Small Unruptured Intracranial Aneurysm Verification Study
SUAVe Study, Japan

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Background and Purpose—The natural history and optimal management of incidentally found small unruptured aneurysms <5 mm in size remain unclear. A prospective study was conducted to determine the optimal management for incidentally found small unruptured aneurysms.

Methods—From September 2000 to January, 2004, 540 aneurysms (446 patients) were registered. Four hundred forty-eight unruptured aneurysms <5 mm in size (374 patients) have been followed up for a mean of 41.0 months (1306.5 person-years) to date. We calculated the average annual rupture rate of small unruptured aneurysms and also investigated risk factors that contribute to rupture and enlargement of these aneurysms.

Results—The average annual risks of rupture associated with small unruptured aneurysms were 0.54% overall, 0.34% for single aneurysms, and 0.95% for multiple aneurysms. Patient <50 years of age (P=0.046; hazard ratio, 5.23; 95% CI, 1.03 to 26.52), aneurysm diameter of ≥4.0 mm (P=0.023; hazard ratio, 5.86; 95% CI, 1.27 to 26.95), hypertension (P=0.023; hazard ratio, 7.93; 95% CI, 1.33 to 47.42), and aneurysm multiplicity (P=0.0048; hazard ratio, 4.87; 95% CI, 1.62 to 14.65) were found to be significant predictive factors for rupture of small aneurysms.

Conclusions—The annual rupture rate associated with small unruptured aneurysms is quite low. Careful attention should be paid to the treatment indications for single-type unruptured aneurysms <5 mm. If the patient is <50 years of age, has hypertension, and multiple aneurysms with diameters of ≥4 mm, treatment should be considered to prevent future aneurysmal rupture. (Stroke. 2010;41:00-00.)

Key Words: annual risk of rupture ■ small unruptured aneurysm ■ multiple-type aneurysms ■ risk factors ■ Small Unruptured Aneurysm Verification Study (SUAVe Study)

In 1998, the International Study of Unruptured Intracranial Aneurysms (ISUIA) obtained the surprising result that the annual risk of rupture associated with unruptured aneurysms <10 mm in diameter without previous subarachnoid hemorrhage (SAH) was only 0.05% per year. The second ISUIA publication showed the annual risk of rupture associated with unruptured aneurysms 7 mm in diameter in the anterior half of the Willis arterial circle with no history of SAH to be 0% and that with a history of SAH 1.5%. These values were much lower than had been thought. However, there is still room for doubt, because the extremely low risk of rupture associated with unruptured aneurysms according to ISUIA was based on an analysis of the retrospective component (Group 1), and also the study population of Group 1 in the ISUIA included a considerable number of patients with symptomatic unruptured aneurysms. In addition, most of the ruptured aneurysms that are seen in daily clinical practice are small. Kassell et al studied the size distribution of ruptured aneurysms based on data from 1092 cases, showing that 13% of ruptured aneurysms were <5 mm in diameter. In other words, there is a discrepancy between the ISUIA data and the sizes of ruptured aneurysms that are seen in daily clinical practice. Strictly speaking, the best way to study the natural history of unruptured aneurysms is to simply observe them without treatment when unruptured aneurysms are incidentally found. However, this is definitely risky. In 1996, the Japan Neurosurgical Society conducted a survey regarding the treatment strategy for incidentally found unruptured cerebral aneurysms by sending questionnaires to 163 major neurosurgical centers in Japan. Based on the results, 87% of neurosurgical centers in Japan agreed that incidentally discovered unruptured aneurysms <5 mm in diameter should be followed up without treatment. In October 2008, the Japanese Society for Detection of Asymptomatic Brain Disease released guidelines outlining the treatment strategy for unruptured aneurysms (www.snh.or.jp/jsbd/gaido.html). It recommended that treatment be considered for unruptured aneurysms ≥5 mm in size. There is, however, no clear evidence as yet that the risk of...
rupture associated with incidentally found small unruptured aneurysms <5 mm in diameter is as low as has been thought. Therefore, in the current study, we prospectively analyzed the annual risk of rupture associated with incidentally found small unruptured aneurysms <5 mm in diameter, that is, those seen in daily clinical practice, and clarified possible risk factors for aneurysm rupture with the ultimate goal of establishing indications for treatment of these aneurysms.

We describe the protocol, methods, and outcomes of the Small Unruptured Aneurysm Verification Study (SUAVe Study, Japan). The SUAVe Study is a multicenter, prospective clinical study conducted by 12 national hospital organization centers in Japan. The SUAVe Study was designed to develop reasonable guidelines for the treatment of unruptured aneurysms.

**Methods**

**Study Design**
This study was undertaken to conform to the SUAVe protocol. The centers enrolled were 12 national hospitals in Japan. Patients were recruited between September 2000 and January 2004. Patients were eligible for the study if (1) they had intracranial unruptured saccular aneurysms <5 mm in diameter confirmed by MR angiography (MRA), CT angiography, and/or digital subtraction angiography; (2) their activities of daily living were independent (modified ranking disability scale 1 or 2); and (3) their baseline clinical data and key images that demonstrated unruptured aneurysms were judged by the Case & Image Judgment Committee to be saccular unruptured aneurysms <5 mm in diameter.

Patients were not eligible if any of the following criteria were met: (1) severe neurological disability (modified ranking disability scale ≥3); (2) unruptured aneurysm <5 mm in size treated at the same time as other intracranial lesions; (3) other severe medical conditions such as malignant neoplasm, cardiac failure, or renal failure requiring hemodialysis; (4) consent refused; or (5) the Case & Image Judgment Committee considered the patient to be ineligible for the study.

All 12 centers participating in the SUAVe Study were national institutions treating a number of patients with cerebral aneurysms on a daily basis. These centers had expertise in neurosurgical management of cerebral aneurysms. If aneurysms enlarged by ≥2 mm in diameter or developed a bleb during the course of observation, the subsequent treatment strategy was based on the policy of each center.

**Procedure**
If the patient met all of the inclusion criteria, all incidentally found unruptured aneurysms <5 mm in diameter were registered and then followed up without surgical or endovascular procedures at 6, 12, 18, 24, 30, and 36 months and then annually for at least 36 months after registration. Nonsurgical treatments such as medications were allowed as needed. All patients were interviewed by contributors to this study, at each participating center, who filled out a structured checklist. The checklist at the beginning of follow-up elicited data on a family history of intracranial aneurysms, the date when an unruptured aneurysm was found, medical history, current smoking status, the reason an unruptured aneurysm was found, characteristics of unruptured aneurysms (multiplicity of aneurysms, location, diameter), and investigation methods (MRA, CT angiography, and/or catheter angiography). CT angiography was obtained with injection of a continuous flow of 2 mL/s and a total of 100 mL of nonionic contrast material so that ≥250 intravascular Hounsfield units could be obtained. Hypertension was defined as a patient having repeated episodes of systolic blood pressure of ≥140 mm Hg, or diastolic pressure of ≥90 mm Hg during visits to a family physician, and/or use of antihypertensive medication. A family history of intracranial aneurysm was defined as any verified aneurysms in first-degree relatives. The checklist for follow-up every 6 months included aneurysm diameter and morphological changes on MRA, CT angiography, and/or catheter angiography; neurological status; rupture; or other medical conditions. The size of the aneurysm was measured in the reference attached on MRA or CT angiography. In the case of catheter angiography, it was measured by the 1-yen coin method, which is used by most neurosurgical centers in Japan. This method is described in detail on the Unruptured Cerebral Aneurysm Study in Japan (UCAS Japan) home page (http://ucas-j.umin.ac.jp/e/measurement.htm). All images and checklists were sent to the Case & Image Judgment Committee after each follow-up examination.

**Patient Population**
Five hundred forty unruptured aneurysms (446 cases), registered in this study during the 3 years 4 months from September 2000 to January 2004, were reviewed by the Case & Image Judgment Committee. Of those initially registered in this study, 92 aneurysms (72 cases) were excluded because 66 were judged to not be aneurysms, 14 were judged to be infundibular dilatations, 10 were ≥5 mm in size, and 2 were judged to be fusiform-type aneurysms. Finally, the Committee concluded that 448 aneurysms (374 cases) met all of the criteria and these were subsequently analyzed. Table 1 shows the baseline characteristics obtained in patients at the beginning of this study. Of the 374 patients, 250 (66.8%) had single unruptured aneurysms and 124 (33.2%) had multiple unruptured aneurysms. The mean duration of follow-up was 42.5 months (range, 6 months to 7 years) with a total of 1306.2 patient-years (1553.5 aneurysm-years) of follow-up. The study population consisted of 238 female and 136 male patients. The mean age at registration was 61.9 years (range, 23 to 89 years). Unruptured aneurysms were discovered for the following reasons: 199 patients (53.2%) were found to have aneurysms on medical checkups of the brain (namely brain dock), 116 (31.0%) were diagnosed in the course of examining patients with brain tumors or brain infarctions, and 37 (9.6%) were found in association with ruptured SAH. The concomitant diseases were hypertension in 93 patients (24.9%), history of cerebral vascular diseases in 59 (15.8%), heart diseases in 26 (7.0%), and diabetes mellitus in 23 (6.1%). There were 31 (8.3%) with a family history of cerebral aneurysms.

Table 1. Baseline Characteristics Obtained in Patients at the Beginning of Follow-Up

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients</th>
<th>No. of aneurysms</th>
<th>No. of multiple aneurysm cases</th>
<th>Age, years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>374</td>
<td>448</td>
<td>124</td>
<td>61.9 ± 10.3</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>59 (15.8%)</td>
<td>26 (7.0%)</td>
<td>36 (9.6%)</td>
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</tr>
<tr>
<td>Median</td>
<td>62</td>
<td>36 (9.6%)</td>
<td>31 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>23–89</td>
<td>199 (53.2%)</td>
<td>116 (31.0%)</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>93 (24.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>59 (15.8%)</td>
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<tr>
<td>Ischemic heart disease</td>
<td>26 (7.0%)</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>23 (6.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histories of SAH</td>
<td>36 (9.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of SAH</td>
<td>31 (8.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm detection</td>
<td>36 (9.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical checkup (brain dock)</td>
<td>199 (53.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated with investigation for brain tumor or stroke</td>
<td>116 (31.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated with ruptured aneurysm</td>
<td>36 (9.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Informed Consent
All patients gave written informed consent, in accordance with criteria established by the local ethics committees at each participating center.

Study End Points
The major end point in this study was rupture of an unruptured aneurysm and treatment of unruptured aneurysms with a surgical or an endovascular procedure. If patients refused further follow-up or failed to return due to other medical conditions, the follow-up periods of these cases were calculated as those from their registration until the last day of follow-up.

Statistical Analysis
All analyses were done with Version 10.0 of Stata software (StataCorp LP, College Station, Texas). Continuous variables (patient age and aneurysm diameter) were compared using the unpaired *t* test in terms of aneurysm growth and aneurysm rupture. Patients were categorized into a ≥50 years group and a <50 years of age group. Aneurysm diameter was divided into a ≥4.0 mm group and a <4.0 mm group. Univariate analyses to assess categorical variables (sex, ≥50 years of age, ≥4.0 mm aneurysm diameter, aneurysm multiplicity, aneurysm site, presence of hypertension, current smoking status, history of SAH, and family history of intracranial aneurysms) associated with aneurysmal rupture and growth were done with the Cox proportional hazards regression. Aneurysm site was compared using the χ² test.

Variables with *P* < 0.2 were retained as covariates and entered together into the multivariate Cox proportional hazards regression model to determine the independent predictive variables associated with future aneurysmal rupture and growth. Hazard ratios (HRs) and 95% CIs were obtained. In life-table analysis and the Cox proportional hazards regression model for aneurysmal rupture, each patient was followed to the time of SAH, death due to any cause other than SAH, or to the last possible follow-up contact. In the cases of aneurysmal growth, follow-up periods were calculated from enrollment until the time of aneurysm growth detected on radiological examinations.

The follow-up period was also expressed using the person-years method. The average annual risk of rupture associated with unruptured aneurysms was calculated by determining the number of first events of rupture divided by the number of person-years of follow-up. The Kaplan-Meier product-limit method was used to estimate the cumulative rates of rupture of incidentally found ruptured aneurysms. The resultant curves of different groups were compared using the generalized Wilcoxon test. Probability values <0.05 were considered statistically significant.

Results

Sizes and Locations of Unruptured Aneurysms <5 mm in Diameter
Table 2 summarizes the distributions of unruptured aneurysms <5 mm in diameter according to size and location. The locations for 448 unruptured aneurysms were as follows: 173 (38.6%) in the internal carotid artery, 158 (35.3%) in the middle cerebral artery, 60 (13.4%) in the anterior communicating artery, 33 (7.4%) in the basilar artery, 12 (2.7%) in the anterior cerebral artery, 4 (0.9%) in the vertebral artery, and 8 (1.8%) at other sites. The most common aneurysm size was 3.0 to 3.9 mm with 193 aneurysms (43.1%) in this group. With regard to aneurysm location, in the 3.0- to 3.9-mm and 4.0- to 4.9-mm aneurysm groups, the percentages of anterior communicating artery aneurysms were only 9.8% and 13.7%, respectively. The percentage of all anterior communicating artery aneurysms was 13.4%, considerably lower than those of internal carotid artery and middle cerebral artery aneurysms. The percentage of all distal anterior cerebral artery aneurysms was also only 2.7%.

Unruptured Aneurysm Cases Lost to Follow-Up
Fifty-three cases were lost to follow-up. Of these, because 16 cases had 2 unruptured aneurysms each, 69 unruptured aneurysms in total were lost to follow-up. There were 7 cases with ruptured aneurysms of which 4 had multiple unruptured aneurysms, that is, 10 aneurysms were lost to follow-up due to rupture events. There were 10 aneurysms considered to be at high risk of rupture because they enlarged by ≥2 mm, changed morphology, or developed blebs. All 10 were treated with direct clipping or endovascular coiling. Of these 10 aneurysms, 2 cases had 2 aneurysms. Therefore, 12 aneurysms were lost to follow-up due to morphological change. Nine cases (12 aneurysms) discontinued follow-up due to death resulting from other medical conditions. Twenty-seven cases (35 aneurysms) were discontinued from follow-up because they refused examination or moved away. There were no patients with morphologically unchanged aneurysms who dropped out of the study because they wished to have an operation for prevention of aneurysmal rupture before the end of follow-up. The calculated observation periods of these cases were from registration until the last observation. Considering the period of time from the beginning until the end of follow-up due to rupture or morphological change, there was a tendency for the majority of long-term follow-up cases to not be those treated for rupture or morphological change.

Ruptured Aneurysm Cases
Seven cases (1.9% of all patients) experienced ruptures during follow-up. Six cases were female and 4 had multiple aneurysms. Five cases had been treated for hypertension. One case had a history of autosomal-dominant polycystic kidney disease. It was noteworthy that although the sizes of aneurysms were unchanged during follow-up, 4 of the 7 rupture cases showed aneurysmal enlargement at the time of rupture. Univariate analysis (Table 3) shows that an aneurysm diameter of ≥4.0 mm (*P* = 0.0069; HR, 5.51; 95% CI, 1.60 to 19.04), multiple aneurysms (*P* = 0.016; HR, 2.62; 95% CI, 1.20 to 5.74), and hypertension (*P* = 0.0023; HR, 7.32; 95%
CI, 2.04 to 26.29) were significantly associated with rupture of small unruptured aneurysms. Because probability values for patient age <50 years, ≥4.0 mm aneurysm diameter, aneurysm multiplicity, and the presence of hypertension were <0.2, these variables were entered as independent variables into multivariate models with a stepwise procedure (Table 4). The significant independent risk factors for aneurysm rupture were revealed to be patient age <50 years (P=0.046; HR, 5.23; 95% CI, 1.03 to 26.52), ≥4.0 mm aneurysm diameter (P=0.023; HR, 5.86; 95% CI, 1.27 to 26.95), hypertension. (P=0.023; HR, 7.93; 95% CI, 1.33 to 47.42), and aneurysm multiplicity (P=0.0048; HR, 4.87; 95% CI, 1.62 to 14.65).

### Annual Risk of Rupture of Small Unruptured Aneurysms <5 mm in Diameter

During the follow-up of 1306.2 person-years (1553 aneurysm-years), 7 (1.9%) of the 374 patients had SAH for average annual rupture incidences of unruptured aneurysms of 0.34%/year and 0.95%/year for single and multiple aneurysm cases, respectively, and 0.54%/year overall. The cumulative risk of rupture overall and for single and multiple unruptured aneurysm cases enrolled in this study based on Kaplan-Meier calculation are shown in the Figure. The cumulative rate of rupture of unruptured aneurysms was 3.36% (95% CI, 0.41 to 6.31) for all cases, 3.14% (95% CI, 0.91 to 10.43) for single aneurysm cases, and 3.44% (95% CI, 1.30 to 8.93) for multiple aneurysm cases at 80 months after unruptured aneurysms were found. The generalized Wilcoxon test revealed that the cumulative rate of rupture differed significantly for cases with aneurysm multiplicity (P=0.029).

### Transition in the Annual Risk of Rupture

We evaluated the transition in the average risk of rupture of unruptured aneurysms according to multiplicity. By 38.5 months on average of follow-up, the average risks of rupture varied widely among groups. At 39.5 months on average
follow-up, however, all groups converged to a certain risk of rupture. In the single aneurysm cases, the average annual risk of rupture was 0.18%/year at 26.1 months on average of follow-up. The risks then converged to 0.34%/year at 42.5 months on average of follow-up. For multiple aneurysm cases, the average annual risk of rupture was 1.96%/year at 17.1 month on average of follow-up and then declined to 0.81%/year at 32.5 months. Ultimately, the rate stabilized at 0.95%/year at an average follow-up of 42.5 months. For all cases, the average risk of rupture plateaued after 38.5 months on average of follow-up and then reached 0.54%/year at 42.5 months on average. These observations suggested that as the follow-up period lengthens, the annual risk of rupture converges to a certain value and plateaus.

**Predictive Values for Aneurysm Enlargement**

During follow-up, 30 aneurysms (25 cases) enlarged. Table 5 shows that aneurysm diameter was significantly associated with growth of small unruptured aneurysms ($P=0.0006$) according to the unpaired $t$ test. Univariate analysis shows that an aneurysm diameter of $\geq 4.0$ mm was significantly associated with growth of small unruptured aneurysms ($P=0.0099$; HR, 2.76; 95% CI, 1.28 to 5.97). Because probability values for women, $\geq 4.0$ mm aneurysm diameter, aneurysm multiplicity, and current smoking were $<0.2$, these variables were entered as independent variables into multivariate models. The significant independent risk factors for aneurysm enlargement were revealed to be women ($P=0.042$; HR, 2.95; 95% CI, 1.04 to 8.35), $\geq 4.0$ mm aneurysm diameter ($P=0.0025$; HR, 3.34; 95% CI, 1.53 to 7.31), aneurysm multiplicity ($P=0.036$; HR, 1.72; 95% CI, 1.24 to 3.75), and current smoking ($P=0.027$; HR, 3.59; 95% CI, 1.19 to 10.86). In the 10 cases with aneurysms growing by $\geq 2$ mm or aneurysms with blebs, rupture was considered to be more likely. Therefore, these aneurysms were surgically clipped or embolized by an endovascular procedure at the center where the patient was followed. All 10 patients were discharged with no impairments in independent activities of daily living.

**Discussion**

**Annual Risk of Rupture of Small Unruptured Aneurysms**

Previously published reports demonstrated that unruptured aneurysms in patients with previous SAH are more likely to rupture than those of the same size in patients without previous SAH. The current study, however, did not find a history of SAH to be associated with aneurysmal rupture, although aneurysm multiplicity was revealed to be significantly associated with rupture of aneurysms. Our data demonstrated the average annual risk of rupture of single unruptured aneurysms $<5$ mm in diameter to be 0.34%/year, that of multiple unruptured aneurysms 0.95%/year, and the overall rate to be 0.54%/year. These rates are slightly lower than the overall annual rupture rate of 1% to 2%/year in previously published articles. During follow-up in the current study, 10 patients with high-risk aneurysms, due to morphological change, were operated on. This may likely have caused bias toward underestimation of the aneurysm rupture rate. Alternatively, our study may have included only small aneurysms. Needless to say, a long duration of follow-up is essential for analyzing the natural history of unruptured aneurysms and the follow-up periods in the current study are somewhat limited. However, we consider follow-ups to have been long enough to study the natural history of small unruptured aneurysms because the transition in the annual rupture rate in the current study showed that the average rate of rupture converged to a certain value and plateaued in the late phase of follow-up. We do not believe that longer follow-up would alter our final results. Also, the current study was prospective, thereby providing optimal analysis of the natural history of small unruptured aneurysms.

**Discrepancy Between Low Rupture Rate of Small Unruptured Aneurysms and Sizes of Ruptured Aneurysms**

With regard to the discrepancy between the very low risk of rupture associated with unruptured aneurysms and the small sizes of ruptured aneurysms, which are seen in daily clinical practice, our data may provide clues possibly explaining this discrepancy. Some authors have hypothesized that certain aneurysms that rupture may decrease in size after the rupture. However, to date, there have been no direct observations to prove this hypothesis. There was 1 unpublished direct observation of rupture events in unruptured aneurysms. Rahman et al studied a collection of aneurysm measurements from patients with pre- and postrupture images obtained by a multicenter collaborative study group. In their study, there
were 9 patients with a total of 9 aneurysms that ruptured. No aneurysms shrank from pre- to postrupture images. Six aneurysms grew postrupture. Our data are similar. Of 7 ruptured aneurysms in the current study, none shrank when they ruptured, whereas 4 enlarged. On the other hand, unruptured aneurysms have a tendency to grow based on the 30 aneurysms that enlarged in the current study and those in other published articles.12–15 It is, therefore, reasonable that new aneurysms form and some then rupture in the process of growing.7,16 The rate of aneurysmal growth is, however, highly variable and unpredictable. From the viewpoint of the relationship between the timing of aneurysm rupture and the process of aneurysmal growth, we previously reported a classification of cerebral aneurysm growth processes starting from formation.17 We classified the growth processes of cerebral aneurysms into 4 patterns: Type 1, the aneurysm ruptures within a time span as short as a few days to a few weeks after its formation; Type 2, the aneurysm grows slowly for a few years after its formation and then ruptures during this process; Type 3, the formed aneurysm keeps growing slowly for a few years without rupturing; and Type 4, the aneurysm grows to a certain size and remains unchanged thereafter. In the current study, there were no Type 1 aneurysms, 7 Type 2 aneurysms (1.6%), 30 Type 3 aneurysms (6.7%), and 411 Type 4 aneurysms (91.7%). If there were numerous small aneurysms that ruptured immediately after forming, that is, Type 1 aneurysms, it could explain the very low risk of rupture associated with unruptured small aneurysms in the ISUIA and the current study, because this type of aneurysm is difficult to follow clinically and radiologically from formation to rupture. Some previous articles suggested that most aneurysms that bleed do so shortly after formation and, thus, are never detected as unruptured aneurysms.10,18 In other words, most acute SAH are from recently formed aneurysms.10,18 After this initial period, the risk of rupture falls to a low level. Mitchell et al proved this based on

### Table 5. Univariate Patient-Related and Aneurysm-Related Risk Factors Associated With Growth of Small Unruptured Aneurysms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients</th>
<th>Growth, %</th>
<th>Nongrowth, %</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>374</td>
<td>25 (6.7)</td>
<td>349 (93.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>238</td>
<td>18 (7.5)</td>
<td>220 (92.5)</td>
<td>1.95</td>
<td>0.78–4.85</td>
<td>0.15</td>
</tr>
<tr>
<td>Men</td>
<td>136</td>
<td>7 (5.1)</td>
<td>129 (94.9)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average†</td>
<td>61.9±10.3</td>
<td>65.0±8.7</td>
<td>61.7±10.4</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>62</td>
<td>65</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>149</td>
<td>3 (2.0)</td>
<td>35 (88.0)</td>
<td>0.35</td>
<td>0.047–2.58</td>
<td>0.30</td>
</tr>
<tr>
<td>≥50</td>
<td>336</td>
<td>22 (6.5)</td>
<td>314 (93.5)</td>
<td>0.0006*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm diameter, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean±SD†</td>
<td>3.3±0.9</td>
<td>3.9±0.9</td>
<td>3.3±0.9</td>
<td>0.0006*</td>
<td></td>
<td></td>
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<tr>
<td>&gt;4.0</td>
<td>116</td>
<td>14 (12.1)</td>
<td>102 (87.9)</td>
<td>2.76</td>
<td>1.28–5.97</td>
<td>0.0099*</td>
</tr>
<tr>
<td>&lt;4.0</td>
<td>258</td>
<td>11 (4.3)</td>
<td>34 (95.7)</td>
<td>1</td>
<td></td>
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<tr>
<td>Multiple aneurysms</td>
<td>124</td>
<td>14 (11.3)</td>
<td>110 (89.7)</td>
<td>2.12</td>
<td>0.98–4.58</td>
<td>0.055</td>
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<tr>
<td>Single aneurysm</td>
<td>250</td>
<td>11 (4.4)</td>
<td>239 (95.6)</td>
<td>1</td>
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<tr>
<td>Site of aneurysm</td>
<td></td>
<td></td>
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<td>0.99</td>
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<td>ICA</td>
<td>173 of 448 (38.6)</td>
<td>11 (6.4)</td>
<td>162 (93.6)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>158 of 448 (35.3)</td>
<td>11 (7.0)</td>
<td>147 (93.0)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ACoA</td>
<td>60 of 448 (13.4)</td>
<td>5 (3.3)</td>
<td>55 (91.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal ACA</td>
<td>12 of 448 (2.7)</td>
<td>1 (8.3)</td>
<td>11 (91.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BA</td>
<td>33 of 448 (7.4)</td>
<td>2 (6.1)</td>
<td>31 (93.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA</td>
<td>4 of 448 (0.9)</td>
<td>0 (0)</td>
<td>4 (100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT</td>
<td>163</td>
<td>10 (6.1)</td>
<td>153 (93.9)</td>
<td>0.87</td>
<td>0.67–1.23</td>
<td>0.24</td>
</tr>
<tr>
<td>Non-HT</td>
<td>211</td>
<td>19 (9.9)</td>
<td>192 (90.1)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>32</td>
<td>5 (15.6)</td>
<td>27 (84.4)</td>
<td>2.53</td>
<td>0.95–6.71</td>
<td>0.062</td>
</tr>
<tr>
<td>Not current smoker</td>
<td>342</td>
<td>20 (5.8)</td>
<td>322 (94.2)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous SAH</td>
<td>36</td>
<td>3 (8.3)</td>
<td>33 (91.7)</td>
<td>0.52</td>
<td>0.070–3.83</td>
<td>0.52</td>
</tr>
<tr>
<td>No previous SAH</td>
<td>338</td>
<td>22 (6.5)</td>
<td>316 (93.5)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of SAH</td>
<td>31</td>
<td>3 (9.7)</td>
<td>28 (90.3)</td>
<td>0.86</td>
<td>0.20–3.67</td>
<td>0.85</td>
</tr>
<tr>
<td>No family history</td>
<td>343</td>
<td>22 (6.4)</td>
<td>321 (93.6)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05.†Unpaired t test for comparisons of growth and no growth groups according to patient age and aneurysm diameter.

ICA indicates internal carotid artery; MCA, middle cerebral artery; ACoA, anterior communicating artery; ACA, anterior cerebral artery; BA, basilar artery; VA, vertebral artery; HT, hypertension.
a mathematical model using data from previously published large studies, concluding that the duration of this high-risk period may be between 1 or 2 days and approximately 8 weeks.\(^{18}\) Our data and some previously published articles support the idea that most unruptured aneurysms detected incidentally have passed into the safe period with a low bleeding rate on follow-up, like Type 4 aneurysms, whereas most of the ruptured small aneurysms we observe in routine daily clinical practice could be Type 1 aneurysms. These observations are consistent with the very low risk of rupture associated with unruptured aneurysms and the small sizes of ruptured aneurysms that are encountered in daily clinical practice.

**Aneurysm Location**

This study showed the overall percentage of anterior communicating artery aneurysms <5 mm in size to be 13.4\%. It is noteworthy that the percentage of unruptured anterior communicating artery aneurysms in the current study is much lower than the usual 30\% reported for ruptured anterior communicating artery aneurysms.\(^{3,19,20}\) Weir et al analyzed site differences between ruptured and unruptured aneurysms based on 337 ruptured and 170 unruptured aneurysm cases.\(^{4}\) In their study population, 35.0\% of ruptured aneurysm cases had anterior communicating artery aneurysms, whereas only 11.2\% of unruptured aneurysms were of this type. Other previously published data related to unruptured intracranial aneurysms also showed 10\% to 15\% of unruptured aneurysms to be anterior communicating artery aneurysms.\(^{1,8}\) These data are consistent with ours. Weir et al thought that midline lesions like anterior communicating artery aneurysms are at greater risk of rupture at a smaller size than are more laterally situated aneurysms.\(^{4}\) Of the 7 ruptured aneurysm cases in the current study, 2 (3.3\%) of 60 anterior communicating artery aneurysms and 1 (8.3\%) of 12 distal anterior cerebral artery aneurysm cases showed rupture (Table 3). These percentages are higher than those of other aneurysm sites and these results are also consistent with their idea. However, statistical significance was not reached, probably due to inadequate statistical power. A larger epidemiological and histological study is needed to confirm this finding.

**Risk Factors for Rupture of Small Unruptured Aneurysms**

Several articles have analyzed the predictive factors for rupture of unruptured aneurysms.\(^{1,2,6,21–25}\) They concluded that a history of SAH, multiple aneurysms, younger patient age, increased aneurysm size, hypertension, and cigarette smoking are risk factors for rupture. Our data revealed age <50 years, ≥4.0 mm aneurysm diameter, hypertension, and aneurysm multiplicity to be significant risk factors for aneurysm rupture. The current study focused only on small unruptured aneurysms, that is, those <5 mm in diameter. However, the risk factors identified in our study are consistent with the results of previous publications.\(^{1,2,6,21–25}\) Most incidentally found small unruptured aneurysms are considered to be stable with a low rate of rupture. However, patients <50 years of age with hypertension and multiple aneurysms with diameters of ≥4 mm have a higher risk of SAH.

**Risk Factors for Enlargement of Small Unruptured Aneurysms**

During follow-up, aneurysms enlarged in 25 of 374 patients (6.7\% of patients who had small unruptured aneurysms). The current study also revealed women, aneurysm diameter ≥4.0 mm, aneurysm multiplicity, and smoking status to be the independent predictive factors for increased size of small unruptured aneurysms. A few studies have investigated risk factors for aneurysmal growth. The size of an aneurysm, the presence of multiple lobes, and cigarette smoking were reported to be associated with aneurysmal growth.\(^{13,14}\) More recently, Miyazawa et al analyzed the risk factors for aneurysmal growth based on analysis of 130 unruptured aneurysm cases studied by serial MRA.\(^{12}\) In their study, aneurysms enlarged in 10.8\% of patients who had unruptured aneurysms. They concluded as well that middle cerebral artery location, multiple aneurysms, aneurysm size of ≥5 mm, and family history of SAH were significant risk factors for aneurysmal growth. The rate of enlargement of small unruptured aneurysms in the current study is lower than that by Miyazawa et al reported, probably because our study included only small unruptured aneurysms. However, our observations that aneurysm size and multiplicity are associated with aneurysmal growth are compatible with their data. Also, another issue that has not yet been clarified is how much risk the growth of small unruptured aneurysms carries for the future rupture of these aneurysms. Aneurysm rupture is much more likely to occur in aneurysms that grow,\(^{2,10,16}\) but rupture could occur in the absence of growth. In this study, there were 7 rupture events of small unruptured aneurysms during the course of follow-up with 4 cases showing diameter increases and 2 showing no size change at the time of rupture. It is, therefore, reasonable to treat unruptured aneurysms that show enlargement or morphological change during the course of follow-up even if they are small.

**Surgical Indications for Incidentally Found Small Unruptured Aneurysms**

Many factors should be considered in determining the management of patients with unruptured intracranial aneurysms. Furthermore, this management should be tailored to the specific risks and benefits of individual aneurysms and patients. The current study showed the average annual risk of rupture of single-type unruptured aneurysms to be 0.34%/year. This is much lower than the risk of treatment because the complication rate related to treating small unruptured aneurysms is reportedly approximately 4\%.\(^{1,2}\) The treatment indications for this type of unruptured aneurysm should be very carefully considered. On the other hand, the annual risk of rupture of multiple-type unruptured aneurysms was 0.95%/year, triple that of single-type cases. The cumulative rate of rupture of multiple unruptured aneurysms was 3.44\% at 80 months. The lifetime rupture probability is calculated by the following formula:

\[
\text{The lifetime rupture probability (\%)} = (1 - \frac{1}{100})^{-Y} \times 100
\]

where X represents the average annual risk of rupture (%/year) and Y the life expectancy (years). The average risk of rupture of 0.95%/year was applied to this formula because
the current study revealed that the average annual risk of rupture had plateaued at the end of follow-up. Based on this formula, the 10-year and 20-year lifetime rupture probabilities of multiple unruptured aneurysms are 9.1% and 17.4%, respectively. These values exceed the risk of treating unruptured aneurysms. Also, regarding risk factors associated with rupture of unruptured aneurysms, only 1 article in the English literature has focused on unruptured aneurysms ≤7 mm.25 Nahed et al noted that hypertension, relatively young age, and posterior circulation aneurysms are significant risk factors for rupture of aneurysms ≤7 mm. Their results were similar to ours, although their study population included unruptured aneurysms up to 7 mm in size. They concluded that given the minimal long-term morbidity and mortality of treating unruptured aneurysms in large, tertiary medical centers, management of unruptured aneurysms ≤7 mm should be governed by factors other than size, specifically age, history of hypertension, and location. In addition, several previous studies have shown that the decision to treat unruptured aneurysms should not be based on aneurysm size alone.4,16,20,26,27 In view of these data, if the patient is <50 years of age, is hypertensive, and harbors multiple aneurysms with diameters of ≥4 mm, surgical or endovascular treatment can reasonably be considered for prevention of future aneurysm rupture. Also, based on our current results, if aneurysm enlargement is documented during follow-up, the aneurysm should be treated with a surgical or an endovascular procedure.

Strengths and Limitations of This Study
Medical checkups of the brain, namely brain dock, are supported by the Ministry of Health, Labor, and Welfare of Japan and are widely available nationwide. These examinations provide healthy asymptomatic people with brain MRI and MRA to identify unruptured aneurysms and other occult abnormal brain lesions. In this study population, more than half of the patients (53.2%) had been found to have unruptured aneurysms during medical checkups of the brain. Also, this study population included no patients with cranial nerve palsy due to an aneurysmal mass effect and only 9.6% of patients had a history of SAH, making the number of patients with obvious risks of aneurysmal rupture small and the study population relatively unbiased. Such study populations provide better conditions for analyzing the natural history of unruptured aneurysms. However, our study also has several limitations. At the beginning of registration, we did not evaluate how many patients with unruptured aneurysms were not included in the study because their aneurysms underwent surgery before potential follow-up, that is, what was the proportion of patients selected because of treatment before potential follow-up. This may have biased the aneurysm rupture rate toward underestimation. Additionally, the proportion of cigarette smokers in the current study was low (only 8.6%). In the general Japanese adult population, 47.9% of men and 12.2% of women are reportedly current smokers based on the National Health and Nourishment survey in Japan conducted by the Japanese Ministry of Health, Labor and Welfare in 2003.28 Considering that the majority of patients in the current study had been found to have unruptured aneurysms during medical checkups of the brain, our study may have included a considerable proportion of patients who were health-conscious. This may also have led to underestimation of the rate of aneurysmal rupture. Finally, the study population size was limited and follow-up was short. A larger study population and longer follow-up periods are needed to obtain more conclusive evidence.

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References


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