The International Study of Unruptured Intracranial Aneurysms (ISUIA) investigated prospectively the natural history of untreated unruptured intracranial aneurysms. Surprisingly, the risk of rupture for aneurysms in the anterior circulation <7 mm in the largest dimension was 0% in patients with no history of subarachnoid hemorrhage (SAH). However, one of the major criticisms of the ISUIA was the low number of patients recruited from each center, which led to the suggestion that the total number of patients included in the study was 10% seen in each center, which would imply an inherent selection bias. Aneurysms deemed at risk for rupture, for example, aneurysm morphology, might have been treated, whereas a small proportion might have undergone observation.

In the Japanese population, Sonobe et al demonstrated that the overall annual risk of rupture for aneurysms <5 mm was 0.54%. Morita et al demonstrated that the annual rate of rupture for aneurysms <5 mm at the middle cerebral artery was 0.23% and at the anterior communicating artery was 0.9% in a Japanese cohort. Nevertheless, the majority of ruptured aneurysms were <10 mm in size, including a substantial percentage of ruptured aneurysms <7 mm in size.

However, data on the natural history of small aneurysms in the European population were scarce. Therefore, the management of unruptured intracranial aneurysms <7 mm in the anterior circulation was controversial.

In our institution, the treatment recommendation for all patients with no history of SAH harboring aneurysms <7 mm in the anterior circulation was conservative treatment, and follow-up was done using magnetic resonance angiography. All patients who underwent conservative treatment were entered into a prospectively conducted database. The objective of the present study was to analyze the natural history of small unruptured intracranial aneurysms in patients with no history of previous SAH in a single cerebrovascular center, with strict, regular follow-up in a European population.

**Background and Purpose**—The natural history of small unruptured intracranial aneurysms of the anterior circulation in the European population is unclear. Therefore, the management of unruptured intracranial aneurysms <7 mm in the anterior circulation is controversial.

**Methods**—Between June 1999 and June 2012, 384 unruptured intracranial aneurysms of the anterior circulation <7 mm in diameter underwent conservative treatment and regular annual follow-up in our institution. Patient- and aneurysm-specific information, as well as information on aneurysm enlargement and rupture, was entered into a prospectively conducted database.

**Results**—The mean follow-up duration was 48.5±37 months. Three aneurysms enlarged during the follow-up period and were treated by surgical clipping. Three aneurysms were ruptured during the follow-up period. The overall annual incidence of subarachnoid hemorrhage was 0.2% during the follow-up. In the multivariate Cox proportional hazard regression analysis, hypertension (P<0.001; hazard ratio, 2.6; 95% confidence interval, 2.1–3.3) and <50 years of age (P=0.04; hazard ratio, 1.3; 95% confidence interval, 1.01–1.7) were significant independent predictors of aneurysm rupture.

**Conclusions**—The present data indicate that the annual incidence of subarachnoid hemorrhage associated with small anterior circulation unruptured intracranial aneurysms is low in this single-institution prospective cohort study. The natural course varies according to arterial hypertension and patient age. (Stroke. 2013;44:3027-3031.)

**Key Words:** aneurysm • subarachnoid hemorrhage
Methods
Starting in June 1999, all patients with intracranial aneurysms at the neurovascular center of Johann Wolfgang Goethe-University (Departments of Neurosurgery, Neurology, and Neuroradiology) were prospectively entered into a SPSS database (version 19, SPSS, Chicago, IL). The local ethics committee approved the study. Besides others, the database included information on aneurysm- and patient-specific characteristics, such as aneurysm size, aneurysm multiplicity, and location, as well as patient age, sex, history of SAH, current smoking status, and presence of arterial hypertension. The indication for treatment of unruptured aneurysms was determined in interdisciplinary meetings in which each aneurysm was discussed by the cerebrovascular neurosurgeon, neurologist, and neuroradiologist. The results of the ISUIA served as a framework for the decision about optimum management. Thus, all patients harboring aneurysms <7 mm of the anterior circulation without previous SAH and the absence of familial and genetic risk factors were treated by annual surveillance with magnetic resonance angiography and were treated only if any change in size or morphology of the aneurysm was detected.

All patients underwent pretreatment with 4-vessel digital subtraction angiography, including 3-dimensional reconstruction starting in the anterior circulation. Of the 553 aneurysms, 387 were <7 mm in size and located in the anterior circulation. Of the 387 aneurysms that had been assigned for observation, 3 were enlarged and were treated by clipping (Table 1; Figure 1). Three hundred eighty-four aneurysms remained untreated. Of the 553 aneurysms, 387 were <7 mm in size and located in the anterior circulation. Of the 387 aneurysms that had been assigned for observation, 3 were enlarged and were treated by clipping (Table 1; Figure 1). Three hundred eighty-four aneurysms remained untreated. The maximum follow-up time was 162 months. Twelve patients were lost to follow-up; however, according to the family doctors, 8 patients died because of malignant tumors and 4 because of cardiopulmonary disease. Data for these 12 patients were censored at the date of last follow-up.

The baseline characteristics are detailed in Table 2. Aneurysm locations are detailed in Table 3.

Statistics
Unpaired t test was used for parametric statistics. Univariate analyses to assess categorical variables associated with aneurysmal rupture were performed with the Cox proportional hazards regression. In the second step, a multivariate Cox proportional hazards regression model was performed to find independent predictors for aneurysm rupture. Hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained. In life-table analysis and the Cox proportional hazards regression model for the time to aneurysmal rupture, each patient was followed up to the time of aneurysm rupture or to the last possible follow-up contact. The variable aneurysm multiplicity was dichotomized into single versus multiple aneurysms.

The follow-up period was expressed using aneurysm-years. The average annual risk of rupture associated with small unruptured aneurysms was calculated by determining the number of first events of rupture divided by the number of aneurysm-years of follow-up. The Kaplan–Meier product limit was used to estimate the cumulative rates of rupture of unruptured aneurysms. The resultant curves of different groups were compared using the generalized Wilcoxon test. Results with P<0.05 were considered statistically significant.

All calculations were made with a standard commercial software (SPSS version 19, Chicago, IL). Statistical analyses were performed in cooperation with the Department of Biostatistics of the Johann Wolfgang Goethe-University.

Results
Three aneurysms ruptured during the follow-up period (Table 4). All patients who experienced aneurysm rupture were women; however, patient sex did not differ between the group of patients with and without aneurysm rupture during follow-up (100% versus 78%; P=0.3). Age did not differ between the group of patients with aneurysm rupture compared with that without aneurysm rupture (55±18 versus 56±13; P=0.9). Aneurysm size was 3±1 mm in patients who experienced aneurysm rupture versus 3.6±1.7 mm in patients without aneurysm rupture (P=0.6). Aneurysm size was stable in patients who experienced aneurysm rupture. Outcome was assessed according to the modified Rankin scale, 6 months after aneurysm rupture. Patients 1 and 2 achieved modified Rankin scale score 1, and patient 3 achieved modified Rankin scale score 2.

All patients who experienced aneurysm rupture during follow-up and 109 of the 260 patients without aneurysm rupture had arterial hypertension (100% versus 42%; P=0.08). All of the patients with aneurysm rupture and 134 of 260 patients without aneurysm rupture during follow-up were current smokers (100% versus 52%; P=0.2).

Table 1. Aneurysm Enlargement During Follow-up

<table>
<thead>
<tr>
<th>No.</th>
<th>Age, y/Sex</th>
<th>Location</th>
<th>Size, mm</th>
<th>No. of Aneurysms</th>
<th>Interval, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48/F</td>
<td>Acom</td>
<td>12</td>
<td>3</td>
<td>1832</td>
</tr>
<tr>
<td>2</td>
<td>49/M</td>
<td>MCA</td>
<td>10</td>
<td>2</td>
<td>1298</td>
</tr>
<tr>
<td>3</td>
<td>73/M</td>
<td>ICA</td>
<td>11</td>
<td>1</td>
<td>2976</td>
</tr>
</tbody>
</table>

Acom indicates anterior communicating artery; F, female; ICA, internal carotid artery; M, male; and MCA, middle cerebral artery.
Table 2. Baseline Characteristics on Admission

| Characteristics                                      | No. of patients | Women | No. of aneurysms | No. of patients with multiple aneurysms | Average no. of aneurysms per patient | Mean age in years (±SD) | Current smoker | Former smoker | Concomitant disease, n (%) | Hypertension | Stroke | Coronary heart disease | Diabetes mellitus | Family history of subarachnoid hemorrhage | Aneurysm detection, n (%) | Medical checkup* | During investigation for brain tumor | During investigation for stroke | Headache | MRI for undefined spells |
|-----------------------------------------------------|-----------------|-------|------------------|-----------------------------------------|-------------------------------------|-----------------------|-----------------|---------------|---------------------------------|---------------|--------|------------------------|---------------------|--------------------------------|-----------------|----------------|--------------------------|----------------|----------------|----------------|----------------|
| Total                                                | 263             | 204 (77.6%) | 384              | 136 (51.7%)                             | 1.46                                 | 55±12                 | 137 (52.1%)    | 14 (5.3%)     | Hypertension (112 (42.6%))        | 18 (6.8%)     | 19 (7.2%) | 14 (5.3%)                       | 8 (3.0%)           | 149 (56.7%)                                         | 149 (56.7%)     | 5 (1.9%)       | 18 (6.8%)               | 39 (14.8%) | 73 (27.8%) |

Aneurysm detection, n (%) includes the following categories: Medical checkup*, During investigation for brain tumor, During investigation for stroke, Headache, MRI for undefined spells.

*MRI was performed during medical checkup to detect any asymptomatic brain lesion in the healthy population or to rule out existing central nervous system disease in patients with other systemic or central nervous system diseases. Not included in this category were symptoms or coexisting diseases listed in the other categories.

The mean follow-up duration was 48.5±37 months. The overall annual incidence of SAH was 0.2% during the follow-up of 1537.5 aneurysm-years. The cumulative rupture rate (calculated using the Kaplan–Meier method) was 0.05% in 4 years, 1.3% in 5 years, and 2.9% within 7 years. The generalized Wilcoxon test revealed that the cumulative rupture rate did not differ with aneurysm multiplicity (P=0.1), but with arterial hypertension (27.1%; P<0.001; Figure 2A) and the smoking status (11.1%; P=0.01; Figure 2B).

Multivariate Analysis

In the multivariate Cox proportional hazard regression analysis, hypertension (P<0.001; HR, 2.6; 95% CI, 2.1–3.3) and <50 years of age (P=0.04; HR, 1.3; 95% CI, 1.01–1.7) were significant independent predictors of aneurysm rupture. The variables such as smoking status, size of the aneurysm, sex, and aneurysm multiplicity were eliminated from the model.

Table 3. Aneurysm Location and Size

<table>
<thead>
<tr>
<th>Location</th>
<th>Total</th>
<th>&lt;3 mm</th>
<th>3.0–4.9 mm</th>
<th>5.0–6.9 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>175 (46%)</td>
<td>75</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>MCA</td>
<td>127 (33%)</td>
<td>28</td>
<td>58</td>
<td>41</td>
</tr>
<tr>
<td>Acom</td>
<td>56 (14%)</td>
<td>11</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>Distal ACA</td>
<td>26 (7%)</td>
<td>11</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>384</td>
<td>125</td>
<td>159</td>
<td>100</td>
</tr>
</tbody>
</table>

ACA indicates anterior cerebral artery; Acom, anterior communicating artery; ICA, internal carotid artery; and MCA, middle cerebral artery.

Table 4. Ruptured Aneurysms During Follow-up

<table>
<thead>
<tr>
<th>No.</th>
<th>Age, y/Sex</th>
<th>Location</th>
<th>Size, mm</th>
<th>SAH History</th>
<th>No. of Aneurysms</th>
<th>Interval, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40/F</td>
<td>Distal ACA</td>
<td>2</td>
<td>No</td>
<td>3</td>
<td>1466</td>
</tr>
<tr>
<td>2</td>
<td>49/F</td>
<td>MCA</td>
<td>3</td>
<td>No</td>
<td>6</td>
<td>1395</td>
</tr>
<tr>
<td>3</td>
<td>76/F</td>
<td>MCA</td>
<td>4</td>
<td>No</td>
<td>1</td>
<td>2495</td>
</tr>
</tbody>
</table>

ACA indicates anterior cerebral artery; F, female; MCA, middle cerebral artery; and SAH, subarachnoid hemorrhage.

Discussion

In the present study of 384 unruptured aneurysms <7 mm in diameter in patients without a history of SAH, the overall annual incidence of SAH was 0.2% during the follow-up. In the multivariate analysis, the natural course of small unruptured aneurysms was influenced by arterial hypertension and patient age.

In the ISUIA trial, aneurysm rupture varied according to aneurysm size and location. Furthermore, patients with previous SAH were more likely to experience aneurysm rupture than those with the same aneurysm size but without previous SAH. Patients harboring unruptured anterior circulation aneurysms <7 mm in diameter without a history of SAH had a minimal probability of aneurysm rupture in ISUIA as well as in the present study.

In the Japanese Small Unruptured Intracranial Aneurysm Verification (SUAVe) study,1 the overall annual risk of aneurysm rupture for aneurysms <5 mm was 0.54%, being higher for patients with multiple aneurysms (0.95%) compared with patients with single aneurysms (0.34%). In the Unruptured Cerebral Aneurysm Study of Japan (UCAS Japan),4 the annual rate of rupture was 0.95%. However, racial differences might be an explanation for the higher rupture rates in the SUAVe study and in the UCAS. Despite the similar incidence of unruptured aneurysms in the Japanese population compared with Western populations, the risk of aneurysm rupture was higher in the Japanese population than in other populations.8 In the present study, patients who experienced aneurysm rupture were not of Japanese or Finnish descent.

Aneurysm size was stable in patients who experienced aneurysm rupture in the present study. This finding is interesting because aneurysms may undergo morphological changes before rupture, for example, increase in size as a sign of instability. The observation that most of the ruptured aneurysms are of small size, whereas small unruptured aneurysms are at low risk to rupture may even be explained by aneurysm shrinkage after rupture so they appear small. In the present study with 3 events, aneurysm size in patients who experienced aneurysm rupture was stable.

Predictors of Aneurysm Rupture

Predictors of aneurysm rupture in the present study were hypertension (P<0.001; HR, 2.6; 95% CI, 2.1–3.3) and <50 years of age (P=0.04; HR, 1.3; 95% CI, 1.01–1.7) in the multivariate Cox proportional hazard regression analysis. The variables such as smoking status, size of the aneurysm, sex, and aneurysm multiplicity had no effect on the rupture rate of anterior circulation aneurysms <7 mm. Arterial hypertension...
was a known and modifiable risk factor for aneurysm rupture.\textsuperscript{2,3,8} Nahed et al\textsuperscript{9} retrospectively analyzed the patients presenting with small ruptured aneurysms and unruptured aneurysms and compared them with respect to aneurysm characteristics and risk factors. In a multivariate analysis, the authors found that for aneurysms $\leq 7$ mm, hypertension, young age, and posterior circulation aneurysms were risk factors for rupture. These results were similar to ours although their study included posterior circulation aneurysms and aneurysms $\leq 7$ mm in size.

Female sex has been reported to be a risk factor for aneurysm rupture in the SUA Ve study.\textsuperscript{3} Our patient population consisted of 77.6% women. All patients who experienced aneurysm rupture in the present study were women. However, female sex was no risk factor for aneurysm rupture according to the multivariate analysis in the present study.

Aneurysm multiplicity did not affect the risk of aneurysm rupture in our cohort, but it was identified as an independent risk factor for rupture in other studies.\textsuperscript{3,10,11} However, this may be because these studies were performed in the Japanese and Finish population with a known higher risk of SAH than other populations. Furthermore, previous studies identifying a higher risk of rupture in patients with multiple aneurysms analyzed the rate of rupture per patient. This would at least double the risk of rupture among patients with multiple aneurysms compared with patients with a single aneurysm.

There still remains an apparently opposing observation that although the risk of rupture of small unruptured incidental aneurysms at the anterior circulation is low, the majority of ruptured aneurysms diagnosed in practice are of small size.\textsuperscript{1,12} One explanation might be that aneurysms that go on to rupture do so relatively soon after formation when the aneurysm wall is weaker and before healing processes can take place. Aneurysms that do not rupture at this initial stage may reach some sort of stable condition with a lower risk for rupture. This is corroborated by the observation that the risk of rupture is higher during the first year after aneurysm diagnosis and decreases thereafter.\textsuperscript{13,14} Furthermore, a higher rate of aneurysm rupture shortly after formation might explain that despite an increased use of surgical and endovascular therapy, the incidence of SAH remained stable during the past decades.\textsuperscript{15} In the present study, the overall annual incidence of SAH from rupture of small incidental aneurysms at the anterior circulation was 0.2% (0.05% cumulative rupture rate in 4 years) in a European population and therefore comparable with data from the ISUIA.\textsuperscript{2}

**Limitations**

One limitation of the present study is a possible case-selection bias. Patients with a presumably high rate of aneurysm rupture, that is, because of aneurysm enlargement, may have undergone treatment. This might bias the aneurysm rupture rate toward underestimation. However, although the overall rate of aneurysm rupture might have been affected by this selection bias, the analysis of risk factors should not have been substantially influenced. Furthermore, the number of aneurysms treated during follow-up is small. Only 3 aneurysms with aneurysm enlargement during follow-up underwent treatment.

The strength of the study is that all patients of a single institution with no history of previous SAH with aneurysms in the anterior circulation $<7$ mm underwent observation in the first instance.
Conclusions
In our single-institution prospective cohort study, the overall annual incidence of SAH was low. The natural course is influenced by arterial hypertension and patient age. Therefore, careful individual decision making is necessary for optimal treatment recommendations.

Acknowledgments
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Disclosures
None.

References
Natural History of Small Unruptured Anterior Circulation Aneurysms: A Prospective Cohort Study
Erdem Güresir, Hartmut Vatter, Patrick Schuss, Johannes Platz, Jürgen Konczalla, Richard Du Mesnil de Rochemont, Joachim Berkefeld and Volker Seifert

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### Supplementary Table I. Baseline characteristics of treated unruptured aneurysms <7mm

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of aneurysms</td>
<td>301</td>
</tr>
<tr>
<td>Aneurysm size</td>
<td>5 ± 1.7</td>
</tr>
<tr>
<td>Aneurysm location</td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>105 (34.9%)</td>
</tr>
<tr>
<td>MCA</td>
<td>119 (39.5%)</td>
</tr>
<tr>
<td>Acom</td>
<td>65 (21.6%)</td>
</tr>
<tr>
<td>Distal ACA</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Reasons for aneurysm treatment</td>
<td></td>
</tr>
<tr>
<td>Previous SAH</td>
<td>187 (62.1%)</td>
</tr>
<tr>
<td>Symptomatic aneurysms</td>
<td>26 (8.6%)</td>
</tr>
<tr>
<td>Family history of SAH</td>
<td>19 (6.3%)</td>
</tr>
<tr>
<td>Other*</td>
<td>69 (23%)</td>
</tr>
</tbody>
</table>

ICA indicates internal carotid artery; Acom, anterior communicating artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; SAH, subarachnoid haemorrhage

* Included in this category are aneurysms treated at the same time of tumor resection, clipping of aneurysms near by other aneurysms undergoing surgical treatment.