significantly reduced risk of stroke on medical treatment alone. This risk is comparable to that distal to complete carotid occlusion. Further research is required to determine whether such patients benefit from carotid endarterectomy. Taken together with other recent observations, these findings support the hypothesis that low flow alone is not usually a sufficient cause of ischemic stroke distal to symptomatic carotid stenosis. We suggest that in patients with carotid stenosis, low poststenotic flow may in fact protect the brain from infarction by reducing the frequency of cerebral embolism.

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References

Low Risk of Ischemic Stroke in Patients With Reduced Internal Carotid Artery Lumen Diameter Distal to Severe Symptomatic Carotid Stenosis: Cerebral Protection Due to Low Poststenotic Flow?

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