ORIGINAL ARTICLE

The Natural Course of Unruptured Cerebral Aneurysms in a Japanese Cohort

The UCAS Japan Investigators*

ABSTRACT

BACKGROUND

The natural history of unruptured cerebral aneurysms has not been clearly defined.

METHODS

From January 2001 through April 2004, we enrolled patients with newly identified, unruptured cerebral aneurysms in Japan. Information on the rupture of aneurysms, deaths, and the results of periodic follow-up examinations were recorded. We included 5720 patients 20 years of age or older (mean age, 62.5 years; 68% women) who had saccular aneurysms that were 3 mm or more in the largest dimension and who initially presented with no more than a slight disability.

RESULTS

Of the 6697 aneurysms studied, 91% were discovered incidentally. Most aneurysms were in the middle cerebral arteries (36%) and the internal carotid arteries (34%). The mean (±SD) size of the aneurysms was 5.7±3.6 mm. During a follow-up period that included 11,660 aneurysm-years, ruptures were documented in 111 patients, with an annual rate of rupture of 0.95% (95% confidence interval [CI], 0.79 to 1.15). The risk of rupture increased with increasing size of the aneurysm. With aneurysms that were 3 to 4 mm in size as the reference, the hazard ratios for size categories were as follows: 5 to 6 mm, 1.13 (95% CI, 0.58 to 2.22); 7 to 9 mm, 3.35 (95% CI, 1.87 to 6.00); 10 to 24 mm, 9.09 (95% CI, 5.25 to 15.74); and 25 mm or larger, 76.26 (95% CI, 32.76 to 177.54). As compared with aneurysms in the middle cerebral arteries, those in the posterior and anterior communicating arteries were more likely to rupture (hazard ratio, 1.90 [95% CI, 1.12 to 3.21] and 2.02 [95% CI, 1.13 to 3.58], respectively). Aneurysms with a daughter sac (an irregular protrusion of the wall of the aneurysm) were also more likely to rupture (hazard ratio, 1.63; 95% CI, 1.08 to 2.48).

CONCLUSIONS

This study showed that the natural course of unruptured cerebral aneurysms varies according to the size, location, and shape of the aneurysm. (Funded by the Ministry of Health, Labor, and Welfare in Japan and others; UCAS Japan UMIN-CTR number, C000000418.)

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*The Unruptured Cerebral Aneurysm Study of Japan (UCAS Japan) investigators are listed in the Supplementary Appendix, available at NEJM.org.

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Although incidentally discovered cerebral aneurysms are common,[1] the management of these lesions has been controversial,[2-6] and the number of patients undergoing repair has been increasing.[7] Previous studies have shown that aneurysms smaller than 5 or 7 mm in the largest dimension rarely rupture and that aneurysms in the posterior circulation have a greater tendency to rupture than do those in the anterior circulation.[5,8] To determine the most appropriate treatment for individual patients, we need to have a better understanding of the risk of rupture of cerebral aneurysms.

We conducted a large, prospective cohort study of unruptured cerebral aneurysms in the Japanese population. The objectives of the study were to elucidate the natural course of such aneurysms and to identify specific independent risk factors for rupture.

METHODS

PATIENTS

We included in the study patients with newly diagnosed, unruptured cerebral aneurysms who visited one of the study centers during the period from January 2001 through April 2004. Patients were eligible for enrollment if they were 20 years of age or older and had an aneurysm that was 3 mm or more in the largest dimension. All patients who visited a study center during the enrollment period and met these criteria were asked to join the study. We excluded patients who had had previous episodes of intracranial hemorrhage of unknown or untreated cause. Patients who presented with a modified Rankin score of more than 2 were also excluded. A modified Rankin scale score of 0 indicates no disability, a score of 1 or 2 indicates slight disability (i.e., the patient requires some help with daily activities but can care for himself or herself), and a score of 3 to 5 indicates moderate disability (i.e., the patient requires some help in daily activity) to severe disability (i.e., the patient requires constant specific care or is bedridden); a score of 6 indicates death.[9] Investigators at each institution obtained the approval of the local institutional review board before joining the study. Each patient was fully informed about the study and provided written consent to participate.

STUDY DESIGN

This study was a project of the Japan Neurological Society. Patients were enrolled prospectively with the use of an electronic data-capture system. The treatment strategy was chosen by the patient or was determined on the basis of the recommendation of the physician. Data were recorded periodically after enrollment. Data were collected through the coordinating office and the data center, which were located at the University Medical Information Network. The protocol of the study, which is summarized briefly here, is available with the full text of this article at NEJM.org. The first member of the writing committee and two comembers assume responsibility for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

DATA COLLECTION

Patients with aneurysms were prospectively identified by the local investigators, and eligible patients who agreed to participate were enrolled. We did not collect information about patients who were not enrolled in the study, and we do not know how many patients were not asked to participate or did not agree to participate.

The date of the patient's initial visit for the current medical condition was designated as day 0 for follow-up. The patient's clinical characteristics, a description of the aneurysm, and the management plan were recorded. After day 0, follow-up data on the patient's clinical status were recorded through either direct interview or telephone contact at 3, 12, and 36 months and at 5 to 8 years if any follow-up data were available (for details, see the protocol). Any change in the patient's condition, any intervention for the aneurysm, and any imaging of the central nervous system during the follow-up period were recorded in detail. Data collection for each patient ended when the aneurysm ruptured or when the patient died or could no longer be followed.

Each patient's clinical status was recorded with the use of the modified Rankin scale. Subarachnoid hemorrhage was identified by means of either computed tomographic (CT) imaging or lumbar puncture or was documented at autopsy (with the exception of five cases for which the diagnosis was made on the basis of sudden severe headache or loss of consciousness).

A diagnosis of aneurysm was based on images obtained through magnetic resonance angiography, high-resolution three-dimensional CT angiography, or digital-subtraction or conventional angiography. For computer images (three-dimensional angiography, three-dimensional CT angiography, or magnetic resonance angiography), the size of the aneurysm was measured with the use of digital data. In the case of digital-subtraction or conventional angiographic machines that were not equipped with size-measurement devices, the 1-yen coin method was used. (A 1-yen coin is exactly 20 mm in diameter and can be visualized on radiographs; therefore, if placed near the patient's head during radiographic examination, it can be used a reference for the size of the aneurysm.) For details on the various imaging techniques, see the protocol. A daughter sac was defined as an irregular protrusion of the aneurysmal wall on the two-dimensional or three-dimensional images. Fusiform or dissecting aneurysms were excluded from the analysis because their pathological characteristics are different from those of the cerebral aneurysms in this study. Aneurysms located at the cavernous portion of the internal carotid artery were excluded because of their specific anatomical location (not directly facing the subarachnoid space) and because they are known to confer a minimal risk of subarachnoid hemorrhage.[2,5]

To confirm the accuracy of the data in the registry, we arranged for outside investigators to verify the data at randomly sampled institutions. For cases of rupture or enlargement of an aneurysm during the follow-up period, all available documentation, including pertinent imaging films, was confirmed by outside investigators (for details of the source-document verification, see the Supplementary Appendix, available at NEJM.org).

STATISTICAL ANALYSIS

To calculate the appropriate sample size for the study, we proposed a working hypothesis: unruptured cerebral aneurysms of 5 mm or more rupture at an annual rate of more than 0.5%. To reject the null hypothesis with an alpha error of 5% (two-sided) and a beta error of 20%, we estimated that 4575 person-years would be required to perform the analysis on the basis of the one-sample binomial distribution if the observed annual rupture rate in this group was 0.75%. We estimated that to obtain this sample size, we would need an enrollment period of 3 years, with 3 years of follow-up for each patient, an estimate that was based on the annual number of untreated, unruptured cerebral aneurysms in a national survey (for details, see the Supplementary Appendix). The incidence of rupture was assessed per aneurysm rather than per patient. Data were censored at the time of a patient's death, a surgical or endovascular intervention, or the last follow-up assessment. When a patient underwent a surgical or endovascular intervention, data from the period up to the time of the intervention were included in the analysis of risk of rupture. Although the patient continued to be followed after the intervention, data from this period were not included in the risk analysis.

The hazard ratios for rupture were analyzed with the use of a Cox proportional-hazards model. Variables associated with rupture in univariate analyses ($P<0.20$) were included in a backward, stepwise, multivariate analysis. We checked the proportional-hazards assumption for each variable by testing Schoenfeld residuals and using the double-log plot method. Statistical analyses were performed with the use of Stata software, version 11.2 (Stata). Two-sided P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 6413 patients with newly diagnosed aneurysms, at 283 institutions, were enrolled during the period from January 1, 2001, through April 30, 2004. At the time of extraction of data from the registry, on April 14, 2010, a total of 5720 patients with 6697 aneurysms met the eligibility criteria. Most patients were asymptomatic, and 91% of the aneurysms were discovered incidentally. Two thirds of the patients were women. The mean (±SD) age of patients was 62.5±10.3 years. The mean size (i.e., the largest dimension) of the aneurysms was 5.7±3.6 mm. Table 1 and Figures 1S through 4S in the Supplementary Appendix show the characteristics of the patients and the aneurysms. An analysis of aneurysms according to the patients' age (in decades) showed that older patients had larger aneurysms. Aneurysms of 7 mm or more were found in 18.0% of patients younger than 50 years of age, in 21.4% of patients 50 to 59 years of age, in 24.7% of patients 60 to 69 years of age, in 32.6% of patients 70 to 79 years of age, and in 39.7% of patients 80 years of age or older ($P<0.001$) (Fig. 1S in the Supplementary Appendix).

During the follow-up period, 2722 patients with 3050 aneurysms underwent surgical repair before rupture of the aneurysm (Fig. 1), through either open or endovascular methods, at a median of 48 days after day 0 (25% by day 28 and 75% by day 82). Patients who underwent surgical repair and those who did not differed according to their age and the size and location of the aneurysm (Table 1).

NATURAL COURSE OF THE ANEURYSMS

Our analysis showed that 111 aneurysms ruptured during the 11,660 aneurysm-years of follow-up, and the annual risk of rupture was 0.95% (95% confidence interval [CI], 0.79 to 1.15). (Individual rates of rupture according to characteristics of the aneurysms are shown in Table 1S in the Supplementary Appendix.) Five cases of subarachnoid hemorrhage were documented only on the basis of loss of consciousness or death after a sudden, severe headache. The Kaplan–Meier curve showed that the rate of rupture was fairly constant throughout the follow-up period (Fig. 2A).

A final review of cases of ruptured aneurysms showed that for 39 ruptured aneurysms (35%), the rupture resulted in the death of the patient, and for 32 aneurysms (29%), the rupture resulted in the patient having a score of 3 to 5 on the modified Rankin scale, indicating moderate-to-severe disability. A total of 131 patients died of causes other than subarachnoid hemorrhage or results of treatment.

The multivariate Cox proportional-hazards model revealed that the size of the lesion, the specific location, and the presence or absence of a daughter sac were significant independent factors affecting the risk of rupture (Table 2), with a clear stratification of risk according to these factors (Fig. 2A and 2B). As compared with aneurysms that were 3 to 4 mm in the largest dimension, aneurysms that were 5 to 6 mm were not associated with a significantly increased risk of rupture, but the risk of rupture was significantly increased for all aneurysms that were 7 mm or larger.

Women and patients with hypertension had an increased risk of rupture, and patients with hyperlipidemia had a decreased risk, but the differences did not reach significance in multivariate analysis. The presence of another aneurysm causing subarachnoid hemorrhage, former or current smoking, a family history of subarachnoid hemorrhage, and the presence of multiple aneurysms

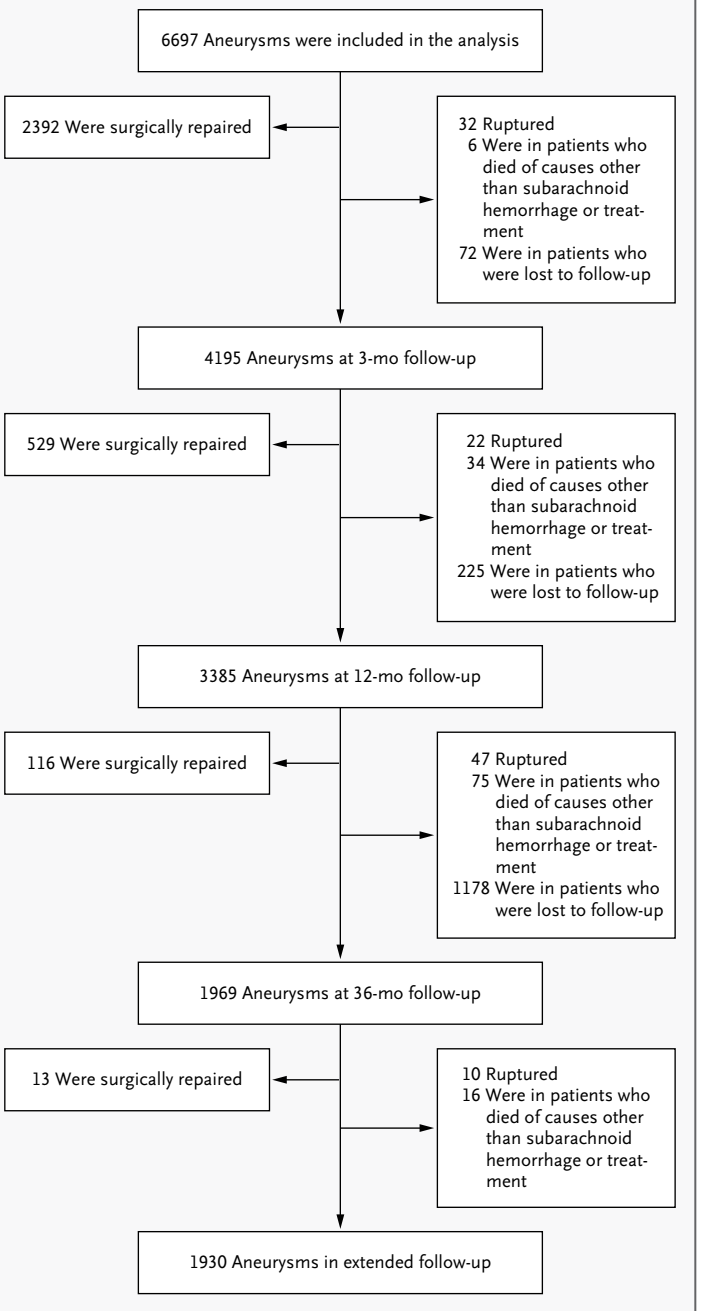

Figure 1. Natural Course of Cerebral Aneurysms in the Study Cohort.
Data were extracted from the registry on April 14, 2010. Aneurysms were assessed among patients with a score on the modified Rankin scale of 0 to 2 (no more than slight disability) at the initial presentation for whom any follow-up data were available. Fusiform and dissecting aneurysms and aneurysms of the cavernous portion of the internal carotid artery were excluded from the analysis. There were various reasons for loss to follow-up, including transfer to a different hospital and the patient's decision to withdraw from follow-up. For the analysis of the 1930 aneurysms that are in the extended follow-up, data were included as of the last follow-up visit.

did not significantly influence the risk of rupture of an aneurysm (P>0.20 for all comparisons) (Table 3S in the Supplementary Appendix). Because we analyzed the rupture risk per aneurysm, the last finding indicates that in patients with multiple aneurysms, each aneurysm is not associated with an increased risk of rupture. However, such patients are subject to the cumulative risk for all individual aneurysms. Thrombosed or calcified aneurysms were often large (83% of thrombosed aneurysms and 71% of calcified aneurysms were 7 mm or larger; P<0.001 for the comparison between the size of aneurysms with and those without thrombosis and for the comparison between the size of aneurysms with and those without calcification) and had an increased tendency to rupture (Table 3S in the Supplementary Appendix), but the number of these aneurysms was small.

The hazard ratio for rupture was significantly higher with aneurysms of the anterior communicating artery and the internal carotid–posterior communicating artery than with those of the middle cerebral artery (Table 2). When aneurysms were stratified by size, the risk of rupture differed

Table 1. Characteristics of the Patients and the Aneurysms.*

Characteristic	Patients (N=5720)	Aneurysms			P Value†
		Total (N=6697)	Not Surgically Treated before Rupture (N=3647)	Surgically Treated before Rupture (N=3050)	
Age					
Mean — yr	62.5±10.3		65.0±10.4	59.7±9.2	<0.001
≥70 yr — no. (%)	1577 (27.6)	1844 (27.5)	1400 (38.4)	444 (14.6)	<0.001
Female sex — no. (%)	3805 (66.5)	4532 (67.7)	2480 (68.0)	2052 (67.3)	0.53
Family history of subarachnoid hemorrhage — no. (%)	736 (12.9)	910 (13.6)	416 (11.4)	494 (16.2)	<0.001
Reason for imaging — no. (%)‡					0.001
Screening	2503 (43.8)	2910 (43.5)	1632 (44.7)	1278 (41.9)	0.001
Headache or dizziness	2714 (47.4)	3172 (47.4)	1713 (47.0)	1461 (47.9)	
Symptoms caused by mass effects or embolic episodes	171 (3.0)	203 (3.0)	100 (2.7)	103 (3.4)	
Subarachnoid hemorrhage	217 (3.8)	273 (4.1)	120 (3.3)	153 (5.0)	
Other	115 (2.0)	137 (2.0)	82 (2.2)	55 (1.8)	
Former or current smoking — no. (%)	960 (16.8)	1173 (17.5)	551 (15.1)	622 (20.4)	<0.001
Medical history — no. (%)					
Hypertension	2480 (43.4)	2969 (44.3)	1665 (45.7)	1304 (42.8)	0.02
Diabetes mellitus	362 (6.3)	396 (5.9)	243 (6.7)	153 (5.0)	0.004
Hyperlipidemia	809 (14.1)	939 (14.0)	484 (13.3)	455 (14.9)	0.05
Ischemic stroke	400 (7.0)	466 (7.0)	308 (8.4)	158 (5.2)	<0.001
Polycystic kidney disease	18 (0.3)	22 (0.3)	11 (0.3)	11 (0.4)	0.67
Multiple aneurysms	793 (13.9)	1770 (26.4)	1003 (27.5)	767 (25.1)	0.03
≥3 Aneurysms	148 (2.6)	480 (7.2)	270 (7.4)	210 (6.9)	0.41
Largest dimension of aneurysm					
Mean — mm		5.7±3.7	5.3±3.3	6.1±3.8	<0.001
Distribution — no. (%)					
≥7 mm		1711 (25.5)	786 (21.6)	925 (30.3)	<0.001
3–4 mm		3132 (46.8)	2000 (54.8)	1132 (37.1)	
5–6 mm		1854 (27.7)	861 (23.6)	993 (32.6)	
7–9 mm		1016 (15.2)	462 (12.7)	554 (18.2)	
10–24 mm		661 (9.9)	310 (8.5)	351 (11.5)	
≥25 mm		34 (0.5)	14 (0.4)	20 (0.7)	

Table 1. (Continued.)

Characteristic	Patients (N=5720)	Aneurysms		P Value†
	Total (N=6697)	Not Surgically Treated before Rupture (N=3628)	Surgically Treated before Rupture (N=3069)	
Location of aneurysm — no. (%)				<0.001
Middle cerebral artery	2425 (36.2)	1210 (33.2)	1215 (39.8)	
Anterior communicating artery	1037 (15.5)	530 (14.5)	507 (16.6)	
Internal carotid artery§	1245 (18.6)	696 (19.1)	549 (18.0)	
Internal carotid–posterior communicating artery	1037 (15.5)	602 (16.5)	435 (14.3)	
Basilar tip and basilar–superior cerebellar artery	445 (6.6)	327 (9.0)	118 (3.9)	
Vertebral artery–posterior inferior cerebellar artery and vertebrobasilar junction	123 (1.8)	80 (2.2)	43 (1.4)	
Other¶	385 (5.7)	202 (5.5)	183 (6.0)	
Other features of aneurysm — no. (%)				
Thrombosed	120 (1.8)	59 (1.6)	61 (2.0)	0.24
Calcified	113 (1.7)	65 (1.8)	48 (1.6)	0.51
Presence of daughter sac	1266 (18.9)	510 (14.0)	756 (24.8)	<0.001

* Plus–minus values are means ±SD. Patients with a score on the modified Rankin scale of 0 (indicating no disability) or 1 or 2 (indicating slight disability) at the time of presentation were enrolled.

† P values are for the comparison between aneurysms that were not surgically treated before rupture and those that were surgically treated before rupture (with either open or endovascular procedures) during follow-up. The P value for the mean age of the patients and for the mean largest dimension of the aneurysms was calculated with the use of Student's t-test. The P value for reason for imaging and for location of the aneurysm was not calculated for individual variables; each of these categories was analyzed as a single variable, with a chi-square test. The P value for distribution of the largest dimension of the aneurysm was calculated for the variables of 3–4 mm, 5–6 mm, 7–9 mm, 10–24 mm, and ≥25 mm as a group, with a Wilcoxon rank-sum test; the analysis of the variable of ≥7 mm was performed separately with a chi-square test.

‡ The reasons for imaging are those that led to the detection of unruptured cerebral aneurysms. Screening was performed to detect any asymptomatic cerebral lesions in the healthy population or to rule out coexisting central nervous system disease in patients with other systemic or central nervous system diseases. Headache or dizziness included aneurysms that were diagnosed incidentally when imaging was performed because of vague, mild symptoms such as mild dizziness or headache; not included in this category were symptoms such as severe headache attributed to sentinel bleeding or enlargement of an aneurysm. Symptoms caused by mass effects or embolic episodes included severe headache with abrupt onset, cranial-nerve palsy, and neurologic deficits that could be associated with aneurysms. Subarachnoid hemorrhage included unruptured cerebral aneurysms coexisting with other aneurysm-induced subarachnoid hemorrhages.

§ This category includes the internal carotid artery paraclinoid location, so-called internal carotid artery dorsal curvature location, internal carotid artery bifurcation, and internal carotid–anterior choroidal artery and excludes other internal carotid artery aneurysms located at the posterior communicating artery and cavernous portion.

¶ "Other" includes aneurysms at the anterior cerebral artery A1 portion, distal anterior cerebral artery, and other supratentorial or infratentorial locations not categorized above.

significantly according to the location of the aneurysm (Table 3). Among small aneurysms, those in the anterior and posterior communicating arteries were associated with a relatively high risk of rupture; this risk was higher than that associated with small aneurysms of the middle cerebral artery, the location that accounted for the largest number of aneurysms in each size group (Table 4S in the Supplementary Appendix).

DISCUSSION

The results of this study showed that the natural course of an unruptured cerebral aneurysm is influenced not only by the size of aneurysm but also by the specific location and shape. The overall rate of rupture of cerebral aneurysms was 0.95% annually. However, this rate may be an underestimate due to possible selection bias, because we censored data when patients underwent surgical intervention, and some of these patients may have been at increased risk for rupture.

Regarding the independent risk factors for rupture, aneurysms of 7 mm or larger were associated with a significantly increased risk of rupture according to our multivariate analysis; large and giant aneurysms were associated with a very high risk of rupture. This finding is similar to

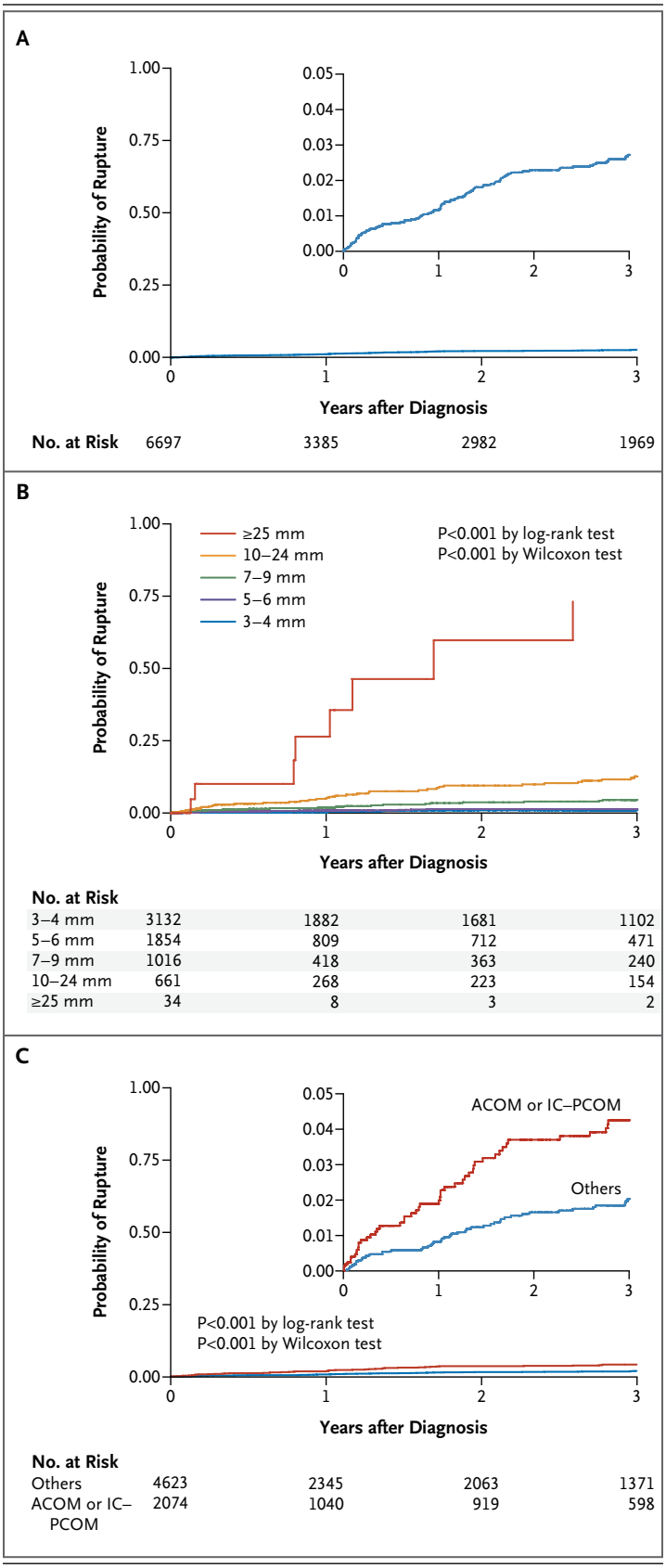

Figure 2. Probability of Rupture of Cerebral Aneurysms.
Shown are the overall probability of rupture of a cerebral aneurysm (Panel A), the probability of rupture according to the size of the aneurysm (Panel B), and the probability of rupture according to the location of the aneurysm (Panel C). The insets in Panels A and C show the same data on an enlarged y axis. ACOM denotes anterior communicating artery, and IC–PCOM internal carotid–posterior communicating artery.

the trend toward an association between size and risk of rupture that was observed in the International Study of Unruptured Intracranial Aneurysms (ISUIA).[5]

The location of the aneurysm is also known to be an important risk factor.[5,6,10] The aneurysms most prone to rupture are located in the anterior communicating and posterior communicating arteries. In our cohort, aneurysms in both locations ruptured at a relatively high rate, even when they were smaller than 7 mm, whereas the ISUIA showed a minimal probability of rupture in patients who had anterior-circulation aneurysms that were smaller than 7 mm and who did not have a history of subarachnoid hemorrhage.[5] Although the ISUIA showed that posterior-circulation aneurysms had a greater tendency to rupture than did anterior-circulation aneurysms,[5] in our analysis, posterior-circulation aneurysms — except for those in the posterior communicating artery and those that were large — were not more prone to rupture (Table 3).

Our multivariate Cox regression model showed that the shape of the aneurysm also influenced the risk of rupture. Aneurysms with a daughter sac were associated with a higher rate of rupture than were aneurysms with a smooth wall. The influence of the shape on the risk of rupture has been suggested in cross-sectional studies comparing ruptured and unruptured cerebral aneurysms.[11,12] Our study shows this association in a prospective cohort.

A history of subarachnoid hemorrhage, former or current smoking, the presence of multiple aneurysms, and hypertension, each of which was identified as an independent risk factor for rupture in other studies,[8,13,14] did not significantly affect the risk of rupture in our cohort. Only 4% of the aneurysms in our study were found in patients who had a history of subarachnoid hemorrhage, and it was therefore difficult to assess the influence of this factor on the risk of rupture. We analyzed the risk of rupture per aneurysm,

whereas previous studies documenting an increased risk among patients with multiple aneurysms have analyzed the rate of rupture per patient. With the latter method, the risk among patients with multiple aneurysms would be at least double the risk among patients with a single aneurysm; therefore, the high risk of rupture reported previously for patients with multiple aneurysms may reflect the cumulative risk of rupture rather than the risk per aneurysm. Regarding the influence of hypertension and smoking, these are modifiable risk factors that might have changed over time. We did not obtain data on such changes over the course of the follow-up period.

One limitation of this study is that we could not exclude a case-selection bias. Patients with aneurysms that are associated with a presumably high rate of rupture could be candidates for early surgical intervention. In this cohort, more than 2000 small aneurysms were treated surgically, and the characteristics of these aneurysms were different from those of the aneurysms that were not treated surgically. Data on aneurysms that were treated surgically were censored at the time of the intervention, and this fact definitely limits the validity of our calculation of the risk of rupture. Although the overall risk of rupture can be affected by this selection bias, the analysis of individual risk factors should not be substantially influenced. The risk of rupture for aneurysms that were smaller than 5 mm (0.36% per year) in our study is very similar to the risk of rupture of single aneurysms in the Small Unruptured Intracranial Aneurysm Verification (SUAVe) study (0.34% per year),[8] in which no surgical intervention was allowed during the follow-up period. Hence, we believe that the influence of selection bias on our analysis of individual risk factors should be acceptably small.

Although most patients were successfully and consecutively enrolled according to the study protocol, not all patients who were eligible were enrolled. The number and characteristics of the unregistered patients were not documented, and we were therefore not able to compare the characteristics of the patients who were included with those of the patients who were not included, to assess potential biases in the selection of patients. However, the characteristics of our cohort were similar to those of cohorts in previous retrospective studies of unruptured cerebral aneurysms from Japan[10,15,16] and should be representative of patients with this disease in Japan.

Table 2. Risk Factors Associated with Rupture of Cerebral Aneurysms.*

Risk Factor	Hazard Ratio (95% CI)	P Value
Female sex	1.54 (0.99–2.42)	0.05
Age ≥70 yr	1.21 (0.81–1.78)	0.34
Hypertension	1.41 (0.96–2.07)	0.08
Hyperlipidemia	0.54 (0.28–1.03)	0.06
Daughter sac	1.63 (1.08–2.48)	0.02
Largest dimension of aneurysm		
3–4 mm	Reference	
5–6 mm	1.13 (0.58–2.22)	0.71
7–9 mm	3.35 (1.87–6.00)	<0.001
10–24 mm	9.09 (5.25–15.74)	<0.001
≥25 mm	76.26 (32.76–177.54)	<0.001
Location of aneurysm		
Middle cerebral artery	Reference	
Anterior communicating artery	2.02 (1.13–3.58)	0.02
Internal carotid artery	0.43 (0.18–1.01)	0.05
Internal carotid–posterior communicating artery	1.90 (1.12–3.21)	0.02
Basilar tip and basilar–superior cerebellar artery	1.49 (0.78–2.83)	0.23
Vertebral artery–posterior inferior cerebellar artery and vertebrobasilar junction	0.68 (0.16–2.87)	0.60
Other	1.48 (0.61–3.60)	0.39

* Hazard ratios for rupture were analyzed with the use of a multivariate Cox proportional-hazards model, with a stepwise selection process adding an age factor. The Harrell's C concordance statistic for this analysis was 0.8172.

Another limitation of the study is that it included only Japanese patients. The risk of subarachnoid hemorrhage is higher in the Japanese population than in other populations, even though the incidence of unruptured cerebral aneurysms is similar to that in Western populations.[1] The current study shows a higher risk of rupture than that shown in the ISUIA.[5] Therefore, caution must be applied in extrapolating the overall risk of rupture in our cohort to other populations. The ISUIA findings represent the natural history of unruptured aneurysms in white populations (more than 90% of the ISUIA cohort is white).[5] Study of the similarities and differences in natural history between these two cohorts should yield valuable information about the natural course of unruptured aneurysms. The explanation for the difference in the risk of rupture between our cohort and the ISUIA cohort may be multifactorial rather than just genetic.

In summary, this study shows that unruptured

Table 3. Annual Rate of Rupture According to Size and Location of Aneurysm.

Location of Aneurysm	Rate of Rupture per Aneurysm per Year (95% CI)				
	3–4 mm	5–6 mm	7–9 mm	10–24 mm	≥25 mm
			percent		
Middle cerebral artery	0.23 (0.09–0.54)	0.31 (0.10–0.96)	1.56 (0.74–3.26)	4.11 (2.22–7.66)	16.87 (2.38–119.77)
Anterior communicating artery	0.90 (0.45–1.80)	0.75 (0.28–2.02)	1.97 (0.82–4.76)	5.24 (197–13.95)	39.77 (9.95–159.00)
Internal carotid artery	0.14 (0.04–0.57)	0	1.19 (0.30–4.77)	1.07 (0.27–4.28)	10.61 (1.49–75.3)
Internal carotid–posterior communicating artery	0.41 (0.15–1.10)	1.00 (0.37–2.66)	3.19 (1.66–6.12)	6.12 (1.66–6.13)	126.97 (40.95–393.68)
Basilar tip and basilar-superior cerebellar artery	0.23 (0.03–1.61)	0.46 (0.06–3.27)	0.97 (0.24–3.89)	6.94 (3.74–12.90)	117.82 (16.60–836.43)
Vertebral artery–posterior inferior cerebellar artery and vertebrobasilar junction	0	0	0	3.49 (0.87–13.94)	0
Other	0.78 (0.25–2.43)	1.37 (0.34–5.50)	0	2.81 (0.40–19.99)	0
Total	0.36 (0.23–0.54)	0.50 (0.29–0.84)	1.69 (1.13–5.93)	4.37 (3.22–5.93)	33.40 (16.60–66.79)

cerebral aneurysms that are larger than 7 mm, are located in the anterior communicating or internal carotid–posterior communicating arteries, and have a daughter sac are associated with an increased risk of rupture. The natural course of unruptured cerebral aneurysms depends on the size, specific location, and the shape of individual aneurysms.

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