Stroke

Journal of the American Heart Association

American Heart Association | American Stroke Association

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Stroke. 2013;44:2414-2421; originally published online July 18, 2013;
doi: 10.1161/STROKEAHA.113.001838
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Natural History of Unruptured Intracranial Aneurysms
A Long-term Follow-up Study

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Background and Purpose—Unruptured intracranial aneurysms are increasingly being detected and are a notable healthcare burden. We investigated the long-term natural history of unruptured intracranial aneurysms and risk factors predictive of subsequent rupture.

Methods—A total of 142 patients with 181 unruptured intracranial aneurysms diagnosed between 1956 and 1978, when these were not treated, were followed up until death or subarachnoid hemorrhage, or until 2011 to 2012. Annual and cumulative incidences of aneurysm rupture and risk factors for rupture were studied using Kaplan–Meier survival analysis and Cox proportional hazards regression models.

Results—The median follow-up time was 21.0 (range, 0.8–52.3) years. During 3064 person-years, there were 34 first episodes of aneurysm rupture, giving an average annual incidence of 1.1%. Eighteen patients died on account of an initial or recurrent aneurysm rupture. The cumulative rate of bleeding was 10.5% (95% confidence interval [CI], 5.2–15.8) at 10 years, 23.0% (95% CI, 15.4–30.6) at 20 years, and 30.1% (95% CI, 21.3–38.9) at 30 years. None of the index aneurysms bled after a follow-up of 25 years. Cigarette smoking (adjusted hazard ratio, 2.44; 95% CI, 1.02–5.88), location of the aneurysm in the anterior communicating artery (adjusted hazard ratio, 3.73; 95% CI, 1.23–11.36), patient age inversely (0.96 per year, 95% CI, 0.92–1.00) and aneurysm diameter ≥7 mm (adjusted hazard ratio, 2.60; 95% CI, 1.13–5.98) independently predicted subsequent aneurysm rupture, as did alcohol consumption (1.27 per 100 g/week; 95% CI, 1.05–1.53; $P<0.05$), but only in univariable analysis.

Conclusions—Cigarette smoking, patient age inversely, and the size and location of the unruptured intracranial aneurysm seem to be risk factors for aneurysm rupture. The risk of bleeding decreases with a very long-term follow-up. **(*Stroke*. 2013;44:2414-2421.)**

Key Words: intracranial aneurysm ■ natural history ■ risk factors ■ smoking ■ subarachnoid hemorrhage

Despite improvements in the management of aneurysmal subarachnoid hemorrhage (SAH), overall case fatality is still high (≈40%).[1,2] For this reason, unruptured intracranial aneurysms (UIA) have been operated on since the 1970s even at quite low-risk levels, to eliminate any conceivable aneurysm rupture.[2]

Most unruptured aneurysms (65% to 85%) are small, <5 to 7 mm in diameter,[3–7] and carry quite a low-rupture risk (≤1% per year).[3–5,7,8] Preventive surgical intervention can eliminate the risk of rupture, but there is no agreement on the indications for treatment or on the screening of small aneurysms.[2–4,9]

Although there is evidence for a low risk of rupture of small aneurysms, the number of hospitalizations and the total costs associated with the diagnosis and treatment of UIAs have increased by 75% and 200%, respectively, in the United States during the past decade.[10] These increases have particularly concerned endovascular treatment for UIAs, even though the long-term durability of such treatment and the overall risks attached to this modality for the occlusion of unruptured aneurysms are still open questions.[2,10,11] The increase in treatment rates are attributed to the more frequent overall use of magnetic resonance (MR) angiography or 3-dimensional computed tomograghy (CT) angiography, leading to the discovery of incidental aneurysms (80% to 90% of UIAs), most of which are small.[4,5,7,8]

The long-term natural history of UIAs in unselected populations is poorly known; however, because the mean follow-up period per patient in most studies has been <5 years. Furthermore, a considerable proportion of the aneurysms have been occluded, leading to a situation in which natural history studies are mostly on the basis of patients of advanced age or with severe diseases and small aneurysms, whereas large, risky UIAs in young patients, who are also more likely to be cigarette smokers, have been operated on, and thus, excluded from natural history cohorts more frequently than others.[4,7,12] It is similarly not known whether the risk of UIA rupture lasts only for few months or years after its discovery or whether it remains constant for the rest of the patient's life, as does the variability of the risk in terms of different risk factors during follow-up.

Received April 17, 2013; final revision received May 22, 2013; accepted June 3, 2013.

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Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.113.001838**

Unruptured aneurysms were not operated on in Finland before 1979, but previous results on the risk of rupture in these patients have been published between 1960 and 2000.[3,13–16] This updated cohort study reports follow-up data on patients with an UIA covering almost the whole of their remaining life.

Patients and Methods

Patient Population

The series included 142 patients with UIAs diagnosed between 1956 and 1978 at the Department of Neurosurgery, Helsinki University Central Hospital, which was the only neurosurgical center in Finland until 1967 and remained responsible for neurosurgical services for 88% of the Finnish population between 1967 and 1976 and for 60% between 1976 and 1978. For the detailed baseline characteristics of the 142 patients and the inclusion and exclusion criteria, see our previous reports.[3,16,17]

Classification of Unruptured Aneurysms

The unruptured aneurysms were classified as follows: asymptomatic incidental aneurysms in 5 patients with angiographies performed for chronic headache, nausea, dizziness, or visual disorders; symptomatic aneurysms in 6, associated mostly with cranial nerve deficits, SAH being excluded by means of a lumbar puncture; and UIAs in 131 patients with a prior SAH.[3,16] The latter group included patients with multiple aneurysms in whom the ruptured one was clipped and occlusion was confirmed by postoperative angiography. For identification of the ruptured aneurysm in all patients with multiple aneurysms, see our previous report.[16]

Follow-up Methods

During the previous follow-up all the patients were personally interviewed (Dr Juvela)[3] by means of a structured questionnaire eliciting data on their height and weight, previous diseases and hospital visits, regular drug use, including analgesics, stimulants, and narcotics, and approximate intake of beer, wine and spirits, and current and previous smoking status and family history of intracranial aneurysms. For the recording of blood pressure (BP) values, see our previous reports.[3,16]

Alcohol consumption was recorded at the beginning of the follow-up in grams of absolute ethanol consumed within 1 week (standard drink 12 g of alcohol). Cigarette smoking was categorized as follows: never a smoker, formerly a regular cigarette smoker (quit before or during the follow-up), and current cigarette smoker. A family history of aneurysms was defined as verified ruptured aneurysm cases in first-degree relatives.

Information on all the patients was also obtained from the medical records of other hospitals and general practitioners to provide a double check on their diseases, medications, and BP readings. Data obtained previously from patients, relatives, and family members by means of repeated telephone interviews and postal questionnaires were available from the 1960s onwards.[3,14–16]

New questionnaires were filled in 2011 and 2012 on the basis of telephone interviews either with patients or with relatives of those patients who had died since the previous follow-up.[3] Autopsy reports and official death certificates from the Causes of Death Register (Statistics Finland) were examined for all the deceased patients. The follow-up was complete.

There were 52 patients alive at the end of our previous follow-up who had not suffered from had SAH, after which unruptured aneurysms between 4 and 6 mm in diameter were occluded in 3 patients (1 by clipping and 2 by coiling at other university hospitals) between 1997 and 1999 after follow-ups of 24.4 to 25.9 years. Two of these aneurysms had increased in diameter by 3 and 5 mm, respectively.

Statistical Analysis

The data were analysed with IBM SPSS Statistics for Windows (release 20.0.0). Categorical variables were compared using Fisher exact 2-tailed test, the Pearson χ^2 test, or the test for linear trends, whereas the continuous variables were compared between groups by means of the Mann–Whitney *U*-test or Student *t* test. Univariable associations between continuous variables were tested using Spearman rank correlation coefficients (r_s).

For the life-table analysis and the Cox proportional-hazards regression model, each patient was followed up until SAH, death from a cause other than SAH, occlusion of the aneurysm (3 cases after follow-up times of 24–26 years), or the last contact. The average annual incidence of SAH was calculated by dividing the number of first events of SAH from the index aneurysms by the number of person-years in the follow-up. Cumulative rates of SAH were estimated by the Kaplan–Meier product-limit method, and the curves for the groups were compared using the log-rank test.

Cox proportional-hazards regression with a backward stepwise procedure (removal if $P>0.1$) and Wald statistics was used to determine hazard ratios (HR) and 95% confidence intervals (CI) for several variables in predicting future aneurysm ruptures. These variables, which were known at the beginning of the follow-up, were the following: age, sex, maximum aneurysm diameter, location of the largest unruptured aneurysm in each patient, presence of multiple unruptured aneurysms, type of aneurysm (symptomatic or incidental versus those with prior SAH), cigarette-smoking status and current smoking, alcohol consumption, a family history of intracranial aneurysms, a history of hypertension (systolic BP >140 mm Hg or diastolic BP >90 mm Hg or use of antihypertensive medication), and BP (systolic, diastolic, and mean) values at the beginning of the follow-up. Interactions between significant predictors of rupture were tested to see the extent to which they deviated from the additive effects of the main risk factors. The proportionality assumption was checked. The test of significance was based on changes in the log (partial) likelihood. The hazard ratios of predictors that were significant in the multivariable models were adjusted for age, sex, and hypertension. A 2-tailed P value <0.05 was considered statistically significant.

Results

Patient Characteristics and Aneurysm Rupture

Subsequent aneurysm ruptures in relation to the baseline characteristics of the patient population are shown in Table 1. Cigarette smoking was closely correlated with the alcohol variables (r_s range, 0.413–0.527; $P<0.001$) and inversely correlated with age (r_s, −0.248; $P<0.01$), but not with BP values which also correlated with age (r_s range, 0.214–0.281; $P<0.05$). Forty-seven patients (33%) received antihypertensive therapy at some offstage during the follow-up period. BP readings were repeatedly high (systolic BP >140 mm Hg or diastolic BP >90 mm Hg) in 49 patients (35%) at the beginning of the follow-up and in 72 (51%) at the end.

The patients with an aneurysm rupture were significantly younger at the end of the follow-up than those without a rupture (mean±SD, 50.4±10.8 versus 67.4±13.5 years; $P<0.001$). In addition, those who died of an aneurysm rupture were significantly younger at the time of death than those who died of unrelated causes (53.8±6.8 versus 66.3±13.5 years; $P<0.001$).

Of the 34 patients with SAH, 18 (53%) died of an aneurysm rupture, 15 of them because of the initial bleeding or early rebleeding, and the remaining 3 on account of rebleeding 7, 21, and 243 days after the initial bleeding, respectively. Of the 16 patients who survived SAH, 8 later died of unrelated causes and 3 of unspecified intracranial bleeding. In addition, 84 patients without SAH from unruptured aneurysm had died of unrelated causes and 4 of them because of rupture of a de novo aneurysm.

Table 1. Baseline Characteristics of Patients at the Beginning of Follow-up, Grouped by Later Aneurysm Rupture

Characteristic	Aneurysm Rupture (34 Patients)	No Aneurysm Rupture (108 Patients)	All Patients (142 Patients)
Women (%)	23 (68)	53 (49)	76 (54)
Age, mean±SD, y	38.5±9.4*	42.8±10.1	41.8±10.1
Body mass index, mean±SD, kg/m^2	27.1±3.9	25.6±3.8	25.9±3.9
Blood pressure, mean±SD, mm Hg	137±19/83±10	140±18/86±9	140±19/85±10
History of hypertension (%)	14 (41)	37 (34)	51 (36)
Smoking status, n=123 (%)			
No	8 (29)	29 (31)	37 (30)
Quit before follow-up	0	15 (16)	15 (12)
Quit during follow-up	0	13 (14)	13 (11)
Current	20 (71)	38 (40)	58 (47)
Alcohol consumption, n=95			
Median (range), g/wk	165 (0–450)*	5 (0–1000)	20 (0–1000)
≥300 g/wk, (%)	5/16 (31)	15/79 (19)	20/95 (21)
Family history of aneurysms, n=94 (%)	3 (14)	6 (8)	9 (10)
Diameter of largest aneurysm (mm)			
Mean±SD	5.6±4.8	4.9±3.2	5.1±3.7
2 to 6 (%)	24 (71)	92 (85)	116 (82)
7 to 9 (%)	6 (18)	10 (9)	16 (11)
10 to 26 (%)	4 (12)	6 (6)	10 (7)
Location of largest aneurysm (%)			
Internal carotid artery	14 (41)	46 (43)	60 (42)
Anterior cerebral artery	1 (3)	5 (5)	6 (4)
Anterior communicating artery	4 (12)	4 (4)	8 (6)
Middle cerebral artery	15 (44)	49 (45)	64 (45)
Vertebrobasilar artery	0	4 (4)	4 (3)
Multiple unruptured aneurysms (%)	7 (21)	26 (24)	33 (23)

A history of hypertension was defined as systolic pressure repeatedly >140 mm Hg or diastolic pressure >90 mm Hg, or as the use of antihypertensive medication. Aneurysm size, largest diameter in mm. A family history of aneurysms was defined as verified ruptured aneurysm cases in first-degree relatives.

*P<0.05 for difference between aneurysm rupture groups.

The 20 patients, who were still alive at the end of the follow-up and had no aneurysm rupture or occlusion, had a mean age of 76.6 years (range, 59.8–93.5 years), and mean follow-up time of 39.7 years (range, 33.8–50.3 years). Of the 20 patients, 13 were women (65%), 9 current smokers (45%), 1 heavy alcohol drinker (5%), 6 persons with hypertension (30%), and 16 (80%) who had had aneurysms of <7 mm in diameter at the beginning of the follow-up. Five patients (25%) had remained current smokers throughout the follow-up period.

Incidence of Aneurysm Rupture

The mean follow-up time per patient was 21.6 years (median, 21.0 years; range, 0.8–52.3 years), and 34 of the 142 patients (24%) had a SAH on account of a UIA during the follow-up of 3064 person-years, yielding an approximate annual incidence of 1.1%, with average annual incidences of 2.2%, 0.8%, and 1.1% for the symptomatic, incidental, and prior SAH aneurysm groups, respectively. Seventy-six patients out of the 142 were still alive and had no aneurysm rupture by 1990, although 7 of them had a rupture during the subsequent follow-up of 918 person-years, yielding an annual incidence of SAH during that period of 0.8%. Correspondingly, 40 patients were alive and had no aneurysm rupture by 2000, but only 1 of them had a rupture during the subsequent follow-up of 361 person-years, yielding an annual incidence of 0.3%.

Annual and cumulative aneurysm rupture rates according to the baseline characteristics known at the beginning of the follow-up are shown in Table 2, and Kaplan–Meier curves for given baseline characteristics are shown in Figures 1 and 2. The risk of bleeding from an unruptured aneurysm remained virtually constant during the first 25 years after diagnosis, except for those aged >50 years, whose risk spanned 10 years.

Current cigarette smoking (P=0.024), heavy alcohol consumption (P=0.043), and aneurysm diameter (particularly ≥7 mm; P=0.028) at the beginning of the follow-up were significantly associated with higher cumulative aneurysm rupture rates, as also was age, although in this case

Table 2. Annual and Cumulative Rupture Rates, Grouped by Factors Known at the Beginning of Follow-up

Characteristic	No. of Patients	Annual Rupture Rate, %	Cumulative Rupture Rates, % (95% CI)		
			10 y	20 y	30 y
All patients	142	1.1 (34/3064)	11 (5–16)	23 (15–31)	30 (21–39)
Prior SAH					
No	11	1.4 (3/210)	27 (1–54)	27 (1–54)	27 (1–54)
Yes	131	1.1 (31/2852)	9 (4–14)	23 (15–30)	30 (21–39)
Sex					
Men	66	0.9 (11/1281)	10 (2–18)	17 (7–26)	23 (10–36)
Women	76	1.3 (23/1781)	11 (4–18)	28 (17–38)	35 (23–47)
Age, y					
≤30	25	1.5 (9/583)	12 (0–26)	31 (12–50)	42 (21–64)
31 to 40	40	1.2 (12/961)	10 (1–20)	30 (15–45)	33 (18–48)
41 to 50	46	0.9 (9/1020)	7 (0–15)	15 (4–27)	27 (11–42)
51 to 60	31	0.8 (4/498)	15 (1–28)	15 (1–28)	15 (1–28)
History of hypertension					
No	91	1.0 (20/2105)	7 (2–13)	21 (12–30)	27 (17–38)
Yes	51	1.5 (14/957)	17 (6–27)	27 (14–40)	35 (19–51)
Current cigarette smoking*					
No	53	0.5 (8/1483)	2 (0–6)	14 (4–24)	17 (6–27)
Yes	70	1.4 (20/1402)	14 (5–22)	27 (16–39)	38 (24–51)
Alcohol consumption*					
<300 g/wk	75	0.5 (11/2156)	4 (0–9)	11 (4–18)	16 (7–24)
≥300 g/wk	20	1.8 (5/276)	23 (3–42)	30 (7–52)	30 (7–52)
Diameter of unruptured aneurysm, mm*					
2 to 6	116	0.9 (24/2583)	9 (4–15)	18 (10–25)	26 (17–35)
7 to 9	16	2.0 (6/306)	7 (0–21)	51 (21–80)	51 (21–80)
10 to 26	10	2.3 (4/173)	30 (2–58)	48 (11–84)	48 (11–84)
Aneurysm in anterior communicating artery					
No	134	1.0 (30/2913)	9 (4–14)	22 (14–30)	28 (19–37)
Yes	8	2.7 (4/149)	38 (4–71)	38 (4–71)	58 (18–98)

The annual rupture rate is calculated by dividing number of patients with aneurysm rupture by the person-years of follow-up, shown in parentheses. CI indicates confidence intervals; and SAH, subarachnoid hemorrhage.

*P<0.05, log-rank test (P=0.024 for smoking; P=0.043 for heavy alcohol consumption; linear trend, P=0.024 for aneurysm diameter).

with an inverse relationship and only in those with a prior SAH (linear trend, P=0.030).

Risk Factors for Aneurysm Rupture

Univariable and multivariable HRs for the risk factors known at the beginning of the follow-up are shown in Table 3. Only cigarette smoking, alcohol consumption (per 100 g/week), and maximum aneurysm diameter ≥7 mm (HR, 2.25; 95% CI, 1.07–4.72; P=0.032) were significant predictors in the univariable analysis.

Using backward stepwise Cox regression to search for independent predictors of aneurysm rupture among the variables with complete data sets as shown in Tables 1 and 2, the predictive variables were the occurrence of anterior communicating artery (ACOA) aneurysm (HR, 2.97; 95% CI, 1.01–8.74; P=0.048), patient age (inversely, 0.96 per year; 95% CI, 0.92–0.99; P=0.022), aneurysm diameter (1.10 per mm; 95% CI, 1.00–1.21; P=0.041), and a history of hypertension (almost significantly, 1.92; 95% CI, 0.94–3.89; P=0.072). When the cigarette smoking and alcohol variables were included in the analysis, current cigarette smoking (HR, 2.23; 95% CI, 0.96–5.18; P=0.063) independently predicted aneurysm rupture but the alcohol variables did not.

In an adjusted multivariable model with the complete set of patient data, it was only patient age that independently predicted aneurysm rupture to a significant extent, whereas ACOA aneurysm (P=0.051), aneurysm diameter (P=0.053), and a history of hypertension (P=0.059) were almost significant predictors after adjustment for confounding factors (Table 3; model I). When cigarette smoking was included in the multivariable model, patient age, ACOA aneurysm, and current smoking were independent significant predictors of a subsequent rupture after adjustment for confounding factors (Table 3; model II). Aneurysm diameter, as a continuous variable, did not reach significance (P=0.088), but if it was replaced by a dichotomous variable, those with an aneurysm

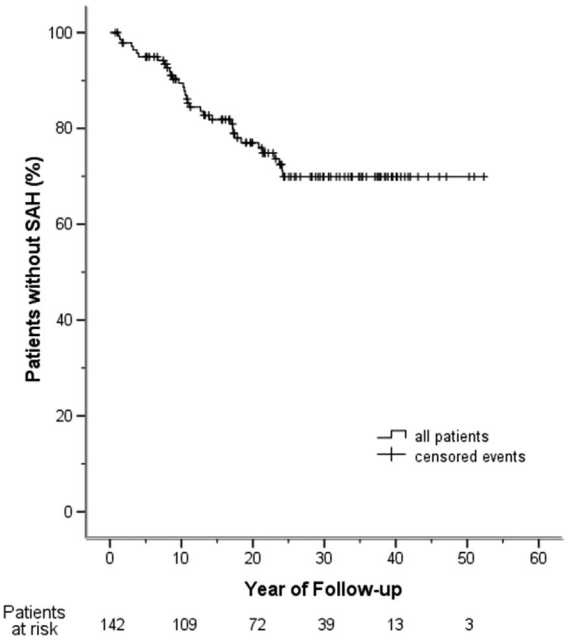

Figure 1. Kaplan–Meier curve showing cumulative rates of aneurysm rupture for all patients. The markers of the curves indicate censored events. SAH indicates subarachnoid hemorrhage.

diameter ≥7 mm had a higher rupture risk than those with smaller aneurysms (adjusted HR 2.60; 95% CI 1.13–5.98; *P*=0.024). Unruptured aneurysms diagnosed in 1970 or before did not have a significantly higher rupture risk attached to them than those with a later diagnosis (adjusted HR 1.90; 95% CI 0.87–4.15), because the annual rupture risk for aneurysms diagnosed in 1970 or before was 1.3% and that for aneurysms diagnosed after 1970 was 0.9% (*P*=0.28). There were no significant interactions between the independent risk factors for aneurysm rupture.

Discussion

Cigarette smoking, the patient's age, and the size and location of the unruptured intracranial aneurysm seem, from the present results, to be independent risk factors for aneurysm rupture, whereas female sex, a history of hypertension, and alcohol consumption may also increase the risk, but verification of these effects would need further testing in a patient population without surgical selection, which would be virtually impossible to perform nowadays. The risk of bleeding seems to decrease in a very long-term follow-up.

The incidence of SAH has shown a moderate decrease in recent decades,[18] but the mean age of the patients has increased by 10 years, although it is still 10 years lower than for other types of stroke.[1,18] Because life expectancy has simultaneously increased considerably, the incidence of SAH should have increased as well, but as this has not been observed anywhere,[2] the decrease in incidence in the younger age groups is probably because of a change in the risk factor profile in general populations. According to our results, the risk of rupture attached to aneurysms diagnosed between 1956 and 1978 decreased slightly but nonsignificantly, an effect that was not because of the patients being of a younger age or to a higher prevalence of risk factors in the earlier phase of this study. This suggests that aneurysms in young adults are more prone to rupture.

Risk of Rupture in Previously Unruptured Aneurysms

Surgical, and later also endovascular, interventions for UIAs have increased in most neurosurgical centers since the 1970s, leading to a considerable selection bias in the patient series used in the natural history studies.[2,10] In recent multicenter studies,[4,7] at least 50% to 60% of the patients had undergone surgical repair of unruptured aneurysms, with those who were younger, were cigarette smokers, or had larger aneurysms having undergone surgery soon after diagnosis more often than the others, leading to the exclusion of patients with high-risk aneurysms from follow-up studies. Furthermore, the significantly increased risk of SAH in patients with aneurysms in the vertebrobasilar or posterior communicating artery compared with aneurysms at other sites may, partly, be explained by the lesser surgical selection of patients with the former aneurysms.[4,7]

Our cohort study covering the rest of the patient's life in the majority of cases (80%), demonstrated an approximate rupture rate for unruptured aneurysms of 1.1% per year, a similar rate to those quoted for earlier prospective studies with short-term follow-up extending up to 5 years after diagnosis (0.8%–1.4% per year).[4,5,7] The risk of aneurysm rupture among patients of working age seemed to remain almost constant for 25 years after diagnosis, except for those aged >50 years, whose risk spanned 10 years. Furthermore, the risk of aneurysm rupture decreased markedly after our last follow-up,[3] when there were only 3 patients with aneurysm ruptures during 489 person-years (3064–2575), yielding an annual incidence of 0.6%. One of these 3 patients had received a diagnosis of UIA at the beginning of the initial cohort study, whereas in the other 2 cases with the aneurysm had been revealed by a CT angiogram taken in the course of the angiographic follow-up study.[17]

Risk Factors for Aneurysm Rupture

Based on our data, the size of the aneurysm, an ACOA location, patient age (inversely), and current cigarette smoking were all independent predictors of subsequent aneurysm rupture without interaction. Hypertension was an almost significant risk factor in a multivariable model without cigarette smoking, and alcohol consumption was significant only in univariable analysis.

Although the incidence of SAH increases with age and is also higher in women after the sixth decade,[18] the risk of aneurysm rupture is not obviously associated with these factors. In fact, it is only in the Small Unruptured Intracranial Aneurysm Verification study[8] and in our assessments that age has been associated independently with aneurysm rupture, and age was inversely related to the risk of aneurysm rupture. The fact that women have a hazard ratio of ≈1.5 may have also increased the risk of aneurysm rupture, which was almost significant in the Unruptured Cerebral Aneurysm Study of Japan (UCAS Japan).[7]

The risk of rupture seems to be associated with the size and location of the aneurysm. As in previous large

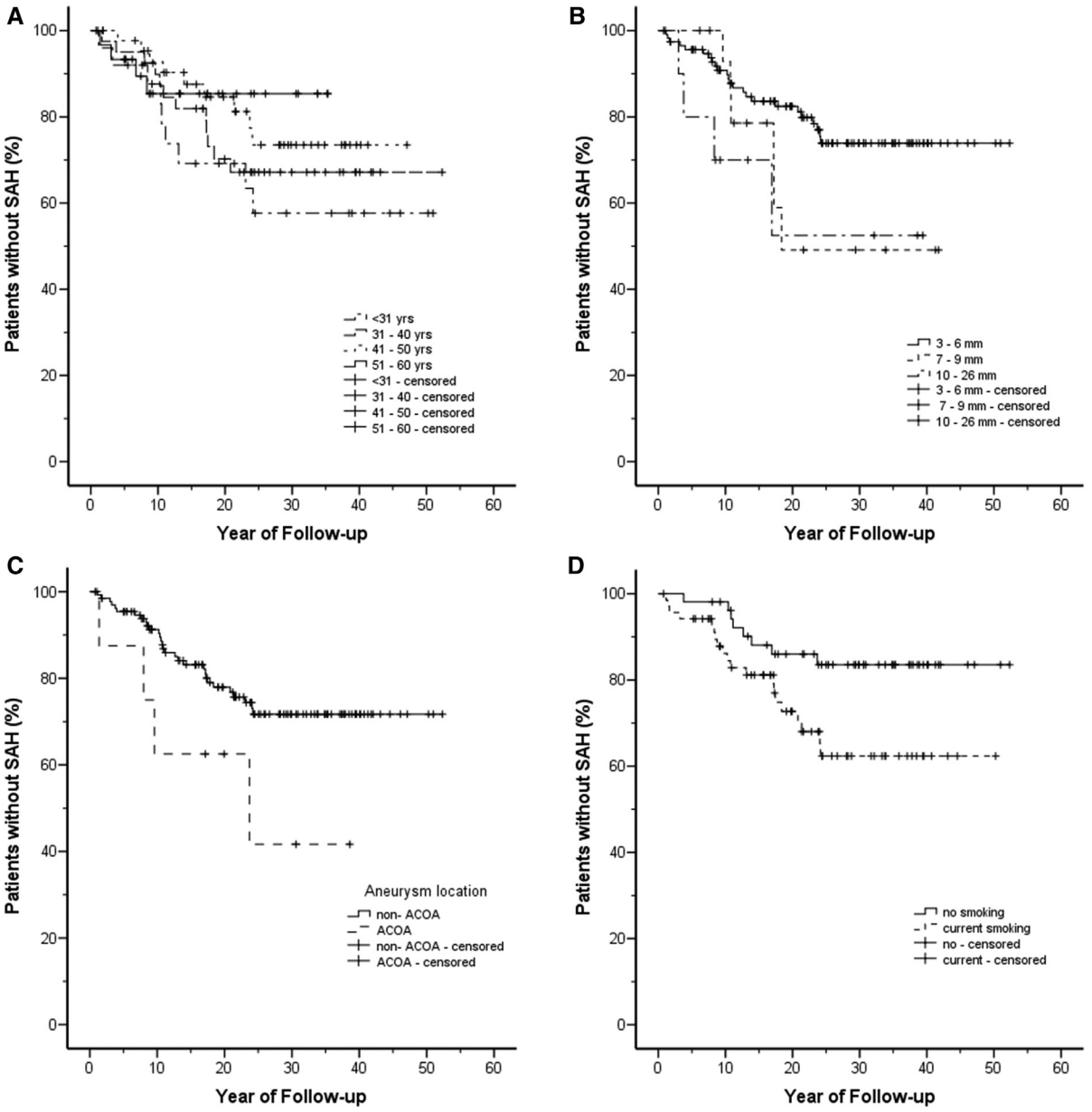

Figure 2. Kaplan–Meier curves showing cumulative rates of aneurysm rupture in relation to background factors: **A**, age groups; **B**, aneurysm diameter (difference between the groups, linear trend, *P*=0.024); **C**, aneurysm location; and **D**, current cigarette smoking (*P*=0.024) at the beginning of follow-up. SAH indicates subarachnoid hemorrhage.

prospective multicenter studies,[4,7] patients with aneurysms larger than ≥7 mm in diameter had a significantly higher rupture risk, and aneurysms located in the anterior[7] or posterior[4,7] communicating artery, or perhaps, in the basilar tip,[4] may also carry an elevated rupture risk. In our study, ACOA location showed a significant association with the risk of rupture, but aneurysm locations in the posterior communicating artery and internal carotid bifurcation did not reach significance, presumably because of the relatively small patient population.

Cigarette smoking has been shown in several studies to be the most important modifiable risk factor for SAH, and 40% of all subarachnoid hemorrhages can be attributed to smoking.[2,19,20] The prevalence of smoking in SAH patients in North America and Europe ranges from 45% to 75%, whereas in the general adult population, it is 20% to 35%. In addition to a high incidence of SAH, lung cancer was also more common in Finland than elsewhere in Scandinavia up to 1992,[21] with a steep decrease in Finnish men from 1980 onwards because of changing smoking habits in the population.[22] The prevalence of cigarette smoking in this series, although high, was similar to that reported previously.[19] Despite the decrease in cigarette smoking in Western countries, the incidence of SAH will not necessarily change, because of improved diagnostic methods and aging of the population. According to our previous cohort of the present patient population,[3] cessation of smoking after diagnosis of UIA is important because continuation of smoking tested as a time-dependent covariate was an even more significant risk factor for aneurysm rupture (adjusted relative risk, 3.04; 95% CI, 1.21–7.66; *P*=0.020) than current

Table 3. Risk Factors for the Rupture of Unruptured Intracranial Aneurysms

Characteristic	No. of Patients	Univariable HR (95% CI)	Multivariable HR (95% CI)	
			Model I	Model II
Sex				
Men	66	1.00	1.00	1.00
Women	76	1.60 (0.78–3.29)	1.63 (0.79–3.36)	1.52 (0.69–3.36)
Age, y				
<31	25	1.00		
31 to 40	40	0.75 (0.32–1.78)		
41 to 50	46	0.52 (0.21–1.30)		
>50	31	0.45 (0.14–1.45)		
Continuous (per y)	142	0.97 (0.94–1.01)	0.96 (0.92–0.99)*	0.96 (0.92–1.00)*
History of hypertension				
No	91	1.00	1.00	1.00
Yes	51	1.50 (0.76–2.97)	1.98 (0.98–4.02)	1.77 (0.81–3.86)
Diameter of unruptured aneurysm, mm				
2 to 6	116	1.00		
7 to 9	16	2.05 (0.83–5.03)		
10 to 26	10	2.64 (0.91–7.64)		
Continuous (per mm)	142	1.08 (0.99–1.18)	1.09 (1.00–1.20)	1.11 (0.99–1.25)
Aneurysm in anterior communicating artery				
No	134	1.00	1.00	1.00
Yes	8	2.53 (0.89–7.18)	2.98 (1.00–8.91)	3.73 (1.23–11.36)*
Current smoking				
No	53	1.00		1.00
Yes	70	2.49 (1.10–5.67)*		2.44 (1.02–5.88)*
Alcohol consumption (per 100 g/wk)	95	1.27 (1.05–1.53)*		

In the multivariable analyses the HR were adjusted for the other variables listed in the table and for prior subarachnoid hemorrhage. CI indicates confidence intervals; and HR, hazard ratios.

*P<0.05.

smoking tested as a fixed covariate obtained at the beginning of follow-up.

Previous natural history studies have either failed to report the prevalence of current cigarette smoking[5] or else it has been somewhat lower than in SAH studies[4] or unexpectedly low.[7,8] Furthermore, those who were cigarette smokers had more often undergone surgery soon after diagnosis than those who were not, leading to the exclusion of many smokers, and perhaps heavy smokers, from follow-up studies.[4,7] Two studies have shown cigarette smoking to increase the risk of aneurysm formation[17] and aneurysm growth,[8,17] the latter also being associated with an increased risk of rupture.[17] A transient increase in BP may also contribute to the rupture of an aneurysm, because smoking a cigarette causes an acute increase in BP for 3 hours.[3,20] Transiently elevated BP levels during alcohol intake and withdrawal may also be an important mechanism for the rupturing of an existing aneurysm, because alcohol consumption has not been shown to cause either aneurysm formation or growth.[17,20,23]

A history of hypertension has not been shown to be associated with the risk of aneurysm rupture, but the definition of hypertension has almost always been inadequate.[12] A history of hypertension when defined as repeated systolic BP measurements >140 mm Hg or diastolic pressure >90 mm Hg, or as the use of antihypertensive medication, has been shown to be an independent risk factor for aneurysm rupture in the Small Unruptured Intracranial Aneurysm Verification study.[8] In our present data, a history of similarly defined hypertension emerges as an almost significant independent risk factor (P=0.059), whereas in our previous assessment,[3] hypertension with a higher BP threshold (160/95) did not increase the risk of aneurysm rupture. Furthermore, BP values correlated significantly with patient age. This may suggest that the even more prevalent borderline hypertension may be a significant risk factor, but these patients are usually younger and also more likely to be cigarette smokers than those with higher blood pressure values.

Patients with either a prior history of SAH or multiple UIAs have not been shown to have a risk higher of aneurysm rupture than others when confounding factors are taken into account.[3,4,7] Only 2 prospective Japanese studies have suggested that either prior SAH[5] or aneurysm multiplicity[8] may increase the risk of SAH.

Strengths and Limitations of This Study

The subjects in this cohort were followed up almost for the rest of their lives, with only a few selective surgical cases emerged after a long period of follow-up (>24 years), and although the long-term follow-up of cases with UIAs was complete, the number of patients was modest compared with that in the International Study of Unruptured Intracranial Aneurysms and UCAS Japan studies. However, the patient populations of the latter studies were highly selected in terms of several predictive factors. Our patients were younger than in the other studies and mostly had multiple aneurysms, with the ruptured aneurysm clipped at the start of the follow-up. However, the presence of multiple aneurysms has rarely been shown to entail a risk of aneurysm rupture. Our results cannot necessarily be generalized to patients of advanced age, in whom usually small aneurysms (<7 mm in diameter) are not considered to be an obvious target for surgical treatment.

Surgery for Unruptured Aneurysms

Our results suggest that unruptured aneurysms should be operated on irrespective of size, at least in patients aged <50 years, provided there are no contraindications for treatment. According to the results of our study and previous ones,[3,4,9,16] the indications for treatment in the case of small aneurysms (<7 mm in diameter) among older patients may be questionable because of the increased risks attached to the treatment with advanced age and the gradually decreasing risk of aneurysm rupture during past few decades. This latter effect may be because of the decreasing prevalence of smoking and the improved treatment available for hypertension. Treatment of small aneurysms in older patients may, nevertheless, be indicated if there are other risk factors. Preventive surgery for UIA should be done by experienced neurosurgeons to achieve the most cost-effective results.[2]

Conclusions

We conclude that UIAs should be operated on irrespective of size in the case of patients aged <50 years if it is technically possible and the surgical risk is not compounded by concurrent diseases. Although cigarette smoking seems to increase the risk of rupture of the aneurysm, it should not mean the rejection of aneurysm surgery, considering the devastating nature of SAH as compared with success rates in modern surgery for unruptured aneurysms. Cessation of smoking is, however, important for all patients with aneurysm.

Acknowledgment

We wish to thank the neurosurgeon, Antti Puntala, for his advocacy.

Sources of Funding

This work was supported, in part, by research grants to Dr Juvela from the Maire Taponen Foundation, the Paavo Nurmi Foundation, and the Paulo Foundation.

Disclosures

None.

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