Immediate Clinical Outcome of Patients Harboring Unruptured Intracranial Aneurysms Treated by Endovascular Approach
Results of the ATENA Study

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Background and Purpose—The management of unruptured intracranial aneurysms remains controversial and the results of endovascular treatment are not precisely known because no prospective data exist. The first prospective multicenter study (ATENA) was conducted in Canada and France to determine clinical outcome and risks of this treatment.

Methods—Six hundred forty-nine patients harboring a total of 1100 aneurysms from 27 Canadian and French neurointerventional centers were prospectively and consecutively treated by endovascular coil embolization. Of these, 739 unruptured intracranial aneurysms were treated during 700 procedures. Aneurysms were selectively treated in the great majority of cases (98.4%) with coils alone (54.5%), the balloon remodeling technique (37.3%), or stenting (7.8%).

Results—Endovascular treatment failed in 32 aneurysms (4.3%). Technical adverse events with or without clinical modification were encountered in 15.4% of patients and included thromboembolic complications (7.1% per procedure), intraoperative rupture (2.6% per procedure), and device-related problems (2.9% per procedure). Adverse events associated with transient or permanent neurological deficit or death were encountered in 5.4% of cases. The 1-month morbidity and mortality rates were 1.7% and 1.4%, respectively.

Conclusions—Endovascular treatment of unruptured intracranial aneurysms is feasible in a high percentage of cases with low morbidity and mortality rates. (Stroke. 2008;39:2497-2504.)

Key Words: cerebral aneurysm • complications • embolization • outcome

The prevalence of intracranial aneurysms has been estimated at 1% to 5% of the adult population.1 Due to noninvasive imaging techniques, including CT, MRI, CT angiography, and MR angiography, unruptured intracranial aneurysms (UIAs) are increasingly diagnosed. Most aneurysms remain asymptomatic until the day they rupture. The annual incidence of rupture is 8 to 10 per 100 000 in the overall population.2,3 Acute rupture resulting in subarachnoid hemorrhage is associated with 30% to 67% mortality and 15% to 30% morbidity.4–6 Clinical management of UIA remains a matter of debate. Preventive treatment is justified if the risks of treatment are low compared with the natural history. The most recent evidence on the natural history and the risk of rupture comes from the International Study of Unruptured Intracranial Aneurysms (ISUIA).7 Conversely, a precise evaluation of the risks of endovascular treatment of UIA is not available. Most series reporting results of this treatment are monocentric and retrospective.8–11 To have a more precise analysis of the results of endovascular treatment (EVT), the first prospective, multicenter study was recently conducted in France and Canada. The short-term clinical and anatomic results are reported in this article. The patients included in this series will have 1 year and 3 years follow-up and results will be subsequently presented as soon as available.

Materials and Methods

Protocol
Analysis of Treatment by Endovascular approach of Non ruptured Aneurysms (ATENA) was conducted by the French Society of Neuroradiology (SFNR) to evaluate short- and long-term results of EVT of UIA. Patients were prospectively and consecutively included from 27 Canadian and French neurointerventional centers. Inclusion criteria included patients harboring unruptured, untreated intracranial aneurysms less than 15 mm. In each center, indication for treatment and its modality was decided by a local multidisciplinary team, including neurosurgeons, neuroanesthesiologists, and neuroradiologists. Thus, in each individual center, all patients selected for EVT were consecutively included in the study.

Fusiform and dissecting aneurysms were excluded as well as aneurysms associated with brain arteriovenous malformations. In case of recent subarachnoid hemorrhage (<1 month) related to another aneurysm, patients were not included.
The protocol was approved by the ethics committee of Reims and informed consent was obtained from all patients.

According to the fact that the goal of the study was to evaluate results of the endovascular treatment, patients harboring aneurysms left untreated or surgically treated were not included and not registered in the database.

Clinical status was defined using the modified Rankin Scale (mRS). Clinical and procedural data were collected and entered through an electronic web site and reviewed anonymously by the principal investigators. Quality of data, exhaustivity, and consecutiveness were controlled independently by clinical research associates on site. The list of patients harboring unruptured aneurysms treated in each center was obtained from each center to control that patients were consecutively included.

Adverse events were reported even if no clinical modification was associated. In case of adverse events, procedural records and charts were reviewed by the clinical research associates. Subsequently, an extensive review of the adverse event was performed anonymously by the study team.

Permanent morbidity and mortality of the treatment was evaluated at 1 month. Morbidity was defined as an mRS of 2 to 5. When preoperative mRS was greater than 1, morbidity was defined by any increase of mRS. Any such modification within 30 days after EVT was designated as treatment-related. Any death within 30 days of endovascular treatment was designated a treatment-related death.

The degree of aneurysmal occlusion was assessed by the neuro-radiologist performing the treatment and a second blinded analysis will be conducted by an independent core laboratory. The degree of aneurysmal occlusion was defined using the modified 3-point Jean Raymond classification scale: complete occlusion, neck remnant, and aneurysm remnant.14

Data management and statistical analysis were independently conducted by the Clinical Research Unit of Reims University Hospital to calculate patient demographics, aneurysm characteristics, treatment, and outcome. Mean and frequency comparisons were performed using Student t test and χ² test or Fisher exact test, respectively. Significance threshold was considered at P=0.05. Statistical analysis was performed using SAS version 8.0 software (SAS Institute, Cary, NC).

### Patient Population

From June 2005 to October 2006 (17 months), 649 patients were prospectively and consecutively included in 27 Canadian and French neurointerventional centers.

The mean number of patients included per center was 24 (range, 4 to 84). Four hundred sixty-eight patients (72.1%) were female and 181 (27.9%) were male, and their ages ranged from 22 to 83 years with a mean of 51.2±11.3 years. Age distribution was as follows: 18 to 30 years in 17 cases (2.6%), 31 to 40 years in 96 cases (14.8%), 41 to 50 years in 199 cases (30.7%), 51 to 60 years in 205 cases (31.6%), 61 to 70 years in 98 cases (15.1%), and >70 years in 34 cases (5.2%).

Aneurysms were discovered incidentally in 420 patients (64.7%), after rupture from another aneurysm in 128 patients (19.7%), during exploration of neurological symptoms related or unrelated to the aneurysm in 85 patients (13.1%), and during familial screening in 16 patients (2.5%).

Cigarette smoking was encountered in 40.8% (260 of 637) and hypertension in 30.2% of patients (192 of 636).

### Description of Aneurysms

The 649 included patients were harboring a total of 1100 aneurysms. Two hundred eighty-nine patients (44.5%) had multiple aneurysms. Among the 1100 aneurysms, 137 were previously ruptured and 963 were unruptured.

Ruptured aneurysms were treated by endovascular approach in 88 cases and by surgical approach in 47 cases; 2 were left untreated. Of the 963 unruptured aneurysms, 224 were treated before the beginning of the study or not treated during the study period (some of them having been treated after the inclusion period). Seven hundred thirty-nine unruptured aneurysms were treated by the endovascular approach during the study period and constitute the study population.

Seven hundred twenty-eight aneurysms were treated once and 11 aneurysms were treated twice during the inclusion period. A total of 700 procedures were performed. The number of aneurysms treated per procedure was one in 657 procedures (93.9%), 2 in 36 procedures (5.1%), and 3 in 7 procedures (1.0%).

Aneurysm characteristics are presented in Tables 1 and 2. Most aneurysms were located in anterior circulation (91.9%), including carotid siphon (38.7%), middle cerebral artery (29.5%), anterior cerebral artery and anterior communicating artery (18.5%), and intracavernous (5.1%); posterior circulation aneurysms were encountered in 8.1% of cases, including the basilar artery (6.2%), vertebral artery (1.5%), and posterior cerebral artery (0.4%).

### Results

#### Modalities of Endovascular Treatment of Unruptured Intracranial Aneurysms

In 12 cases (1.6%), occlusion of the parent vessel was performed. Seven hundred twenty-seven aneurysms (98.4%) were selectively treated using coils. For selective treatment, coils alone were used in 396 aneurysms (54.5%). The balloon remodeling technique was used in 271 cases (37.3%), intracranial stenting in 57 cases (7.8%), and Trispan in 3 cases (0.4%).
Intraoperative systemic heparinization was used in all cases. Anticoagulation therapy was continued during the days after treatment in 441 procedures (63.0%). Antiplatelet medication was used before the endovascular treatment in 139 procedures (19.9%), during the treatment in 350 cases (50.0%), and after the treatment in 402 cases (57.4%).

### Feasibility of Endovascular Treatment of Unruptured Intracranial Aneurysms

Endovascular treatment failed in 32 aneurysms (4.3%). In 2 patients with multiple aneurysms, treatment was interrupted due to occurrence of rupture of another aneurysm during the treatment; thus, one of the aneurysms planned to be treated within the same session remained untreated and was considered a failure of the EVT.

In 22 cases, treatment failed due to anatomic reasons: wide neck not controllable with the remodeling technique, vessel arising from the neck of the aneurysm, and small size of the aneurysm making deposition of coils difficult and unsafe.

In 8 cases, treatment failed due to technical problems: difficulty to navigate the microcatheter inside the aneurysm due to tortuosity of the cervical or intracranial vessels or to vasospastic conditions and difficulty to deploy the coils inside the aneurysm due to instability of the microcatheter.

The treatment failed in 14 aneurysms located in the middle cerebral artery (MCA), 7 aneurysms located in the anterior cerebral artery (ACA) and anterior communicating artery (Acom), 7 aneurysms located in the internal carotid artery (ICA), including carotid siphon and intracavernous aneurysms, and 4 aneurysms located in the posterior circulation.

The rate of failure was 6.7% in the posterior circulation group, 6.4% in the MCA group, 5.1% in the ACA/Acom group, and 2.2% in the ICA group. There is no significant difference among groups according to the location, but there is a trend to significance of lower failure rate in the ICA group (P=0.07).

The size of the aneurysm was 1 to 6 mm in 25 cases and 7 to 15 mm in 7 cases. The rate of failure was significantly different in 1- to 6-mm aneurysms (5.7%) and in 7- to 15-mm aneurysms (2.3%; P=0.022).

Dome-to-neck ratio was ≤1.5 in 21 cases and >1.5 in 11 cases. The rate of failure was 5.4% when the dome-to-neck ratio was ≤1.5 (broad-based aneurysm) and 3.1% when the dome-to-neck ratio was >1.5. This difference was not significant (P=0.78).

The management of UIA after failure of EVT was not asked and it is not possible to know which therapeutic strategy was finally used in these patients (conservative or surgical treatment or another EVT).

### Adverse Events Related to Endovascular Treatment of Unruptured Intracranial Aneurysms

One patient died just before the treatment (even before the femoral puncture) due to an anesthetic complication. This patient was obviously kept for the whole analysis of complications. This death was not considered as a treatment-related technical adverse event but was taken because of the 1-month mortality rate.

Among 649 patients, 104 treatment-related technical adverse events with or without clinical modification were encountered in 100 patients (15.4%).

Specific complications (thromboembolic events, aneurysm rupture, or device-related problems) were encountered in 88 procedures (12.6%) in 87 patients (13.4%). Among 700 procedures, 50 thromboembolic complications (7.1% per procedure) occurred in 49 patients; intraprocedural aneurysmal rupture occurred in 18 procedures (2.6% per procedure); coil-related complications (coil stretching, inappropriate coil detachment) occurred in 20 procedures (2.9% per procedure).

Nonspecific complications were encountered in 16 procedures (2.3%); most of them occurred at the puncture site.

Forty-eight thromboembolic complications occurred during or just after the EVT. In 2 cases, thromboembolic complication occurred a few days after the treatment (7 and 11 days). Treatment of thromboembolic complications was tailored to the specific situation of each patient: no specific treatment in 12 cases, modification of the medical treatment in 23 cases, intra-arterial chemical or mechanical fibrinolysis in 14 cases, and surgery in one case (craniotomy). In 25 of 49

### Table 2. Size of the Neck and Dome-to-Neck Ratio of Treated Aneurysms According to Location

<table>
<thead>
<tr>
<th>Neck Size</th>
<th>Dome-to-Neck Ratio</th>
<th>≤4 mm</th>
<th>N</th>
<th>%</th>
<th>&gt;4 mm</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>476</td>
<td>70.1</td>
<td>203</td>
<td>29.9</td>
<td>356</td>
<td>52.4</td>
<td>323</td>
</tr>
<tr>
<td>Carotid siphon</td>
<td>201</td>
<td>70.3</td>
<td>85</td>
<td>29.7</td>
<td>137</td>
<td>47.9</td>
<td>149</td>
</tr>
<tr>
<td>ACA, Acom</td>
<td>97</td>
<td>70.8</td>
<td>40</td>
<td>29.2</td>
<td>80</td>
<td>58.4</td>
<td>57</td>
</tr>
<tr>
<td>MCA</td>
<td>153</td>
<td>70.2</td>
<td>65</td>
<td>29.8</td>
<td>124</td>
<td>56.9</td>
<td>94</td>
</tr>
<tr>
<td>Intracavernous</td>
<td>25</td>
<td>65.8</td>
<td>13</td>
<td>34.2</td>
<td>15</td>
<td>35.9</td>
<td>23</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>35</td>
<td>58.3</td>
<td>25</td>
<td>41.7</td>
<td>31</td>
<td>51.7</td>
<td>29</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>28</td>
<td>60.9</td>
<td>18</td>
<td>39.1</td>
<td>25</td>
<td>54.3</td>
<td>21</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>5</td>
<td>45.5</td>
<td>6</td>
<td>54.5</td>
<td>4</td>
<td>36.4</td>
<td>7</td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>2</td>
<td>66.6</td>
<td>1</td>
<td>33.3</td>
<td>2</td>
<td>66.6</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>511</td>
<td>69.1</td>
<td>228</td>
<td>30.9</td>
<td>387</td>
<td>52.4</td>
<td>352</td>
</tr>
</tbody>
</table>
patients, no clinical worsening was observed (51.0%). Ten patients had a transient deficit (20.4%), 12 patients had a permanent neurological deficit (24.5%), and 2 patients died (4.1%).

Intraprocedural aneurysmal rupture was observed in 18 patients. In most cases, treatment of the rupture consisted of immediate reversal of heparin and continuation of coiling to achieve maximum filling of the aneurysm to stop bleeding. In 9 cases (50.0%), no clinical worsening was observed after the intraoperative rupture. In one case (5.6%), a transient neurological deficit was observed, although in 5 cases (27.8%), a permanent clinical aggravation was noticed; in 3 cases (16.7%), rupture led to death.

In 20 cases, technical complications occurred as a direct result of the device used (stretching of the coil, problem of detachment); no clinical modification was observed in 18. One had a transient deficit and one died.

**Neurological Complications**

Among 649 patients, 35 adverse events were associated with a modification of the neurological status (5.4% of patients): 12 transient neurological deficits (1.9%), 17 permanent neurological deficits (2.6%), and 6 deaths (0.9%). Including the patient who died preoperatively from anesthetic complications, the global postoperative death rate was 1.1%.

Transient neurological deficits were related to thromboembolic complications in 10 cases, to intraoperative aneurysm rupture in one case, and to a device problem in one case.

Permanent complications were related to thromboembolic complications in 12 cases and to intraoperative aneurysm rupture in 5 cases. At 1 month, mRS was 0 or 1 in 7 cases and 2 to 5 in 10 cases.

Deaths were related to intraoperative rupture in 3 cases, thromboembolic complications in 2 cases, and device-related problem associated with thromboembolic complication in one case.

Three patients had brain hematomas that were anatomically unrelated to the treated aneurysm several days after the EVT. Two of them died and one had a permanent deficit with a 1-month mRS at 4.

**Factors Affecting Complications of Endovascular Treatment of Unruptured Intracranial Aneurysms**

The rate of thromboembolic complications was 8.8% in ACA/Acom aneurysms, 9.6% in MCA aneurysms, 4.6% in ICA aneurysms (intracavernous and supraclinoid), and 3.3% in posterior circulation aneurysms (Tables 3 and 4). The rate of thromboembolic complications was not different according to dome-to-neck ratio ($\leq 1.5$: 5.4%; $>1.5$: 8.2%, nonsignificant). On the contrary, the rate of thromboembolic events was significantly different according to the size of aneurysms.

<p>| Table 3. Rates of Complications According to Aneurysm Location, Size, and Dome-to-Neck Ratio* |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Location</th>
<th>ACA/Acom (n=136)</th>
<th>MCA (n=218)</th>
<th>ICA (n=324)</th>
<th>Posterior Circulation (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysm Size</td>
<td>1 to 6 (n=434)</td>
<td>7 to 15 (n=304)</td>
<td>$\leq 1.5$ (n=386)</td>
<td>$&gt;1.5$ (n=352)</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>12</td>
<td>21</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Percent</td>
<td>8.8</td>
<td>9.6</td>
<td>4.6</td>
<td>3.3</td>
</tr>
<tr>
<td>Intraoperative rupture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3</td>
<td>9</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Percent</td>
<td>2.2</td>
<td>4.1</td>
<td>1.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Device problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>5</td>
<td>4</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Percent</td>
<td>3.7</td>
<td>1.8</td>
<td>2.8</td>
<td>3.3</td>
</tr>
</tbody>
</table>

* Aneurysm harbored by the patient who died before the treatment was not included in these analyses. Aneurysm size is given in millimeters.

| Table 4. Rates of Complications According to the EVT Technique Used* |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Nonselective Treatment (n=12) | Coiling (n=398) | Remodeling (n=271) | Stenting+Coiling (n=57) |
| Thromboembolic complications | | | |
| N | 0 | 29 | 15 | 6 |
| % | 0.0 | 7.3 | 5.5 | 10.5 |
| Intraoperative rupture | | | |
| N | 0 | 8 | 9 | 1 |
| % | 0.0 | 2.0 | 3.3 | 1.7 |
| Device problems | | | |
| N | 0 | 8 | 8 | 4 |
| % | 0.0 | 2.0 | 3.0 | 7.0 |

* Aneurysm harbored by the patient who died before the treatment was not included in these analyses.
One-Month Clinical Results

One-month mortality and morbidity rates were 1.4% (9 of 649) and 1.7% (11 of 649), respectively (Table 5). Among the 9 deaths, one patient died just before the treatment due to an anesthetic complication. Six patients died during or immediately after treatment (see “Neurological Complications”). Two patients died several days after the treatment from intracranial bleeding not anatomically related to the aneurysm. Due to the 2 patients who died several days after the treatment, the 1-month mortality rate (1.4%) is higher than the postoperative mortality rate (1.1%).

Among the 11 patients with 1-month worsening of clinical status, morbidity was due to thromboembolic complications in 6 patients, to intraoperative rupture in 4 patients, and to intracranial hematoma unrelated to aneurysm occurring a few days after discharge of the patient in one case. The morbidity rate at 1 month (1.7%) was lower than the percentage of postoperative permanent complications (2.6%) due to the clinical improvement to mRS 1 or 0 observed in some patients.

Improvement of the mRS at 1 month versus preoperative mRS was observed in patients harboring multiple aneurysms in which one was ruptured or in patients presenting with neurological symptoms related or unrelated to the aneurysm. In these cases, endovascular treatment of unruptured aneurysms was performed during a phase of improvement of the clinical status.

Morbidity and mortality were not significantly different according to sex and preoperative mRS (Table 6). On the contrary, morbidity and mortality rates were higher in patients older than 60 years (mortality: nonsignificant; morbidity: \( P = 0.036 \)). Morbidity and mortality were, respectively, 1.2% (3 of 260) and 1.5% (4 of 260) in the nonsmoking group and 2.1% (8 of 377) and 1.3% (5 of 377) in the smoking group and 2.6% (5 of 192) and 2.1% (4 of 192) in hypertensive patients compared with 1.4% (6 of 444) and 1.1% (5 of 444) in nonhypertensive patients (nonsignificant for both).

Anatomic Results

According to the analysis conducted by the treating neuroradiologist, the postoperative aneurysmal occlusion was: complete occlusion: 436 aneurysms (59.0%); neck remnant: 160 aneurysms (21.7%); and aneurysm remnant: 143 aneurysms (19.3%).

Table 5. One-Month Clinical Results (mRS)*

<table>
<thead>
<tr>
<th>1 Month</th>
<th>Preoperative</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6 (deaths)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>0</td>
<td>13†</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>8</td>
<td>536</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>18</td>
<td>58</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>528</td>
<td>77</td>
<td>17</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>9</td>
<td>649</td>
<td></td>
</tr>
</tbody>
</table>

*Comparison between preoperative mRS (horizontal lines) and 1-month postoperative mRS (columns). Bolded values include patients that were considered clinically stable (no morbidity). Italicized values include patients with a 1-month postoperative worsening of mRS (morbidity). Bolded/italicized values correspond to death. Values located below the bolded values correspond to patients clinically improved 1 month after treatment.

†In this group, 1-month mRS 1 is related to nonspecific complications in some patients.

(1 to 6 mm: 4.6%; 7 to 15 mm: 9.9%; \( P = 0.005 \)). The rate of thromboembolic complications was 7.3% in the coil alone group, 5.5% in remodeling group, 10.5% in the stenting group, and 0.0% in the nonselective treatment group.

The rate of perioperative aneurysmal perforation was 2.2% in ACA/Acom aneurysms, 4.1% in MCA aneurysms, 1.9% in ICA aneurysms (intracavernous and supraclinoid), and 0.0% in posterior circulation aneurysms. The rate of perioperative aneurysmal rupture was significantly different according to the size of aneurysms (1 to 6 mm: 3.7%; 7 to 15 mm: 0.7%; \( P = 0.008 \), but not to the dome-to-neck ratio (\( \leq 1.5: 2.6\); \( >1.5: 2.3\); nonsignificant). The rate of perioperative aneurysmal perforation was 2.0% in the coil alone group, 3.3% in the remodeling group, 1.7% in the stenting group, and 0.0% in the nonselective treatment group.

Regarding complications versus aneurysm location and treatment technique, it is not possible to have a valid statistical analysis due to the small number of events in each subgroup.

Table 6. Morbidity and Mortality According to Sex, Age, and Preoperative mRS

<table>
<thead>
<tr>
<th>Sex</th>
<th>Preoperative mRS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F (n=468)</td>
<td>M (n=181)</td>
</tr>
<tr>
<td>Morbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>%</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>%</td>
<td>1.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>%</td>
<td>2.8</td>
<td>3.9</td>
</tr>
</tbody>
</table>
Analysis of factors affecting postoperative aneurysmal occlusion will be performed after completion of the independent analysis of the postoperative angiograms by the core laboratory and is not presented in this article.

Discussion
The management of unruptured intracranial aneurysms is still a matter of debate and depends on a full understanding of the natural history balanced against the risks of treatment and long-term protection provided. The natural history of UIAs was analyzed in a large cohort of patients and percentages of rupture were determined according to the location and size of aneurysms. The outcome after surgery of unruptured aneurysms is well documented. On the contrary, results of EVT have not been analyzed in a high methodological quality series including a large number of patients. ATENA is the first prospective, multicentric study investigating a large population of patients treated by the endovascular approach. The goal was to describe the results of the EVT of UIA in France (and Canada) without changing the indications, the strategies, and the techniques that were usually performed in each individual center. The goal of ATENA was not to describe the global management of UIA in France or to evaluate the respective place and results of conservative, surgical, and endovascular treatment. It was also not to compare neurosurgical and endovascular treatment.

The strategy of treatment of UIA is in France (like probably in the other countries) decided on a case-by-case basis. This case-by-case basis was the rule for enrolment in ATENA and the decision of EVT of UIA was made in each center by a local multidisciplinary team. The rationale of the decision of EVT was not asked in ATENA.

As described in the ISUIA study, most patients included in ATENA were females (72.1%) and the mean age was 51.2 years. Anatomic distribution of UIA was usual with a large predominance of anterior circulation aneurysms (91.9%). Surprisingly, the majority of treated aneurysms were less than 7 mm (58.7%) despite the fact that the risk of bleeding was reported to be low in this group in the ISUIA study. It reflects the current practice in France. It is probably linked to the fact that the 7-mm threshold is not considered in France as the only criteria to decide whether an UIA has to be treated. Effectively, indications of treatment for UIA are not only based on the size criteria, but also on clinical factors, including age and previous subarachnoid hemorrhage, morphological factors (daughter sac, irregular shape of the sac), and potential modifications of the aneurysmal sac along time (increase in size, modifications of the shape).

Analysis of Complications Occurring During the Endovascular Treatment of Unruptured Intracranial Aneurysms
The global rate of technical adverse events with or without clinical modification in our series is 15.4% per patient (100 of 649). Adverse events specifically related to the treatment of aneurysms were encountered in 12.6% of procedures: thromboembolic events (7.1%), intraoperative aneurysm rupture (2.6%), and device-related problems (2.9%). Adverse events with postoperative modification of the neurological status or death were encountered in 5.4% of patients. It is comparable to published data. In the retrospective series of UIA provided by Gonzalez et al., the percentage of specific technical complications is 6.9%, including cerebral embolization (3.7%), aneurysm perforation (1.4%), arterial dissection (0.9%), and device-related problems (1%). In large series mixing ruptured and unruptured aneurysms, the rate of complications related to the treatment is between 8.3% and 18.2% of cases.

The percentage of thromboembolic events may also differ from one series to another according to the technique used to treat the aneurysm; the medication administered before, during, and after treatment; and the technique used to detect complications (CT, MRI, angiography, transcranial Doppler). However, the percentage of thromboembolic complications in our series (7.1%) is close to what has been reported in unruptured series: 3.7%, 6.9%, and in series mixing ruptured and unruptured aneurysms: 11.0%, 9.1%, and 12.7%. Outcome of thromboembolic events is variable. Death is directly related to thromboembolic complication in 2 of 49 (4.1%) in our series, and permanent deficit is observed in 12 of 49 patients (24.5%).

Intraoperative aneurysm perforation is observed in 2.6% of procedures. In previous small series, no intraoperative aneurysmal rupture is reported but it is probably due to the small number of patients treated. In the Gonzalez and Terada series, the rate of intraoperative aneurysmal rupture is 1.4% and 1.3%, respectively. In our series, intraoperative perforation was a severe complication leading to 3 deaths (16.7%) and 5 permanent deficits (27.8%).

Factors Affecting Complications of Endovascular Treatment of Unruptured Intracranial Aneurysms
Due to the large size of our series, it is for the first time possible to analyze the role of anatomical and technical factors in the occurrence of adverse events. Interestingly, occurrence of thromboembolic complications or intraoperative rupture was not significantly different according to the location or dome-to-neck ratio of aneurysms. On the contrary, the rate of thromboembolic events was significantly higher in large-sized aneurysms (1 to 6 mm: 4.6%; 7 to 15 mm: 9.9%; P=0.008). The rate of intraoperative aneurysmal rupture was significantly higher in smaller aneurysms (1 to 6 mm: 3.7%; 7 to 15 mm: 0.7%; P=0.008) as was previously suggested by some authors.

Results of the Endovascular Treatment of Unruptured Intracranial Aneurysms
A small number of series are specifically evaluating the results of the endovascular treatment of UIA. Most of them are monocentric and retrospective and include a small number of patients (from 39 to 217 patients). Failure of the endovascular treatment is reported in 5.0% to 9.5% of cases, mortality in 0.0% to 0.5% of cases, and morbidity in 3.7% to 5.1%. In the endovascular cohort of ISUIA, mortality is 1.7% and morbidity (mRS of 3 to 5) 2.2% in 451 patients. In the aggregate analysis published by Lee, the adverse outcome rate (defined as combined all-cause early or in-hospital morbidity or mortality) varied from 0.0% to 30.0% and
mortality from 0.0% to 12.0%. The cumulative coils adverse outcome rate is 8.8%.

ATENA is the first prospective, multicentric study dealing with a high number of patients harboring UIA treated by the endovascular approach. The rate of failure of EVT in the treatment of UIA is low: 4.3%. Interestingly, the rate of failure is significantly different according to the size: 5.7% in 1- to 6-mm aneurysms and 2.3% in 7- to 15-mm aneurysms. The rate of failure is lower in the basilar siphon group (2.2%) than in the posterior circulation group (6.7%), MCA group (6.4%), and ACA/Acom group (5.1%), but it is not significant. The rate of failure is not significantly different according to dome-to-neck ratio.

At 1 month posttreatment, mortality is 1.4% and morbidity 1.7%. Compared with previous series, morbidity was more severely defined in our study as an mRS >1. Indeed, if a patient was unable to carry out all previous activities after endovascular treatment (mRS 2), we have considered it more relevant to classify this patient as having morbidity. In ATENA, morbidity was defined as mRS of 2, 3, 4, or 5 and in ISUIA as mRS 3, 4, or 5. As a hypothesis, if morbidity in the ATENA study was defined as mRS >2 or any increase of mRS in case of preoperative mRS >1, morbidity would have been 0.9% instead of 1.4%.

Deaths were directly related to EVT in 6 of 9 cases: 3 perioperative ruptures, 2 thromboembolic complications, and one device-related problem with a subsequent thromboembolic complication. In another case, the patient died just before the treatment due to complications related to anesthesia. In 2 other cases, intracerebral bleeding unrelated to the aneurysm occurred several days after EVT.

ATENA results are not directly comparable to the results of ISUIA regarding the endovascular cohort. In ISUIA, patients were included during a relatively long period of time (1991 to 1998) and took place at a time when indications and results of the EVT of UIA were probably not the same as in the ATENA study conducted recently within a short period of time (17 months). In ISUIA, patients with preoperative mRS >2 and aneurysms less than 2 mm were not included. In ISUIA, morbidity of the treatment was defined by using mRS and cognitive tests (Mini Mental State Examination or telephone interview for cognitive status). On the contrary, in ATENA, morbidity was defined by using only mRS.

Results of the Surgical Treatment of Unruptured Intracranial Aneurysms

In the largest meta-analysis published by Raaymakers et al in 1998, which included a total of 2460 patients from 61 studies, mortality was 2.6% and permanent morbidity 10.9%. In the open surgical cohort of ISUIA, surgery-related death was reported in 1.5% and disability (mRS of 3 to 5) in 2.9%. In an aggregate analysis published by Lee et al in 2005, the cumulative clipping adverse outcome rate (defined as combined all-cause early or in-hospital morbidity or mortality) was 17.8% in a group of 11 363 subjects.

Comparison of the Results of the Surgical and Endovascular Treatment of Unruptured Intracranial Aneurysms

No direct comparison has been made between surgical and endovascular treatment of UIA in a randomized study as was the case for ruptured aneurysms with ISAT. However, in assessment of single-center series and meta-analysis dealing with surgical or endovascular treatment of UIA, mortality of the endovascular treatment is reported between 0% and 1.7% as compared with 1.5% to 2.6% for surgical treatment. Similarly, morbidity is higher with surgical treatment than with endovascular treatment, 2.9% to 10.9% and 2.1% to 5.1%, respectively.

Database analysis by Johnston et al compared the clinical outcome of patients with unruptured aneurysms treated by surgery and endovascular therapy. Adverse outcomes were significantly higher in the surgical group (18.5%) than in the endovascular group (10.6%). Mortality was 2.3% after clipping and 0.4% after coiling. Shorter hospital stay, shorter recovery period, and reduced costs are also reported in the endovascular group. With a similar methodology, Higashida et al showed that endovascular treatment was associated with fewer adverse outcomes (6.6% versus 13.2%), decreased mortality (0.9% versus 2.5%), shorter lengths of hospital stay (4.5 versus 7.4 days), and lower hospital charges compared with neurosurgical treatment.

Limitations of Our Study

There are 2 main limitations to our study. First, untreated or surgically treated UIA were not registered; therefore, it is not possible to determine if the local team decision has induced an inclusion bias when deciding which treatment strategy was the most appropriate. Thus, it is not possible to determine if our population is representative of the whole population of patients harboring UIAs. However, our population is perfectly representative of the daily practice in French centers, because all aneurysms treated by EVT were consecutively collected during a certain period of time for the study. Second, cognitive status of the patients was not evaluated, as ISUIA did.

Summary

Endovascular treatment of unruptured intracranial aneurysms can be achieved in a high percentage of cases (95.7%) with low morbidity and mortality rates (1.7% and 1.4%, respectively). The first cause of mortality is intraoperative rupture followed by thromboembolic complications. Morbidity is mainly due to thromboembolic complications. According to the literature, morbidity–mortality of the endovascular treatment seems to be lower than for surgical treatment. The rate of complications is significantly affected by aneurysm size. Intraoperative rupture rate is higher in small aneurysms and thromboembolic complications are more frequent in aneurysms greater than 7 mm. Morbidity and mortality at 1 month is higher in patients older than 60 years. Midterm outcome of the endovascular treatment will be analyzed after follow-up of 1 and 3 years.

Appendix

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Disclosures

None.

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