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Lifelong Rupture Risk of Intracranial Aneurysms Depends on Risk Factors

A Prospective Finnish Cohort Study

Miikka Korja, MD, PhD; Hanna Lehto, MD; Seppo Juvela, MD, PhD

Background and Purpose—Our aim was to define for the first time the lifelong natural course of unruptured intracranial aneurysms (UIAs) and identify high-risk and low-risk patients for the rupture.

Methods—One hundred and eighteen patients (61 women) with UIAs were diagnosed between 1956 and 1978 and followed up until death or subarachnoid hemorrhage (SAH). The median age at the diagnosis was 43.5 years (range, 22.6–60.7 years). The median size of the UIA at the diagnosis was 4 mm (range, 2–25 mm). Analyzed risk factors for a rupture included sex, age, cigarette smoking, systolic blood pressure values, diagnosed hypertension, UIA size, and number of UIAs.

Results—Thirty four (29%) out of 118 people had SAH during the lifelong follow-up. The median age at SAH was 51.3 years (range, 30.1–71.8 years). The annual rupture rate per patient was 1.6%. Female sex, current smoking, and aneurysm size of ≥ 7 mm in diameter were risk factors for a lifetime SAH. Depending on the risk factor burden, the lifetime risk of an aneurysmal SAH varied from 0% to 100%, and the annual rupture rate from 0% to 6.5%. Of the 96 patients with small (< 7 mm) UIAs, 24 (25%) had an aneurysmal SAH during the follow-up.

Conclusions—Almost 30% of all UIAs in people of working age ruptured during a lifelong follow-up. The risk varied substantially on the basis of risk factor burden. Because even small UIAs ruptured, treatment decisions of UIAs should perhaps be based on the risk factor status. (*Stroke*. 2014;45:1958-1963.)

Key Words: follow-up studies ■ intracranial aneurysm ■ risk factors ■ smoking ■ subarachnoid hemorrhage

It has been speculated that the true natural course of unruptured intracranial aneurysms (UIAs) will never be described.¹ Because so-called preventive treatments of UIAs have become common, current natural course studies are biased.² The temptation to treat UIAs is based on the fear of subarachnoid hemorrhage (SAH), which has a 30-day mortality of 40%.³ In this light, it seems logical to deal with any fortuitously discovered UIA before a conceivable rupture, as stated already over 30 years ago.⁴ Moreover, as patients with UIAs are informed to be at a risk of SAH, the knowledge of which often creates anxiety among patients and doctors, this may lead to a shared illusion of controlling future events by conducting preventive treatments. However, the treatment decisions should be based on comparisons between preventive treatment results and the natural course, not on comparisons between preventive treatment results and outcome after SAH.

In Finland, UIAs were left untreated until 1979, which enabled us to identify a patient cohort with untreated UIAs. The cohort has been followed up for > 20 years on average.^{5–8} In the previous publications based on the cohort,^{5–8} like in other recent studies on the natural course of UIAs,^{9–12} the focus has been on the annual UIA rupture risk. In this study,

we included only 118 UIA patients with lifelong follow-up data and defined the annual UIA rupture risk, lifelong rupture risk, and risk factors for the rupture.

Methods

Lifelong UIA Cohort

The original study cohort has previously been described in detail.^{5–8} In brief, patients who were diagnosed with a UIA between 1956 and 1978 in Helsinki University Central Hospital were identified from the hospital patient registry in the mid-1980s. The first 61 patients were diagnosed with UIAs between 1956 and 1970, and they had 2 follow-up assessments by 1980.¹³ The final cohort with additional 81 patients diagnosed before 1979 had follow-up assessments in the late 1980s, 1990s, and between 2011 and 2012.^{5–8} One hundred and eighteen patients had died or had an aneurysmal SAH during the follow-up. At the beginning of the follow-up, 110 (93%) of these 118 patients presented with a SAH, 4 (3%) with incidental (angiography for unrelated symptoms) UIAs, and 4 (3%) with symptomatic UIAs. Ruptured intracranial aneurysms were treated with surgery, whereas UIAs were left untreated. For identification of the ruptured aneurysm in patients with multiple aneurysms, see our previous report.⁶

Of the 118 patients (61 women), 28 (24%) had multiple (≥ 2) UIAs. The mean and median age at the time of diagnosis of UIAs was 42.8 and 43.5 years (range, 22.6–60.7 years), respectively. Follow-up time

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was counted as the time from the diagnosis of UIA(s) until death or SAH. Follow-up was complete.

Data Gathering

The data gathering protocol has been described previously.⁵⁻⁸ In brief, the data on risk factors were collected using telephone interviews (patients and relatives), written questionnaires, and medical records obtained from the study hospital, other hospitals, and healthcare centers. Those who were alive between 1996 and 1998 were also interviewed in the outpatient clinic. At the same time, a follow-up computed tomography angiogram was performed.^{7,14} For all patients who died, autopsy reports and death certificates were scrutinized. The approval for the surveys and follow-up data collection had been obtained in 1995 and 2009 from Helsinki University Central Hospital and Turku University Hospital ethics committees.

Studied Risk Factors

Age, sex, systolic blood pressure (SBP) values (dichotomized at 140 mm Hg), diagnosed hypertension (defined as repeated SBP >140 mm Hg or repeated diastolic blood pressure >90 mm Hg, or as the use of antihypertensive medication), smoking status (divided into never-smokers, ex-smokers, and current smokers), number of the UIA(s) (single or multiple), and size of the UIA(s) (maximum aneurysm diameter <7 mm [small] or ≥7 mm [large]; Table 1).

Systolic Blood Pressure

SBP values available in medical data in hospitals and healthcare centers were recorded at the follow-ups. The mean SBP value of all measurements (mean 3 measurements per person, range, 0–15) within the last 5 years before death or SAH was used in statistical analyses. If only one SBP value (24 patients) was recorded within the last 5 years, this was used as a cross-sectional data in statistical analyses. When only 5 years older SBP values were available, the most recent SBP was used in statistical analyses.

Smoking Status

Smoking status was recorded as a never-smoker if the patient had no regular smoking history and did not report smoking at any of the follow-ups. If the patient quit smoking 12 months before the death or SAH, he/she was considered as an ex-smoker. In other occasions, patients were considered to be current smokers.

Aneurysm Growth and De Novo Aneurysms

The change in the maximum diameter of the aneurysm(s) and the number of de novo aneurysms during the follow-up were recorded if follow-up imaging studies were taken for any reason.¹⁴ For SAH patients, follow-up imaging studies were available at the time of the bleed. For fatal SAH cases without angiographies, autopsy reports with aneurysm measurements were used.

Statistical Analysis

Continuous variables were dichotomized and compared according to occurrence of SAH with the Pearson χ^2 or Fisher's exact tests. Unconditional logistic regression was used to calculate univariable and multivariable odds ratios (ORs) with 95% confidence intervals. The lifetime risk of SAH is expressed both in terms of a percentage and as ORs. Multivariable analyses were adjusted for previously identified significant risk factors for SAH.^{9,10,15-17} *P* values <0.05 were considered significant. Data were analyzed with the IBM SPSS Statistics version 22.0 for Windows (IBM Corp., Armonk, NY).

Results

Characteristics of the Lifelong UIA Cohort

Follow-Up Times and Age Characteristics

The overall follow-up time of 118 patients from the diagnosis of UIA(s) until death or SAH was 2187 person-years (mean, 18.5 years per patient [range, 0.8–52.3 years]). During the lifelong follow-up, 34 (29%) and 38 (32%) out of 118 patients had a SAH from a known or any UIA. The mean follow-up time was 11.9 and 13.6 years (range, 1.2–51.0 years) for these 34 and 38 patients, respectively. Mean follow-up time from diagnosis of a UIA to the rupture of de novo aneurysm (n=2) or aneurysm diagnosed during follow-up (n=2, diagnosed in follow-up computed tomography angiograms in 1996) was 28.5 years (range, 13.4–51.0 years).

Median and mean age at SAH from a UIA were 51.3 and 50.4 years (range, 30.1–71.8 years), respectively. Four patients with SAH from an aneurysm other than the previously

Table 1. Lifetime Risk (%) of SAH in Patients With UIAs and Various Risk Factors for SAH

Risk Factor (No. of Patients)	Subcategory	Overall	Women	Men
All patients (118)		29% (34/118)	38% (23/61)	19% (11/57)
Age at UIA diagnosis (118)	<50 y	34% (30/88)	46% (20/44)	23% (10/44)
	≥50 y	13% (4/30)	18% (3/17)	8% (1/13)
SBP (117)	≤140 mm Hg	30% (18/61)	33% (10/30)	26% (8/31)
	>140 mm Hg	27% (15/56)	40% (12/30)	12% (3/26)
Diagnosed hypertension (117)	No	33% (14/42)	42% (8/19)	26% (6/23)
	Yes	25% (19/75)	34% (14/41)	15% (5/34)
Smoking (99)	Never-smoker	27% (8/30)	31% (8/26)	0% (0/4)
	Ex-smoker	0% (0/17)	0% (0/5)	0% (0/12)
	Current smoker	39% (20/52)	45% (9/20)	34% (11/32)
Aneurysm size (118)	<7 mm	25% (24/96)	30% (15/50)	20% (9/46)
	≥7 mm	46% (10/22)	73% (8/11)	18% (2/11)
Multiple UIAs (118)	No	30% (27/90)	41% (19/46)	18% (8/44)
	Yes	25% (7/28)	27% (4/15)	23% (3/13)

Total number of patients with information on the risk factor in parenthesis. SAH indicates subarachnoid hemorrhage; SBP, systolic blood pressure; and UIA, unruptured intracranial aneurysm.

diagnosed UIA had the mean and median age of 70.5 and 69.2 years (range, 63.4–80.2 years), respectively. Out of the 118 patients, 22 (19%) died from a SAH (18 because of a UIA and 4 because of other aneurysms). Median and mean age at unrelated death were 67.8 and 66.6 years (range, 33.9–93.6 years), respectively.

Incidence of SAH

The average annual UIA rupture rate was 1.6% for patients (34 SAH cases during 2187 person-years) and 1.2% for aneurysms (34 ruptured aneurysms during the total follow-up of 2782 aneurysm-years). The crude incidence of SAH from a known or any (de novo/nonindex aneurysms included) UIAs was 1555 (95% confidence interval, 1080–2170) and 1738 (95% confidence interval, 1230–2370) per 100000 person-years, respectively.

Univariable Analyses of Risk Factors for SAH

Age and Sex

The OR for a lifetime risk of SAH among the patients younger than 50 and 40 years at the baseline was 3.36 (95% confidence interval, 1.07–10.53) and 3.41 (1.49–7.82) compared with others (Table 2). Of the 48 patients who were younger than 40 years at the baseline, 21 (44%) had a SAH during the lifelong follow-up. On the contrary, 13 (19%) out of the 70 patients who were 40 years old or older at the beginning of the follow-up had SAH during the follow-up. The unadjusted OR for a lifetime SAH in women was 2.53 in comparison with men (Table 2).

SBP and Smoking

The risk of a lifetime SAH did not associate with SBP or diagnosed hypertension (Tables 1 and 2). Current smokers had an OR of 3.05 for a lifetime SAH in comparison with never-/ex-smokers (Table 2). Overall, 71% and 53% of SAH patients and all cohort patients, respectively, were current smokers (Table 1). Corresponding rates for ever-smoking were 71% and 70%.

Aneurysm Size, Growth, and Multiplicity

In unadjusted analyses, the patients with UIAs of 7 mm or more in size had an increased risk of a lifetime SAH, particularly among women, compared with the patients with smaller UIAs (Tables 1 and 2). Sixty four (54%) out of 118 patients had follow-up angiographies or autopsy with aneurysm measurements, and in 33 (52%) out of 64 patients ≥ 1 aneurysm had increased (≥ 2 mm) in the size. Of the 27 patients with SAH from a previously diagnosed UIA and follow-up data on the size of the aneurysm, 25 (93%) had an increase in the aneurysm size (≥ 2 mm) at the time of SAH, whereas 8 (22%) out of 37 patients without SAH had such an increase ($P < 0.001$). Twenty-eight patients with multiple UIAs did not have a higher risk of a lifetime SAH than patients with a single UIA (Tables 1 and 2).

Multivariable Analyses of Risk Factors for SAH

Our and previously identified risk factors^{9,10,15–17} for SAH were included in a multivariable analysis (Table 3). The multivariable analysis suggested that current smoking and the UIA size of ≥ 7 mm are independent risk factors for a lifetime SAH (Table 3). Female sex and young age at the beginning of the follow-up approached significance (Table 3).

Variation in the Lifetime SAH Risk Depending on Risk Factors

The study cohort was divided into subgroups of patients by the risk factor status, and the risk of a lifetime SAH in each subgroup was calculated (Table 4). The lifetime risk of SAH varied from 0% to 100% between the groups (Table 4). Smoking women with the UIA size of ≥ 7 mm seemed to have an exceptionally high lifelong UIA rupture risk.

Discussion

Less than one third of UIAs ruptured during the lifetime follow-up of a working-age patient cohort. Rupture risks of UIAs depended on the combination of risk factors in the UIA

Table 2. Univariable Odds Ratios for a Lifetime SAH in Patients With UIAs and Various Potential Risk Factors for SAH

Risk Factor (No. of Patients)	Subcategory	Overall (CI)	Women (CI)	Men (CI)
All		N/A	2.53 (1.10–5.85)*	1
Age at UIA diagnosis (118)	<50 y	3.36 (1.07–10.53)*	3.89 (0.98–15.47)	3.53 (0.41–30.56)
	≥ 50 y	1	1	1
SBP (117)	≤ 140 mm Hg	1	1	1
	> 140 mm Hg	0.87 (0.39–1.96)	1.33 (0.47–3.82)	0.38 (0.09–1.59)
Diagnosed hypertension (117)	No	1	1	1
	Yes	0.68 (0.30–1.55)	0.71 (0.23–2.18)	0.49 (0.13–1.85)
Smoking (99)	Never- and ex-smoker	1	1	N/A
	Current smoker	3.05 (1.19–7.83)*	2.35 (0.71–7.76)	N/A
Aneurysm size (122)	<7 mm	1	1	1
	≥ 7 mm	2.50 (0.96–6.52)	6.22 (1.45–26.75)*	0.91 (0.17–4.98)
Multiple UIAs	No	1	1	1
	Yes	0.78 (0.30–2.05)	0.52 (0.14–1.87)	1.35 (0.30–6.05)

All men with SAH were current smokers, and thus, no odds ratios for smoking could be defined. CI indicates 95% confidence intervals; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; and UIA, unruptured intracranial aneurysm.

* $P < 0.05$, N/A, not applicable or no cases.

Table 3. Multivariable Analysis of Risk Factors for a Lifetime SAH for 98 Patients

Risk Factor	Overall (95% CI)	Women (95% CI)	Men (95% CI)
Female sex	2.50 (0.87–7.17)	N/A	N/A
Age at UIA diagnosis <50 y	7.50 (0.89–62.99)	N/A	3.05 (0.33–28.51)
SBP >140 mm Hg	1.04 (0.38–2.84)	2.07 (0.50–8.66)	0.38 (0.08–1.88)
Current smoking	3.44 (1.11–10.68)*	2.70 (0.68–10.78)	N/A
Aneurysm size ≥ 7 mm	4.02 (1.14–14.19)*	14.02 (2.01–98.05)*	1.79 (0.26–12.28)

Previously identified risk factors^{9,10,15–17} for SAH have been included in the analysis. Because none of the 50-year-old or older nonsmoking women with UIAs had SAH, age-dichotomized odds ratios for women could not be calculated. All men with SAH were current smokers, and thus, no odds ratios for smoking men could be defined. Odds ratios and 95% CIs. CI indicates confidence interval; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; and UIA, unruptured intracranial aneurysm.

* $P < 0.05$, N/A, not applicable or no cases.

carriers. For example, the risk of a lifetime aneurysmal SAH was 73% in women with UIAs of ≥ 7 mm in size, whereas none of the never-smoking men had a SAH. Similarly, in the recent long-term study on the risk of SAH among general population,¹⁷ the incidence of SAH was >20 times higher in smoking and hypertensive women in comparison with never-smoking and normotensive men.¹⁷ Overall, the findings of this study are in accordance with the previous large, long-term, prospective, and population-based SAH risk factor study results,^{15–17} suggesting that female sex and current smoking are the major risk factors for aneurysmal SAH. Because the increasing age of the patients associated with increasing SBP values and diagnosed hypertension (data not shown), SBP and diagnosed hypertension were not significant risk factors for aneurysm rupture in this UIA cohort.

One fourth (22 UIAs) of the ruptured UIAs were small at baseline, but 17 out of these 22 small UIAs grew to the size of ≥ 7 mm by the time of the rupture. This considered, rupture

risk estimates cannot be based solely on the initial size of a UIA. Furthermore, the UIA size at baseline played an insignificant role in the rupture risk particularly in men, and the overall effect of risk factors on the risk of SAH seemed to vary significantly between men and women, like in the recent study.¹⁷ The rupture risk of UIAs of <7 mm in size has been reported to be minimal (<1% per year).^{9,10} If small UIAs have a low risk of rupture,^{9,10} and higher risk large UIAs (≥ 7 mm) are relatively rare,¹⁸ preventive treatments of asymptomatic UIAs cannot have significant effect on the incidence of SAH. Half a century ago, Freytag et al¹⁹ studied 250 ruptured aneurysms and found that 66% were 6 to 10 mm in size and 13% were <5 mm. Kassell et al²⁰ reported similar results in 1983, showing that 71% of ruptured aneurysms were <10 mm in diameter and 13% were <5 mm. According to our results, 25% and 27% of the UIAs of <7 mm and ≤ 10 mm in size at the baseline, respectively, ruptured during the lifelong follow-up. At the time of rupture, 19% and 70% of the UIAs were <7 mm and

Table 4. Variation in Annual and Lifetime Rupture Risks in Patients With UIAs and Various Combinations of Risk Factors for SAH

UIA Patient Groups	ARR, %	LTRR, %	No. of pts	Mean UIA Size, mm	Median UIA Size, mm	Median Age at Diagnosis, y	Median FU Time PP, y
Never-smoking men	0	0	4	8.5	5.5	51.2	27.1
Men ≥ 50 y old with ≥ 7 mm UIAs	0	0	5	10.4	8	55.6	13.2
Men ≥ 50 y	0.6	8	13	6.5	5	55.6	13.2
Never-smoking women with <7 mm UIAs	0.9	23	22	3.6	3.5	47.1	25.7
Women ≥ 50 y	1.0	18	17	5.0	4	55.0	17.4
Men with <7 mm UIAs	1.1	20	46	3.8	4	41.6	17.6
Men	1.2	19	57	4.8	5	42.6	15.7
Never-smoking women	1.3	31	26	5.0	4	46.1	24.6
Men with ≥ 7 mm UIAs	1.3	18	11	9.2	8	47.5	11.3
Women with <7 mm UIAs	1.4	30	50	3.7	4	45.5	21.9
Women	1.8	38	61	5.2	4	45.1	18.4
Current smoking men	2.5	34	32	4.3	4.5	36.8	14.1
Current smoking women	2.7	45	20	4.6	4	39.9	16.9
Current smoking men with ≥ 7 mm UIAs	4.0	50	4	8.0	8	41.6	10.2
Women with ≥ 7 mm UIAs	4.6	73	11	12.3	8	45.1	16.9
Current smoking women with ≥ 7 mm UIAs	6.5	100	4	8.3	8	37.4	17.2

ARR indicates annual rupture risk; LTRR, lifetime rupture risk; No. of pts, number of patients; PP, per person; and UIA, unruptured intracranial aneurysm.

≤10 mm in size, respectively. Even though the multivariable analysis suggested that the size was an independent risk factor for the UIA rupture, the multivariable analysis cannot fully adjust for all confounding factors. Indeed, of the 10 out of 22 ruptured UIAs of ≥7 mm in size, 8 were found in women (4 were current smokers and 4 were hypertensive) and 2 in actively smoking men.

The current study may have a couple of advantages. The study is based on a lifelong follow-up cohort without a treatment selection bias prior to or during the follow-up. In the short-term UCAS⁹ and ISUIA¹⁰ studies, it has been impossible to identify lifelong or long-term risk factors for aneurysmal SAH. If the risk of rupture is not stable over time, lifelong studies may be more reliable than short-term studies. In the previous studies,^{9,10} nearly half of UIAs were treated before or during the follow-up, leaving mostly low-risk UIAs in the natural course cohort. The annual rupture risk for UIAs has been reported to be between 0.5% and 1.4% in the most recent cohort (>100 people) studies,^{5,9–12} despite highly different demographics, risk factor occurrences, and UIA characteristics between the patient populations. This raises a question, how reliable and useful the reported average annual rupture risk estimates are, especially if they are given on the basis of the UIA characteristics only. The lifelong follow-up time enabled us to define also the annual UIA rupture risk on the basis of risk factors, and the risk varied between 0% and 6.5%, which varied, however, less than lifelong rupture risk. Finally, no patients were lost from the follow-up, and therefore, we were also able to prospectively identify true UIA patients, that is, patients with never-rupturing aneurysms.

The study has also shortcomings. For example, if the risk of SAH is higher in the UIA patients with a previous SAH,¹² the calculated risks in this study may be overestimates. The major shortcoming is the small sample size, and for example, reliable estimates of more detailed subgroups could not be calculated. However, because the increase in the size of biased cohorts may increase the magnitude of inaccurate estimates and conclusions, the number of SAH events probably defines more reliably the significance of a natural course study. The current one has the second highest number of end points (SAHs and deaths) after the ISUIA study,¹⁰ and the third highest number of SAH events after the ISUIA and UCAS Japan study.^{9,10} It is worth mentioning that <5% in the ISUIA and UCAS study patients had a rupture of a UIA during the follow-up. Aneurysm morphology could not be analyzed as an additional risk factor for SAH in this study. This was because of the fact that only conventional angiographies with standard imaging projections were available, but no 3-dimensional reconstructions, during the period when the follow-ups were started.

Although diagnosed hypertension and SBP values have been shown to increase the risk of SAH in general population,^{15–17} these have not been shown to increase risk of rupture of existing UIAs in the largest natural history studies.^{5,9,10} In fact, the marginal statistical significance (hazards ratio, 1.4; 95% CI, 1.1–1.8) was obtained only in a large meta-analysis of 8382 patients with a follow-up of 29 166 person years.²¹

Thus, hypertension may have a more substantial role in aneurysm formation than in its rupture. Finnish people have also been considered to have a higher risk of UIA rupture.²¹ However, none of the 32 Finns in the ISUIA^{10,21} had an aneurysm rupture within >200 follow-up years, suggesting that the selection bias was significant, and established risk factors are much more important than nationality when estimating aneurysm rupture risk.

Whether the study has a high external validity is somewhat irrelevant, as the study is suggesting that the risk factors and especially their specific combinations have a high impact on the UIA rupture risk, similar to a previous report.¹⁷ In brief, the study reports that the lifelong risk of a UIA rupture depends strongly on the risk factors, also other than the size of the UIA, and these should perhaps be taken into account when making treatment decisions. It would be exceptional if the risk factor-dependent relative UIA rupture risk was significantly different in other Western populations, even though this needs to be confirmed in future studies.^{9,10} Furthermore, a similar lifelong follow-up study will likely never be repeated.

In conclusion, the presented results provide the first evidence of a lifetime course of UIAs, and the risk factor-based results may be of assistance in making treatment decisions. Never-smoking men seem to have a low lifetime risk of an aneurysmal SAH and may be a UIA patient group that can be safely followed up for a long time. Hopefully, the future analyses of the ongoing prospective UIA studies^{9,10} will also focus on similar subgroup analyses, thus strengthening or weakening the external validity of our results.

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Disclosures

None.

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