

Intracranial Aneurysm Parameters for Predicting a Future Subarachnoid Hemorrhage: A Long-Term Follow-up Study

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BACKGROUND: Retrospective studies have suggested that aneurysm morphology is a risk factor for subarachnoid hemorrhage (SAH).

OBJECTIVE: To investigate whether various morphological indices of unruptured intracranial aneurysms (UIAs) predict a future rupture.

METHODS: A total of 142 patients with UIAs diagnosed between 1956 and 1978 were followed prospectively until SAH, death, or the last contact. Morphological UIA indices from standard angiographic projections were measured at baseline and adjusted in multivariable Cox proportional hazards regression analyses for established risk factors for SAH.

RESULTS: During a follow-up of 3064 person-years, 34 patients suffered from an aneurysm rupture. In multivariable analyses, aneurysm volume, volume-to-ostium area ratio, and the bottleneck factor separately as continuous variables predicted aneurysm rupture. All the morphological indices were higher ($P < .01$) after the rupture than before. In final multivariable analyses, current smoking (adjusted hazard ratio 2.50, 95% CI 1.03-6.10, $P = .044$), location in the anterior communicating artery (4.28, 1.38-13.28, $P = .012$), age (inversely; 0.95 per year, 0.91-1.00, $P = .043$), and UIA diameter ≥ 7 mm at baseline (2.68, 1.16-6.21, $P = .021$) were independent risk factors for a future rupture. Aneurysm growth during the follow-up was associated with smoking ($P < .05$) and SAH ($P < .001$), but not with the aneurysm indices.

CONCLUSION: Of the morphological indices, UIA volume seems to predict a future rupture. However, as volume correlates with the maximum diameter of the aneurysm, it seems to add little to the predictive value of the maximum diameter. Retrospective studies using indices that are measured after rupture are of little value in risk prediction.

KEY WORDS: Cigarette smoking, Intracranial aneurysm, Morphology, Natural history, Risk factors, Subarachnoid hemorrhage

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Subarachnoid hemorrhage (SAH) is a deadly disease with high case fatality (about 40%).^{1,2} This is one of the reasons why unruptured intracranial aneurysms (UIAs) are often treated when found.²⁻⁴ Because of the increasing use of magnetic resonance imaging (MRI), MR angiography, and 3-dimensional CT angiography (CTA) for examining symptoms unrelated to UIAs (chronic headache, dizziness, nausea, visual disorders, etc.), asymptomatic UIAs are being detected more and more

frequently.²⁻⁴ As numbers of neuroimaging examinations are likely to increase in the future, numbers of diagnosed UIAs will probably also increase.

According to a recent review,⁵ the prevalence of UIAs in adult populations is approximately 3%, and 93% of these are < 10 mm in size and 66% are < 5 mm. According to the largest and most comprehensive follow-up studies of UIAs,⁶⁻⁹ the risk factors for a rupture are reported to be a maximum UIA size of ≥ 7 mm, location in the anterior communicating, posterior communicating, or vertebrobasilar artery, smoking, age, a history of hypertension, and female sex. In addition to the size of the

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UIA, retrospective studies have identified several morphological parameters as potential predictors of a rupture: volume of the aneurysm,¹⁰ aspect ratio,¹¹⁻¹⁵ the bottleneck factor,¹³ height–width ratio,¹³ and volume-to-ostium area ratio (VOR).¹⁵ The results have been conflicting, however. In all these studies the indices were measured after the rupture of the aneurysm, questioning the reliability and predictive value of the measures. Prospective follow-up studies are therefore needed to estimate the true predictive value of UIA indices. Until very recently, only 2 prospective studies had been done.¹⁶⁻¹⁷ In these multicenter studies with a treatment selection bias (exclusion of aneurysms with a higher rupture risk) and with a short-term follow-up (mean 2 yr), there were only 0¹⁷ and 3¹⁶ aneurysm ruptures. Therefore, morphology parameters for rupture could not be analyzed. In the first study,¹⁶ bottleneck factor (dome/neck ratio), however, predicted aneurysm growth.

As it is nowadays difficult, or even impossible, to conduct an unselected prospective study of UIA indices as risk factors for a future SAH, we made use of our long-term cohort of patients with UIAs, which were not operated on in our country prior to 1979. This prospective follow-up study investigates the significance of UIA indices in predicting a future SAH.

METHODS

Patient Population

The cohort included 142 patients with 182 UIAs diagnosed between 1956 and 1978 at our institution, which was at that time responsible for neurosurgical services for near the whole population of our country. All the patients gave their written informed consent. Approval for the surveys and follow-up data collection was obtained from the local ethics committee and all aspects of the study were in compliance with national legislation and the Declaration of Helsinki.

Classification of Unruptured Aneurysms

Most patients ($n = 131$) had multiple aneurysms, but only the ruptured one was treated surgically. Verification of the ruptured aneurysm was based on intraoperative surgical observations and the results of the treatment were confirmed by postoperative angiography. Additional evidence supporting the identification of the rupture site was based on the following findings: the greater size of the ruptured aneurysm in 10 patients, aneurysm size, and the presence of a secondary sac in 69 patients, intracerebral hematoma at the site of the ruptured aneurysm in 38 patients, and oculomotor palsy associated with a ruptured internal carotid artery aneurysm in 14 patients. Patients with SAH and 2 or more aneurysms of equal size but without any other evidence of aneurysm rupture were treated conservatively at that time and were excluded from this study. The remaining 11 patients had either incidental ($n = 5$; chronic headache, nausea, dizziness, visual disorders) or symptomatic ($n = 6$; cranial nerve deficits or cerebral infarction) UIAs (confirmed by a lumbar puncture).

Follow-up Methods

The detailed follow-up protocols have been reported previously.^{8-10,18-22} The follow-up evaluations were based on postal questionnaires and telephone interviews obtained from patients or proxies every 10 yr from the 1960s onwards. During the previous

follow-up evaluations,^{8,10,18,19} the patients had been interviewed using a structured questionnaire focused on patient characteristics, previous diseases, hospital visits, medication, and health behavior. Patients who were alive between 1996 and 1998 were also interviewed at the outpatient clinic and a follow-up CTA was performed. The last questionnaires, based on telephone interviews, were filled in between 2011 and 2012.

Additional information on all the patients was obtained from medical records supplied by other hospitals and general practitioners, and the accuracy of the data collected with regard to diseases, medication, health behavior, and blood pressure (BP) levels was verified. Autopsy reports and official death certificates from the Causes of Death Register (Statistics Finland, Helsinki, Finland) were examined for all deceased patients. The follow-up was complete.

Risk Factors

BP values before the baseline data collection were acquired from other hospitals and general practitioners, and further measurements were obtained during the follow-up visits. “Acute phase” BP values obtained within 3 mo of SAH were excluded. In patients with multiple BP measurements, the values in the first and last quarter of the follow-up period were averaged. Hypertension was defined as a systolic pressure repeatedly > 140 mm Hg or a diastolic pressure > 90 mm Hg.

Alcohol consumption was recorded in approximate grams of absolute ethanol consumed within 1 wk (1 standard drink = 12 g of alcohol) throughout the follow-up period. Cigarette smoking was categorized as follows: never a smoker, formerly a regular smoker (quit before or during the follow-up), or a current smoker at the last follow-up. A family history of SAH was defined as ≥ 2 first-degree relatives with verified ruptured aneurysms.

Aneurysm Indices

Aneurysm volume,¹⁰ aspect ratio,¹¹⁻¹⁶ the bottleneck factor,^{13,16} height–width ratio,¹³ and VOR¹⁵ were calculated using standard projections of 2-dimensional conventional angiograms. The maximum (D), transverse (d), and height (h) diameters together with the neck width (n) were measured from each angiographic image of a UIA and used to calculate the aneurysm indices as follows: (1) aneurysm volume ($\pi \times D \times d^2/6$); (2) aspect ratio maximum (D/n); (3) aspect ratio (h/n); (4) the bottleneck factor (d/n); (5) height–width ratio (h/d); and (6) VOR ($4D \times d^2/6n^2$).

Statistical Analysis

Data were analyzed with IBM SPSS Statistics, version 23.0, for Windows (IBM Corp., Armonk, NY, USA). Categorical variables were compared using Fisher’s exact 2-tailed test, while continuous variables were compared between groups by means of the Mann–Whitney U -test or Student’s t -test. Changes in aneurysm indices before and after rupture were compared using the Wilcoxon Signed Rank test. Univariable associations between parameters were tested using the Spearman rank correlation coefficients (r_s).

For the life-table analysis and Cox proportional hazards regression model, each patient was followed up until SAH, death from a cause other than SAH, treatment of UIA (3 cases after follow-up lasting from 24.4 to 25.9 yr), or the final follow-up in 2011 or 2012. A Cox proportional hazards regression with a forward stepwise procedure (entry into the model if $P < .1$) and Wald statistics were employed to estimate hazard ratios (HRs) and 95% confidence intervals (CI). The test of significance was based on changes in the log (partial) likelihood. The

variables known at the beginning of the follow-up included age, sex, morphological indices, and location of the largest UIA (that also was the ruptured one in all cases with multiple UIAs except for 1 patient where the second largest one later ruptured and was included in the analysis), presence of multiple UIAs, smoking status, alcohol consumption, a family history of ruptured intracranial aneurysms, a history of hypertension, and BP values. Interactions between significant predictors of a future rupture were analyzed in order to evaluate their possible deviation from the simple additive risk factor effects. In circumstances where morphological indices correlated closely with each other, the statistical models were adjusted for each parameter and for known SAH risk factors such as smoking, sex, age, and systolic BP. The proportionality assumption was confirmed. A *P*-value less than .05 was considered statistically significant.

RESULTS

Patient Characteristics and Follow-up Time

The baseline characteristics and aneurysm rupture status of the patients are shown in Table 1. Age (inversely), cigarette smoking, and alcohol consumption associated with a future UIA rupture. All the morphological parameters were higher ($P < .01$) after the rupture than before (measured for 2 groups: 131 aneurysms with a prior SAH, and 21 index UIAs after rupture). A correlation matrix for the continuous variables is shown in Table 2. Most of the UIA indices correlated with each other (eg, maximum diameter and volume, $r_s = 0.958$, $P < .01$).

The median follow-up time per patient was 21.0 yr (mean 21.6, range 0.8-52.3 yr), and 34 (24%) of the 142 patients suffered from an SAH during the follow-up of 3064 person-years (annual incidence of SAH, 1.1%; Figure). The cumulative rate of SAH at 30 yr of follow-up was 30.1% (95% CI, 21.3-38.9). The median time between diagnosis and a subsequent aneurysm rupture was 10.6 yr (mean 11.9, range 1.2-24.2 yr), and the median duration of follow-up in patients without an aneurysm rupture was 24.4 yr (mean 24.6, range 0.8-52.3 yr).

If UIAs were used as observation units instead of patients (aneurysm-based calculation), incidence rates were understandably lower since none of the additional UIAs ruptured in the same patient (see Table 1, Supplemental Digital Content).

Risk Factors for Future Aneurysm Rupture

Univariable HRs for the risk factors for aneurysm rupture are shown in Table 3. Current smoking, alcohol consumption, volume, aspect ratio maximum, the bottleneck factor, and VOR were all significant risk factors for the future aneurysm rupture, whereas the maximum diameter as a continuous variable did not achieve significance ($P = .081$; Table 3).

In multivariable analysis, the independent predictors for aneurysm rupture were current smoking (adjusted HR 3.15, 95% CI 1.31-7.56, $P = .010$), location in the anterior communicating artery (ACOA; 3.50, 1.20-10.23, $P = .022$), and aneurysm volume (1.06, 1.03-1.09 per 100 mm³, $P < .001$). Since the UIA indices were closely intercorrelated, each index was also tested

separately. Apart from UIA volume, only the bottleneck factor and VOR as continuous variables were risk factors for SAH. The adjusted Cox regression models, including smoking, ACOA location, sex, age, systolic BP and all the aneurysm indices at baseline, are shown in Table 4.

Since most of the ruptured aneurysms ($n = 34$) were small at baseline (maximum diameter, median 4 mm; range 2-26 mm; less than 7 mm in 24 cases; median volume 18 mm³), the UIA indices were poor predictors for a future rupture when treated as categorical variables (analyzed in quartiles). In fact, only a UIA volume of 63 mm³ or more (the highest quartile) was an independent risk factor for SAH with a comparable significance of maximum diameter of ≥ 7 mm obtained in large cohort studies (Table 5).⁶⁻⁹ We did also an aneurysm-based analysis and the risk factors were essentially the same (see Table 2, Supplemental Digital Content).

Risk Factors for UIA Growth

Eighty-seven patients had an angiographic imaging examination, either at the time of rupture during the follow-up ($n = 27$; all of whom had maximum diameter measurements, although only 21 had indices available because of missing data in 6 cases) or else at a follow-up visit ($n = 60$), and these images were used to assess any growth in the UIA (Figure). The mean follow-up time for these 87 patients was 19.2 yr, and the maximum diameter of the UIA had increased by ≥ 1 mm in 40 cases (46.0%) and by ≥ 3 mm in 31 cases (36%), implying a mean growth of 2.48 ± 3.74 (SD) mm (median 0, range 0-17 mm, interquartile range 0-4 mm). The estimated annual growth rate was 0.31 ± 0.86 mm. The maximum diameter of the ruptured aneurysms ($n = 27$) had grown by ≥ 1 mm in all 27 patients and by ≥ 3 mm in 23 (74%) patients (mean growth 6.11 ± 4.20 mm, median 5 mm, range 1-17 mm, annual rate 0.92 ± 1.36 mm/yr), which was more ($P < .001$) than in the aneurysms that did not rupture, ($n = 60$), which had grown by ≥ 1 mm in 13 cases (22%) and by ≥ 3 mm in 8 (13%) cases (mean 0.85 ± 1.96 mm, median 0, range 0-9 mm, annual rate 0.04 ± 0.09 mm/yr). Since angiographic follow-up terminated at aneurysm rupture, the follow-up for the 27 patients in that group was shorter ($P < .001$) than for the 60 patients without a rupture (mean 12.0 ± 6.9 vs 22.4 ± 9.3 yr). Only 2 of the 27 patients with an aneurysm rupture (2 nonsmoking women) had had a control angiography before the rupture. The first of these had bilateral middle cerebral artery aneurysms of 4 mm in diameter, which grew by 1 and 5 mm, respectively, during the follow-up of 8.0 yr, leading to a fatal SAH 4.7 yr later, in 1974. The second patient had an ACOA aneurysm of 4 mm which did not grow at all during a follow-up time of 21.3 yr but grew thereafter by 2 mm and ruptured after a total follow-up of 23.7 yr, in 2000.

Current smokers at the end of the follow-up ($n = 34$) had ($P < .05$) higher UIA growth rates during the follow-up than those who had never smoked or the ex-smokers ($n = 47$; 3.44 ± 4.73 vs 1.57 ± 2.72 mm, 0.52 ± 1.27 vs 0.14 ± 0.35 mm/yr). An increase

TABLE 1. Baseline Characteristics of Patients Stratified by Aneurysm Rupture Status

Characteristic	Patients with prior subarachnoid hemorrhage (131 patients)	Patients with UIAs at the beginning of follow-up		Patients with later UIA rupture and aneurysm measurement after rupture (21 patients)	All UIA patients (142 patients)
		Aneurysm rupture (34 patients)	No aneurysm rupture (108 patients)		
Women (%)	68 (52)	23 (68)	53 (49)	13 (62)	76 (54)
Age (mean ± SD, years)	41.4 ± 9.9	38.5 ± 9.4*	42.8 ± 10.1	34.5 ± 7.1	41.8 ± 10.1
Body mass index (mean ± SD, kg/m ²)	25.7 ± 3.8	27.2 ± 3.9	25.6 ± 3.8	27.3 ± 3.4	25.9 ± 3.9
Blood pressure (mean ± SD, mm Hg)	140 ± 19/85 ± 10	137 ± 19/83 ± 10	140 ± 18/86 ± 9	132 ± 16/80 ± 9	140 ± 19/85 ± 10
History of hypertension (%)	48 (37)	14 (41)	37 (34)	6 (29)	51 (36)
Smoking status, n = 123 (%)					
Nonsmoker	32/115 (28)	8/28 (29)	29/95 (31)	7/19 (37)	37/123 (30)
Quit before follow-up	14/115 (12)	0	15/95 (16)	0	15/123 (12)
Quit during follow-up	11/115 (10)	0	13/95 (14)	0	13/123 (11)
Current smoker	58/115 (50)	20/28 (71)	38/95 (40)	12/19 (63)	58/123 (47)
Alcohol consumption, n = 95					
Median (IQR), g/wk	20 (0-225)	165 (5-400)*	5 (0-150)	65 (4-200)	20 (0-200)
> 300 g/wk (%)	19/89 (21)	5/16 (31)	15/79 (19)	2/14 (14)	20/95 (21)
Family history of ruptured aneurysms (n = 94) (%)	9/88 (10)	3/22 (14)	6/72 (8)	3/15 (20)	9/94 (10)
Diameter of largest aneurysm (mean ± SD, mm)	10.3 ± 4.2 [†]	5.6 ± 4.8	4.9 ± 3.2	10.7 ± 6.7 [†]	5.1 ± 3.7
Volume of largest aneurysm (mm³)					
Mean ± SD	319 ± 492 [†]	319 ± 1347	95 ± 350	1006 ± 3214 [†]	149 ± 726
Median (IQR)	150 (72-320)	18 (6-91)	23 (14-63)	144 (75-374)	20 (8-63)
Aspect ratio max. (mean ± SD)	3.1 ± 1.1 [†]	1.9 ± 1.0	1.6 ± 0.6	2.5 ± 0.9 [†]	1.7 ± 0.8
Aspect ratio (mean ± SD)	3.1 ± 1.1 [†]	1.8 ± 1.0	1.6 ± 0.6	2.5 ± 0.9 [†]	1.7 ± 0.7
Bottleneck factor (mean ± SD)	1.9 ± 0.7 [†]	1.5 ± 0.8	1.3 ± 0.5	1.8 ± 0.8 [†]	1.3 ± 0.6
Height-width ratio (mean ± SD)	1.7 ± 0.5 [†]	1.2 ± 0.4	1.3 ± 0.3	1.5 ± 0.3 [†]	1.3 ± 0.4
Volume-to-ostium area ratio					
Mean ± SD	29.0 ± 31.7 [†]	20.4 ± 68.2	8.4 ± 18.8	41.9 ± 111.5 [†]	11.2 ± 37.2
Median (IQR)	17.8 (11.5-38.1)	3.7 (1.8-13.3)	3.3 (1.9-7.8)	14.1 (7.9-25.1)	3.3 (1.9-8.2)
Location of largest aneurysm (%)					
Internal carotid artery	41 (31)	14 (41)	46 (43)	11 (52)	60 (42)
ACA + A2	4 (3)	1 (3)	5 (5)	1 (5)	6 (4)
Anterior communicating artery	31 (24)	4 (12)	4 (4)	1 (5)	8 (6)
Middle cerebral artery	55 (42)	15 (44)	49 (45)	8 (38)	64 (45)
Vertebrobasilar artery	0	0	4 (4)	0	4 (3)
Irregularity or lobulation (%)	97 (74) [†]	3 (9)	19 (18)	8/16 (50) [†]	22 (15)
Multiple unruptured aneurysms (%)	28 (21)	7 (21)	26 (24)	4 (19)	33 (23)

Aneurysm size = largest diameter in mm.

UIA: unruptured intracranial aneurysm.

ACA: anterior cerebral artery, A2 = pericallosal artery.

IQR: interquartile range (range between 25th and 75th percentiles).

*P < .05 for difference in unruptured aneurysms between subsequent aneurysm rupture groups.

[†]P < .01 for difference of aneurysm indices between ruptured (measured after the rupture) and unruptured aneurysms.

TABLE 2. Spearman Rank Correlation Coefficients for Age, Blood Pressure and Morphometric Indices of 142 Unruptured Aneurysms at Baseline

Characteristic	Age	Systolic blood pressure	Diastolic blood pressure	Diameter of aneurysm	Volume of aneurysm	Aspect ratio max.	Aspect ratio	Bottleneck factor	Height-width ratio	Volume-to-ostium area ratio
Age	1.0									
Systolic blood pressure (mm Hg)	0.281 [†]	1.0								
Diastolic blood pressure (mm Hg)	0.214*	0.681 [†]	1.0							
Diameter of aneurysm (mm)	0.118	-0.076	-0.020	1.0						
Volume of aneurysm (mm ³)	0.116	-0.084	-0.015	0.958 [†]	1.0					
Aspect ratio max.	0.127	0.008	-0.042	0.770 [†]	0.652 [†]	1.0				
Aspect ratio	0.121	0.012	-0.037	0.746 [†]	0.629 [†]	0.982 [†]	1.0			
Bottleneck factor	0.095	-0.028	-0.041	0.705 [†]	0.786 [†]	0.682 [†]	0.659 [†]	1.0		
Height-width ratio	0.085	0.035	-0.005	0.263 [†]	0.030	0.507 [†]	0.537 [†]	-0.196*	1.0	
Volume-to-ostium area ratio	0.112	-0.066	-0.033	0.920 [†]	0.940 [†]	0.803 [†]	0.788 [†]	0.904 [†]	0.079	1.0
Aneurysm growth (mm)	-0.145	-0.040	-0.144	-0.193	-0.185	-0.126	-0.166	-0.095	-0.107	-0.189
Aneurysm growth (mm/year)	-0.154	0.020	-0.120	-0.185	-0.186	-0.149	-0.189	-0.111	-0.118	-0.211

Correlation coefficients are for the largest unruptured aneurysm (maximum diameter: mean 5.1, median 4, range 2-26 mm) of each patient except for one patient whose second largest aneurysm (2 mm in diameter) later ruptured and was included in the analysis instead of the largest one (4 mm). Of 33 multiple unruptured aneurysm cases, the second largest aneurysm was in 7 patients equal to the largest one.

*P < .05

†P < .01

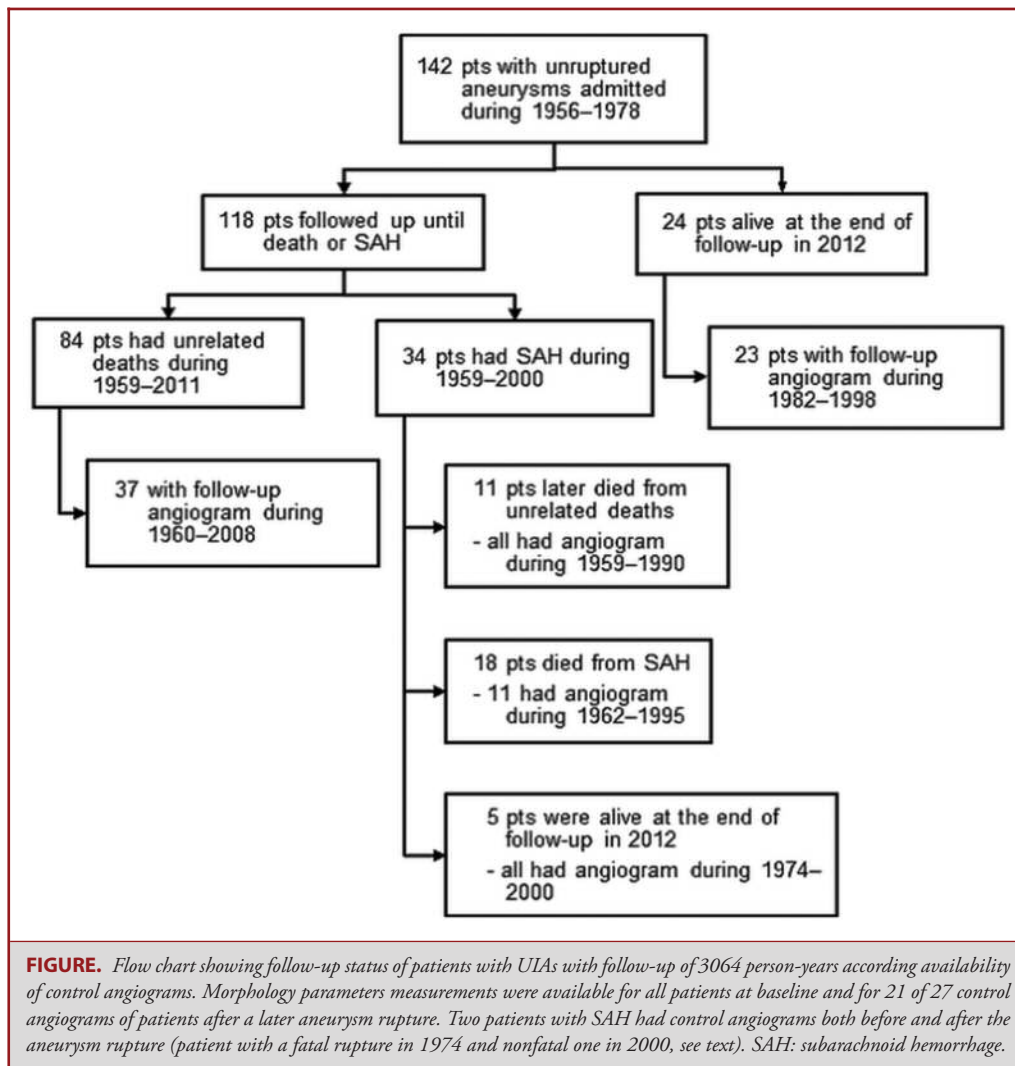
of ≥ 1 mm was observed in 19/34 vs 16/47 patients and an increase of ≥ 3 mm in 15/34 vs 11/47 patients. Aneurysm growth rates did not correlate significantly with the baseline UIA indices or any risk factor other than smoking (Table 2).

DISCUSSION

Our prospective data suggest that baseline measurements of aneurysm volume, the bottleneck factor and VOR as continuous variables, and the maximum aneurysm diameter (≥ 7 mm) as a categorical variable seem to be independent risk factors for a future UIA rupture in a virtually lifelong follow-up. Other independent risk factors for rupture seem to be smoking, age (inversely), and an ACOA location. Aneurysm growth is likely to be associated with a future rupture. Smoking in particular, but not the aneurysm indices at baseline would seem to increase the likelihood of future growth of the aneurysm. Consequently, future morphological studies of UIAs should try to take into account smoking status or preferably cumulative dose of smoking.^{23,24} Smoking, which is the most important modifiable risk factor for SAH,^{19,25,26} is likely to affect UIA formation and growth via hitherto unknown molecular mechanisms. The optimal angiographic follow-up interval for monitoring the growth rate of

UIAs is obscure, as the growth rate and subsequent time of rupture remain unclear. In one of the cohort patients, a small UIA remained stable for over 20 yr but then ruptured.

A maximum UIA diameter of ≥ 7 mm was an independent risk factor for rupture, as has also been suggested in previous prospective studies.^{6-9,18,20} In any case, UIA diameter correlated closely with UIA volume, and a volume of ≥ 63 mm³ (the largest quartile, the median maximum diameter of these UIAs was 8 mm, range 6-25 mm) was also associated with an increased risk of rupture. None of the other indices showed any comparable cutoff values for an increased risk of future rupture, most likely because 70% of the ruptured UIAs were less than 7 mm in diameter at baseline suggesting also that treatment decisions of small UIAs cannot be based on the widely used cutoff value of 7 mm. It is important to recognize that morphological parameters are designed especially for predicting the future rupture of small UIAs, which comprise the vast majority of all UIAs, as larger ones are less troublesome when determining the need for treatment. Unfortunately, without taking into account modifiable risk factors such as cumulative dose of smoking and BP, UIA volume or other morphological parameters do not seem to be optimal predictors for SAH, similar to what have been reported about the maximum baseline diameter of UIAs.^{8,9}



The natural history of UIAs is not well known, especially since the various cohort studies have inevitably incorporated selection and treatment biases. Many have excluded, for example, patients with UIAs which entail a higher lifelong rupture risk, ie young patients, patients with large or growing UIAs, and smokers.^{6,7,20} It is on account of such contradicting results and conclusions that a search has been undertaken for additional risk factors for UIA rupture. Along with the current increased interest in the flow dynamics of UIAs, various morphological parameters have recently been studied as predictors of future SAH,¹¹⁻¹⁵ but these investigations share 1 fundamental and crucial shortcoming: they have measured the predictor indices from already ruptured aneurysms and compared them with those of UIAs. As shown here, the morphological parameters of ruptured aneurysms are significantly higher than those of the same aneurysms prior to rupture. Thus, they represent the morphological features of ruptured aneurysms shortly before, during, or even after rupture,

and it is clear that retrospective results cannot have predictive value with respect to estimating the long-term risk of rupture. This shortcoming may explain some of the conflicting results emerging from retrospective studies.¹¹⁻¹⁵

As in most previous follow-up studies, our study showed that observations and risks should be analyzed per patient, not per aneurysm, since the latter approach may lead to misleading incidence rates. Our and the Unruptured Cerebral Aneurysm Study of Japan (UCAS Japan) data^{7,20} showed also that in multiple UIA cases, additional UIAs did not rupture during remaining follow-up if one UIA had already ruptured (see **Tables 1 and 2, Supplemental Digital Content**).

Limitations

The strengths of this prospective study include the completeness and long duration of the follow-up and the limited treatment selection bias.⁸ On the other hand,

TABLE 3. Univariable Risk Factors for the Rupture

Characteristic	No. of patients	Univariate HR (95% CI)
Female sex	76/142	1.60 (0.78-3.29)
Age (per 10 yr)	142	0.76 (0.54-1.07)
Systolic blood pressure (per 10 mm Hg)	142	0.97 (0.79-1.18)
Current smoking	70/123	2.49 (1.10-5.67)*
Alcohol consumption (per 100 g/wk)	95	1.27 (1.05-1.53)*
Aneurysm in ACOA	8/142	2.53 (0.89-7.18)
Maximum diameter of unruptured aneurysm (per mm)	142	1.08 (0.99-1.18)
Volume of aneurysm (per 100 mm ³)	142	1.04 (1.02-1.07) [†]
Aspect ratio max. (per unit)	142	1.58 (1.03-2.42)*
Aspect ratio (per unit)	142	1.45 (0.92-2.27)
Bottleneck factor (per unit)	142	1.84 (1.12-3.02)*
Height-width ratio (per unit)	142	0.61 (0.21-1.72)
Volume-to-ostium area ratio (per 10 mm)	142	1.09 (1.03-1.15) [†]
Irregularity or lobulation	22/142	0.60 (0.18-1.95)

Hazard ratios (HRs) represent comparisons with patients without a risk factor [male sex, no hypertension, no current smoking, aneurysm location other than the anterior communicating artery (ACOA)].

*P < .05

[†]P < .01

the overall cohort size was modest by comparison with the large multicenter cohorts with short follow-up times.^{6,7} This was due to the historical policy governing aneurysm treatment, according to which only ruptured aneurysms of good-grade patients of working age were treated, leaving us the possibility of following up unruptured UIAs. Despite the small cohort size, however, the number of SAHs was relatively high because of the long duration of the follow-up by comparison with the much larger landmark studies.^{6,7} Furthermore, as a considerable number of patients had been excluded from previous natural history studies (treatment bias based on UIA size, UIA growth, young age, cigarette smoking, etc.) either before (58%)^{6,20} or during (32%, 48%)^{6,7,20} the follow-up, our results may reflect the natural history more reliably.²⁰ Even so, the findings presented here cannot necessarily be generalized, at least not to patients of advanced age. Finnish people have also been considered to be subject to a higher risk of aneurysm rupture.²⁰ In Finland, the incidence of SAH is not higher than elsewhere when the study design with inclusion and exclusion criteria, accuracy of diagnosis, and distribution of sex and age of population (standardization) are taken into account.^{27,28} In fact, the Nordic countries seem to have similar SAH incidences.²⁸ Finally, all our initial UIA measurements were obtained from 2-dimensional conventional angiograms, which may yield less accurate measures than 3-dimensional angiograms. Moreover, we could measure only the most commonly used indices and not 3-dimensional parameters. However, even though this shortcoming creates an

TABLE 4. Multivariable Cox Regression Models for the Aneurysm Indices With Respect to Rupture

	Multivariable HR (95% CI)
Model I	
Maximum diameter of unruptured aneurysm (per mm)	1.11 (0.98-1.25) [†]
Current smoking	2.72 (1.12-6.60)*
Aneurysm in anterior communicating artery	3.82 (1.23-11.83)*
Model II	
Volume of aneurysm (per 100 mm ³)	1.05 (1.02-1.09) [†]
Current smoking	3.12 (1.24-7.85)*
Aneurysm in anterior communicating artery	4.34 (1.42-13.22)*
Model III	
Aspect ratio max. (per unit)	1.49 (0.89-2.51)
Current smoking	2.45 (1.01-5.94)*
Aneurysm in anterior communicating artery	4.01 (1.31-12.21)*
Model IV	
Aspect ratio (per unit)	1.29 (0.74-2.25)
Current smoking	2.52 (1.04-6.09)*
Aneurysm in anterior communicating artery	4.06 (1.33-12.39)*
Model V	
Bottleneck factor (per unit)	1.98 (1.09-3.60)*
Current smoking	2.56 (1.07-6.12)*
Aneurysm in anterior communicating artery	3.41 (1.12-10.42)*
Model VI	
Height-width ratio (per unit)	0.52 (0.17-1.62)
Current smoking	2.69 (1.12-6.42)*
Aneurysm in anterior communicating artery	3.77 (1.23-11.59)*
Model VII	
Volume-to-ostium area ratio (per 10 mm)	1.11 (1.05-1.18) [†]
Current smoking	3.05 (1.22-7.64)*
Aneurysm in anterior communicating artery	4.33 (1.43-13.16)*
Model VIII	
Irregularity or lobulation	0.21 (0.03-1.57)
Current smoking	2.81 (1.15-6.85)*
Aneurysm in anterior communicating artery	4.79 (1.54-14.96) [†]

Abbreviations: CI: confidence interval; HR = hazard ratio.

In the various multivariable models, the HRs for each parameter index were adjusted for current smoking and for the nonsignificant variables sex, age, and systolic blood pressure at baseline.

*P < .05

[†]P < .01

[‡]P = .098

TABLE 5. Multivariable models of risk factors for rupture

	Multivariable HR (95% CI)	
	Model I	Model II
Female sex	1.45 (0.65-3.26)	1.49 (0.67-3.34)
Age (per 10 yr)	0.62 (0.39-0.99)*	0.62 (0.39-0.98)*
Current smoking	2.50 (1.03-6.10)*	2.59 (1.06-6.33)*
Systolic blood pressure (per 10 mm Hg)	1.09 (0.86-1.39)	1.11 (0.88-1.41)
Aneurysm in anterior communicating artery	4.28 (1.38-13.28)*	4.42 (1.43-13.64)*
Maximum diameter of unruptured aneurysm (≥ 7 mm)	2.68 (1.16-6.21)*	
Volume of aneurysm (≥ 63 mm ³)		2.54 (1.08-5.99)*

Abbreviations: CI: confidence interval; HR: hazard ratio.

In the multivariable analyses, the hazard ratios (HRs) were adjusted for the other variables listed in the models.

* $P < .05$

inherent but as yet unknown measurement bias, the distributions of the morphological indices were similar to those obtained in previous studies, supporting the view that our results are in all probability reasonable.¹¹⁻¹⁵

CONCLUSION

The various morphological parameters of UIAs do not seem to offer significant additional benefit when estimating the long-term risk of UIA rupture, especially in comparison with the simple and widely used maximum size of the UIA. Importantly, morphological measurements performed after rupture cannot be used in prediction models. However, given the relatively small cohort size, studied parameters might evolve as modest predictors in larger prospective cohorts. Whether any modest value improves the reliability of predictive models, or adds to clinical decision-making processes, remain unclear. Modifiable risk factors still play an essential role in the estimation of the lifelong risk of UIA rupture, but morphological features may perhaps serve as supportive tools in decision-making processes.

Disclosures

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COMMENT

The authors should be congratulated for further examining and analyzing this cohort that has brought us so much information of importance regarding the risk of future hemorrhage of UIAs. This is the cohort that has been followed most completely for the longest period of time originating from a period in which few UIAs were treated. In the past, this cohort has been questioned with regard to its relevance to populations outside of Finland, because of the high detection rate of aneurysms in Finland, and the identification of a proportion of these cases at the time of another aneurysm that had ruptured. However, the hypothesis for a predilection of the Finnish population for aneurysm development (as discussed by Korja and Kaprio¹), and the increased likelihood of aneurysm to rupture, may both be misplaced.² Furthermore, the difference between those with and without a preceding rupture is minimal or nonexistent.³ Therefore, results of this study are likely to be applicable generally.

Although the small number of cases limits the number of variables that might significantly be associated with rupture to only a few, the importance of finding every variable that might have an impact is of less importance than finding those variables with an impact of greater magnitude (smoking history, ACOA location, and increasing size).

Why this small series is of unparalleled importance is because it is the least affected by biases, such as selection bias, that can never be eliminated from more recent cohort studies. That 25% of their cohort with

size less than 7 mm have been demonstrated to subsequently rupture,⁴ a group predicted to be extremely unlikely to rupture by ISUIA II,² raises the importance of selection bias and the difficulties in adjusting for this from recently studied cohorts. An assumption that is required for survival analyses, and the subsequent calculation of risk of hemorrhage, is that patients censored to treatment will have the same risk of future hemorrhage as those that remain in the study and followed. The discrepancy between ISUIA II's finding and the Helsinki cohort can almost certainly be accounted for by this bias of removing patients for treatment, once treatment became reliably safe, with a perceived greater risk of hemorrhage (such as irregular fundus or fundus size to parent artery ratio), perception widely accepted after the Helsinki cohort was closed to additional cases.

This cohort, bound to the past, is the richer for its failure of contamination with selection bias for treatment. Although somewhat limited by size, the length of follow-up will ensure that this remains an unparalleled source of knowledge. The meticulous mining of information from this cohort with recently generated questions maintains its currency as one of the most important epidemiological studies of all times regarding UIAs.

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SUPPLEMENTAL DIGITAL CONTENT

Table 1. Annual rupture risk of 142 patients with 182 unruptured aneurysms based on person-year and aneurysm-year follow-up.

No of aneurysms per patient	No. of patients / aneurysms	No. of ruptures	Person-years of follow-up	Annual incidence per person-year follow-up (%)	Aneurysm-years of follow-up	Annual incidence per aneurysm-year follow-up (%)
1	109 / 109	27	2407	1.12	2407	1.12
2	27 / 54	6	542	1.11	1123	0.53
3	5 / 15	1	99	1.01	296	0.34
4	1 / 4	0	17	0	67	0
Total	142 / 182	34	3064	1.11	3893	0.87

During the follow-up, none of the patients had a rupture from more than one aneurysm. Of 7 patients with multiple unruptured aneurysms and an aneurysm rupture during the follow-up, 5 have a fatal SAH. Of the 27 patients with a single unruptured aneurysm, the rupture caused death in 12 patients.

Using person-years in follow-up, the number of unruptured aneurysms or multiplicity was not associated with the rupture risk. When using aneurysm-years instead, the number of aneurysms decreased the risk of rupture [log rank test, $p=0.029$; Cox proportional hazards regression model, hazard ratio (HR) 0.48, 95% confidence interval (CI) 0.24-0.95 per no. of aneurysms, $p=0.034$] as did also multiplicity (log rank test, $p=0.029$; HR 0.41, 95% CI 0.18-0.94, $p=0.034$). This was because after aneurysm rupture in multiple unruptured aneurysms cases no additional aneurysms ruptured during remaining life time.

Of 142 patients, 34 had an aneurysm rupture during 3064 person years yielding an approximate annual rupture risk of 1.11% per person-year (see above).¹ In the Unruptured Cerebral Aneurysm Study of Japan (UCAS Japan), 5720 patients with 6697 unruptured aneurysms were followed up for 11660 aneurysm-years (aneurysm-based analysis) and 111 aneurysms ruptured yielding an annual rupture rate of 0.95% per aneurysm-year.²

Both the Finnish study and UCAS Japan were included in a meta-analysis called the PHASES score study where follow-up was based on person-years (Supplementary webappendix).³ In the UCAS Japan, 5720 patients with 6697 aneurysms were followed up a total of 9596 person-years. Again 111 patients had an aneurysm rupture and the annual rupture rate was 1.16%. This meant that only one aneurysm per patient could have ruptured and none of the 793 additional aneurysms in patients with multiple aneurysms ruptured during the follow-up of 2064 aneurysm-years. Because these additional aneurysms were smaller with a lower rupture risk, likelihood of rupture is very low during the remaining lifetime.

Table 2. Multivariable models of risk factors for rupture according to method of analysis.

Characteristic at baseline	Multivariable HR (95% CI)		
	Model I	Model II	Model III
Current smoking	2.92 (1.12-7.62)*	3.15 (1.31-7.56)†	2.87 (1.20-6.88)*
Aneurysm in anterior communicating artery	3.36 (1.07-10.52)*	3.50 (1.20-10.23)*	3.86 (1.32-11.26)*
Maximum diameter of unruptured aneurysm (per mm)	1.05 (0.89-1.24)		
Volume of aneurysm (per 100 mm ³)		1.06 (1.03-1.09)†	1.06 (1.03-1.09)†

Model I: patients with a single unruptured aneurysm (n=109)

Model II: all patients (person-years of follow-up; n=142)

Model III: all aneurysms (aneurysm-years of follow-up; n=182)

In the multivariable analyses the hazard ratios (HR) were adjusted for the other variables listed in the models.

* $p < 0.05$, † $p \leq 0.01$

It is important understand that if independent observation units are not patients but aneurysms, patients with 2 or more unruptured aneurysms are counted more than once in risk analyses. A patient with several aneurysms of which only one rupture has simultaneously both response and censored follow-up event status. Such an approach is difficult to interpret due to this illogical statistical presumption.

The only correct method to analyze whether patients with multiple aneurysms have an increased risk for rupture is to follow patients with person-years and use number of aneurysms or aneurysm multiplicity as a covariate which can show whether aneurysms are more prone to rupture in patients with multiple unruptured aneurysms, especially after adjustment for smoking, female sex, and patient age which are also independent risk factors for multiple aneurysms.⁴

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