ABSTRACT

Background  The management of unruptured intracranial aneurysms requires knowledge of the natural history of these lesions and the risks of repairing them.

Methods  A total of 2621 patients at 53 participating centers in the United States, Canada, and Europe were enrolled in the study, which had retrospective and prospective components. In the retrospective component, we assessed the natural history of unruptured intracranial aneurysms in 1449 patients with 1937 such aneurysms; 727 of the patients had no history of subarachnoid hemorrhage from a different aneurysm (group 1), and 722 had a history of subarachnoid hemorrhage from a different aneurysm that had been repaired successfully (group 2). In the prospective component, we assessed treatment-related morbidity and mortality in 1172 patients with newly diagnosed unruptured intracranial aneurysms.

Results  In group 1, the cumulative rate of rupture of aneurysms that were less than 10 mm in diameter at diagnosis was less than 0.05 percent per year, and in group 2, the rate was approximately 11 times as high (0.5 percent per year). The rupture rate of aneurysms that were 10 mm or more in diameter was less than 1 percent per year in both groups, but in group 1, the rate was 6 percent the first year for giant aneurysms (≥25 mm in diameter). The size and location of the aneurysm were independent predictors of rupture. The overall rate of surgery-related morbidity and mortality was 17.5 percent in group 1 and 13.6 percent in group 2 at 30 days and was 15.7 percent and 13.1 percent, respectively, at 1 year. Age independently predicted surgical outcome.

Conclusions  The likelihood of rupture of unruptured intracranial aneurysms that were less than 10 mm in diameter was exceedingly low among patients in group 1 and was substantially higher among those in group 2. The risk of morbidity and mortality related to surgery greatly exceeded the 7.5-year risk of rupture among patients in group 1 with unruptured intracranial aneurysms smaller than 10 mm in diameter. (N Engl J Med 1998;339:1725-33.)

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ment of such patients. For the prospective portion of the study, the objectives were to evaluate the risks of morbidity and mortality associated with treatment of unruptured intracranial aneurysms and to determine whether these risks are higher for some patients than for others.

Identification and Recruitment of Patients

The retrospective cohort included patients with unruptured intracranial aneurysms that had been diagnosed during the period from 1970 to 1991. At each center, retrospective cases could be included only as far back as hard-copy arteriograms and medical records were available for all patients at that center. Central medical records systems, admission records, and records from departments of radiology, neurosurgery, and neurology were used as sources for identifying patients.

Prospective patients were identified by study coordinators at the participating centers, who conducted surveillance of patients with diagnosed intracranial aneurysms between 1991 and 1995.

Patient Eligibility

Retrospective Component

Patients were eligible for enrollment in the retrospective component if they had had at least one unruptured intracranial aneurysm, whether or not they had symptoms (e.g., cranial-nerve palsies). Patients may have had a previous ruptured aneurysm at another location that was clipped, completely trapped, or isolated from the circulation by endovascular obliteration, as confirmed arteriographically. Patients had to have been able to care for themselves after the previous aneurysm had been treated (i.e., a score of 1 or 2 on the Rankin scale of neurologic disability, with scores ranging from 1 [no disability] to 5 [severe disability]). Patients with fusiform, traumatic, or mycotic aneurysms were not eligible for the study. Also, patients with aneurysms that were found to be less than 2 mm in maximal diameter with the use of a standard measuring device were excluded. Patients with subarachnoid hemorrhage from a single ruptured aneurysm or an unknown source were excluded. In addition, patients in whom the aneurysm was manipulated within 30 days after diagnosis were not eligible. Patients with a history of intracranial hemorrhage were excluded if the cause was unknown or if an underlying structural lesion was not repaired. Patients were excluded if they did not consent to follow-up, if they had a malignant brain tumor, or if they were bedridden or unable to communicate at the time the aneurysm was identified.

Prospective Component

Eligibility criteria for patients in the prospective component were similar to those for the patients in the retrospective component, except that in the prospective component, the investigators decided whether to enroll the patients without planned surgical or endovascular treatment or with planned surgical or endovascular treatment of at least one intracranial aneurysm. All patients were required to undergo cerebral arteriography in order to confirm the presence, location, and size of intracranial aneurysms.

Radiology

Hard copies of cerebral arteriograms from all patients were reviewed at the central study office at the Mayo Clinic, Rochester, Minnesota, by two neuroradiologists. The size of the aneurysm was corrected for magnification by methods reported previously.11 A pilot study was conducted to establish criteria for measurement, standards for evaluating the size and morphologic characteristics of the aneurysm, and interobserver reliability.15

Follow-up

For the retrospective cohort, follow-up information was obtained by means of an annual standardized questionnaire and a review of medical records. Neurologic symptoms, intracranial surgery, or repeated arteriographic studies undertaken since the previous assessment were recorded.

For the prospective cohort, base-line assessments were made. Prospective patients who did not undergo planned surgical treatment were followed with the use of an annual questionnaire. For patients who underwent surgical treatment, assessments were made 7 days after the procedure, at hospital discharge, at 30 days, and at yearly intervals. For both cohorts, neurologic status was measured with the use of the Rankin scale at each follow-up assessment, and cognitive status was determined with the Mini-Mental State Examination14 or the Telephone Interview for Cognitive Status15 at the same intervals. All complications of surgical treatment were recorded.

Determination of Events

Detailed information was obtained on all end points (definite or questionable subarachnoid or intracerebral hemorrhage and death). Comprehensive adjudication was performed centrally for all hemorrhages, strokes, and deaths on the basis of uniform criteria, with the use of available clinical, radiologic, autopsy, and other information, and hemorrhages were classified according to the location of the rupture. Subarachnoid or intracerebral hemorrhage was classified as definite (symptoms of subarachnoid or intracerebral hemorrhage and positive findings on computed tomography [CT] or magnetic resonance imaging [MRI], surgery, or autopsy), highly probable (symptoms and positive findings on cerebrospinal fluid analysis), or probable (symptoms only). All definite, highly probable, and probable aneurysmal hemorrhages were included in the primary analysis.

In the prospective component of the study, evidence of surgery-related cerebral infarction, hemorrhage, or death was confirmed centrally. Neurologic deficits 30 days or 1 year after treatment were evaluated for their relation to treatment or coexisting disorders.

Morbidity related to surgical treatment was defined as a Rankin score of 3, 4, or 5 (moderate-to-severe neurologic disability) or a score of less than 24 on the Mini–Mental State Examination or less than 27 on the Telephone Interview for Cognitive Status (both indicating a serious cognitive abnormality) at 30 days and 1 year.14,15 Mortality was considered separately.

Statistical Analysis

The retrospective component included two groups designated by their eligibility for enrollment. Group 1 and group 2 were analyzed as separate strata. Between-group comparisons of the distributions of demographic and clinical characteristics were made by the chi-square test for categorical variables and the t-test for continuous variables. Estimates of the risk of hemorrhage were made with the use of life-table methods, with data on death, surgical intervention, and last follow-up assessment censored. Predictors of hemorrhage were ascertained with the use of a proportional-hazards regression model.

For the prospective cohort, survival, morbidity (a Rankin score of 3, 4, or 5), and diminished mental status (a score of less than 24 on the Mini–Mental State Examination or less than 27 on the Telephone Interview for Cognitive Status), as well as overall morbidity and mortality, were analyzed. Survival estimates and 95 percent confidence intervals were calculated with life-table methods 30 days and 1 year after treatment. The risk of morbidity was estimated as the proportion of patients with impairment at the 30-day and 1-year examinations. The overall risk of morbidity or mortality was estimated as the proportion of patients who were disabled or died at 30 days and 1 year. Surgery-related morbidity and mortality were estimated on the basis of only those events attributed to treatment of the aneurysm. Factors related to overall morbidity and mortality were determined with the use of logistic regression. (An expanded description of the methods used in this study is available on the Internet at www.mayo.edu/ISUIA or by writing to the ISUIA Coordinating Center.)
RESULTS

Retrospective Cohort

Demographic and Clinical Characteristics

Fifty-three centers in the United States, Canada, and Europe enrolled a total of 1449 patients with 1937 unruptured intracranial aneurysms (727 patients in group 1 and 722 patients in group 2). The aneurysms were diagnosed at the participating centers between 1970 and 1991.

Of the 1449 patients, 1085 (75 percent) had single unruptured intracranial aneurysms and 364 (25 percent) had multiple unruptured intracranial aneurysms, with similar distributions in groups 1 and 2 (Table 1). The mean age at diagnosis was higher in group 1 than in group 2 (Table 1). Almost three fourths of the patients were women. The mean duration of follow-up was 8.3 years, with a total of approximately 12,023 patient-years of follow-up.

Conditions leading to the diagnosis of unruptured intracranial aneurysms included headaches in 36 percent of patients, ischemic cerebrovascular disease in 17.6 percent, cranial-nerve deficits in 15.4 percent, aneurysmal mass effect in 5.7 percent, ill-defined spells in 4.8 percent, convulsive disorder in 4.2 percent, subdural or intracerebral hemorrhage in 2.7 percent, brain tumor in 1.7 percent, and nervous system degenerative disease in 0.5 percent. The diagnosis was suspected on the basis of CT findings in 39.8 percent and MRI findings in 5.6 percent.

Aneurysmal Characteristics

The distribution of unruptured intracranial aneurysms according to size and location (parent artery) is shown for groups 1 and 2 in Table 1. Forty-one of the patients in group 1 with small aneurysms (<10 mm in diameter) (9.7 percent) and 153 patients in the entire retrospective group (10.6 percent) had single cavernous carotid aneurysms.

Overall, 32 percent of the patients in group 1 and 11 percent of those in group 2 had unruptured aneurysms that caused symptoms other than those associated with rupture (e.g., cranial-nerve palsies).

Risk Factors

Potential risk factors for the development of an unruptured aneurysm or for subsequent rupture were documented at the time of diagnosis (Table 2). Among patients for whom data on smoking were available, 60.6 percent were current smokers and 18.6 percent were former smokers (a precise history of smoking was unavailable for 31 percent of the patients). Other potential risk factors for which there were substantial numbers of patients with missing...
of the 1449 patients, 32 had confirmed aneurysmal ruptures during follow-up, and in 28 of the 32, the rupture occurred within the first 7.5 years of follow-up. Two other patients with subarachnoid hemorrhage 2 years and 5.6 years after diagnosis had coexisting arteriovenous malformations. In neither patient was it possible to delineate whether the aneurysm or the arteriovenous malformation had ruptured. Patients with both aneurysms and arteriovenous malformations (20 in group 1 and 13 in group 2) were not included in the analysis of end points.

Of the 12 patients in group 1 who had confirmed aneurysmal subarachnoid hemorrhage, only 1 had an aneurysm that was less than 10 mm in diameter, whereas 17 of the 20 patients in group 2 with ruptures had aneurysms that were less than 10 mm in diameter. Two of the 32 ruptures occurred in patients with cavernous carotid aneurysms.

Prediction of Rupture

In group 1, the only significant predictors of rupture were the size and location of the aneurysm. Aneurysms that were less than 10 mm in diameter were much less likely to rupture than those that were 10 to 24 mm in diameter (relative risk for larger aneurysms, 11.6; P = 0.03) or 25 mm or more in diameter (relative risk, 59.0; P < 0.001). The relative risk of rupture was 13.8 for aneurysms at the basilar tip and 13.6 for those in the vertebrobasilar or posterior cerebral distribution, as compared with other locations (P = 0.001 and P = 0.007, respectively). For posterior communicating aneurysms, the relative risk of rupture was 8.0 (P = 0.02). In group 2, the relative risk of rupture was 5.1 for aneurysms at the basilar tip (P = 0.004) and 1.31 for older age (P = 0.04). The size of the aneurysm did not predict the risk of rupture.

Rupture Rates

Rates of confirmed subarachnoid hemorrhage 7.5 years after diagnosis are shown in Figures 1 and 2. The cumulative rate of rupture for patients in group 1 with aneurysms that were less than 10 mm in diameter at the time of discovery was 0.4 percent, or about 0.05 percent per year. In contrast, the rupture rate for patients in group 1 with aneurysms that were 10 mm or more in diameter was about 20 times that of the rate for smaller aneurysms, approaching 1 percent per year (Fig. 1). In group 2,

### Table 2. Risk Factors for Rupture in the Retrospective and Prospective Cohorts.

<table>
<thead>
<tr>
<th>COHORT AND RISK FACTOR</th>
<th>GROUP 1</th>
<th>GROUP 2</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>308/697 (44.2)</td>
<td>200/676 (29.6)</td>
<td>508/1373 (37.0)</td>
</tr>
<tr>
<td>Treatment for hypertension</td>
<td>264/698 (37.8)</td>
<td>124/698 (17.8)</td>
<td>388/1396 (27.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>16/691 (2.3)</td>
<td>6/691 (0.9)</td>
<td>22/1382 (1.6)</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>41/688 (6.0)</td>
<td>16/683 (2.4)</td>
<td>57/1371 (4.2)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>15/695 (2.2)</td>
<td>2/693 (0.3)</td>
<td>17/1388 (1.2)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>39/689 (5.7)</td>
<td>21/671 (3.1)</td>
<td>60/1360 (4.4)</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>11/691 (1.6)</td>
<td>2/673 (0.3)</td>
<td>13/1364 (1.0)</td>
</tr>
<tr>
<td>Alcohol use (&gt;5 drinks in 24 hr)</td>
<td>38/202 (18.8)</td>
<td>74/155 (47.7)</td>
<td>112/357 (31.4)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>284/540 (52.6)</td>
<td>321/459 (69.9)</td>
<td>605/999 (60.6)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>120/540 (22.2)</td>
<td>66/459 (14.4)</td>
<td>186/999 (18.6)</td>
</tr>
<tr>
<td>Use of stimulants</td>
<td>4/129 (3.1)</td>
<td>6/125 (4.8)</td>
<td>10/254 (3.9)</td>
</tr>
<tr>
<td>Use of oral contraceptives by women</td>
<td>38/143 (26.6)</td>
<td>31/94 (33.0)</td>
<td>69/237 (29.1)</td>
</tr>
</tbody>
</table>

Prospective cohort

<table>
<thead>
<tr>
<th>COHORT AND RISK FACTOR</th>
<th>GROUP 1</th>
<th>GROUP 2</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>295/798 (37.0)</td>
<td>70/197 (35.5)</td>
<td>365/995 (36.7)</td>
</tr>
<tr>
<td>Treatment for hypertension</td>
<td>251/798 (31.5)</td>
<td>54/197 (27.4)</td>
<td>305/995 (30.7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>22/798 (2.8)</td>
<td>0/197</td>
<td>22/995 (2.2)</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>45/798 (5.6)</td>
<td>5/197 (2.5)</td>
<td>50/995 (5.0)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>5/798 (0.6)</td>
<td>0/197</td>
<td>5/995 (0.5)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>32/798 (4.0)</td>
<td>7/197 (3.6)</td>
<td>39/995 (3.9)</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>17/798 (2.1)</td>
<td>3/197 (1.5)</td>
<td>20/995 (2.0)</td>
</tr>
<tr>
<td>Alcohol use (&gt;5 drinks in 24 hr)</td>
<td>244/798 (30.6)</td>
<td>7/197 (36.0)</td>
<td>315/995 (31.7)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>359/798 (45.0)</td>
<td>106/197 (53.8)</td>
<td>465/995 (46.7)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>255/798 (32.0)</td>
<td>61/197 (31.0)</td>
<td>316/995 (31.8)</td>
</tr>
<tr>
<td>Use of stimulants</td>
<td>15/798 (5.9)</td>
<td>5/197 (3.1)</td>
<td>20/995 (2.0)</td>
</tr>
<tr>
<td>Use of oral contraceptives by women</td>
<td>285/379 (49.2)</td>
<td>98/159 (61.6)</td>
<td>383/738 (51.9)</td>
</tr>
</tbody>
</table>
the smaller aneurysms were approximately 11 times as likely to rupture as aneurysms of the same size in group 1, with a rate of approximately 0.5 percent per year. The rupture rate of larger aneurysms was similar to that in group 1, approaching 1 percent per year. Figure 2 shows rupture rates over time for groups 1 and 2 according to the size of the aneurysm. In group 1, aneurysms that were 25 mm or more in diameter had a rupture rate of 6 percent in the first year (Fig. 2A).

Mortality

Among the 32 patients with initially unruptured aneurysms and subsequent hemorrhage, the case fatality rate was 66 percent (83 percent in group 1 and 55 percent in group 2). Of the 205 patients who died during the 7.5 years of follow-up, 42 died of intracranial hemorrhage, 36 of cancer, 30 of cardiac disease, 14 of respiratory tract disease, 11 of cerebral infarction, and 72 of other, unrelated causes. On an actuarial basis, the estimated survival rate at five years for the entire retrospective cohort was 89 percent.

Prospective Cohort

Surgical Intervention

In the prospective cohort, 1172 patients were enrolled in the treatment group (961 patients in group 1 and 211 in group 2). Intracranial surgery was performed in 798 patients (83 percent) in group 1 and in 198 (94 percent) in group 2. The rest of the patients were treated with various endovascular procedures.

Demographic and Clinical Characteristics

The mean age at diagnosis was 52 years (range, 19 to 91), with a higher mean age in group 1 than in group 2 (53 vs. 47 years) (Table 3). Approximately three fourths of the patients were women.

Conditions leading to the diagnosis of an unruptured intracranial aneurysm and enrollment in the treatment group included headache in 34 percent of patients, cranial-nerve deficits in 14 percent, ischemic cerebrovascular disease in 11 percent, ill-defined spells in 10 percent, aneurysmal mass effect in 6 percent, convulsive disorder in 5 percent, subdural or intracerebral hemorrhage in 0.4 percent, brain tumor in 0.4 percent, and nervous system degenerative disease in 0.3 percent. The diagnosis was suspected on the basis of CT findings in 40 percent of patients and MRI findings in 37 percent.
### Table 3. Base-Line Characteristics of the Prospective Cohort.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (N=798)</th>
<th>Group 2 (N=197)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>53.0</td>
<td>47.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Range</td>
<td>19–91</td>
<td>24–78</td>
<td></td>
</tr>
<tr>
<td>Female sex — no. of patients (%)</td>
<td>598 (74.9)</td>
<td>163 (82.7)</td>
<td></td>
</tr>
<tr>
<td>White race — no. of patients (%)</td>
<td>735 (92.1)</td>
<td>175 (88.8)</td>
<td></td>
</tr>
<tr>
<td>Total no. of aneurysms</td>
<td>1039</td>
<td>262</td>
<td></td>
</tr>
<tr>
<td>Diameter of largest aneurysm — mm</td>
<td>11.6</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2–50</td>
<td>2–60</td>
<td></td>
</tr>
<tr>
<td>Size of largest aneurysm — no. of patients (%)</td>
<td>128 (16.0)</td>
<td>128 (16.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2–5 mm</td>
<td>262 (32.8)</td>
<td>79 (40.1)</td>
<td></td>
</tr>
<tr>
<td>6–9 mm</td>
<td>203 (25.4)</td>
<td>39 (19.8)</td>
<td></td>
</tr>
<tr>
<td>10–14 mm</td>
<td>148 (18.5)</td>
<td>11 (5.6)</td>
<td></td>
</tr>
<tr>
<td>15–24 mm</td>
<td>57 (7.1)</td>
<td>3 (1.5)</td>
<td></td>
</tr>
<tr>
<td>»25 mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location of aneurysm — no. of aneurysms (%)</td>
<td>24 (2.3)</td>
<td>3 (1.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Cavernous carotid artery</td>
<td>393 (37.8)</td>
<td>82 (31.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>167 (16.1)</td>
<td>23 (8.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>Anterior communicating or anterior cerebral artery</td>
<td>305 (29.4)</td>
<td>116 (44.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>48 (4.1)</td>
<td>15 (5.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Posterior communicating artery</td>
<td>50 (4.8)</td>
<td>15 (5.7)</td>
<td>0.54</td>
</tr>
<tr>
<td>Vertebral or posterior cerebral artery</td>
<td>57 (5.5)</td>
<td>8 (3.1)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

**Aneurysmal Characteristics**

The distribution of unruptured intracranial aneurysms according to size and location (parent artery) is shown for groups 1 and 2 in Table 3. The distributions of aneurysms were very similar to those in the retrospective cohort. Overall, 21 percent of the patients had specific symptoms, including 23 percent of the patients in group 1 and 10 percent of those in group 2.

**Risk Factors**

Various potential risk factors for the development of an intracranial aneurysm as well as treatment-related morbidity and mortality were documented at the time of diagnosis (Table 2). Overall, 47 percent of the patients were current smokers, and 32 percent were former smokers.

With regard to base-line neurologic status, 94 percent of the patients had a Rankin score of 1 (96 percent in group 1 and 89 percent in group 2). The Barthel score was 100 (indicating normal ability to perform the activities of daily living) for 98 percent of patients, and the score on the Mini–Mental State Examination was higher than 23 (indicating no serious cognitive abnormality) for 98 percent of the patients.

**Surgical Outcome**

The morbidity and mortality rates at 30 days and 1 year are shown in Table 4. Thirty days after surgery, 18 of 996 patients (all in group 1) had died. Ten deaths were due to cerebral infarction, five to intracranial hemorrhage, and two to pulmonary embolism; one death was related to respiratory complications. One year after surgery, 34 deaths had occurred in group 1 (30 related to surgery) and 2 in group 2 (both related to surgery).

Seventy-eight patients in group 1 and eight in group 2 had a Rankin score of 3, 4, or 5 at 30 days. Ninety-three patients in group 1 and 21 in group 2 had impaired cognitive status. Age was the only independent predictor of a poor surgical outcome. In group 1, surgery-related morbidity and mortality at one year among patients younger than 45 years was 6.5 percent, as compared with 14.4 percent for those between 45 and 64 years old and 32 percent for those over 64 (P<0.001).

**DISCUSSION**

Among patients without a history of subarachnoid hemorrhage (group 1), those with unruptured intracranial aneurysms that were less than 10 mm in diameter had an exceedingly low risk of rupture (approximately 0.05 percent per year). Unruptured aneurysms of the same size in patients with a history of subarachnoid hemorrhage (group 2) were approximately 11 times as likely to rupture (a risk of approximately 0.5 percent per year). The size and location of the aneurysm were significant independent predictors of rupture in patients in group 1 (larger
aneurysms and those in the tip of the basilar artery, vertebrobasilar or posterior cerebral artery, or posterior communicating artery (where they were more likely to rupture). In group 2, only the basilar-tip location was predictive of rupture. In view of these findings, it is pertinent to begin considering patients with previous subarachnoid hemorrhage and those without previous hemorrhage differently when making decisions about the management of unruptured intracranial aneurysms.

The overall rupture rate for the 1449 patients in the retrospective component of our study (0.5 percent per year) was lower than the rates reported in previous natural-history studies, and the rate in group 1 was significantly lower than that in group 2. The aneurysms were considerably larger in group 1 (mean diameter, 10.9 mm) than in group 2 (mean diameter, 5.7 mm), and the number of giant aneurysms was markedly lower in group 2. These differences are most likely the result of the rupture or repair (or both) of larger aneurysms in the patients in group 2 before enrollment in the study. The exceedingly low rupture rate in the patients in group 1 with aneurysms that were less than 10 mm in diameter is consistent with the findings of previous studies.

Although the retrospective component of our study provides indispensable long-term follow-up data as a basis for determining future rupture rates, it is possible that a systematic bias we cannot identify has been introduced because of the nature of this cohort.

The overall morbidity and mortality rates associated with surgical repair of unruptured intracranial aneurysms were higher than those reported previously. The 30-day rates of mortality and morbidity (a score of 3, 4, or 5 on the Rankin scale) were only slightly higher than those predicted on the basis of a systematic review of previous reports on repair of unruptured aneurysms. In our study, however, impaired mental status added substantially to morbidity at 30 days and 1 year, and this variable was not assessed in the previous studies.

In the surgically treated cohort, age was the only significant independent predictor of surgical outcome. The rates of surgery-related morbidity and mortality were higher in group 2 (mean diameter, 5.7 mm), and the number of giant aneurysms was markedly lower in group 2. These differences are most likely the result of the rupture or repair (or both) of larger aneurysms in the patients in group 2 before enrollment in the study. The exceedingly low rupture rate in the patients in group 1 with aneurysms that were less than 10 mm in diameter is consistent with the findings of previous studies.

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In the surgically treated cohort, age was the only significant independent predictor of surgical outcome. The rates of surgery-related morbidity and mortality were higher in group 2 (mean diameter, 5.7 mm), and the number of giant aneurysms was markedly lower in group 2. These differences are most likely the result of the rupture or repair (or both) of larger aneurysms in the patients in group 2 before enrollment in the study. The exceedingly low rupture rate in the patients in group 1 with aneurysms that were less than 10 mm in diameter is consistent with the findings of previous studies.

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mortality were substantially lower for younger pa-
ients than for older patients. Other potential predic-
tors of surgery-related morbidity and mortality (in-
cluding the location and size of the aneurysm) and
endoavascular results could not be assessed ade-
cately with the number of patients in the prospective cohort.

With aneurysmal size and location included in the
multivariate model, the presence of aneurysmal symp-
toms other than those related to rupture was not a pre-
cident of rupture. Similarly, the presence of symp-
toms did not independently predict the outcome of the
surgery.

The management of unruptured intracranial an-
eurysms depends on the natural history of these le-
sions and on morbidity and mortality rates associ-
ated with repair. On the basis of the rupture rates and
treatment risks in our study, it appears unlikely that
surgery will reduce the rates of disability and death
in patients with unruptured intracranial aneurysms
smaller than 10 mm in diameter and no history of sub-
arachnoid hemorrhage. Data on treatment-related
morbidity and mortality rates according to aneurys-
mal size and location and specific symptoms are re-
quired to determine whether surgical or endovascular
intervention may be warranted in various subgroups
of patients with unruptured intracranial aneurysms,
including those with acute symptomatic unruptured
aneurysms.

Supported by a grant (R01-NS-28492) from the National Institute of Neurological Disorders and Stroke.

APPENDIX


A full listing of investigators, committees, and institutions is available on the Internet at www.mayo.edu/ISUAA.

REFERENCES

2. Housepian EM, Posl JL. A systematic analysis of intracranial aneurysms from the autopsy file of the Presbyterian Hospital, 1914 to 1956. J Neu-

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CORRECTION

Unruptured Intracranial Aneurysms

To the Editor: The conclusions reached by Wiebers et al. (Dec. 10 issue) about the natural history of aneurysmal subarachnoid hemorrhage arouse concern because of the inhomogeneous grouping of patients and the differences in the rates of subarachnoid hemorrhage at different sites. Since they included intracavernous aneurysms in their determination of rupture rates, the rates for aneurysms truly within the subarachnoid space may be underestimated, since intracavernous aneurysms rarely cause subarachnoid hemorrhage. To a lesser extent, the same caveat may apply to proximal infraclinoid ophthalmic aneurysms and those arising from the clinoidal segment of the carotid artery, since they are often protected by dura and bone. The grouping of aneurysms in these locations with aneurysms that are free within the subarachnoid space combines categories of aneurysms that entail very different risks of hemorrhage. Of the 1937 aneurysms, 669 (34.5 percent) were in these proximal locations, a point that may have important implications for the overall findings (Table 1).

From the data provided, we cannot determine the effect of this distribution of aneurysms on the much higher (by a factor of 11) risk of subarachnoid hemorrhage among the patients in group 2. Certainly, the difference of 15 percentage points between the two groups in the proportion of aneurysms free in the subarachnoid space may account for some of the results. The data shown in Table 1 of the article by Wiebers et al. suggest that the incidence of single aneurysms was the same in the two groups. Since patients in group 2 had had a previous subarachnoid hemorrhage that had been treated, they represent a population with a higher rate of multiple aneurysms and are not comparable to the patients in group 1. This factor may also have contributed to the difference in the natural history of unruptured intracranial aneurysms between the groups and must be acknowledged in any discussion of the natural history.

Another concern of ours is the relation between subarachnoid hemorrhage and the size of the aneurysm. Although Wiebers et al. have written about the absence of subarachnoid hemorrhage in patients with aneurysms that are less than 10 mm in diameter, many large series have shown that the mean diameter of aneurysms in patients who present with subarachnoid hemorrhage is less than 10 mm, as noted by Dr. Caplan in his editorial. Therefore, we conclude that there is little assurance that an aneurysm that is less than 10 mm will not bleed.

We believe that the conclusions of this article should be modified to reflect a higher risk of subarachnoid hemorrhage at certain sites, since this will affect the manner in which treatment options are presented to patients.

Table 1. Distribution of Aneurysms.

<table>
<thead>
<tr>
<th>Type</th>
<th>Location*</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unprotected in sub-</td>
<td>ACA, MCA,</td>
<td>570 (58)</td>
<td>698 (73)</td>
</tr>
<tr>
<td>arachnoid space</td>
<td>PCA, VB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protected from sub-</td>
<td>CCA, ICA</td>
<td>407 (42)</td>
<td>262 (27)</td>
</tr>
<tr>
<td>arachnoid space</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of aneurysms</td>
<td></td>
<td>977</td>
<td>960</td>
</tr>
</tbody>
</table>

*ACA denotes anterior communicating artery, MCA middle cerebral artery, PCA posterior communicating artery, VB vertebrobasilar arteries, CCA cavernous carotid artery, and ICA internal carotid artery.

Alejandro Berenstein, M.D.
Eugene S. Flamm, M.D.
Mark J. Kupersmith, M.D.
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References


To the Editor: Although we were encouraged to see a report on the important problem of unruptured intracranial aneurysms, we are concerned that selection bias, especially in the retrospective cohort, may have undermined the study’s findings and recommendations.

We were approached to participate in this study and include any patients with unruptured intracranial aneurysms who were being followed. Although we had several such patients, we declined the invitation because of our concern that the cohort would not be representative of the overall population of patients with unruptured aneurysms. For instance, the vast majority of patients with unruptured aneurysms who are referred to our institution have already been surgically treated, leaving only a small minority with aneurysms with a
low risk on the basis of the natural history, and these aneurysms were, for example, heavily calcified, partly intracavernous, tiny and laterally located, or in elderly patients with other medical problems. Unfortunately, aneurysms such as these also often pose a greater surgical risk, further complicating the issue of their inclusion in a study.

We think that the data reported confirm our concern about selection bias. The cohort consisted of 1449 patients at 53 centers who were given a diagnosis over a period of 21 years (1970 to 1991). All the centers are regional referral institutions that would be expected, on the basis of the volume at our institution, to see 60 to 80 patients with newly diagnosed unruptured aneurysms annually. Assuming this to be the case, outcome data would have been reported for only 1.3 patients per year (2 percent of all patients seen). Even if one assumes the volume in the referral centers to be only 10 percent of this value, the cohort would represent only 20 percent of the patients in these centers, which is still too small a percentage to be representative of the population at large.

Thus, although we applaud any plans for a true population-based assessment and some type of randomized trial addressing this problem and hope that this article will trigger enough controversy to see that goal accomplished, we recall the initial impressions that carotid artery disease was benign and not in need of treatment, which were reversed by definitive studies showing that intervention was appropriate for patients who were properly identified. The same could apply to unruptured aneurysms, which the study shows still have a case fatality rate of 66 percent when they are left to bleed.

For those of us treating this disease, the identification of appropriate surgical candidates, combined with more cost-effective screening, probably offers the greatest hope, since ongoing efforts to prevent early rebleeding, cure vasospasm, reverse severe brain damage, and refine microsurgical and endovascular techniques are having little effect on overall morbidity due to this disease.

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J.P. Mohr, M.D.
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To the Editor: The annual rupture rate reported by Wiebers et al. is considerably lower than that reported in other respected studies.1, 2 One study found that unruptured aneurysms smaller than 5 mm in diameter that subsequently ruptured were larger after rupture.3 The Aneurysmal Subarachnoid Hemorrhage Cooperative Study2 demonstrated that 24 percent of ruptured aneurysms are 5 mm or less. Rupture of aneurysms smaller than 10 mm is not uncommon in our practice. The low rate of rupture of small aneurysms reported by Wiebers et al. is most likely explained by the fact that growth and rupture are time-dependent. Follow-up was not long enough to allow the expansion and rupture of aneurysms.

The rates of surgical morbidity and mortality were higher in this study than in other series.4 There have been microneurosurgical advances since 1970, when the retrospective component began. It would not be accurate to use high complication rates when one is analyzing the risks and benefits of the obliteration of aneurysms. We are sure that the authors accept the seriousness of these lesions and the potential for poor outcomes (a mortality rate of up to 50 percent after rupture). In addition, in 42 of the 205 patients who died during the 7.5 years of follow-up, death was caused by intracranial hemorrhage. Was this due to the aneurysm? Were autopsy data available?

Patients in whom the aneurysm was manipulated within 30 days after diagnosis were excluded. This cohort most likely represents younger patients who have aneurysms with worrisome features that make the decision to operate straightforward. If these assumptions are true, the rate of surgical complications would be lower in this group. The number of such patients and the reasons for treatment are not reported.

The locations of the aneurysms in this study differ from those in previous studies and suggest that there may have been a location-specific bias.5 There were 256 cavernous aneurysms. The likelihood of rupture is low if the lesion is completely intracavernous. These lesions account for 18 percent of aneurysms in the retrospective study, but for only 6 percent of cases of subarachnoid hemorrhage.

To advise patients with unruptured aneurysms properly, three factors require consideration: the size and location of the aneurysm and the patient's age. The study does not provide information regarding the rates of surgical complications as a function of the location or the size of the aneurysm or the patient's age. Unfortunately, all patients are combined into one group that reflects various microneurosurgical techniques. This approach is very misleading. We hope that this report will prompt further investigation into this important clinical issue.

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Robert Friedlander, M.D.
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References
To the Editor: In his editorial, Dr. Caplan states that “patients with previously ruptured aneurysms had 11 times the rate of rupture of patients without prior hemorrhage.” As I interpret the data of Wiebers et al., this excess is applicable only to the subgroup of patients with aneurysms that were less than 10 mm in diameter. Among patients with aneurysms that were 10 mm or more, the rates of rupture are roughly similar in the group with prior hemorrhage and the group without it.

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The authors reply:

Approximately half the patients with cavernous aneurysms also had noncavernous unruptured aneurysms. Although intracavernous aneurysms can cause subarachnoid hemorrhage, most are protected from the subarachnoid space. Other internal carotid aneurysms are not protected. The annual rates of rupture are only slightly increased by the exclusion of patients with cavernous aneurysms (Table 1); patients in group 2 who had small (<10 mm) unruptured aneurysms remain approximately 10 times as likely to have a subsequent rupture as patients with small aneurysms in group 1.

Currently, the numbers of patients are too small (only a total of 32 aneurysmal ruptures) to determine meaningful rupture rates in group 1 and group 2 according to the six different locations and two size categories (24 subgroups). The presence of multiple unruptured intracranial aneurysms was not a predictor of future rupture independent of the size and location of the largest unruptured aneurysm. Unruptured aneurysms were more likely to rupture in patients in group 2, but this risk does not appear to be related to the presence of multiple unruptured intracranial aneurysms.

The concern about microneurosurgical advances that have occurred since 1970 and the exclusion of patients who underwent surgery in the first 30 days after diagnosis is not relevant, since operative morbidity and mortality were assessed only in the patients in the prospective group, beginning in late 1991. The base-line characteristics of the surgically treated patients and those who were not so treated were virtually identical, with minor differences in the mean age and aneurysmal size only among patients in group 1, underscoring the lack of consensus about the selection of patients with unruptured intracranial aneurysms as candidates for surgery.

Comparison of our retrospective results with those of a 30-year study (1965 to 1995) in Rochester, Minnesota, of a population-based sample of patients with intracranial aneurysms (and unpublished data) yielded strikingly similar demographic characteristics, aneurysmal characteristics, and associated medical conditions, suggesting that our group (representing approximately 40 percent of patients with unruptured aneurysms who were seen at participating centers) may be representative of the general population. A randomized trial would involve a much greater prospective selection bias than our study because many patients would refuse to participate.

Data on the natural history of unruptured intracranial aneurysms confirm the conclusion that judgments about the probability of the rupture of such aneurysms cannot be extrapolated from data on patients with ruptured aneurysms. It appears that most aneurysms that are going to rupture do so when they form or soon afterward and that the critical size in terms of rupture is smaller for aneurysms that rupture early.

In our cohort, the patient’s age significantly predicted operative morbidity and mortality. The influences of the size and location of aneurysms in this study are not yet clear because of insufficient numbers of patients; this is one of the central reasons that the study has been extended to involve a total of 5500 patients.

Table 1. Mean Annual Rates of Confirmed Subarachnoid Hemorrhage.

<table>
<thead>
<tr>
<th>Diameter of Unruptured Aneurysm</th>
<th>All Patients</th>
<th>All Patients Except Those with Cavernous Aneurysms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (no subarachnoid hemorrhage)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 mm</td>
<td>0.85</td>
<td>0.67</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>0.95</td>
<td>1.38</td>
</tr>
<tr>
<td>Group 2 (subarachnoid hemorrhage)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 mm</td>
<td>0.56</td>
<td>0.68</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>0.64</td>
<td>0.72</td>
</tr>
</tbody>
</table>

David O. Wiebers, M.D.
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References

To the Editor: Dr. Brett is correct. Aneurysms that were less than 10 mm in diameter were 11 times as likely to rupture in patients who had prior bleeding from other aneurysms as in patients without prior subarachnoid hemorrhage. Aneurysms that were at least 10 mm had a similar rate of rupture whether or not there had been prior subarachnoid hemorrhage.

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CORRECTION

Unruptured Intracranial Aneurysms — Risk of Rupture and Risks of Surgical Intervention

Unruptured Intracranial Aneurysms — Risk of Rupture and Risks of Surgical Intervention. On page 1729, in Figure 2B, the curves were mislabeled. The upper curve, with the square symbols, should have been labeled “10–24 mm,” and the lower curve should have been labeled “<10 mm.”