Original Contribution

Endovascular Therapy for Asymptomatic Unruptured Intracranial Aneurysms
JR-NET and JR-NET2 Findings

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Background and Purpose—National registration studies (the Japanese Registry of Neuroendovascular Therapy [JR-NET] and JR-NET2) have determined the current status and outcomes of neuroendovascular therapy (neuro-EVT). We analyzed short-term outcomes of EVT for asymptomatic unruptured intracranial aneurysms (UIAs).

Methods—We extracted periprocedural information about EVT for 4767 asymptomatic UIAs from 31 968 registered procedural records of all EVT in the JR-NET and JR-NET2 databases. We assessed the features of the aneurysms and procedures, immediate radiographic findings, procedure-related complications, and clinical outcomes at 30 days after the procedures.

Results—We located 80.0% of UIAs in the anterior circulation, and the most frequent were paraclinoid. The diameter of 2.5%, 32.9%, 51.9%, 12.0%, and 0.7% of the UIAs was <3, 3 to 4, 5 to 9, 10 to 19, and >20 mm, respectively. EVT failed in only 2.1%. Adjunctive techniques were applied in 54.8% of procedures. Pre- and postprocedural antiplatelet agents were prescribed in 85.6% and 84.0%, respectively, of the procedures. The immediate radiographic outcomes of 57.7%, 31.9%, and 10.0% of the UIAs comprised complete occlusion, residual necks, and residual aneurysms, respectively. Complications that were associated with 9.1% of procedures comprised 2.0% hemorrhagic and 4.6% ischemic, and the 30-day morbidity and mortality rates were 2.12% and 0.31%, respectively.

Conclusions—The radiographic results of EVT for asymptomatic UIAs in Japan were acceptable, with low mortality and morbidity rates. (Stroke. 2013;44:00-00.)

Key Words: complications ■ embolization ■ endovascular procedures ■ intracranial aneurysm ■ treatment outcome ■ unruptured aneurysm

The management of incidental unruptured intracranial aneurysms (UIAs) remains undefined. After the International Study of Unruptured Intracranial Aneurysms (ISUIAs) prospecctively showed very low rupture rates of small aneurysms of the anterior circulation, others described the natural course of UIAs. Although the reported rupture rate of small UIAs is low, when they do rupture, they lead to life-threatening subarachnoid hemorrhage (SAH).

To determine how to manage patients with UIAs, the risks of various treatments with respect to the natural history and other risk factors should be assessed. The outcomes of clipping have been systematically described. Some retrospective single-center outcomes of endovascular therapy (EVT) have been excellent, and prospective data from France and Canada have been published, but the actual risks of EVT remain poorly understood.

The Japanese Registry of Neuroendovascular Therapy (JR-NET) and JR-NET2 are surveys that the Japanese Society for Neuroendovascular Therapy conducted in 2007 and 2010, respectively, to determine the status of EVT in Japan, and to standardize endovascular procedures and plan education for Japanese neurointerventionists on the basis of outcomes. The primary end point was the 30-day clinical outcome (modified Rankin Scale [mRS]) and secondary end points comprised technical success, adverse events arising within 30 days, and procedure-related complications arising after 30 days.

We collected a considerable amount of clinical data about EVT for UIAs through the JR-NET and JR-NET2 investigations. Here, we evaluated the outcomes of EVT for asymptomatic UIAs in Japan.

Methods

JR-NET and JR-NET2 Protocols

All EVT specialists certified by Japanese Society for Neuroendovascular Therapy were invited to register consecutive procedures on the JR-NET 2007 and JR-NET2 2010 databases. Patients...
in the JR-NET study were registered from 122 Japanese neurointerventional centers with 200 EVT specialists. The inclusion criteria comprised all patients who underwent EVT performed by EVT specialists between January 2005 and December 2006. Overall, 10715 patients who underwent 11114 EVT procedures were registered. Similarly, included in JR-NET2 were patients who underwent EVT at 150 neurointerventional centers with 255 EVT specialists between January 2007 and December 2009. Overall, 20272 patients who underwent 20854 EVT procedures were registered. The participants in these studies are listed in Appendix in the online-only Data Supplement.

Clinical and procedural data were entered through a Web site constructed by the Translation Research Informatics Center (Kobe, Japan) and anonymously reviewed by the principal investigators. Each JR-NET and JR-NET2 data set of cerebral aneurysms included the following parameters: demographics (sex, age, date of treatment), clinical data (mRS before and 30 days after EVT), complication data (procedure-related complications, adverse events), treatment parameters (aneurysmal location, size, shape, associated or not with SAH, symptomatic or asymptomatic), and procedural data (number of cerebral aneurysms treated in a single procedure, endovascular techniques, immediate radiographic outcomes, antithrombotic regimen). Table 1 shows the 16 locations of cerebral aneurysms listed in the registra

Data Extraction
All data sets registered as aneurysmal treatment and initially extracted from the JR-NET and JR-NET2 databases were screened in a single session to collect only information about treatment of asymptomatic UIAs. In other words, ruptured aneurysms, dissecting aneurysms, symptomatic UIAs, extracranial aneurysms, aneurysms associated with ruptured or symptomatic aneurysms, and treated UIAs comitant with other diseases were excluded. We also screened procedures for eligibility criteria comprising pre- (sex, age, date of treatment, preprocedural mRS, aneurysm characteristics), intra- (techniques), and postprocedural status (radiographic outcomes, procedure-related adverse events, and mRS at 30 days). Treatment for intentional parent artery occlusion and nonsaccular aneurysms was also excluded. We thus isolated 1506 (1571 UIAs) and 3067 (3,196 UIAs) procedures from JR-NET and JR-NET2, respectively, with complete data for almost all variables on which this analysis was based (Figure). Combining these data from 4573 (4767 UIAs) procedures, 1262 (27.6%) and 3311 (72.4%) men and women, respectively, ranging in age from 6 to 93 (mean, 60.6±11.1) years underwent procedures. The numbers of treated UIAs were 1 (96.1%) of 4395, 2 of 164, 3 of 12, and 4 of 2 procedures (Table 2).

Statistical Analysis
Mean and frequency data were compared using Student’s t test and the χ² test or Fisher exact test, respectively. Trends were analyzed using the Cochran–Armitage test. All data were statistically analyzed using JMP version 10.0 software (SAS Institute, Cary, NC). The significance threshold was established at P<0.05.

### Table 1. Treated Aneurysms

<table>
<thead>
<tr>
<th>Location</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior circulation</td>
<td>3814 (80.0)</td>
</tr>
<tr>
<td>ICA-cav</td>
<td>201 (4.2)</td>
</tr>
<tr>
<td>ICA-para</td>
<td>1575 (33.0)</td>
</tr>
<tr>
<td>ICA-Pcom</td>
<td>682 (14.3)</td>
</tr>
<tr>
<td>ICA-AchoA</td>
<td>157 (3.3)</td>
</tr>
<tr>
<td>ICA-bif</td>
<td>142 (3.0)</td>
</tr>
<tr>
<td>MCA</td>
<td>301 (6.3)</td>
</tr>
<tr>
<td>ACRBA</td>
<td>39 (0.8)</td>
</tr>
<tr>
<td>Acom</td>
<td>588 (12.3)</td>
</tr>
<tr>
<td>Daca</td>
<td>101 (2.1)</td>
</tr>
<tr>
<td>Other (AC)</td>
<td>28 (0.6)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>953 (20.0)</td>
</tr>
<tr>
<td>VA</td>
<td>132 (2.8)</td>
</tr>
<tr>
<td>BA-trunk</td>
<td>44 (0.9)</td>
</tr>
<tr>
<td>BA-Sca</td>
<td>188 (3.9)</td>
</tr>
<tr>
<td>BA-bif</td>
<td>520 (10.9)</td>
</tr>
<tr>
<td>PCA</td>
<td>42 (0.9)</td>
</tr>
<tr>
<td>Other (PC)</td>
<td>27 (0.6)</td>
</tr>
<tr>
<td>Size (r, mm)</td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>119 (2.5)</td>
</tr>
<tr>
<td>3 to &lt;5</td>
<td>1569 (32.9)</td>
</tr>
<tr>
<td>5 to &lt;10</td>
<td>2476 (51.9)</td>
</tr>
<tr>
<td>10 to &lt;20</td>
<td>570 (12.0)</td>
</tr>
<tr>
<td>≥20</td>
<td>33 (0.7)</td>
</tr>
<tr>
<td>Appearance (% of UIA&lt;10 mm)</td>
<td></td>
</tr>
<tr>
<td>Narrow neck†</td>
<td>1816 (43.6)</td>
</tr>
<tr>
<td>Wide neck‡</td>
<td>2348 (56.4)</td>
</tr>
</tbody>
</table>

*Acim indicates anterior communicating artery; ACRBA, anterior cerebral artery proximal to anterior communicating artery; BA, basilar artery; BA-bif, bifurcation of BA; BA-Sca: superior cerebellar artery of basilar artery; BA-trunk, trunk of basilar artery; Daca, anterior cerebral artery distal to anterior communicating artery; ICA-AchoA, anterior choroidal artery; ICA-bif, bifurcation of internal carotid artery; ICA-cav, cavernous segment of ICA; ICA-para, paraclinoid segment of ICA; ICA-Pcom, posterior communicating artery; MCA, middle cerebral artery; Other (AC), other locations in anterior circulation; Other (PC), other locations in posterior circulation; PCA, posterior cerebral artery; and VA, vertebral artery.

†Neck, ≤4 mm and Dome-to-neck (D/N) ratio ≥1.5.
‡Neck >4 mm or D/N ratio <1.5.

Results

Aneurysm Characteristics

We analyzed periprocedural data from 4767 asymptomatic UIAs. Table 1 shows the features of the aneurysms, 3814 (80.0%) and 953 (20.0%) of which were located in the anterior and posterior circulation, respectively. One third was located in the internal carotid artery-paraclinoid, followed by the internal carotid artery-posterior communicating artery (14.3%), anterior communicating artery (12.3%), bifurcation of basilar artery (10.9%), and middle cerebral artery (6.3%). The maximal diameters of 2476 (51.9%) and 1569 (32.9%) aneurysms were 5 to 9 and 3 to 4 mm,
respectively. The maximal diameters of 570 (12.0%), 33 (0.7%), and 119 (2.5%) aneurysms were 10 to 19, >20, and <3 (very small) mm, respectively. Among UIAs <10 mm, 1816 (43.6%) and 2348 (53.4%) had narrow and wide necks, respectively.

Modalities of EVT for UIAs
Of 2155 (45.2%) aneurysms that were scheduled for intraaneurysmal embolization, all were treated by intrasaccular coil embolization using a single microcatheter and coils, and the remaining 2612 (54.8%) underwent adjunctive therapies, including balloon remodeling,13 double catheters,14 and intracranial stenting. Intracranial stents were applied to only 51 (1.1%) aneurysms because they were not approved in Japan until 2010. Systemic heparinization was included in 4488 (98.1%) procedures. Continuous anticoagulation and post- and preprocedural antiplatelet medications were applied in 3108 (68.0%), 3841 (84.0%), and 3914 (85.6%) procedures, respectively. Preferences for adjunctive techniques increased annually (P<0.001), and the rates of post- and preprocedural antiplatelet therapy also statistically increased annually (P<0.001, each; Table I in the online-only Data Supplement).

EVT Feasibility and Immediate Radiographic Outcomes
EVT for 102 (2.1%) aneurysms failed (Table 3) at rates of 4.2%, 2.9%, 1.7%, 1.4%, and 3.0% for aneurysms with diameters of <3, 3 to 4, 5 to 9, 10 to 19, and >20 mm, respectively. The failure rate statistically decreased along with increasing aneurysmal size (P=0.003; Table II in the online-only Data Supplement). Failure rates did not significantly differ between aneurysms of the anterior and posterior circulation (2.2% versus 1.9%; Table III in the online-only Data Supplement). The immediate radiographic outcomes of 4665 successfully treated aneurysms (Table 3) showed that 2690 (57.7%) were completely occluded, 1490 (31.9%) had residual necks, 468 (10.0%) had residual aneurysmal domes, and 17 (0.4%) ended in unpredicted parent artery occlusion. The rate of residual aneurysm tended to increase annually (P=0.03; Table 4).

Adverse Events Related to EVT
Procedure-related adverse events occurred in 417 (9.1%) patients and 23.0% of those (n=96; 2.1% of total) had a reduced 30-day mRS (Table 3). Intracranial hemorrhagic and ischemic complications developed after 90 (2.0%) and 210 (4.6%) procedures, respectively, and 65 aneurysms ruptured intraprocedurally (1.4% per each aneurysm and procedure). We also found 5 aneurysms that had ruptured during the post-treatment period. Ischemic complications significantly decreased annually (P=0.01), but the total complication rates had no significant trend (Table 4). Analysis according to aneurysm size revealed that total complication rates were higher in aneurysms with very small (<3 mm) and large (≥10 mm) diameters than in those with diameters between 3 and 9 mm (Table II in the online-only Data Supplement). Rates of ischemic and hemorrhagic complications were significantly higher in larger (P<0.001) and smaller aneurysms (P<0.001), respectively. The complication rates were significantly lower for aneurysms in the anterior than in the posterior circulation: 8.3% (316/3,814) versus 11.2% (113/953), P=0.005 (Table III in the online-only Data Supplement). Furthermore, among UIAs <10 mm in diameter, complication rates were lower in those with

Table 2. Characteristics of Patients and Procedures

<table>
<thead>
<tr>
<th>UIAs (n)</th>
<th>4767</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedures (n)</td>
<td>4573</td>
</tr>
<tr>
<td>Age (y, range)</td>
<td>60.6±11.1 (6–93)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>3311 (72.4)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>1262 (27.6)</td>
</tr>
<tr>
<td>Preprocedural mRS (n %)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4262 (93.2)</td>
</tr>
<tr>
<td>1</td>
<td>182 (4.0)</td>
</tr>
<tr>
<td>2</td>
<td>75 (1.6)</td>
</tr>
<tr>
<td>3</td>
<td>24 (0.5)</td>
</tr>
<tr>
<td>4</td>
<td>26 (0.6)</td>
</tr>
<tr>
<td>5</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td>Aneurysms/procedure, n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4395 (96.1)</td>
</tr>
<tr>
<td>2</td>
<td>164 (3.4)</td>
</tr>
<tr>
<td>3</td>
<td>12 (0.3)</td>
</tr>
<tr>
<td>4</td>
<td>2 (0.0)</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin scale; and UIA, unruptured intracranial aneurysm.

Figure. Included and excluded data sets. Preprocedural status: sex, age, date of treatment, preprocedural modified Rankin Scale (mRS) and aneurysm characteristics. Intraprocedural status: techniques. Postprocedural status: radiographic outcome, procedure-related adverse events and mRS 30 days after EVT. JR-NET indicates the Japanese Registry of Neuroendovascular Therapy; and UIA, unruptured intracranial aneurysm.
Table 3. Summary of Overall Outcomes of EVTs

<table>
<thead>
<tr>
<th>Technique (pa)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>2155</td>
<td>45.2</td>
</tr>
<tr>
<td>Adjunctive</td>
<td>2612</td>
<td>54.8</td>
</tr>
<tr>
<td>Antithrombotic regimen (pp)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE antiplatelet therapy</td>
<td>3914</td>
<td>85.6</td>
</tr>
<tr>
<td>INTRA systemic heparinization</td>
<td>4488</td>
<td>98.1</td>
</tr>
<tr>
<td>CONT anticoagulation</td>
<td>3108</td>
<td>68.0</td>
</tr>
<tr>
<td>POST antiplatelet therapy</td>
<td>3841</td>
<td>84.0</td>
</tr>
</tbody>
</table>

Feasibility (pa)

| Success       | 4665 | 97.9 |
| Failure        | 102  | 2.1  |

Anatomic outcome (per successfully treated UIA)

| CO            | 2690 | 57.7 |
| RN            | 1490 | 31.9 |
| RA            | 468  | 10.0 |
| uPAO          | 17   | 0.4  |

Adverse events (pp)*

| Procedure-related complications | 417 (96) | 9.1 (2.1) |
| Hemorrhagic                     | 90 (29)  | 2.0 (0.7) |
| Intraprocedural aneurysmal rupture | 65 (18) | 1.4 (0.3) |
| Aneurysmal rupture in post-treatment period | 5 (5) | 0.1 (0.1) |
| Ischemic                        | 210 (59) | 4.6 (1.3) |
| Puncture site                   | 33     | 0.7   |
| Other                           | 84     | 1.8   |

mRS 30 days after EVT

<table>
<thead>
<tr>
<th>mRS 30 days after EVT</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4193</td>
<td>91.7</td>
</tr>
<tr>
<td>1</td>
<td>207</td>
<td>4.5</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>0.7</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>0.7</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>0.8</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>0.2</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Clinical outcome (pp)

<table>
<thead>
<tr>
<th>Clinical outcome (pp)</th>
<th>97</th>
<th>2.12</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day morbidity</td>
<td>2.12</td>
<td></td>
</tr>
<tr>
<td>30-day mortality</td>
<td>0.31</td>
<td></td>
</tr>
</tbody>
</table>

CO indicates complete occlusion; CONT, continuous; EVT, endovascular therapy; INTRA, intraprocedural; pa, per aneurysm; mRA, modified Rankin Scale; POST, postprocedural; pp, per procedure; PRE, preprocedural; RA, residual aneurysm; RN, residual neck; and uPAO, unpredicted parent artery occlusion.

*With mRS deterioration.

favorable than in those with wide necks (Table IV in the online-only Data Supplement).

Clinical Outcomes at 30 Days

The 30-day morbidity and mortality rates were 97 (2.12%) and 14 (0.31%) of 4573 procedures, respectively (Table 3). All deaths were accompanied by hemorrhagic complications (aneurysmal ruptures, n=10; arterial dissections, n=2; arterial perforation, n=1) except one with ischemic complications caused by branch occlusion. No death was associated with other systemic conditions, such as coronary disease, pneumonia, or cancer.

Discussion

The incidence of detecting incidental asymptomatic UIAs has recently increased together with increasing opportunities for radiological assessments and developments in neuroimaging devices. However, consensus has not been reached on UIA management, which requires understanding of the natural history balanced against risks of treatment and long-term protection.

The largest study of the natural course of UIAs was compiled in 1998 by ISUIA investigators who first reported 0.5% annual rates of SAH for aneurysms <10 mm and 0.05% annual rates in patients with and without a history of SAH. On the basis of reports thereafter about the natural history, especially of small UIAs, risk factors for aneurysmal rupture and SAH resulting from small aneurysms, the Japan Stroke Society released statements for the management of UIAs within guidelines for the management of stroke, and relatively clear recommendations for UIA management have also been reported. Morita et al documented 111 patients with a 0.95% annual rate of rupture during a follow-up comprising 11 660 aneurysm-years. However, the results of clipping UIAs and coiling are difficult to compare. Although some prospective randomized studies, such as the ISAT or Barrow Trial, have compared coiled with clipped ruptured aneurysms, the results for UIAs were determined from aggregate analyses or analyses of recent databases because designing randomized controlled trials is difficult.

We aimed to clarify the current risks and short-term outcomes of EVT for UIAs in Japan, considering individual UIA management. We analyzed the outcomes of EVT for asymptomatic UIAs between 2005 and 2009 on the basis of information accumulated from the JR-NET and JR-NET2 databases created from information provided by >100 institutions throughout Japan. Most EVT for asymptomatic UIAs was performed by Japanese Society for Neuroendovascular Therapy–certified EVT specialists. Thus, this study is the first large cohort investigation of the nationwide results of EVT for asymptomatic UIAs.

In the present study, most of the patients were women and anterior circulation aneurysms were the most prevalent, which reflected the findings of the ISUIA and Analysis of Treatment by Endovascular approach of Non ruptured Aneurysms (ATENA) studies. However, the patients were a mean of 10 years, and most aneurysms (87.3%) were <10 mm. Although the Japanese guidelines recommend treating UIAs ≥5 mm in maximal diameter, UIAs <5 mm account for 35.4% of the total; Oishi et al reported that 223 (44.6%) of 500 small (<10 mm in diameter) treated UIAs were <5 mm. As part of the annual health checks characteristic of the unique Japanese healthcare system, complete physical examinations and whole brain screenings are widespread, and more small UIAs have been discovered through these routine procedures than elsewhere. Moreover, the Japanese insurance system covers treatment for such UIAs if the patient elects to proceed. Thus, small UIAs have abundant opportunities for treatment in Japan.
others describe small patient cohorts. The ATENA study11 prospectively studied EVT outcomes at seven neuroradiological centers in France and Canada during 2005 and 2006. Table V in the online-only Data Supplement lists the case series of EVT for UIAs reported after the 1998 ISUIA study and Table 5 summarizes them and compares the ATENA and present studies.

### Feasibility and Clinical Outcomes of EVT

The 2.1% failure rate in the present study was lower than those in the ATENA (4.3%) and other (3.8% to 10%) studies. The failure rates were significantly higher and lower for small aneurysms with wide and narrow necks, respectively, and tended to increase as aneurysms decreased. Failure rates did not significantly differ between aneurysms of the anterior and aneurysms of the posterior circulation.

The ATENA study that defined morbidity at 1 month after treatment as mRS 2 to 5 and a preoperative mRS >1 as any increase in the mRS, reported morbidity and mortality rates of 2.6% and 1.1%, respectively. These rates in retrospective case series range from 0% to 7.7% and from 0% to 1.7%, respectively. One systematic review found that at 1 month, 1.8% of patients had died in addition to 4.7% with unfavorable outcome rates, including death.22 We determined 2.1% and 0.3% morbidity and mortality rates from JR-NET and JR-NET2 data, respectively, which we think are justified. We could not evaluate cognitive status as in the ISUIA study, and because neurologists did not always perform independent neurological examinations, we might have underestimated morbidity.

### Radiographic Outcomes

The other case series used various classifications. To compare rates of insufficient radiographic outcomes of coil embolization among studies, we determined how many were defined as incomplete occlusion (<90%) or residual aneurysm. The radiographic outcomes of coil embolization were insufficient in 19.3% of aneurysms in the ATENA study, 1.2% to 20.8% in other studies, and 10.0% in the present study. We also determined the initial radiographic outcomes of the HELPS23 and the Cerecyte trial24; 14.5% were insufficient in the former and 11.7% were insufficient in the latter,24 which used bare platinum coils. The radiographic outcomes herein usually depended on the judgment of the treating physicians, and thus poor outcomes might have been underestimated, which the second report of the ATENA study also considers.25

### Adverse Events

The rate of procedure-related complications is 15.4% in the ATENA study (including 2.6% and 7.1% hemorrhagic and ischemic complications, respectively) and 2.5% to 28% in...
other studies. This variation might be associated with studies defining complications differently. We found that intra- or postprocedural complications were associated with 417 (9.1%) of 4573 procedures within 30 days and comprised intracranial hemorrhagic and ischemic complications in 2.0% and 4.6% of those, respectively. About 75% of these were asymptomatic or transiently symptomatic and did not result in mRS deterioration. Systemic heparinization is recommended before placing guiding catheters to maintain activated coagulation times within 250 to 300 seconds and to avoid thromboembolic or ischemic complications of UIAs. Antiplalet therapy has also been recommended to prevent thromboembolic complications. Here, intraprocedural systemic heparinization was applied in 98.1% of procedures, and pre- and postprocedural oral antiplatelet agents were applied significantly more often every year. Continuous intravenous anticoagulation therapy with not only heparin but also antithrombin agents (Argatroban) has also been added. Ischemic complications decreased annually, and the frequency of thrombogenic adjunctive techniques has increased. We could not identify the efficacy of antiplatelet medication against ischemic complications, and thus prospective studies are required.

We found significantly higher complication rates, especially ischemic, for aneurysms of the posterior as compared with the anterior circulation, which contradicted the findings of a recent systematic review. Recently, UCAS Japan found similar rupture rates of aneurysms in the posterior and anterior circulation, but those of aneurysms in the internal carotid artery-posterior communicating artery and anterior communicating artery were higher. The lower complication rate associated with aneurysms of the posterior circulation should be further investigated. Notably, larger and smaller aneurysms were associated with higher ischemic and hemorrhagic complication rates, respectively, and the risks of hemorrhagic complications and insufficient radiographic results were significantly higher in tiny aneurysms <3 mm than in those of UIAs 5 to 9 mm (odds ratios, 2.8 [P=0.04] and 2.1 [P=0.09], respectively). In contrast, risks of failure or total complications were not significantly increased in tiny aneurysms <3 mm. These findings should be considered in the management of small UIAs. Intraprocedural aneurysmal rupture occurred at a rate of 2.6% per procedure in the ATENA study, 1.4% per aneurysm in the series of Oishi et al, and 1.9% per patient treated for a UIA in the Cerecyte trial. We found similar rates of 1.4%. Because 10 of 65 aneurysmal ruptures led to mortality, intraprocedural aneurysmal rupture must be scrupulously avoided. We found 5 (0.1%) post-treatment aneurysmal ruptures, although such events in the HELPS or the Cerecyte trial were not reported. Of these 5 ruptures, only 1 was associated with intraprocedural rupture. All of them led to poor clinical outcomes (mRS, 4–6). On the basis of our findings of complication rates, physicians should reconsider treatment indications for smaller aneurysms, such as those that were treated in the Japanese system and which we determined before comparing the risk of complications with the low risk of rupture (ISUIA2 or UCAS Japan).

**Limitations**

We extracted information about the outcomes of EVT for asymptomatic UIAs from those of all EVTs that were retrospectively registered by physicians at several neurointerventional centers but they do not represent the nationwide total. The Japan Neurosurgical Society found that 3053 EVTs were performed to treat unruptured cerebral aneurysms during 2006. Our database included 1103 unruptured cerebral aneurysms for the same period, which was 36.1% of the total. Furthermore, aneurysms that were treated more than once could not be excluded from the present study. Our results could be inherently biased because the treating physicians assessed radiographic and clinical outcomes and procedure-related complications. Decisions on treatment indications might have also introduced inclusion bias. To understand the full outcomes of EVTs for UIAs in Japan, Japanese Society for Neuroendovascular Therapy will continue to collect data from all certified neurointerventionists throughout Japan. In addition, a prospective study, especially of EVT for unruptured aneurysms, might be warranted. Intracranial stent-assisted techniques and bioactive coil usage were not assessed because these devices were not fully approved in Japan during the study period. This report simply describes the outcomes of EVT for asymptomatic UIAs, which did not include surgically treated or untreated UIAs, and the population of patients with asymptomatic UIAs was not representative of the total.

**Conclusions**

This is the largest nationwide study of the outcomes of EVT for UIAs in Japan in which the immediate radiographic

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**Table 5. Case Series After ISUIA (1–9), Including ATENA and Present Study**

<table>
<thead>
<tr>
<th>Study</th>
<th>Case Series Summary*</th>
<th>ATENA Study (Pierré et al)†</th>
<th>Present Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOP</td>
<td>39–457</td>
<td>649</td>
<td>4573</td>
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<tr>
<td>UIAs</td>
<td>42–500</td>
<td>739</td>
<td>4767</td>
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<tr>
<td>F, %</td>
<td>51–89</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>Age, y</td>
<td>48–73</td>
<td>51</td>
<td>61</td>
</tr>
<tr>
<td>UAC, %</td>
<td>53–91</td>
<td>92</td>
<td>80</td>
</tr>
<tr>
<td>PMORB, %</td>
<td>0–7.7</td>
<td>2.6</td>
<td>2.1</td>
</tr>
<tr>
<td>MORT, %</td>
<td>0–1.7</td>
<td>1.1</td>
<td>0.3</td>
</tr>
<tr>
<td>IA0†, %</td>
<td>1.2–20.8</td>
<td>19.3</td>
<td>10.0</td>
</tr>
<tr>
<td>FAIL, %</td>
<td>0–10.0</td>
<td>4.3</td>
<td>2.1</td>
</tr>
<tr>
<td>PRC†, %</td>
<td>2.5–28.0</td>
<td>15.4</td>
<td>9.1</td>
</tr>
<tr>
<td>Ischemic complications, %</td>
<td>0.8–18.0</td>
<td>7.1</td>
<td>4.6</td>
</tr>
<tr>
<td>Hemorrhagic complications‡, %</td>
<td>0–2.6</td>
<td>2.9</td>
<td>2.0</td>
</tr>
</tbody>
</table>

EVT indicates endovascular therapy; F, female; FAIL, failure; IA0, insufficient anatomic outcome; ISUIA, International Study of Unruptured Intracranial Aneurysms; LIM, limitation; MORT, mortality; NOP, number of patients or procedures; PMORB, permanent morbidity; PRC, procedure-related complications; RA, residual aneurysms; and UAC, UIAs in anterior circulation.

*Summary of data from case series of EVT for UIAs reported after ISUIA study (1998). Details are shown in online supplement.
†Total number of incomplete occlusions (<90%) or RA in each report.
‡Complications manually determined when complications were not specified.
results, short-term outcomes, and actual status were retrospectively analyzed. We found that EVT for UIAs was feasible (98.4%), with low morbidity and mortality rates (2.12% and 0.31%, respectively), although the total complication rate was relatively high (9.1%). Nevertheless, because complication rates tended to be higher for very small UIAs, treatment indications should be reconsidered, considering their low risk of rupture. These results could be used as a reference for deciding strategies to manage asymptomatic UIAs in routine clinical practice.

Acknowledgments
The authors express heartfelt thanks to the doctors who devoted their time to this investigation.

Sources of Funding
This study was supported by research grants for cardiovascular diseases (17C-1, 20C-2) from the Ministry of Health, Labor, and Welfare of Japan.

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References


Endovascular Therapy for Asymptomatic Unruptured Intracranial Aneurysms: JR-NET and JR-NET2 Findings
Tomoyoshi Shigematsu, Toshiyuki Fujinaka, Toshiki Yoshimine, Hirotoshi Imamura, Akira Ishii, Chiaki Sakai and Nobuyuki Sakai

Stroke. published online July 30, 2013;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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ONLINE SUPPLEMENT

Endovascular therapy for asymptomatic unruptured intracranial aneurysms: JR-NET and JR-NET2 findings
Supplementary Table I. Annual endovascular techniques and antithrombotic regimens.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>57.2</td>
<td>49.8</td>
<td>45.9</td>
<td>39.9</td>
<td>38.6</td>
<td>&lt;0.001</td>
<td>45.2</td>
</tr>
<tr>
<td>Adjunctive</td>
<td>42.8</td>
<td>50.2</td>
<td>54.1</td>
<td>60.1</td>
<td>61.4</td>
<td></td>
<td>54.8</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Antithrombotic regimen (pp)</th>
<th>Overall (2005-2009)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE antiplatelet therapy</td>
<td>85.6</td>
</tr>
<tr>
<td>INTRA systemic heparinization</td>
<td>NS 98.1</td>
</tr>
<tr>
<td>CONT anticoagulation</td>
<td>NS 68.0</td>
</tr>
<tr>
<td>POST antiplatelet therapy</td>
<td>84.0</td>
</tr>
</tbody>
</table>

All values except p values are shown as ratios (%). CONT, continuous; INTRA, intra-procedural; NS, not significant; pa, per aneurysm; POST, post-procedural; pp, per procedure; PRE, pre-procedural.

Supplementary Table II. Insufficient anatomic outcome, failure rate and complication rates in each size subgroups.

<table>
<thead>
<tr>
<th>Maximal radius (mm %)</th>
<th>Failure rate</th>
<th>RA</th>
<th>Procedure-related complications</th>
<th>Hemorrhagic</th>
<th>Ischemic</th>
<th>p</th>
<th>Overall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>4.2</td>
<td>16.7</td>
<td>8.4</td>
<td>5.0</td>
<td>2.5</td>
<td>0.003</td>
<td>2.1</td>
</tr>
<tr>
<td>≥3</td>
<td>2.9</td>
<td>10.2</td>
<td>7.9</td>
<td>2.5</td>
<td>3.6</td>
<td>NS</td>
<td>10.0</td>
</tr>
<tr>
<td>&lt;5</td>
<td>1.7</td>
<td>8.7</td>
<td>8.5</td>
<td>1.9</td>
<td>4.4</td>
<td>&lt;0.001</td>
<td>8.9</td>
</tr>
<tr>
<td>&lt;10</td>
<td>1.4</td>
<td>13.5</td>
<td>8.5</td>
<td>0.7</td>
<td>7.7</td>
<td>&lt;0.001</td>
<td>2.0</td>
</tr>
<tr>
<td>&lt;20</td>
<td>3.0</td>
<td>18.8</td>
<td>12.8</td>
<td>0</td>
<td>18.2</td>
<td>&lt;0.001</td>
<td>4.6</td>
</tr>
</tbody>
</table>

NS, not significant; RA, residual aneurysm.
Supplementary Table III. Feasibility and complication rates of anterior and posterior circulation.

<table>
<thead>
<tr>
<th></th>
<th>Anterior circulation (%)</th>
<th>Posterior circulation (%)</th>
<th>p</th>
<th>Overall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure rate</td>
<td>2.2</td>
<td>1.9</td>
<td>NS</td>
<td>2.1</td>
</tr>
<tr>
<td>RA</td>
<td>10.0</td>
<td>10.2</td>
<td>NS</td>
<td>10.0</td>
</tr>
<tr>
<td>Procedure-related</td>
<td>8.3</td>
<td>11.2</td>
<td>0.005</td>
<td>8.9</td>
</tr>
<tr>
<td>complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>1.9</td>
<td>2.3</td>
<td>NS</td>
<td>2.0</td>
</tr>
<tr>
<td>Aneurysmal rupture</td>
<td>1.3</td>
<td>1.5</td>
<td>NS</td>
<td>1.4</td>
</tr>
<tr>
<td>Ischemic</td>
<td>4.0</td>
<td>6.9</td>
<td>&lt;0.001</td>
<td>4.6</td>
</tr>
</tbody>
</table>

All values except p values area shown as ratios (%). NS, not significant; RA, residual aneurysm.

Supplementary Table IV. Results of coil embolization for aneurysms < 10 mm with wide and favorable necks.

<table>
<thead>
<tr>
<th></th>
<th>Favorable neck* (%)</th>
<th>Wide-neck† (%)</th>
<th>p</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure rate</td>
<td>1.4</td>
<td>2.9</td>
<td>0.002</td>
<td>2.2</td>
</tr>
<tr>
<td>RA</td>
<td>7.0</td>
<td>11.4</td>
<td>&lt;0.001</td>
<td>9.5</td>
</tr>
<tr>
<td>Procedure-related</td>
<td>6.4</td>
<td>9.7</td>
<td>&lt;0.001</td>
<td>8.3</td>
</tr>
<tr>
<td>complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>1.5</td>
<td>2.7</td>
<td>0.01</td>
<td>2.2</td>
</tr>
<tr>
<td>Aneurysmal rupture</td>
<td>1.3</td>
<td>1.7</td>
<td>NS</td>
<td>1.5</td>
</tr>
<tr>
<td>Ischemic</td>
<td>2.9</td>
<td>5.0</td>
<td>&lt;0.001</td>
<td>4.1</td>
</tr>
</tbody>
</table>

RA, residual aneurysm; *Favorable neck: neck, ≤4 mm and dome-to-neck (D/N) ratio ≥ 1.5; NS, not significant; †Wide neck: neck >4 mm or D/N ratio <1.5.
Supplementary Table V. Case series of EVT for UIAs reported after ISUIA study (1998).

<table>
<thead>
<tr>
<th>Authors</th>
<th>LIM UIAs</th>
<th>Study period</th>
<th>NOP</th>
<th>UIAs</th>
<th>F</th>
<th>Age (y)</th>
<th>UAC</th>
<th>PMORB</th>
<th>MORT</th>
<th>IAO*</th>
<th>FAIL</th>
<th>PRC†</th>
<th>Ischemic complications</th>
<th>Hemorrhagic complications†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murayama et al., 1999</td>
<td>-</td>
<td>1991.8-1998.1</td>
<td>115</td>
<td>120</td>
<td>79</td>
<td>51</td>
<td>73</td>
<td>3.4</td>
<td>0</td>
<td>4.2</td>
<td>5.0</td>
<td>6.7</td>
<td>5.0</td>
<td>0.9</td>
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<tr>
<td>Roy et al., 2001</td>
<td>r ≥ 3 mm</td>
<td>1992.8-1999.6</td>
<td>116</td>
<td>125</td>
<td>78</td>
<td>51</td>
<td>78</td>
<td>4.3</td>
<td>0</td>
<td>4.8</td>
<td>5.6</td>
<td>10.3</td>
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<td>2.6</td>
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<tr>
<td>Wanke et al., 2002</td>
<td>-</td>
<td>1997.7-2000.12</td>
<td>39</td>
<td>42</td>
<td>59</td>
<td>48</td>
<td>74</td>
<td>4.8</td>
<td>0</td>
<td>10.5</td>
<td>10.0</td>
<td>2.5</td>
<td>2.5</td>
<td>0</td>
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<tr>
<td>Gonzalez et al., 2004</td>
<td>-</td>
<td>1991.8-2000.5</td>
<td>217</td>
<td>247</td>
<td>77</td>
<td>54</td>
<td>76</td>
<td>5.5</td>
<td>0.9</td>
<td>1.2</td>
<td>5.7</td>
<td>6.9</td>
<td>3.7</td>
<td>1.4</td>
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<tr>
<td>Terada et al., 2005</td>
<td>-</td>
<td>1999.7-2004.5</td>
<td>76</td>
<td>78</td>
<td>68</td>
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<td>53</td>
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<td>20.3</td>
<td>-</td>
<td>7.3</td>
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<td>1.2</td>
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<tr>
<td>van Rooij et al., 2006</td>
<td>-</td>
<td>1995.1-2005.7</td>
<td>149</td>
<td>176</td>
<td>89</td>
<td>52</td>
<td>72</td>
<td>2.6</td>
<td>1.3</td>
<td>4.6</td>
<td>-</td>
<td>3.4</td>
<td>2.8</td>
<td>0.6</td>
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<tr>
<td>Gallas et al., 2008</td>
<td>-</td>
<td>1998.1-2005.1</td>
<td>290</td>
<td>321</td>
<td>63</td>
<td>49</td>
<td>-</td>
<td>7.7</td>
<td>1.7</td>
<td>3.7</td>
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<td>14.4</td>
<td>9.0</td>
<td>2.6</td>
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<td>Standhardt et al., 2008</td>
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<td>1992.2-2004.8</td>
<td>173</td>
<td>202</td>
<td>73</td>
<td>52</td>
<td>79</td>
<td>3.5</td>
<td>0.5</td>
<td>8.5</td>
<td>-</td>
<td>19.3</td>
<td>10.9</td>
<td>2.0</td>
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<tr>
<td>Im et al., 2009</td>
<td>r ≤ 7 mm</td>
<td>2002.5-2006.12</td>
<td>370</td>
<td>435</td>
<td>75</td>
<td>58</td>
<td>90</td>
<td>0.3</td>
<td>0</td>
<td>5.1</td>
<td>-</td>
<td>10.1</td>
<td>5.5</td>
<td>0.9</td>
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<tr>
<td>Benes et al., 2010</td>
<td>-</td>
<td>1996.12-2005.9</td>
<td>131</td>
<td>151</td>
<td>71</td>
<td>51</td>
<td>87</td>
<td>0.8</td>
<td>0.8</td>
<td>6.0</td>
<td>4.0</td>
<td>10.5</td>
<td>7.0</td>
<td>0.7</td>
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<tr>
<td>Hwang et al., 2011</td>
<td>age ≥ 70 y</td>
<td>2003.5-2010.2</td>
<td>96</td>
<td>122</td>
<td>83</td>
<td>73</td>
<td>91</td>
<td>0</td>
<td>0</td>
<td>12.2</td>
<td>0.0</td>
<td>4.1</td>
<td>0.8</td>
<td>0.8</td>
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<tr>
<td>Yue, 2011</td>
<td>-</td>
<td>2008.1-2011.1</td>
<td>74</td>
<td>80</td>
<td>51</td>
<td>49</td>
<td>64</td>
<td>1.3</td>
<td>1.3</td>
<td>13.8</td>
<td>-</td>
<td>4.1</td>
<td>-</td>
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<td>Khosla et al., 2012</td>
<td>-</td>
<td>2000.1-2010.1</td>
<td>355</td>
<td>394</td>
<td>76</td>
<td>57</td>
<td>73</td>
<td>3.3</td>
<td>0.5</td>
<td>12.2</td>
<td>6.3</td>
<td>28.0</td>
<td>≤18.0</td>
<td>2.0</td>
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<tr>
<td>Oishi et al., 2012</td>
<td>r &lt; 10 mm</td>
<td>2001.6-2009.12</td>
<td>457</td>
<td>500</td>
<td>73</td>
<td>60</td>
<td>90</td>
<td>0.8</td>
<td>0.2</td>
<td>20.8</td>
<td>3.8</td>
<td>7.6</td>
<td>3.8</td>
<td>2.2</td>
</tr>
</tbody>
</table>

All values except NOP, UIAs and Age area shown as ratios (%). *Total number of incomplete occlusions (<90%), residual aneurysms (RA) or body filling (BF), in each report. †Complications manually determined when unspecified. IAO, Insufficient anatomic outcome; F, female; FAIL, failure; LIM, limitation; MORT, mortality; NOP, Number of patients or procedures; PRC, procedure-related complications; UAC, UIAs in anterior circulation.
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