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CLINICAL ARTICLE

Rupture risk of small unruptured cerebral aneurysms

Fusao Ikawa, MD, PhD,[1] Akio Morita, MD, PhD,[2] Shinjiro Tominari, MD, PhD,[3] Takeo Nakayama, MD, PhD,[4] Yoshiaki Shiokawa, MD, PhD,[5] Isao Date, MD, PhD,[6] Kazuhiko Nozaki, MD, PhD,[7] Susumu Miyamoto, MD, PhD,[8] Takamasa Kayama, MD, PhD,[9] Hajime Arai, MD, PhD,[10] and The Japan Neurosurgical Society for UCAS Japan Investigators

[1]Department of Neurosurgery, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima; [2]Department of Neurological Surgery, Nippon Medical School, Tokyo; [3]Department of Health Informatics, Kyoto University School of Public Health, Kyoto; [4]Graduate School of Medicine and Faculty of Medicine, Kyoto University, Kyoto; [5]Department of Neurosurgery, Kyorin University School of Medicine, Tokyo; [6]Department of Neurological Surgery, Okayama University Graduate School of Medicine, Okayama; [7]Department of Neurosurgery, Shiga University of Medical Science, Shiga; [8]Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto; [9]Department of Advanced Medicine, Yamagata University School of Medicine, Yamagata; and [10]Department of Neurosurgery, Juntendo University, Tokyo, Japan

OBJECTIVE The annual rupture rate of small (3–4 mm) unruptured cerebral aneurysms (UCAs) is 0.36% per year, however, the proportion of small ruptured aneurysms < 5 mm is 35%. This discrepancy is explained by the hypothesis that most acute subarachnoid hemorrhage (SAH) is from recently formed, unscreened aneurysms, but this hypothesis is without definitive proof. The authors aimed to clarify the actual number of screened, ruptured small aneurysms and risk factors for rupture.

METHODS The Unruptured Cerebral Aneurysm Study Japan, a project of the Japan Neurosurgical Society, was designed to clarify the natural course of UCAs. From January 2001 through March 2004, 6697 UCAs among 5720 patients were prospectively registered. At registration, 2839 patients (49.6%) had 3132 (46.8%) small UCAs of 3–4 mm. The registered, treated, and rupture numbers of these small aneurysms and the annual rupture rate were investigated. The rate was assessed per aneurysm. The characteristics of patients and aneurysms were compared to those of larger unruptured aneurysms (≥ 5 mm). Cumulative rates of SAH were estimated per aneurysm. Risk factors underwent univariate and multivariate analysis.

RESULTS Treatment and rupture numbers of small UCAs were 1132 (37.1% of all treated aneurysms) and 23 (20.7% of all ruptured aneurysms), respectively. The registered, treated, rupture number, and annual rupture rates were 1658 (24.8%), 495 (16.2%), 11 (9.9%), and 0.30%, respectively, among 3-mm aneurysms, and 1474 (22.0%), 637 (20.9%), 12 (10.8%), and 0.45%, respectively, among 4-mm aneurysms. Multivariate risk-factor analysis revealed that a screening brain checkup (hazard ratio [HR] 4.1, 95% confidence interval [CI] 1.2–14.4), history of SAH (HR 10.8, 95% CI 2.3–51.1), uncontrolled hypertension (HR 5.2, 95% CI 1.8–15.3), and location on the anterior communicating artery (ACoA; HR 5.0, 95% CI 1.6–15.5) were independent predictors of rupture.

CONCLUSIONS Although the annual rupture rate of small aneurysms was low, the actual number of ruptures was not low. Small aneurysms that ruptured during follow-up could be detected, screened, and managed based on each risk factor. Possible selection criteria for treating small UCAs include a history of SAH, uncontrolled hypertension, location on the ACoA, and young patients. Further large prospective and longitudinal trials are needed.

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KEYWORDS small unruptured cerebral aneurysm; risk factor; ruptured cerebral aneurysm; screening; vascular disorders

ABBREVIATIONS ACoA = anterior communicating artery; BA = basilar artery; CI = confidence interval; HR = hazard ratio; ICA = internal carotid artery; IQR = interquartile range; MCA = middle cerebral artery; MRA = MR angiography; PCoA = posterior communicating artery; SAH = subarachnoid hemorrhage; UCA = unruptured cerebral aneurysm; UCAS = Unruptured Cerebral Aneurysm Study; VA = vertebral artery.

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Asymptomatic unruptured cerebral aneurysms (UCAs) are frequently discovered incidentally through screening. In 2015, the American Heart Association and the American Stroke Association updated guidelines for managing patients with UCAs;[36] however, these guidelines do not specify separate recommendations for managing small (3–7 mm) aneurysms.

Most UCAs are < 5 mm in diameter.[14,27,28] According to the natural course of UCAs in a Japanese cohort, the overall annual rupture rate has been reported as 0.95% per year (Unruptured Cerebral Aneurysm Study [UCAS] Japan).[27] However, it was 0.36% per year in UCAs that were 3–4 mm in diameter. A recent systematic review of small UCAs found that the reported annual rupture rate of lesions ≤ 5 mm was < 0.5%.[23] However, the proportion of small aneurysms in general is not low; 85%–90% of ruptured cerebral aneurysms are ≤ 10 mm.[5,25,26,42] According to recent reports, the proportion of small ruptured aneurysms ≤ 5 mm and < 5 mm among total ruptured aneurysms was 45%–50%[6,20,25,42] and 35%,[4] respectively.

Some aneurysms are likely to bleed shortly after formation and are rarely detected through screening.[34] However, it is unknown how many of these aneurysms exist. Furthermore, there are no precise published data from a large, prospective cohort study of the natural history and management of small UCAs, even though size is one of the risk factors of rupture.[27] Here, we aimed to clarify the actual number of screened and ruptured small UCAs and the risk factors for rupture of small UCAs in a post hoc subgroup analysis of UCAS Japan.

Methods

UCAS Japan

UCAS Japan,[27] a project of the Japan Neurosurgical Society, was designed to clarify the natural course of UCAs. In this study, patients at least 20 years of age were eligible to enroll if they had an aneurysm ≥ 3 mm in diameter. The study excluded patients with a past history of intracranial hemorrhage from an unknown or untreated cause, those with a decreased ability to engage in activities of daily life (modified Rankin Scale score > 2), and those with an aneurysm located at the cavernous portion of the internal carotid artery (ICA). Detailed inclusion and exclusion criteria are available in the protocol described in a previously published report.[27]

Standard Protocol Approval, Registration, and Patient Consent

This study was approved by the IRB of Hiroshima University and the Japan Neurosurgical Society. Investigators at each participating institution obtained the approval of their local IRB to conduct this study, and the procedures followed were in accordance with institutional guidelines. Written informed consent was obtained from all patients participating in this study. This study was registered with the UMIN Clinical Trials Registry (no. C000000418; https://www.umin.ac.jp/ctr).

Enrollment Criteria and Categorization

Over a period of 39 months (January 2001 through March 2004), patients were registered from any one of the 283 institutions participating in the UCAS study. Hiroshima University was one of the participating sites for this multicenter trial. There were 6 reasons for imaging that led to detection of the UCAs: a screening brain checkup, incidental examination (other than brain checkup), unspecified symptoms (headache, dizziness), symptoms from mass effects or embolic episodes, subarachnoid hemorrhage (SAH), and other. Medical checkups of the brain, namely the "brain dock," are supported by some organizations and municipalities and are widely available in Japan. The brain checkup system, which uses MRI and MR angiography (MRA) of the brain and neck for screening purposes, has been used in Japan since approximately 1995; use of this system is not standard, but is popular.[29]

At the time patients were registered, we recorded data such as age, sex, smoking habits, the reason for imaging, and family or past history of SAH and other diseases. Hypertension was categorized as controlled or uncontrolled according to the hypertension guidelines in Japan, which recommend controlled hypertension as 140/90 mm Hg or less. For this study, we defined lesions of 3 mm as those ranging from 2.5 mm to 3.4 mm, 4-mm lesions as those ranging from 3.5 mm to 4.4 mm, and 5-mm lesions as the range from 4.5 to 5.4 mm. We excluded UCAs smaller than 3 mm because diagnosis with low-tesla MR images decreases in accuracy in this population. The patients' clinical status, a description of the aneurysm, and the treatment plan were recorded 3, 12, and 36 months after diagnosis, and 5–8 years later in some patients. Therapy was chosen by the patient or determined by the physician. When a patient underwent surgery, we included data up to the time of surgery in our analysis of the rupture risk. We also gathered information about the aneurysm, including the largest diameter, thrombosed or calcified components on the aneurysmal wall, and the presence of a daughter sac, which was defined as an irregular protrusion of the aneurysmal wall on imaging.

The location of each aneurysm was categorized as follows: middle cerebral artery (MCA), anterior communicating artery (ACoA), ICA, ICA–posterior communicating artery (IC-PCoA), basilar artery (BA), vertebral artery (VA), and "other." The ICA includes the ICA paraclinoid and dorsal curvature locations, the ICA bifurcation, and the anterior choroidal artery of the ICA. It excludes other ICA aneurysms at the PCoA and cavernous portion. The BA includes the tip and superior cerebellar artery. The VA includes the VA posterior-inferior cerebellar artery and the vertebrobasilar junction. The "other" category includes aneurysms located at the A_1 section of the anterior cerebral artery, and the distal anterior cerebral artery as well as other supratentorial or infratentorial locations not included in the categories listed above. SAH was identified through the use of CT or lumbar puncture, or at autopsy.

Previous Findings

The primary results of the UCAS Japan study have been published previously.[27] The annual rupture risk of unruptured aneurysms was 0.95%, and the independent risk factors for rupture were size (> 7 mm), location (ACoA or

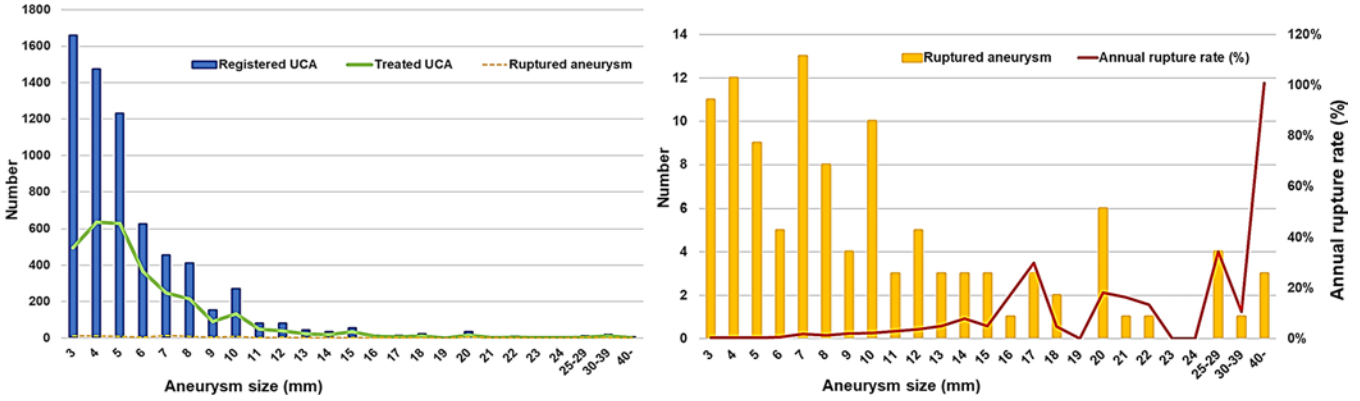

FIG. 1. Left: The numbers of registered, treated UCAs and ruptured aneurysms according to aneurysm size. **Right:** The number of ruptured and the annual rupture rate of UCAs according to aneurysm size. Figure is available in color online only.

PCoA), and shape (the presence of a daughter sac) of the aneurysm.

Analysis of Aneurysm Size in UCAS Japan

We investigated the registration, treatment, and annual rupture rate of 6697 eligible aneurysms in the total cohort of 5720 patients in the UCAS Japan study. Aneurysm size was classified from 3 to 24 mm in 1-mm increments, and then in groups of 25–29 mm, 30–39 mm, and > 40 mm in maximum diameter. The registration, treatment, number of ruptured UCAs, and annual rupture rate for each size were calculated. The rate of rupture was assessed per aneurysm rather than per patient.

Extracting the Small UCA Subgroup for Analysis

Comparisons between UCAs ≤ 4 mm and ≥ 5 mm were made for patients and aneurysms by using patient-specific factors such as age, sex, the reason for discovery of the UCA, hypertension (none, controlled, and uncontrolled), hyperlipidemia, smoking, polycystic kidneys, and old cerebral infarction, as well as aneurysm-specific factors such as size, location, calcification, thrombosis, and shape. In a subgroup of small UCAs, aneurysms that led to SAH were extracted for this post hoc analysis, and the risk factors of rupture underwent univariate and multivariate analysis.

Statistical Analysis

Statistical tests were two-sided and differences were considered to be significant when the p value was < 0.05. Characteristics of patients and aneurysms in this subgroup were compared to those of patients with UCAs ≥ 5 mm by using the t-test for mean values and the chi-square test for proportional values. The cumulative rates of SAH were estimated per aneurysm with the Kaplan-Meier product-limit method, and the curves between groups were compared by using the log-rank test. Cox proportional hazard regression analyses were performed to calculate hazard ratios (HRs) for the predictor variables. When variables associated with aneurysm rupture had a p value < 0.2 with univariate analysis, they were selected for a multivariate analysis. We defined the p value in univariate analysis as p < 0.20 to capture any potential variable in the analysis and minimize the risk of excluding an important contributor. We checked the proportional hazards assumption for each variable by testing Schoenfeld residuals. All statistical analyses were conducted using Stata software (version 14.2, StataCorp). When a patient had multiple aneurysms, the largest of these, along with its location and with or without the daughter sac, was used to categorize the patient.

Results

Size Distribution of UCAS Japan

In the total cohort of 5720 patients with 6697 UCAs eligible for the UCAS Japan study, 2839 patients (49.6%) had 3132 small UCAs (46.8%) of 3–4 mm in diameter at the time of registration, and these were subjected to this post hoc subgroup analysis. Figure 1 left shows the number of registered, treated, and ruptured UCAs according to their size. The largest number of registered aneurysms was the 3-mm category with 1658 aneurysms (24.8%), followed by 1474 aneurysms (22.0%) of 4 mm and 1229 aneurysms (18.4%) of 5 mm. Small UCAs of 3 and 4 mm comprised 46.8% of all UCAs. The total number treated was 3050 (45.5%) and the highest treatment category was 4 mm (637 aneurysms, 20.9%), followed by 629 aneurysms (20.6%) of 5 mm, and 495 aneurysms (16.2%) of 3 mm. Aneurysms of 3 and 4 mm totaled 37.1% of all treated UCAs.

Figure 1 right shows the number of ruptures and annual rupture rate of UCAs according to size. The total number of ruptured UCAs was 111 (1.7%) and the highest category of ruptured aneurysms was 7 mm, with 13 aneurysms (11.7%). Twelve of the 4-mm lesions ruptured (10.8%), and 11 of the 3-mm aneurysms ruptured (9.9%), comprising 20.7% of all ruptured UCAs. The highest annual rupture rate by size occurred in the > 40-mm category, with 100% per year, 34.3% per year in the 25–29 mm category, and 30.0% per year for 17-mm lesions. For 3- and 4-mm UCAs, the annual rupture rates were 0.30% per year and 0.45% per year, respectively.

Small UCAs Compared With Larger UCAs

A total of 2839 patients with 3132 UCAs ≤ 4 mm were investigated in this post hoc subgroup analysis. The mean

TABLE 1. Patient characteristics of UCAs ≤ 4 mm compared to those ≥ 5 mm

Characteristic	Total Cohort	UCA (mm)		p Value
		≤4	≥5	
No. of patients	5720	2839	2881	
Age, yrs				**<0.001**
Mean ± SD	62.5 ± 10.3	61.7 ± 10.2	63.4 ± 10.3	
Median (IQR)	63 (55–70)	62 (55–69)	64 (56–71)	
Range	23–98	25–93	23–98	
Females, n (%)	3805 (66.5)	1868 (65.8)	1937 (67.2)	0.25
Multiplicity, n (%)	793 (13.9)	600 (21.1)	193 (6.7)	**<0.001**
Reason for imaging, n (%)				**<0.001**
Screening brain checkup	1044 (18.3)	591 (20.8)	453 (15.7)	
Incidental other than brain checkup	1459 (25.5)	710 (25.0)	749 (26.0)	
Unspecified Sx (headache, dizziness)	2714 (47.4)	1294 (45.6)	1420 (49.3)	
Sxs caused by mass effects or embolic episodes	171 (3.0)	47 (1.7)	124 (4.3)	
w/ SAH	217 (3.8)	137 (4.8)	80 (2.8)	
Other	115 (2.0)	60 (2.1)	55 (1.9)	
Modality of diagnosis, n (%)				**0.016**
DSA	2338 (40.9)	1155 (40.7)	1183 (41.1)	
MRA	2896 (50.6)	1362 (48.0)	1534 (53.2)	
CTA	1559 (27.3)	807 (28.4)	752 (26.1)	
Family history of SAH, n (%)	736 (12.9)	396 (14.0)	340 (11.8)	**0.015**
Past & medical history, n (%)				
History of SAH	187 (3.3)	101 (3.6)	86 (3.0)	0.22
Former or current smoker	960 (16.8)	492 (17.3)	468 (16.2)	0.27
Hypertension, n (%)				**<0.001**
None	3240 (56.6)	1652 (58.2)	1588 (55.1)	
Controlled	1989 (34.8)	939 (33.1)	1050 (36.4)	
Uncontrolled	491 (8.6)	248 (8.7)	243 (8.4)	
Diabetes mellitus, n (%)	362 (6.3)	164 (5.8)	198 (6.9)	0.49
Hyperlipidemia, n (%)	809 (14.1)	416 (14.7)	393 (13.6)	0.27
Ischemic stroke, n (%)	400 (7.0)	193 (6.8)	207 (7.2)	0.57
Polycystic kidney disease, n (%)	18 (0.3)	8 (0.3)	10 (0.3)	0.66

CTA = CT angiography; DSA = digital subtraction angiography; Sx = symptom.
Boldface type indicates statistical significance.

(± SD) age of patients was 61.7 ± 10.2 years. Tables 1 and 2 show the characteristics of patients and aneurysms in comparison with UCAs ≥ 5 mm. Age, multiplicity, reason for imaging, modality of diagnosis, family history of SAH, hypertension, location, and shape of the aneurysm were significant variables in the two groups.

Risk Factors for Small UCA Rupture

The results of univariate and multivariate analyses of factors related to small UCA ruptures per aneurysm are summarized in Table 3. The HRs for rupture were analyzed with the use of a Cox proportional hazards model of multivariate analysis. Statistically significant predictors for rupture in small UCAs included the screening brain checkup (HR 4.1, 95% confidence interval [CI] 1.2–14.4), a history of SAH (HR 10.8, 95% CI 2.3–51.1), uncontrolled hypertension (HR 5.2, 95% CI 1.8–15.3), and the location of the ACoA (HR 5.0, 95% CI 1.6–15.5).

Treated Small UCAs Compared With Untreated Small UCAs

Tables 4 and 5 show the results of comparison between treated and untreated small UCAs of 3-mm and 4-mm diameter. Variables showing significant differences between the groups included age, modality of diagnosis, family history of SAH, history of SAH, and former or current smoking. History of ischemic stroke was the only unique significant factor among 4-mm UCAs.

Rate of Small UCA Rupture

The median (interquartile range [IQR]) and mean follow-up periods were 1019 (IQR 75–1112) and 743.0 days, respectively. Twenty-three patients (0.7%) experienced SAH during the follow-up period, and the overall annual rupture risk was 0.36% in small UCAs (23 SAHs per 6371 patient-years). The cumulative rate of SAH for all

TABLE 2. Characteristics of UCAs ≤ 4 mm compared to those ≥ 5 mm

Characteristic	Total Cohort	UCA (mm)		p Value
		≤4	≥5	
No. of aneurysms	6697	3132	3565	
Age, yrs				**<0.001**
Mean ± SD	62.6 ± 10.1	61.7 ± 10.1	63.4 ± 10.2	
Median (IQR)	63 (56–70)	62 (55–69)	64 (56–71)	
Range	23–98	25–93	23–98	
Multiplicity, n (%)	1770 (26.4)	893 (28.5)	877 (24.6)	**<0.001**
Females, n (%)	4532 (67.7)	2083 (66.5)	2449 (68.7)	0.056
Reason for imaging, n (%)				**<0.001**
Screening brain checkup	1212 (18.1)	641 (20.5)	571 (16.0)	
Incidental other than brain checkup	1698 (25.4)	763 (24.4)	935 (26.2)	
Unspecified Sx (headache, dizziness)	3174 (47.4)	1435 (45.8)	1739 (48.8)	
Sxs caused by mass effects or embolic episodes	203 (3.0)	54 (1.7)	149 (4.2)	
w/ SAH	273 (4.1)	167 (5.3)	106 (3.0)	
Other	137 (2.0)	72 (2.3)	65 (1.8)	
Modality of diagnosis, n (%)				**0.008**
DSA	2825 (42.2)	1291 (41.2)	1534 (43.0)	
MRA	3336 (49.8)	1486 (47.4)	1850 (51.9)	
CTA	1788 (26.7)	887 (28.3)	901 (25.3)	
Family history of SAH, n (%)	910 (13.6)	460 (14.7)	450 (12.6)	**0.014**
Past & medical history, n (%)				
History of SAH	225 (3.4)	119 (3.8)	106 (3.0)	0.061
Former or current smoker	1173 (17.5)	545 (17.4)	628 (17.6)	0.82
Hypertension, n (%)				**0.005**
None	3728 (55.7)	1808 (57.7)	1920 (53.9)	
Controlled	2365 (35.3)	1046 (33.4)	1319 (37.0)	
Uncontrolled	604 (9.0)	278 (8.9)	326 (9.1)	
Diabetes mellitus, n (%)	396 (5.9)	176 (5.6)	220 (6.2)	0.34
Hyperlipidemia, n (%)	939 (14.0)	454 (14.5)	485 (13.6)	0.30
Ischemic stroke, n (%)	466 (7.0)	217 (6.9)	249 (7.0)	0.93
Polycystic kidney disease, n (%)	22 (0.3)	8 (0.3)	14 (0.4)	0.33
No. of ruptured aneurysms, n (%)	111 (1.7)	23 (0.7)	88 (2.5)	**<0.001**
Annual rupture rate	0.95	0.36	1.66	**<0.001**
Surgical/endovascular treatment, n (%)	3050 (45.5)	1132 (36.1)	1918 (53.8)	**<0.001**
Mean size of aneurysm ± SD, mm	5.7 ± 3.7	3.5 ± 0.5	7.6 ± 4.0	**<0.001**
Location of aneurysm, n (%)				**<0.001**
MCA	2425 (36.2)	1150 (36.7)	1275 (35.8)	
ACoA	1037 (15.5)	467 (14.9)	570 (16.0)	
ICA	1245 (18.6)	638 (20.4)	607 (17.0)	
IC-PCoA	1037 (15.5)	434 (13.9)	603 (16.9)	
BA	445 (6.6)	184 (5.9)	261 (7.3)	
VA	123 (1.8)	36 (1.1)	87 (2.4)	
Other	385 (5.7)	223 (7.1)	162 (4.5)	
Shape, n (%)				
Thrombosed	120 (1.8)	10 (0.3)	110 (3.1)	**<0.001**
Calcified	113 (1.7)	19 (0.6)	94 (2.6)	**<0.001**
Presence of daughter sac	1266 (18.9)	283 (9.0)	983 (27.6)	**<0.001**

Boldface type indicates statistical significance.

TABLE 3. Univariate and multivariate Cox proportional hazard risk factors associated with rupture of small UCAs ≤ 4 mm

Variable	Univariate Analysis		Multivariate Cox Proportional Hazard Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, yrs	0.99 (0.95–1.03)	0.70		
<50	1.57 (0.53–4.61)	0.41		
Female sex	2.42 (0.82–7.12)	0.11*	2.89 (0.96–8.70)	0.06
Multiplicity	0.50 (0.17–1.46)	0.20		
Reason for imaging				
Screening brain checkup	2.43 (0.73–8.07)	0.15*	4.09 (1.16–14.40)	0.028†
Incidental other than brain checkup	Ref		Ref	
Unspecified Sx (headache, dizziness)	1.43 (0.45–4.49)	0.54	1.92 (0.60–6.22)	0.27
Sxs caused by mass effects or embolic episodes	(omitted)			
w/ SAH	(omitted)			
Other	(omitted)			
Past & medical history				
Family history of SAH	0.29 (0.04–2.16)	0.23		
Past history of SAH	2.96 (0.69–12.63)	0.14*	10.83 (2.29–51.13)	0.003†
Smoking	0.55 (0.13–2.33)	0.41		
Hypertension				
None	Ref			
Controlled	1.16 (0.44–3.06)	0.76	1.10 (0.40–3.07)	0.85
Uncontrolled	4.17 (1.52–11.49)	0.01*	5.21 (1.77–15.30)	0.003†
Diabetes mellitus	1.48 (0.35–6.30)	0.60		
Hyperlipidemia	0.27 (0.04–2.02)	0.20		
Ischemic stroke	0.58 (0.08–4.33)	0.60		
Location of aneurysm				
MCA	Ref			
ACoA	3.96 (1.30–12.12)	0.02*	4.98 (1.60–15.52)	0.006†
ICA	0.64 (0.12–3.29)	0.59	0.69 (0.13–3.64)	0.67
IC-PCoA	1.85 (0.50–6.89)	0.36	2.34 (0.62–8.88)	0.21
BA	1.02 (0.12–8.74)	0.99	1.13 (0.13–9.80)	0.91
VA	(omitted)	0	(omitted)	
Other	3.46 (0.83–14.50)	0.09*	3.42 (0.80–14.59)	0.10
Shape				
Thrombosed	(omitted)			
Calcified	(omitted)			
Presence of daughter sac	2.18 (0.65–7.37)	0.21		
Size, mm				
3	Ref			
4	1.49 (0.66–3.37)	0.34		

* $p < 0.2$.
† $p < 0.05$.

patients with small UCAs was 0.91% (95% CI 0.57–1.45) at 2 years after diagnosis, and 1.86% (95% CI 1.02–3.38) at 5 years (Fig. 2A). The probability of rupture in patients with hypertension and an ACoA aneurysm is shown in Fig. 2B and C. However, the number of patients whose lesions were detected through the screening brain checkup was not significantly high with either the Kaplan-Meier product-limit method or the log-rank test (Fig. 2D). A total of 56 patients died during follow-up, but only 2 deaths were related to SAH.

Discussion

There have been several studies of UCAs,[18,27,28,32,39] however, none has described the actual number and proportion of small UCA ruptures among all ruptured UCAs. This study shows the actual number and proportion of small UCA ruptures among all ruptured UCAs, and the risk factor analysis was performed in specific reference to small UCAs in a large prospective cohort. The proportion of small UCA rupture among all ruptured UCAs in the total

TABLE 4. Patient characteristics of treated UCAs compared to untreated UCAs of 3-mm diameter

Characteristic	Treated UCA Before Rupture	Untreated UCA	p Value
No. of patients	356	849	
Age, yrs			**<0.001**
Mean ± SD	58.4 ± 9.0	62.0 ± 10.8	
Median (IQR)	59 (53–65)	63 (55–70)	
Range	25–77	25–93	
Females, n (%)	232 (65.2)	536 (63.1)	0.50
Multiplicity, n (%)	26 (7.3)	49 (5.8)	0.32
Reason for imaging, n (%)			**0.044**
Screening brain checkup	77 (21.6)	173 (20.4)	
Incidental other than brain checkup	78 (21.9)	233 (27.4)	
Unspecified Sx (headache, dizziness)	169 (47.5)	385 (45.3)	
Sxs caused by mass effects or embolic episodes	6 (1.7)	14 (1.6)	
w/ SAH	24 (6.7)	30 (3.5)	
Other	2 (0.6)	14 (1.6)	
Modality of diagnosis, n (%)			
DSA	179 (50.3)	270 (31.8)	**<0.001**
MRA	152 (42.7)	442 (52.1)	**0.003**
CTA	103 (28.9)	268 (31.6)	0.37
Family history of SAH, n (%)	58 (16.3)	115 (13.5)	0.22
Past & medical history, n (%)			
History of SAH	20 (5.6)	16 (1.9)	**0.001**
Former or current smoker	75 (21.1)	125 (14.7)	**0.007**
Hypertension, n (%)			0.44
None	207 (58.1)	518 (61.0)	
Controlled	116 (32.6)	269 (31.7)	
Uncontrolled	33 (9.3)	62 (7.3)	
Diabetes mellitus, n (%)	14 (3.9)	55 (6.5)	0.083
Hyperlipidemia, n (%)	55 (15.4)	142 (16.7)	0.59
Ischemic stroke, n (%)	19 (5.3)	60 (7.1)	0.27
Polycystic kidney disease, n (%)	0 (0.0)	2 (0.2)	0.36

Boldface type indicates statistical significance.

TABLE 5. Patient characteristics of treated UCAs compared to untreated UCAs of 4-mm diameter

Characteristic	Treated UCA Before Rupture	Untreated UCA	p Value
No. of patients	547	683	
Age, yrs			**<0.001**
Mean ± SD	59.6 ± 9.0	63.9 ± 10.4	
Median (IQR)	59 (54–66)	65 (57–71)	
Range	29–80	35–91	
Female sex, n (%)	348 (63.6)	446 (65.3)	0.54
Multiplicity, n (%)	61 (11.2)	60 (8.8)	0.17
Reason for imaging, n (%)			**<0.001**
Screening brain checkup	140 (25.6)	126 (18.4)	
Incidental other than brain checkup	109 (19.9)	178 (26.1)	
Unspecified Sx (headache, dizziness)	242 (44.2)	316 (46.3)	
Sxs caused by mass effects or embolic episodes	2 (0.4)	14 (2.0)	
w/ SAH	37 (6.8)	27 (4.0)	
Other	17 (3.1)	22 (3.2)	
Modality of diagnosis, n (%)			
DSA	292 (53.4)	204 (29.9)	**<0.001**
MRA	229 (41.9)	353 (51.7)	**0.001**
CTA	112 (20.5)	235 (34.4)	**<0.001**
Family history of SAH, n (%)	101 (18.5)	62 (9.1)	**<0.001**
Past & medical history, n (%)			
History of SAH	32 (5.9)	21 (3.1)	**0.017**
Former or current smoker	109 (19.9)	91 (13.3)	**0.002**
Hypertension, n (%)			0.75
None	332 (60.7)	400 (58.6)	
Controlled	169 (30.9)	223 (32.7)	
Uncontrolled	46 (8.4)	60 (8.8)	
Diabetes mellitus, n (%)	28 (5.1)	46 (6.7)	0.24
Hyperlipidemia, n (%)	80 (14.6)	88 (12.9)	0.38
Ischemic stroke, n (%)	25 (4.6)	64 (9.4)	**0.001**
Polycystic kidney disease, n (%)	3 (0.5)	1 (0.1)	0.22

Boldface type indicates statistical significance.

cohort was 20.7%, which is not insignificant. Aneurysms that bleed shortly after formation are difficult to follow clinically and radiologically from formation to rupture; therefore, they were never detected as UCAs and most acute SAH in patients with small aneurysms was from recently formed aneurysms.[23,34,40] According to the present prospective study, however, at least 20.7% of small UCAs among all ruptured UCAs were already detected as UCAs. This fact told us that the number of aneurysms that bleed shortly after formation and were unscreened was rare. For small UCAs with risk factors, we can manage the control of risk and treat those with higher risk factors. On the other hand, according to Kassell and Torner,[17] the proportion of small ruptured cerebral aneurysms among 1092 cases was 13% in those ≤ 5 mm. However, this proportion has been increasingly reported as up to 50% recently.[2,4,6,22,25,42] There are likely two reasons for the relatively lower proportion of small UCA ruptures in this study. One is that about half of the small UCAs were treated before rupture and managed according to the risk factors of rupture. The reasons to treat small UCAs included the patient's young age, modality of diagnosis, family history of SAH, history of SAH, and former or current smoking (Tables 4 and 5). The second reason is that UCAS Japan did not include 2-mm UCAs. According to other studies,[14,28] the rate of small UCAs from 2 to 4 mm was no less than 87.6%,[3] with lesions of 2.0 to 2.9 mm at 46.3%.[14] Therefore, 2-mm UCAs occur more frequently than 3- or 4-mm UCAs. However, the natural his-

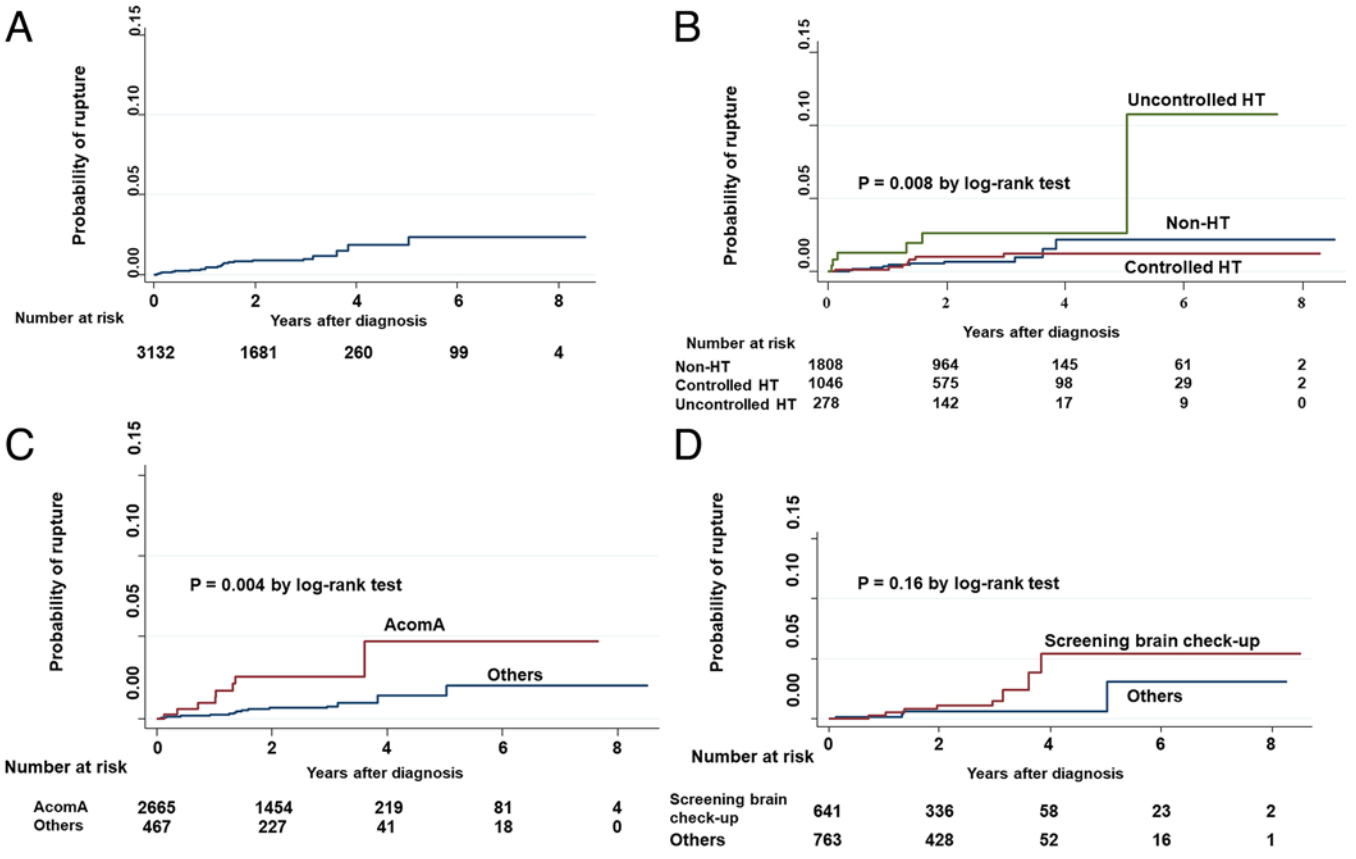

FIG. 2. A: Kaplan-Meier curve showing the probability of rupture for all patients. **B:** Kaplan-Meier curve showing the probability of rupture in patients with hypertension (HT). **C:** Kaplan-Meier curve showing the probability of rupture in patients with an anterior communicating artery (AcomA) aneurysm. **D:** Kaplan-Meier curve showing the probability of rupture in patients detected through the screening brain checkup. Figure is available in color online only.

tory of small UCAs remains poorly understood, and only 0.25%[8,31,35] to 0.54% per year[34] eventually rupture.

The reported risk factors for rupture of small UCAs are the patient's age (< 50 years), hypertension, multiple aneurysms, initial aneurysm size, location of the posterior circulation and ACoA, and size ratio.[10,16,34] In this study, according to multivariate analysis, the significant risk factors were the screening brain checkup, past history of SAH, uncontrolled hypertension, and the location of the ACoA. A possible reason that age < 50 years was not a risk factor in our study could be that patients undergoing treatment for a small UCA were significantly younger than the untreated group (Tables 4 and 5). Many reports regard the location of the ACoA as one risk factor for rupture of UCAs[5,9,13,14,27,37] because of morphological[3] and associated anomalies.[20] Additionally, many reports of hypertension as a risk factor have been published;[5,9,13,14,27,37] however, hypertension is more the essential fact of actual high systolic blood pressure than the hypertension itself in patients with SAH.[19] Nonetheless, the role of blood pressure level in patients with small UCAs has never been researched.

The screening brain checkup was one of the risk factors of UCA rupture in our Cox proportional hazard regression analysis; however, this risk factor was not significantly high according to the log-rank test. The risk of early aneurysmal rupture after the discovery of a UCA was higher than expected based on the aneurysm's characteristics.[7] Psychological stress has been increasingly suggested as a potential risk factor for hemorrhagic strokes,[12] and a sudden increase in blood pressure as a result of startling emotion is related to aneurysm rupture.[38] In fact, anxiety and depression were apparent in patients with untreated UCAs.[21,30] Therefore, explanations to patients whose small UCA has just been detected should be undertaken carefully to avoid the startled emotion. Further study regarding the stress caused just by the detection of an aneurysm and its concomitant risk is necessary.

To date, many published reports about small UCAs have noted that direct treatment of small lesions without risk factors was ineffective because of too many background and general management issues. This strategy could be the best way to reduce the rate of SAH. Two recent papers describe managing small UCAs without risk by using a Markov decision model for lifetime rupture; they state that, in most situations, prophylactic treatment of such lesions is unlikely to improve patient outcomes over the natural history.[1] According to another paper, no preventive treatment and even no imaging follow-up were the most effective strategies in patients with UCAs of 3 mm or less, resulting in better health outcomes.[24]

We found that the common features of small UCAs were younger patients, multiplicity, detection through screening checkup, and family history of SAH (Tables 1 and 2). If possible, the treatable risk factors, such as hypertension, should be managed as soon as possible. The psychological stress of having a UCA varies according to the sensitivity of the individual patient. The timing of interventional treatment for a UCA is controversial. If the patient has high anxiety and depression, relatively immediate treatment in a high-volume center by an experienced doctor might be an option after proper and informed consent, as rupture after discovery is most likely during the early period.[15,21,33] In general, however, we cannot reduce the incidence of SAH through interventional treatment of individual small UCAs based on the large numbers of small UCAs. Currently, some drugs show promise in preventing the rupture of UCAs.[11,41]

According to the present study, if any small aneurysms are found incidentally, patients should be treated for hypertension and stressful communication of the risks should be avoided. Aneurysms located on the ACoA or associated with previous SAH should be followed with imaging at appropriate intervals or might be interventionally treated under limited conditions. Finally, we should further investigate small UCAs and manage them according to the patient's individual background.

Limitations

This study has several limitations. First, the population in this pooled analysis was limited to Japanese patients with UCAs. The rate of UCA rupture in the Japanese population has been reported to be high, and Japanese ethnicity is an independent predictor of aneurysm rupture, according to previously reported pooled data.[9] Therefore, the results in this report should be applied with caution to small UCAs in other populations because the geographical region is related to the risk of rupture. Although a study such as this prospective cohort is possible only in Japan, nonetheless, the results contribute to the study of UCAs across the globe.

Second, this study has a case-selection bias. Tables 4 and 5 show the treated UCA characteristics of patients. Those with age, past and medical history were significantly different factors. Third, the small number of variables investigated is the result of our choice to assess only variables common to this group. Thus, rates of smoking and intake of aspirin or a statin were not investigated because patients undergoing brain checkups tend to be highly health conscious and healthy. And fourth, this study did not include very small UCAs of 1 or 2 mm, which appear often in screening images. Therefore, further study should include 1- or 2-mm UCAs. Finally, the study had relatively short follow-up durations, with 45% at 2 years and 29% at 3 years.

Conclusions

Despite the annual rupture rate of small UCAs being low, the actual number of ruptures was not low in the total group. Small UCAs that ruptured during follow-up could be detected, screened, and managed based on each risk factor. Possible selection criteria for treating small UCAs include a history of SAH, uncontrolled hypertension, location on the ACoA, and young patients. Further large prospective and longitudinal registered trials are needed to elucidate these issues.

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References

1. Aishima K, Shimizu T, Aihara M, Yoshimoto Y: Lifetime effects of small unruptured intracranial aneurysms. **World Neurosurg 95:**434–440, 2016
2. Bender MT, Wendt H, Monarch T, Beaty N, Lin LM, Huang J, et al: Small aneurysms account for the majority and increasing percentage of aneurysmal subarachnoid hemorrhage: a 25-year, single institution study. **Neurosurgery 83:**692–699, 2018
3. Cai W, Hu C, Gong J, Lan Q: Anterior communicating artery aneurysm morphology and the risk of rupture. **World Neurosurg 109:**119–126, 2018
4. Dolati P, Pittman D, Morrish WF, Wong J, Sutherland GR: The frequency of subarachnoid hemorrhage from very small cerebral aneurysms (< 5 mm): a population-based study. **Cureus 7:**e279, 2015
5. Forget TR Jr, Benitez R, Veznedaroglu E, Sharan A, Mitchell W, Silva M, et al: A review of size and location of ruptured intracranial aneurysms. **Neurosurgery 49:**1322–1326, 2001
6. Froelich JJ, Neilson S, Peters-Wilke J, Dubey A, Thani N, Erasmus A, et al: Size and location of ruptured intracranial aneurysms: a 5-year clinical survey. **World Neurosurg 91:**260–265, 2016
7. Geurts M, Timmers C, Greebe P, Algra A, Rinkel GJ: Patients with unruptured intracranial aneurysms at the waiting list for intervention: risk of rupture. **J Neurol 261:**575–578, 2014
8. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al: Heart disease and stroke statistics—2014 update: a report from the American Heart Association. **Circulation 129:**e28–e292, 2014
9. Greving JP, Wermer MJ, Brown RD Jr, Morita A, Juvela S, Yonekura M, et al: Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. **Lancet Neurol 13:**59–66, 2014
10. Güresir E, Vatter H, Schuss P, Platz J, Konczalla J, de Rochement RduM, et al: Natural history of small unruptured anterior circulation aneurysms: a prospective cohort study. **Stroke 44:**3027–3031, 2013
11. Hasan DM, Mahaney KB, Brown RD Jr, Meissner I, Piepgras DG, Huston J, et al: Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture. **Stroke 42:**3156–3162, 2011
12. Henderson KM, Clark CJ, Lewis TT, Aggarwal NT, Beck T, Guo H, et al: Psychosocial distress and stroke risk in older adults. **Stroke 44:**367–372, 2013
13. Hostettler IC, Alg VS, Shahi N, Jichi F, Bonner S, Walsh D, et al: Characteristics of unruptured compared to ruptured intracranial aneurysms: a multicenter case-control study. **Neurosurgery 83:**43–52, 2018
14. Imaizumi Y, Mizutani T, Shimizu K, Sato Y, Taguchi J: Detection rates and sites of unruptured intracranial aneurysms according to sex and age: an analysis of MR angiography-

based brain examinations of 4070 healthy Japanese adults. **J Neurosurg 6:**1–6, 2018
15. International Study of Unruptured Intracranial Aneurysms Investigators: Unruptured intracranial aneurysms—risk of rupture and risks of surgical intervention. **N Engl J Med 339:**1725–1733, 1998
16. Kashiwazaki D, Kuroda S: Size ratio can highly predict rupture risk in intracranial small (<5 mm) aneurysms. **Stroke 44:**2169–2173, 2013
17. Kassell NF, Torner JC: Size of intracranial aneurysms. **Neurosurgery 12:**291–297, 1983
18. Korja M, Lehto H, Juvela S: Lifelong rupture risk of intracranial aneurysms depends on risk factors: a prospective Finnish cohort study. **Stroke 45:**1958–1963, 2014
19. Korja M, Silventoinen K, Laatikainen T, Jousilahti P, Salomaa V, Hernesniemi J, et al: Risk factors and their combined effects on the incidence rate of subarachnoid hemorrhage—a population-based cohort study. **PLoS One 8:**e73760, 2013
20. Kwak R, Niizuma H, Hatanaka M, Suzuki J: Anterior communicating artery aneurysms with associated anomalies. **J Neurosurg 52:**162–164, 1980
21. Lee EJ, Lee HJ, Hyun MK, Choi JE, Kim JH, Lee NR, et al: Rupture rate for patients with untreated unruptured intracranial aneurysms in South Korea during 2006–2009. **J Neurosurg 117:**53–59, 2012
22. Lee GJ, Eom KS, Lee C, Kim DW, Kang SD: Rupture of very small intracranial aneurysms: incidence and clinical characteristics. **J Cerebrovasc Endovasc Neurosurg 17:**217–222, 2015
23. Malhotra A, Wu X, Forman HP, Grossetta Nardini HK, Matouk CC, Gandhi D, et al: Growth and rupture risk of small unruptured intracranial aneurysms: a systematic review. **Ann Intern Med 167:**26–33, 2017
24. Malhotra A, Wu X, Forman HP, Matouk CC, Gandhi D, Sanelli P: Management of tiny unruptured intracranial aneurysms: a comparative effectiveness analysis. **JAMA Neurol 75:**27–34, 2018
25. Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, et al: International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. **Lancet 360:**1267–1274, 2002
26. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, et al: International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. **Lancet 366:**809–817, 2005
27. Morita A, Kirino T, Hashi K, Aoki N, Fukuhara S, Hashimoto N, et al: The natural course of unruptured cerebral aneurysms in a Japanese cohort. **N Engl J Med 366:**2474–2482, 2012
28. Murayama Y, Takao H, Ishibashi T, Saguchi T, Ebara M, Yuki I, et al: Risk analysis of unruptured intracranial aneurysms: prospective 10-year cohort study. **Stroke 47:**365–371, 2016
29. Nakagawa T, Hashi K: The incidence and treatment of asymptomatic, unruptured cerebral aneurysms. **J Neurosurg 80:**217–223, 1994
30. Otawara Y, Ogasawara K, Kubo Y, Tomitsuka N, Watanabe M, Ogawa A, et al: Anxiety before and after surgical repair in patients with asymptomatic unruptured intracranial aneurysm. **Surg Neurol 62:**28–31, 2004
31. Rinkel GJ, Djibuti M, Algra A, van Gijn J: Prevalence and risk of rupture of intracranial aneurysms: a systematic review. **Stroke 29:**251–256, 1998
32. Ronkainen A, Hernesniemi J, Puranen M, Niemitukia L, Vanninen R, Ryynänen M, et al: Familial intracranial aneurysms. **Lancet 349:**380–384, 1997
33. Sato K, Yoshimoto Y: Risk profile of intracranial aneurysms: rupture rate is not constant after formation. **Stroke 42:**3376–3381, 2011
34. Sonobe M, Yamazaki T, Yonekura M, Kikuchi H: Small unruptured intracranial aneurysm verification study: SUAVe study, Japan. **Stroke 41:**1969–1977, 2010
35. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G: European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. **Cerebrovasc Dis 35:**93–112, 2013
36. Thompson BG, Brown RD Jr, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly ES Jr, et al: Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. **Stroke 46:**2368–2400, 2015
37. Tominari S, Morita A, Ishibashi T, Yamazaki T, Takao H, Murayama Y, et al: Prediction model for 3-year rupture risk of unruptured cerebral aneurysms in Japanese patients. **Ann Neurol 77:**1050–1059, 2015
38. Vlak MH, Rinkel GJ, Greebe P, van der Bom JG, Algra A: Trigger factors and their attributable risk for rupture of intracranial aneurysms: a case-crossover study. **Stroke 42:**1878–1882, 2011
39. Wiebers DO, Whisnant JP, Huston J III, Meissner I, Brown RD Jr, Piepgras DG, et al: Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. **Lancet 362:**103–110, 2003
40. Wiebers DO, Whisnant JP, Sundt TM Jr, O'Fallon WM: The significance of unruptured intracranial saccular aneurysms. **J Neurosurg 66:**23–29, 1987
41. Yoshimura Y, Murakami Y, Saitoh M, Yokoi T, Aoki T, Miura K, et al: Statin use and risk of cerebral aneurysm rupture: a hospital-based case-control study in Japan. **J Stroke Cerebrovasc Dis 23:**343–348, 2014
42. Zhao L, Zhang L, Zhang X, Li Z, Tian L, Wang YX: An analysis of 1256 cases of sporadic ruptured cerebral aneurysm in a single Chinese institution. **PLoS One 9:**e85668, 2014

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Ikawa, Morita. Acquisition of data: Ikawa, Morita, Shiokawa, Date, Nozaki, Miyamoto. Analysis and interpretation of data: Ikawa, Tominari. Drafting the article: Ikawa, Morita, Tominari. Critically revising the article: Ikawa, Shiokawa, Nozaki, Miyamoto. Reviewed submitted version of manuscript: Ikawa, Morita, Date. Approved the final version of the manuscript on behalf of all authors: Ikawa. Statistical analysis: Tominari, Nakayama. Administrative/technical/material support: Tominari, Nozaki. Study supervision: Morita, Nakayama, Shiokawa, Date, Miyamoto, Kayama, Arai.

Correspondence

Fusao Ikawa: Hiroshima University, Hiroshima, Japan. fikawa-nsu@umin.ac.jp.