Incidental Intracranial Aneurysms in Patients With Internal Carotid Artery Stenosis

A CT Angiography Study and a Metaanalysis

Laura M. Héman, MD; Lisa M. Jongen, MD; H. Bart van der Worp, MD, PhD; Gabriel J.E. Rinkel, MD, PhD; Jeroen Hendrikse, MD, PhD

Background and Purpose—Smoking and hypertension are important risk factors for atherosclerotic carotid artery disease, but also for intracranial aneurysms. We studied the presence of aneurysms in a series of patients with internal carotid artery (ICA) stenosis and performed a systematic review of the literature to assess in patients with ICA stenosis the prevalence of intracranial aneurysms, gender differences in prevalence, and the size of the aneurysms found.

Methods—In a prospectively collected series of patients with symptomatic ICA stenosis >50% on CTA we assessed the proportion with intracranial aneurysms. We performed “Embase” and “Pubmed” searches for studies on patients with ICA stenosis (domain) and intracranial aneurysms (outcome measurement). We calculated overall prevalence and relative risks for gender, both with corresponding 95% confidence intervals (CI).

Results—We found an intracranial aneurysm in 8 of our 194 patients (4.1%; [95% CI 1.3 to 6.9]). The literature search resulted in 5 relevant and valid articles, totaling 4251 patients. The overall prevalence in all series combined was 3.2% (95% CI 2.7 to 3.7); the prevalence of aneurysms larger than 5 mm was 0.9% (95% CI 0.6 to 1.1). Women had a higher risk than men (relative risk 1.6; [59% CI 1.1 to 2.3]).

Conclusion—About 1% of patients with a symptomatic ICA stenosis have an intracranial aneurysm with a higher than negligible risk of rupture, but in deciding aneurysms treatment the risk of cardiovascular diseases other than aneurismal rupture should be taken into account. The proportion of patients with aneurysms seems higher in series of patients with ICA stenosis than in the general population. (Stroke. 2009;40:1341-1346.)

Key Words: intracranial aneurysm ■ carotid stenosis ■ CT angiography

In a systematic review on the prevalence of incidental aneurysms in autopsy and angiography studies, atherosclerotic diseases seem to increase the risk of incidental aneurysms. This relation may be explained by the fact that atherosclerotic diseases and intracranial aneurysms share common risk factors. However, in that review a broad domain for atherosclerotic diseases was chosen ranging from angina pectoris to ischemic cerebrovascular disease. This broad domain may explain the substantial differences between studies in aneurysm prevalence. These facts make it difficult to subtract a conclusion exclusively for the prevalence of intracranial aneurysms in patients with atherosclerotic carotid stenosis. Moreover, at the time of that review, only studies that used conventional angiography were available. Nowadays, there are various diagnostic techniques that can discover cerebral aneurysms as incidental findings. The disadvantage for DSA when used to assess internal carotid artery (ICA) stenosis is that the vertebrobasilar system often is not visualized properly. Accordingly, aneurysms at the posterior circulation may go undetected. CT angiography (CTA) is routinely used in patients with subarachnoid hemorrhage, but can also be used in aneurysm screening, follow-up, and anatomic characterization, and includes the most important parts of the vertebrobasilar circulation. Accuracy of CTA is 89% for detecting aneurysms and 96% for detection of aneurysms larger than 3 mm. Therefore, CTA images of the intracranial circulation acquired for the assessment of the carotid stenosis and the carotid bifurcation could also be used to assess the prevalence of cerebral aneurysms in patients with symptomatic ICA stenosis.

The aim of this study is to provide an overview of the prevalence of asymptomatic intracranial aneurysms in patients with internal carotid artery stenosis. We assessed the proportion with intracranial aneurysms in a prospectively collected series of patients with a symptomatic ICA stenosis >50% on CTA. Furthermore, we performed a
literature review on the prevalence of intracranial aneurysms in patients with carotid artery stenosis, assessed sex differences in prevalence, and evaluated the sizes of the aneurysms found.

Materials and Methods

Patients
Participants in the present study were prospectively included in the “International Carotid Stenting Study” (ICSS). The study design and protocol of this trial have been described elsewhere. All patients were over the age of 40 years and had a recently symptomatic atherosclerotic ICA stenosis >50%. None of the patients had current or past evidence of a subarachnoid hemorrhage. For research purposes, both CTA and carotid ultrasound investigations were performed in patients with a symptomatic carotid artery stenosis included in the ICSS study in our center. We included 194 patients (132 men and 62 women, mean age 70 ± 10 years) with symptomatic ICA stenosis who underwent CTA before carotid endarterectomy (CEA) or carotid artery stenting. Ten patients had a symptomatic ICA stenosis of 50% to 70% and 184 a stenosis greater than 70%.

CT Angiography
CT angiography was performed with a 16 to 40 or 64-slice scanner (Philips Medical Systems). To minimize dental artifacts patients were scanned in supine position with the head tilted so that the mandible was perpendicular to the table. The scan range started 3 cm under the vertex and ended below the aortic arch. Either a 16×0.75 mm, 40×0.625 mm, or 64×0.625 mm collimation was used, with a pitch between 0.77 and 0.85 (depending on the scanner options) and a rotation time of 0.42 s. Exposure settings were 120 kVp and 180 mAs. Overlapping sections of 1.0 mm (16 slice) or 0.9 mm slice thickness (40 or 64 slice) were reconstructed at a reconstruction interval of 0.5 mm and a field of view of 160 mm. CTA was performed after injection of 50 mL contrast material (Ultravist 300, Schering) at 5 mL/s, followed by a saline chaser bolus of 50 mL injected at the same flow rate. The scan delay was determined from injection of a bolus of 40 mL contrast...

Figure 1. Flowchart literature search.

Figure 2. CTA images show a 4.5-mm aneurysm of the right middle cerebral artery with an axial (A), coronal (B), and sagittal (C) MIP reconstruction. CTA images show an 8-mm aneurysm of the basilar artery with an axial (D), coronal (E), and sagittal (F) MIP reconstruction. CTA images show a 4-mm aneurysm of the anterior communicating artery with an axial (G), coronal (H), and sagittal (I) MIP reconstruction.
material that was used for a brain perfusion study. The resulting images were sent to a dedicated CT workstation (Extended Brilliance Workspace, Philips) for further evaluation.

Assessment of Incidental Findings
We reviewed the CTA scans made from October 2003 until February 2008. All scans were read by experienced neuroradiologists. For this study, we screened all 194 CTA reports for aneurysms. The location of the aneurysms and the size of the ICA stenosis were recorded. We measured the largest size of the aneurysms. Furthermore, we determined the prevalence of aneurysms in women and men separately.

Literature Review
We performed a systematic literature search to determine the prevalence of aneurysms in patients with ICA stenosis (Figure 1). We defined a domain (patients with carotid artery stenosis), a determinant (imaging of the head), and an outcome (aneurysms or incidental findings). We compiled a query with synonyms of these components. Synonyms were connected with “OR” in the search string, while the domain, determinant and outcome were connected with “AND.” With this procedure we created a query for the databases “EMBASE” and “PubMed.” However, after screening related articles we seemed to have missed some relevant articles. This was explained by the fact that some articles did not mention the determinant, namely the way of imaging, in their title or abstract. Therefore, we compiled a new search string with only the domain and outcome incorporated. Then, the missing articles were included in the search results, but the number of hits was very high (3146 articles). To reduce the number of articles we performed two actions. First, we searched for articles with the word “carotid” mentioned in the title, because of its relevance of including patients with carotid stenosis. Second, we limited the articles to those in English, German, and Dutch. This search resulted in 1086 hits. We excluded all articles that did not contain our domain, determinant, and outcome. Furthermore, we excluded all case reports.

Data Analysis
First, we calculated the prevalence of the aneurysms. More than one aneurysm found in a single patient was counted as a single finding, both in our patient study as in studies found in the literature. In the patients study, descriptive statistical analyses in the patient study were performed to define characteristics of the patients, carotid artery stenosis and aneurysms. We pooled the results and calculated an overall prevalence and 95% confidence interval in the retrieved articles and our series. To analyze sex differences we used a subset, because not all articles provided the relevant information. With the available results we calculated the relative risk and 95% confidence interval for men and women. Furthermore, we described characteristics of the aneurysms we found in our patient study and of the aneurysms described in the articles of the systematic literature review and calculated the prevalence of aneurysms larger than 5 mm.

Results
Patient Study
We found 9 aneurysms in 8 of our 194 patients: a prevalence of 4.1% (95% CI 1.3 to 6.9%). Figure 2 shows axial, coronal,

### Table 1. Baseline Characteristics of Patients Included in the CTA Study

<table>
<thead>
<tr>
<th>Year of Publication</th>
<th>Population</th>
<th>No of Participants</th>
<th>Mean Age</th>
<th>% Female</th>
<th>Imaging Method</th>
<th>No of Patients</th>
<th>% Aneurysms</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>(2003–2008)</td>
<td>Symptomatic patients with ICA stenosis &gt;50%</td>
<td>194</td>
<td>70</td>
<td>CTA</td>
<td>8</td>
<td>4.1%</td>
<td>1.3 to 6.9</td>
</tr>
<tr>
<td>Kappelle et al⁵²</td>
<td>2000 (1987–1991)</td>
<td>Symptomatic patients with ICA stenosis 30% to 99%</td>
<td>2885</td>
<td>66</td>
<td>Angiography</td>
<td>90</td>
<td>3.1%</td>
<td>2.5 to 3.8</td>
</tr>
<tr>
<td>Ballotta et al¹³</td>
<td>2006 (1992–1999)</td>
<td>Patients with (asymptomatic ICA stenosis &gt;70% who underwent CEA</td>
<td>474</td>
<td>±72</td>
<td>DSA (81.3%); MRA/CTA (18.7%)</td>
<td>11</td>
<td>2.3%</td>
<td>1.0 to 3.7</td>
</tr>
<tr>
<td>Griffiths et al⁴⁵</td>
<td>1996 (1993)</td>
<td>Patients before possible CEA</td>
<td>100</td>
<td>62</td>
<td>Angiography</td>
<td>7</td>
<td>7%</td>
<td>2.0 to 12.0</td>
</tr>
<tr>
<td>Pappada et al⁵⁶</td>
<td>1996 (unknown)</td>
<td>Patients for intervention of carotid stenosis</td>
<td>389</td>
<td>67</td>
<td>Angiography</td>
<td>10</td>
<td>2.6%</td>
<td>1.0 to 4.1</td>
</tr>
<tr>
<td>Kann et al⁶⁶</td>
<td>1997 (unknown)</td>
<td>Patients with asymptomatic carotid disease</td>
<td>209</td>
<td>±68</td>
<td>Unknown</td>
<td>10</td>
<td>4.8%</td>
<td>1.9 to 7.7</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ICA, internal carotid artery; CEA, carotid endarterectomy; DSA, digital subtraction angiography; MRA, magnetic resonance angiography; CTA, computed tomography angiography; ±, mean age abstracted from given information in article.
and sagittal CTA images of patients with a middle cerebral artery aneurysm, a basilar artery aneurysm, and an anterior communicating artery aneurysm. The mean size of the aneurysms ± SD was 4.3 mm ± 2.0 mm (range, 2 to 8 mm). Two aneurysms were larger than 5 mm: 1 MCA aneurysm of 7 mm and 1 basilar artery aneurysm of 8 mm. Six aneurysms were located at the middle cerebral artery. Other locations were the posterior inferior cerebellar artery, the basilar artery, and the anterior communicating artery. One patient had 2 MCA aneurysms. The prevalence in women was higher (8.1% [95% CI 1.3 to 10.8]) than in men (2.3% [95% CI 0.3 to 3.6]). In 6 of the 8 patients with aneurysms, the aneurysm was located ipsilateral to the symptomatic ICA stenosis. The mean age of the patients with an aneurysm (69 ± 9 years) did not differ from the mean age of patients without an aneurysm (70 ± 9 years). Table 1 shows the prevalence of other cardiovascular risk factors in the patients with and without incidentally found intracranial aneurysms.

### Table 3. Characteristics of Patients and Aneurysms Found in Our Study and in the Literature

<table>
<thead>
<tr>
<th>Mean Age Patients With Aneurysms (Mean Age Study Population)</th>
<th>% Female</th>
<th>% Male</th>
<th>Location % (No. of Patients)</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>68 (70)</td>
<td>8.1</td>
<td>Anterior communicating artery 12.5% (n=1)</td>
<td>&lt;5 mm: 77.8% (n=7)</td>
</tr>
<tr>
<td>Ma C 62.5% (n=5)</td>
<td></td>
<td></td>
<td>Cerebellar 12.5% (n=1)</td>
<td>6–9 mm: 22.2% (n=2)</td>
</tr>
<tr>
<td>Ma C 62.5% (n=1)</td>
<td></td>
<td></td>
<td>Basilar artery 12.5% (n=1)</td>
<td>&gt;10 mm: 0% (n=0)</td>
</tr>
<tr>
<td>Kappelle et al²</td>
<td>66 (66)</td>
<td>4.0</td>
<td>Cavernous carotid 26.7% (n=24)</td>
<td>&lt;5 mm: 82.8% (n=82)</td>
</tr>
<tr>
<td>Supraclinoid carotid 50% (n=45)</td>
<td></td>
<td></td>
<td>Anterior communicating artery 12.2% (n=11)</td>
<td>6–9 mm: 13.1% (n=13)</td>
</tr>
<tr>
<td>Ma C 20% (n=18)</td>
<td></td>
<td></td>
<td>Cerebellar 1.1% (n=1)</td>
<td>&gt;10 mm: 4.0% (n=4)</td>
</tr>
<tr>
<td>Ballotta et al³</td>
<td>72 (unknown)</td>
<td>...</td>
<td>Anterior communicating artery 27.3% (n=3)</td>
<td>&lt;5 mm: 50% (n=6)</td>
</tr>
<tr>
<td>Ma C (n=8)</td>
<td></td>
<td></td>
<td>Cerebellar 9.1% (n=1)</td>
<td>6–9 mm: 25% (n=3)</td>
</tr>
<tr>
<td>Griffiths et al⁴</td>
<td>unknown (62)</td>
<td>...</td>
<td>Cavernous carotid 26.8% (n=2)</td>
<td>&lt;5 mm: 85.7% (n=6)</td>
</tr>
<tr>
<td>Supraclinoid carotid 14.3% (n=1)</td>
<td></td>
<td></td>
<td>Ma C 42.9% (n=3)</td>
<td>6–9 mm: 14.3% (n=1)</td>
</tr>
<tr>
<td>Ma C 14.3% (n=1)</td>
<td></td>
<td></td>
<td>Basilar artery 14.3% (n=1)</td>
<td>&gt;10 mm: 0% (n=0)</td>
</tr>
<tr>
<td>Pappada et al⁵</td>
<td>63 (67)</td>
<td>3.1</td>
<td>Supraclinoid carotid 30% (n=3)</td>
<td>&lt;5 mm: 22.2% (n=1)</td>
</tr>
<tr>
<td>Anterior communicating artery 20% (n=2)</td>
<td></td>
<td></td>
<td>Ma C 30% (n=3)</td>
<td>6–9 mm: 55.5% (n=7)</td>
</tr>
<tr>
<td>Anterior cerebral artery 20% (n=2)</td>
<td></td>
<td></td>
<td>Ma C 30% (n=3)</td>
<td>&gt;10 mm: 22.2% (n=2)</td>
</tr>
<tr>
<td>Kann et al⁶</td>
<td>68 (unknown)</td>
<td>...</td>
<td>Cavernous carotid 30% (n=3)</td>
<td>&lt;5 mm: 80% (n=8)</td>
</tr>
<tr>
<td>Supraclinoid carotid 40% (n=4)</td>
<td></td>
<td></td>
<td>Ma C 20% (n=2)</td>
<td>6–9 mm: 10% (n=1)</td>
</tr>
<tr>
<td>Posterior communicating artery 10% (n=1)</td>
<td></td>
<td></td>
<td>Ma C 20% (n=2)</td>
<td>&gt;10 mm: 10% (n=1)</td>
</tr>
</tbody>
</table>

MCA indicates middle cerebral artery.

### Metaanalysis

In Table 2 we summarize the results of the literature search and our patient study of aneurysms detected in patients with ICA stenosis. In Table 3 we compare the characteristics of the aneurysms in our patient study with those of the literature search. We found 5 relevant and valid studies, including a total of 4251 patients. Mean ages ranged from 62 to 72 years old. The populations were North American², six or European (Italy,³,⁵ Great Britain,²,⁴). A total of 147 aneurysms was found in 136 patients. The overall prevalence of intracranial aneurysms in all series combined was 3.2% [95% CI 2.7 to 3.7] (Figure 3). Of the 147 aneurysms, 37 were larger than 5 mm (0.9% [95% CI 0.6 to 1.1]), and 10 were larger than 10 mm (0.2% [95% CI 0.1 to 0.4]). The locations of the intracranial aneurysms were as follows: cavernous internal carotid artery (n = 29), supraclinoid internal carotid artery (n = 53), anterior communicating artery (n = 17), middle cerebral artery (n = 40), cerebellar (n = 5), basilar (n = 2), and
The prevalence of intracranial aneurysms appears higher in patients with ICA stenosis than in a general population. Recent large studies in the general population with mean age between 20 and more than 70 years of age found prevalences of intracranial aneurysms of 0%, 0.1%, 0.11%, 0.2%, and 1.8%. However, comparison between these studies of healthy populations and the results of our literature review is difficult. First, age is an important risk factor in the prevalence of aneurysms, with an increase in prevalence in more elderly populations. Secondly, prevalences may be affected by differences in the percentage of women included and by the fact that the studies were performed in different countries. Nevertheless, our results suggest a higher prevalence of asymptomatic aneurysms in patients with ICA stenosis than in the general population. A higher prevalence of asymptomatic intracranial aneurysms in patients with ICA stenosis may be explained by risk factors that intracranial aneurysms and atherosclerotic ICA stenosis have in common. Athero-sclerosis can produce morphological changes causing fibrous tissue deposition. Weakened vessels can dilate and form an aneurysm. Another explanation for the higher prevalence of intracranial aneurysms in patients with carotid artery disease could be an alteration in flow pattern associated with ICA stenosis. In the presence of an ICA stenosis the flow velocity in the internal carotid artery increases drastically, and this may have effects on the vasculature downstream and may in turn influence the development of cerebral aneurysms. Because of the small number of patients with aneurysms in our own series and because of insufficient data in the literature, we were not able to study the relation between the side of the stenosis and the side of the aneurysm.

We found a higher risk in women than in men. This corresponds with the observed higher prevalence of aneurysms in women in general populations. Overall, prevalence of cardiovascular disease is lower in women than in men. The higher prevalence of aneurysms in women within the subset of patients with ICA stenosis suggests involvement of factors other than atherosclerosis, smoking, and hypertension in aneurysm formation, such as hormonal factors.

The search string in the literature search was broad to decrease the possibility that relevant articles were missed. The broad search resulted in 1086 articles that fulfilled the search criteria. However, most of these articles had to be excluded because the studies were not performed in patients with an internal carotid artery stenosis, no imaging of the head was performed, or the studies did not investigate the presence of intracranial aneurysms. Therefore, only 5 articles fulfilled all the inclusion criteria. Of the 5 reported studies, those with the smallest populations found the highest incidence of aneurysms. Therefore, publication bias cannot be disproved. Another remarkable fact is the higher percentages of medium-sized (6 to 9 mm) and large (>10 mm) aneurysms found in the Italian studies, which also found the lowest prevalence of aneurysms. The high proportion of large aneurysms in these studies might therefore be explained by underdiagnosis of small aneurysms. In our patient study, which is the first using CTA to determine the prevalence of intracranial aneurysms in patients with ICA stenosis, we also could have missed a few aneurysms because of a sensitivity of 89% of CTA compared to conventional angiography. We presume that this possible underestimation is of minor importance because the prevalence of 4.1% in our series is higher than the mean calculated prevalence of 3.2%, because aneurysms of the posterior circulation are more likely to be detected with CTA than with conventional angiography within this subset of patients, and because we did find 3 aneurysms of 3 mm or smaller. This suggests that the sensitivity of CTA for the detection of intracranial aneurysms in our study may have been higher than in a review on test characteristics of CTA. Finally, not detecting very small aneurysms in this subset of patients is probably of minor clinical importance, as most of these small aneurysms will not be treated because of their small risk of rupture.

Current imaging techniques used for the detection and grading of carotid artery stenosis, such as the CTA technique in the present study, have a large coverage. This large coverage introduces the risk of finding asymptomatic intracranial cerebral aneurysms. These incidentally detected aneurysms will have only clinical consequences in the few patients with very large aneurysms, which have a high risk of future rupture. In the vast majority of patients with symptomatic ICA stenosis and incidental aneurysms the stroke risk of
ischemic stroke or heart disease will exceed the rupture risk of aneurysms, especially in elderly patients. Furthermore, there are no reliable data available that carotid revascularization increases the rupture risk of intracranial aneurysms. For these reasons we think that active screening for intracranial aneurysms in patients with internal carotid artery stenosis is not required. When imaging techniques are used with a large coverage, such as the CTA technique, this may result in the finding of incidental intracranial aneurysms. In most patients such a finding should not influence the treatment of the internal carotid artery stenosis.

We showed that when performing CT angiography from the aortic arch toward the top of the skull for detection and grading of ICA stenosis, incidentally intracranial aneurysms may be detected. The prevalence of intracranial aneurysms is probably higher in patients with ICA stenosis than in the general population. In deciding aneurysms treatment the risk of cardiovascular diseases other than aneurismal rupture should be taken into account.

Disclosures
None.

References
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