Importance of Intracranial Atherosclerotic Disease in Patients With Symptomatic Stenosis of the Internal Carotid Artery

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Background and Purpose—The estimated prevalence of intracranial atherosclerotic disease (IAD) in patients with stenosis of the extracranial internal carotid artery (ICA) varies between 20% and 50%. The benefits of carotid endarterectomy (CE) in patients with both IAD and symptomatic extracranial ICA stenosis are uncertain.

Methods—The association between IAD and other vascular risk factors and with the risk of stroke at 3 years were studied in patients with symptomatic extracranial ICA stenosis who participated in the North American Symptomatic Carotid Endarterectomy Trial (NASCET). Since the NASCET protocol excluded severe IAD, only a modest number of patients in this category could be studied.

Results—IAD was observed in one third of the patients. In medically treated patients, the relative risk of stroke associated with IAD varied from 1.3 (95% CI, 0.9 to 1.9) with extracranial ICA stenosis of 50% to 1.8 (95% CI, 1.1 to 3.2) with 85% to 99% ICA stenosis. In contrast, IAD did not affect the risk of stroke among surgically treated patients. To prevent 1 stroke ipsilateral to the symptomatic ICA stenosis over 3 years in patients who have also IAD, 12 patients with 50% to 69%, 5 patients with 70% to 84%, and 3 patients with 85% to 99% ICA stenosis have to undergo CE. In patients without IAD these numbers are 26, 7, and 6, respectively.

Conclusions—IAD is an independent risk factor for subsequent stroke in medically treated patients with symptomatic ICA stenosis. CE reduces this risk. The additional risk imposed by IAD in medically treated patients enhances the value of CE in patients with moderate symptomatic extracranial ICA stenosis. Detection of IAD, requiring angiography, is an important prelude to planning CE in symptomatic patients with moderate extracranial ICA stenosis. (Stroke. 1999;30:282-286.)

Key Words: angiography ■ carotid artery diseases ■ carotid endarterectomy ■ outcome ■ risk factors

Carotid endarterectomy (CE) has been shown to be beneficial in patients who have had a transient ischemic attack (TIA) or nondisabling stroke attributable to a 70% to 99% stenosis of the internal carotid artery (ICA). For patients with an ICA stenosis between 50% and 70%, the decision about whether they should undergo CE is less certain and is dependent on other vascular risk factors and concomitant vascular diseases. One of the factors that has received little attention within this decision-making process is intracranial atherosclerotic disease (IAD). IAD has been associated with a poor prognosis.

Because CE is particularly beneficial in patients with risk factors that confer poor prognosis on those treated medically, it may be hypothesized that the procedure is useful in patients who have both an extracranial ICA stenosis and IAD. On the other hand, IAD may lower the benefits of CE, since the removal of a stenotic lesion in the proximal part of the vascular tree may yield a lesser benefit in the presence of a more distally localized stenosis. Another reason for concern may be that CE has been reported to have an increased perioperative risk in the presence of carotid siphon stenosis. As a consequence, the benefits of CE in reducing future stroke in patients with both IAD and extracranial ICA stenosis remain uncertain. Resolving this issue is of increased importance because CE is being advocated by some with anecdotal evidence on the basis of ultrasound examination or MR angiography only, for which usually no or only partial intracranial imaging is performed.

The purpose of the present study is to assess the role of IAD in making decisions regarding CE by using data from the North American Symptomatic Carotid Artery Trial (NASCET).

Subjects and Methods

NASCET was a randomized, multicenter clinical trial designed to determine the role of CE in patients with symptomatic ICA stenosis. The patients randomized into NASCET had a recent TIA or
nondisabling ischemic stroke in the territory of an ICA with an extracranial atherosclerotic lesion that narrowed the artery by ≥30% and was accessible for surgery. The methods and the final results have been published elsewhere.1–3,15 Patients were not eligible if they had a probable source of embolism in the heart, if they had other serious diseases likely to cause death within 5 years, or if they had ICA stenosis distal to the second cervical vertebral body or MCA stenosis proximal to or at the trifurcation that was judged to be more significant than the surgically accessible ICA lesion.

Before randomization, all patients underwent selective carotid angiography with a minimum of 2 projections showing both the cervical and the intracranial portions of the carotid arteries and their main intracranial branches. The stenosis of the extracranial carotid artery was measured at the site of the maximal residual diameter and compared with the diameter of the distal artery at the point at which the walls became parallel.16 All angiograms were reviewed by the principal neuroradiologist of NASCET (A.J.F.). IAD was defined as any atherosclerotic wall irregularity or stenosis in the intracranial portion of the ICA or in the main trunk of the anterior or middle cerebral artery. Lateral or oblique projections were reviewed to assess IAD in the intracranial part of the ICA, whereas anteroposterior projections were used for the middle and anterior cerebral arteries. The stenosis of the intracranial arteries was also measured at the site of the maximal residual diameter (numerator) and compared with the estimated original diameter (denominator). In performing this measurement, we used the diameter of the artery above the diseased segment to estimate the original diameter of the diseased portion. IAD was classified as absent, mild (atherosclerotic wall irregularities but no stenosis), moderate (stenosis of <50% of the original diameter), or severe (stenosis of ≥50% of the original diameter or occlusion). The location of IAD (infraclinoid ICA disease, supraclinoid ICA disease, or anterior or middle cerebral artery disease) was also recorded. Ipsilateral IAD refers to IAD in the hemisphere corresponding to the symptomatic lesion for which the patient was randomized. Fifty angiograms were also reviewed by L.J.K., without knowledge of the assessments by A.J.F., to determine the interobserver variability with respect to the presence and severity of IAD. Interobserver agreement was assessed by means of a \( \kappa \) statistic.

For the present study, a composite of any stroke or death within 30 days after randomization or the occurrence of stroke ipsilateral to the symptomatic ICA lesion (further defined as “ipsilateral stroke”) was the primary outcome. Patients who changed treatment group during follow-up were included in the analyses up to the time of crossover. For the primary analysis, patients were categorized into 2 groups, those with and those without ipsilateral IAD. In a secondary analysis, outcome events were correlated to the site and severity of IAD. We also studied the association between future stroke and IAD in the supply territory of the ICA contralateral to the side of randomization in patients with a stenosis of that artery.

Characteristics of patients with and without intracranial disease were compared by use of a \( \chi^2 \) test. The prognostic impact of IAD on subsequent risk of stroke in patients with different degrees of ICA stenosis was assessed with Kaplan-Meier survival analyses and Cox proportional hazards regression modeling. The likelihood ratio test was used to assess the significance of the risk factors. The “change-in-estimate” strategy was used to measure the level of confounding among the risk factors in the model.17

**Results**

Mild ipsilateral IAD was found in 776 patients (26.9%), moderate IAD in 166 (5.8%), and severe ipsilateral IAD in 14 (0.5%). In 1633 patients (56.6%) IAD was absent, and in 296 (10.3%) the angiogram did not allow the assessment of IAD. The infraclinoid portion of the ICA was affected approximately 7 times more often than the supraclinoid portion or the anterior or middle cerebral artery (Table 1). The 2 observers agreed on the presence and severity of IAD in 44 of the 50 angiograms (88%) that were reviewed for the interobserver study, resulting in an interobserver agreement coefficient (\( \kappa \)) of 0.74.

Baseline characteristics are shown in Table 2. In general, patients with IAD were more likely to harbor the common vascular risk factors: smoking, hypertension, diabetes mellitus, coronary artery disease, and intermittent claudication.18 The presence of IAD was also associated with race other than white, higher degree of ICA stenosis, and irregular or ulcerated plaques. Patients without IAD more often had TIAIs as the presenting event whereas patients with IAD more often had longer lasting deficits, but this difference was not statistically significant (\( P=0.11 \)). The risk of any stroke or death within 30 days after CE (perioperative risk) was 6.7% in the group without IAD and 6.1% in the group with IAD (\( P=0.64 \)). Multivariate analyses performed with Cox proportional hazards regression did not identify any baseline characteristics as confounders, and therefore no statistical adjustments were made to the Kaplan-Meier risk estimates.

The Kaplan-Meier risks of ipsilateral stroke at 3 years are summarized in Figure 1 and Table 3. For patients who received best medical care only, the risk of stroke was increased by the presence of IAD and further modified by the degree of extracranial ICA stenosis. However, the risk of stroke for the patients who underwent CE was not altered by either the degree of ICA stenosis or by the presence of IAD (\( P=0.014 \) for the test of interaction between IAD, degree of ICA stenosis, and type of treatment). To increase the precision of the risk estimates, the results from the patients who underwent CE are reported as single values in Figure 1. The difference in the ipsilateral stroke risk at 3 years between medically treated patients with and without ipsilateral IAD was 5 times less in the group with <50% ICA stenosis (4.2%) than in the group with 85% to 99% ICA stenosis (20.4%) (Table 3). The corresponding relative risks (RRs) of stroke in the presence of IAD increased from 1.3 to 1.8 as the degree of extracranial ICA stenosis ranged from mild to very severe (Table 3). In terms of surgical benefits, the number of patients with IAD and an extracranial ICA stenosis of 85% to 99% needed to undergo CE to prevent 1 additional stroke in 3 years is only 3. This number rapidly increases with lesser degrees of ICA stenosis and is further accentuated by the absence of intracranial disease (Table 4). To prevent 1 ipsilateral stroke in 3 years, 12 patients with IAD and an extracranial ICA stenosis of 50% to 69% have to undergo CE.
The RR for ipsilateral stroke associated with moderate or severe ipsilateral IAD versus none in the medically treated patients was 1.4 (95% CI, 0.9 to 2.1) and was in the same range as the RRs found in the total group of medically treated patients with IAD (Table 3). The RR for ipsilateral stroke in medically treated patients with atherosclerotic lesions of the middle or anterior cerebral artery was 1.9 (95% CI, 1.3 to 2.8), but in patients with lesions of the intracranial ICA it was 1.3 (95% CI, 1.0 to 1.7).

The effect of IAD on outcome was also examined in NASCET patients with an asymptomatic 30% to 99% stenosis of the extracranial ICA contralateral to the side of randomization. These asymptomatic lesions were not operated on. Among 1796 patients, 518 (28.8%) also had IAD on the asymptomatic side. The 3-year risk of stroke in the supply territory of the contralateral ICA was 6.2% in patients with IAD versus (4.8%) in those without IAD (RR, 1.3; 95% CI, 0.8 to 2.0). As was observed in the patients with IAD ipsilateral to the symptomatic extracranial ICA stenosis, the risk of future stroke was dependent on both the presence of IAD and the severity of the asymptomatic extracranial ICA stenosis (Figure 2).

Discussion

Ipsilateral IAD is an independent risk factor for subsequent stroke in patients with symptomatic ICA stenosis who are treated with the best medical care only but not in patients who have undergone CE. Therefore, the risk estimate for this group is reported in aggregate form as a single value. A test of interaction between IAD, degree of stenosis, and type of treatment yielded a value of $P=0.0014$.

<table>
<thead>
<tr>
<th>Degree of ICA stenosis:</th>
<th>Absent, % (n=1929)</th>
<th>Present, % (n=956)</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50%</td>
<td>49.6</td>
<td>43.1</td>
<td></td>
</tr>
<tr>
<td>50–69%</td>
<td>28.4</td>
<td>32.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>70–84%</td>
<td>12.7</td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td>85–99%</td>
<td>9.4</td>
<td>7.8</td>
<td></td>
</tr>
</tbody>
</table>

*Refers to the overall association between a risk factor and IAD.

Figure 1. Kaplan-Meier estimates of ipsilateral stroke risk at 3 years by appearance of IAD, degree of extracranial ICA stenosis, and treatment group. The presence of IAD did not affect the risk of stroke in the patients who underwent CE. Therefore, the risk estimate for this group is reported in aggregate form as a single value. A test of interaction between IAD, degree of stenosis, and type of treatment yielded a value of $P=0.0014$. Widespread atheromatous disease also may enhance thrombogenesis systemically and thus increase the likelihood of embolism from a stenotic proximal ICA lesion. Because CE may increase intracranial flow, another possibility may be that low flow is an important contributor in the genesis of an infarction in the presence of both an extracranial
ICA stenosis and ipsilateral IAD. Alternatively, an embolus from the extracranial part of the ICA may be more likely to cause permanent obstruction of an intracranial artery in the presence of IAD, but only transient obstruction in its absence. This suggestion may be supported by the observation that patients without IAD more often had TIAs whereas patients with IAD more often had longer-lasting deficits, although this was not statistically significant (Table 1).

The prevalence of IAD in one third of the NASCET patients is within the range that has been described before in patients considered suitable for CE. Depending on the definition of IAD, the prevalence varied between 20% and 50%. The $\kappa$ value of 0.74 reflected good interobserver agreement. One previous study of IAD has been published with similar good intraobserver agreement. Consequently, it should be possible to extrapolate our observations to the future management of patients with symptomatic extracranial ICA stenosis and IAD.

Both the risk of stroke and the risk factors that were observed in the NASCET patients with IAD who did not undergo CE correspond with those in earlier studies. However, IAD has not previously been reported as an independent risk factor for future stroke. The site of IAD is dependent on race. In white subjects the extracranial arteries are affected more often, whereas the middle cerebral artery is most common in blacks and Chinese. Although only 7% of the NASCET population was nonwhite, we also found that IAD was more common in these patients. IAD affecting the major intracerebral arteries was associated with a worse prognosis than IAD affecting the intracranial portion of the ICA, but this finding is based on small numbers in the subgroups. The impact on long-term outcome of different sites of IAD in the presence of extracranial ICA stenosis has not been reported previously.

In the European Carotid Surgery Trial, ipsilateral stenosis of the carotid siphon was associated with an increased perioperative risk. In NASCET the presence of ipsilateral IAD did not alter the perioperative risk, as has been described before in other studies. Our study could not give final answers to the issue of whether severe intracranial stenosis should contraindicate CE, but this is probably of minor clinical relevance. During the early years of NASCET, records were kept in 93 participating centers of all patients who were not eligible for the trial. Only 23 of 1059 symptomatic patients who could not be randomized (2.3%) had a more significant intracranial stenosis than the surgically accessible lesions. (NASCET, unpublished data, 1998) In 14 patients who were randomized into NASCET with severe intracranial stenosis, the operative risk was not different from that for patients with mild or moderate stenosis.

Subgroup analyses arising from clinical trials must be interpreted cautiously. The NASCET angiograms were primarily meant to assess the extracranial ICA. However, intracranial views were requested in all patients, and one of the strengths of the present study is the consistent assessment of IAD and its relationship to the risk of stroke.

### Table 3. Three-year Risk of Ipsilateral Stroke Associated with IAD, According to Degree of ICA Stenosis

<table>
<thead>
<tr>
<th>Degree of ICA Stenosis</th>
<th>Patients Treated With Medical Care</th>
<th>Patients Who Underwent CE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IAD Absent</td>
<td>IAD Present</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>13.8</td>
<td>18.0</td>
</tr>
<tr>
<td>50%–69%</td>
<td>14.7</td>
<td>19.4</td>
</tr>
<tr>
<td>70%–84%</td>
<td>23.5</td>
<td>28.8</td>
</tr>
<tr>
<td>85%–99%</td>
<td>25.3</td>
<td>45.7</td>
</tr>
</tbody>
</table>

Risk values are given as percentages.
of all angiograms by the same experienced neuroradiologist. In addition, all data recorded in the NASCET database was obtained prospectively. As we could not compare our results with other studies dealing with the same type of patients, because none are available, we decided to study the influence of IAD also in the hemisphere contralateral to the side of randomization. Although the number of strokes that occurred in the contralateral hemisphere was small, the RR associated with IAD was in the same range as was found in the hemisphere ipsilateral to side of randomization. In addition, the same pattern of increased stroke risk was observed when moderate or severe ipsilateral IAD was analyzed.

In conclusion, the present results indicate that in patients in whom CE is being considered, information about intracranial arteries obtained from angiography is useful. IAD is an independent risk factor for patients with a symptomatic ICA stenosis that is not surgically removed. The presence of IAD should not be a reason to abandon CE in patients with symptomatic 70% to 99% ICA stenosis. Our observations need confirmation, but CE may be taken into consideration in patients with symptomatic, moderate ICA stenosis who have also IAD.

Acknowledgments

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References

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