

# Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment

*International Study of Unruptured Intracranial Aneurysms Investigators\**

## Summary

**Background** The management of unruptured intracranial aneurysms is controversial. Investigators from the International Study of Unruptured Intracranial Aneurysms aimed to assess the natural history of unruptured intracranial aneurysms and to measure the risk associated with their repair.

**Methods** Centres in the USA, Canada, and Europe enrolled patients for prospective assessment of unruptured aneurysms. Investigators recorded the natural history in patients who did not have surgery, and assessed morbidity and mortality associated with repair of unruptured aneurysms by either open surgery or endovascular procedures.

**Findings** 4060 patients were assessed—1692 did not have aneurysmal repair, 1917 had open surgery, and 451 had endovascular procedures. 5-year cumulative rupture rates for patients who did not have a history of subarachnoid haemorrhage with aneurysms located in internal carotid artery, anterior communicating or anterior cerebral artery, or middle cerebral artery were 0%, 2.6%, 14.5%, and 40% for aneurysms less than 7 mm, 7–12 mm, 13–24 mm, and 25 mm or greater, respectively, compared with rates of 2.5%, 14.5%, 18.4%, and 50%, respectively, for the same size categories involving posterior circulation and posterior communicating artery aneurysms. These rates were often equalled or exceeded by the risks associated with surgical or endovascular repair of comparable lesions. Patients' age was a strong predictor of surgical outcome, and the size and location of an aneurysm predict both surgical and endovascular outcomes.

**Interpretation.** Many factors are involved in management of patients with unruptured intracranial aneurysms. Site, size, and group specific risks of the natural history should be compared with site, size, and age-specific risks of repair for each patient.

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## Introduction

Unruptured intracranial aneurysms are diagnosed with greater frequency as imaging techniques improve. The management of unruptured intracranial aneurysms remains controversial because of incomplete and conflicting data about the natural history of these lesions and the risks associated with their repair.<sup>1–9</sup>

Results of phase 1 of this study have been reported previously,<sup>1</sup> and include a retrospective study of the natural history and a prospective assessment of morbidity and mortality associated with surgical repair of unruptured aneurysms. Here, we include only prospective data on the natural history of unruptured intracranial aneurysms, the clinical outcomes of endovascular treatment, and a more comprehensive assessment of the risks of surgical treatment. With these combined data, the study aim is to provide information about the magnitude and determinants of the risks associated with the natural history and repair of unruptured intracranial aneurysms.

## Methods

### Patients

Study coordinators identified eligible patients prospectively from people who were diagnosed between 1991 and 1998, and visited International Study of Unruptured Intracranial Aneurysms (ISUIA) centre. They used the system's central inpatient and outpatient admission records, and records from departments of radiology, neurosurgery, and neurology to identify eligible patients.

Patients were eligible for enrolment if they had at least one unruptured intracranial aneurysm, whether or not they had aneurysmal symptoms other than rupture (eg, cranial nerve palsy). Patients might have had a previous ruptured aneurysm at another location that was clipped, trapped, or completely isolated from the circulation by endovascular obliteration, as confirmed by arteriography. We included patients only if they could care for themselves after the previous aneurysm was treated (ie, a score of 1 or 2 on the Rankin scale of neurologic disability, in which scores range from 1 [no disability] to 5 [severe disability]).

Patients were excluded if they had any of: (1) fusiform, traumatic, or mycotic aneurysms; (2) aneurysms with a maximum diameter less than 2 mm, as measured with a standard measuring device; (3) subarachnoid haemorrhage from a single ruptured aneurysm or an unknown source; (4) an unruptured aneurysm that was manipulated before entry into the study; (5) a history of intracranial haemorrhage if the cause was unknown or if an underlying structural lesion was not repaired; or (6) a malignant brain tumour. Also, patients were excluded if they were bedridden or unable to communicate when the aneurysm was identified.

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	No surgery (n=1692)	Surgery		p*	p†
		Open surgical (n=1917)	Endovascular (n=451)		
Subarachnoid haemorrhage					
No (group 1)	1077	1591	409	<0.0001	<0.0001
Yes (group 2)	615	326	42		
Age (years) (mean [SD])	55.2 (13.1)	51.5 (11.4)	53.7 (13.1)	<0.0001	<0.0001
Women (%)	1261 (74.5%)	1456 (75.9%)	351 (77.8%)	0.302	0.399
White	1550 (91.6%)	1734 (90.4%)	427 (94.7%)	0.015	0.004
Number with unruptured aneurysms					
Single	1006 (59.7%)	1284 (67.5%)	309 (70.7%)	<0.0001	0.298
Multiple	679 (40.3%)	623 (32.5%)	132 (29.3%)		
Total number of unruptured aneurysms	2686	2884	651		
Maximum diameter of aneurysms (mm) (mean [SD])	7.4 (6.9)	9.6 (6.7)	13.1 (9.7)	<0.0001	<0.0001
Size of aneurysm (mm), (number of patients [%])				<0.0001	<0.0001
2-7	1049 (62.0%)	735 (38.6%)	126 (27.9%)		
7-12	390 (23.0%)	758 (39.8%)	137 (30.4%)		
13-24	198 (11.7%)	332 (17.4%)	133 (29.5%)		
≥25	55 (3.2%)	80 (4.2%)	55 (12.2%)		
Aneurysm location (number of patients [%])				<0.0001	<0.0001
Cavernous part of carotid artery	210 (12.4%)	38 (2.0%)	89 (19.7%)		
Internal carotid artery	387 (22.9%)	681 (35.6%)	145 (32.2%)		
Anterior communicating or anterior cerebral artery	175 (10.3%)	284 (14.8%)	41 (9.1%)		
Middle cerebral artery	475 (28.1%)	650 (34.0%)	54 (12.0%)		
Posterior communicating artery	246 (14.5%)	84 (4.4%)	15 (3.3%)		
Vertebrobasilar system (other than basilar tip)	87 (5.1%)	72 (3.8%)	40 (8.9%)		
Tip of basilar artery	112 (6.6%)	105 (5.5%)	67 (14.9%)		

Data missing for some categories. \*For comparisons of patients in all three groups (patients who had no operations, those who had open surgery, and those who had endovascular procedures). †For comparisons of patients from two groups (patients who had open surgery and those who had endovascular procedures).

Table 1: **Patients' baseline characteristics**

All patients gave written informed consent, in accordance with criteria set by the local ethics committees at each participating centre.

### Procedures

Patients were assigned to one of two cohorts—operated or unoperated—based on whether surgical or endovascular treatment of at least one unruptured intracranial aneurysm was planned on clinical grounds at the time the patient was first seen at the ISUIA centre. All patients underwent catheter cerebral arteriography to confirm the presence, location, and size of intracranial aneurysms.

There were two study objectives for the unoperated cohort. First, to describe the natural history of unruptured intracranial aneurysms in patients without subarachnoid haemorrhage from a separate aneurysm (group 1), and in patients with subarachnoid haemorrhage from a separate aneurysm (group 2). Second, to determine whether specific subgroups of patients have a greater risk of rupture and, if so, to provide evidence for the most appropriate management of those patients.

Study objectives for the operated cohort (in which patients were treated with surgical or endovascular repair) were to assess the risks of morbidity and mortality associated with treatment of unruptured intracranial aneurysms and to determine whether these risks are higher for some categories of patients than for others.

Hard copies of cerebral arteriographs from all patients were reviewed at the central study office at Mayo Clinic, Rochester, Minnesota, by two neuroradiologists. The size of the aneurysm was corrected for magnification by standardised methods reported previously.<sup>10</sup> A pilot study established standards for measuring the size and morphological characteristics of the aneurysm and interobserver reliability.<sup>10</sup>

### Follow-up

Baseline characteristics were recorded for all patients. Patients who did not undergo planned surgical treatment were followed up with the use of an annual standardised questionnaire. Neurological symptoms, intracranial operative findings, and results of repeated arteriographic

studies undertaken since the previous assessment were recorded. For patients who underwent surgical or endovascular treatment, assessments were made 7 days after the procedure, at hospital discharge, at 30 days after treatment, and then at yearly intervals.

Neurological status was measured with the use of the Rankin scale at each follow-up assessment, and cognitive status was determined with the mini-mental state examination<sup>11</sup> or the telephone interview for cognitive status<sup>12</sup> at every follow-up. Annual questionnaire assessments included questions about employment status, medical and smoking history, medications, and quality of life (quality-of-life questions were first asked in follow-up assessments in 1996; questions were from the medical outcomes study 36-item short-form health survey [SF-36]). All complications of surgical and endovascular treatment were noted.

### Determination of events

Detailed information was obtained for all endpoints (definite or questionable subarachnoid or intracerebral haemorrhage and death). Patient assessments were done by trained investigators and coordinators. Haemorrhages were classified in accordance with the location of the rupture. Subarachnoid or intracerebral hemorrhage were classified as (1) definite (symptoms of subarachnoid or intracerebral haemorrhage and positive findings on CT or MRI during surgery, or at autopsy); (2) highly probable (symptoms and positive findings on cerebrospinal fluid analysis); or (3) probable (symptoms only). All patients with definite, highly probable, and probable aneurysmal haemorrhages were included in the primary analysis.

Evidence of cerebral infarction, haemorrhage, or death related to surgery was confirmed centrally with use of standard criteria and information from clinical, radiological, and autopsy records. Neurological deficits at 30 days or 1 year after treatment were assessed for their relation to treatment or coexisting disorders. Deficits clearly related to a coexisting disorder were not attributed to aneurysmal treatment.

Morbidity related to surgical treatment was defined as a Rankin score of 3, 4, or 5 (moderate to severe

	No surgery	Surgery		p*	p†
		Open surgical	Endovascular		
Subarachnoid haemorrhage	514 (30.4%)	263 (13.7%)	38 (8.5%)	<0.0001	0.003
Cranial nerve deficit	135 (8.0%)	197 (10.3%)	113 (25.2%)	<0.0001	<0.0001
Other aneurysm mass effect	45 (2.7%)	103 (5.4%)	38 (8.5%)	<0.0001	0.012
Ischaemic cerebrovascular disease	178 (10.5%)	102 (5.3%)	22 (4.9%)	<0.0001	0.746
Subdural or intracerebral haematoma	21 (1.2%)	6 (0.3%)	2 (0.4%)	0.003	0.662
Brain tumour	13 (0.8%)	6 (0.3%)	3 (0.7%)	0.165	0.270
Central nervous system degenerative condition	7 (0.4%)	4 (0.2%)	3 (0.7%)	0.267	0.147
Convulsive disorder	49 (2.9%)	85 (4.4%)	18 (4.0%)	0.049	0.696
Headaches	401 (23.7%)	643 (33.6%)	166 (37.0%)	<0.0001	0.161
Transient ischaemic attack	180 (10.6%)	133 (6.9%)	26 (5.8%)	<0.0001	0.387
Undefined spells	121 (7.1%)	200 (10.4%)	46 (10.3%)	0.002	0.915
CT	510 (30.1%)	748 (39.0%)	190 (42.4%)	<0.0001	0.189
MRI	434 (25.6%)	826 (43.1%)	235 (52.5%)	<0.0001	<0.0001
Other	502 (29.7%)	565 (29.5%)	116 (25.9%)	0.130	0.130

\*For comparisons of patients in all three groups (patients who had no operations, those who had open surgery, and those who had endovascular procedures). †For comparisons of patients from two groups (patients who had open surgery and those who had endovascular procedures).

Table 2: **Reasons for diagnostic angiography**

neurological disability); a score less than 24 on the minimal state examination; or a score less than 27 on the telephone interview for cognitive status (both indicate a serious cognitive abnormality) at 30 days and 1 year.<sup>11-13</sup>

### Statistical analysis

Data from the two cohorts and group 1 and group 2 were analysed as separate strata. Between-cohort comparisons of the distributions of baseline characteristics were done with the  $\chi^2$  test for categorical variables and *t* test for continuous variables. Estimates of the risk of haemorrhage for the unoperated cohort were made with the use of life-table methods, with censoring on the date of death, surgical intervention, and latest follow-up assessment.

Predictors of haemorrhage were ascertained from a proportional-hazards regression model.

For the prospective operated cohort survival, morbidity (one or both of a Rankin score of 3, 4, or 5, or diminished mental status as indicated by a score <24 on the minimal state examination or <27 on the telephone interview for cognitive status), as well as the combined overall morbidity and mortality were analysed. Survival estimates and 95% CI were calculated with life-table methods at 30 days and 1 year after treatment. The risk of morbidity was estimated from the proportion of patients with disability at the 30-day and 1-year examinations; Likewise, overall risk of morbidity or mortality was the proportion of patients who were disabled or dead at

	No surgery	Surgery		p*	p†
		Open surgical	Endovascular		
Medical history					
Hypertension	732 (43.6%)	730 (38.3%)	188 (42.1%)	0.004	0.143
Hypertension therapy	637 (37.8%)	640 (33.5%)	162 (36.1%)	0.002	0.294
Atrial fibrillation	57 (3.4%)	44 (2.3%)	12 (2.7%)	0.133	0.636
Cardiac arrhythmias	78 (4.7%)	95 (5.0%)	21 (4.7%)	0.916	0.822
Congestive heart failure	18 (1.1%)	8 (0.4%)	5 (1.1%)	0.054	0.102
Myocardial infarction	109 (6.5%)	77 (4.0%)	23 (5.2%)	0.004	0.299
Valvular disease	37 (2.2%)	40 (2.1%)	12 (2.7%)	0.740	0.450
Family history					
Aneurysms	276 (18.4%)	400 (22.9%)	65 (16.2%)	0.001	0.003
Subarachnoid haemorrhage	271 (18.0%)	350 (20.2%)	64 (15.8%)	0.070	0.042
Indeterminate haemorrhage	147 (10.0%)	209 (12.2%)	38 (9.4%)	0.075	0.118
Indeterminate stroke	553 (36.2%)	631 (32.7%)	144 (35.0%)	0.895	0.766
Coronary artery disease	662 (43.0%)	793 (45.0%)	174 (41.6%)	0.326	0.215
Intermittent claudication	107 (8.0%)	111 (7.0%)	26 (6.8%)	0.521	0.902
Focal cerebral ischaemic episodes‡	143 (10.5%)	180 (11.5%)	42 (11.0%)	0.702	0.768
Behavioural history					
Alcohol (>5 drinks per 24 h)	502 (30.2%)	498 (26.3%)	97 (21.7%)	0.001	0.045
Current smoker	693 (41.1%)	900 (47.2%)	174 (38.6%)	<0.0001	<0.0001
Former smoker	602 (35.7%)	608 (31.9%)	145 (32.2%)		
Use of stimulants	79 (4.7%)	145 (7.6%)	22 (4.9%)	0.001	0.042
Use of oral contraceptives	542 (44.7%)	753 (52.8%)	167 (48.7%)	<0.0001	0.174
Associated disorders					
Coarctation of aorta	9 (0.5%)	2 (0.1%)	0 (0.0%)	0.023	0.493
Polycystic kidney disease	25 (1.6%)	39 (2.1%)	7 (1.6%)	0.531	0.487
Arteriovenous malformation	34 (2.0%)	38 (2.0%)	13 (2.9%)	0.465	0.235
Ehlers-Danlos syndrome	0 (0%)	0 (0.0%)	0 (0.0%)		
Neurofibromatosis	0 (0%)	2 (0.1%)	2 (0.5%)	0.044	0.162
Tuberous sclerosis	0 (0%)	2 (0.1%)	0 (0.0%)	0.225	0.494
Moyamoya disease	0 (0%)	0 (0.0%)	0 (0.0%)		
Hypocoagulable state	6 (0.4%)	4 (0.2%)	1 (0.2%)	0.672	0.952
Fibromuscular disease	14 (0.9%)	22 (1.1%)	7 (1.6%)	0.453	0.482

Data are number (%); the denominator is the number of patients for whom information was available. \*For comparisons of patients in all three groups (patients who had no operations, those who had open surgery, and patients who had endovascular procedures). †For comparisons of patients from two groups (patients who had open surgery and those who had endovascular procedures). ‡Includes ischaemic stroke, reversible ischaemic neurological deficit, and transient ischaemic attack.

Table 3: **Medical and behavioural risk factors and associated disorders that might predict rupture of an unruptured intracranial aneurysm**

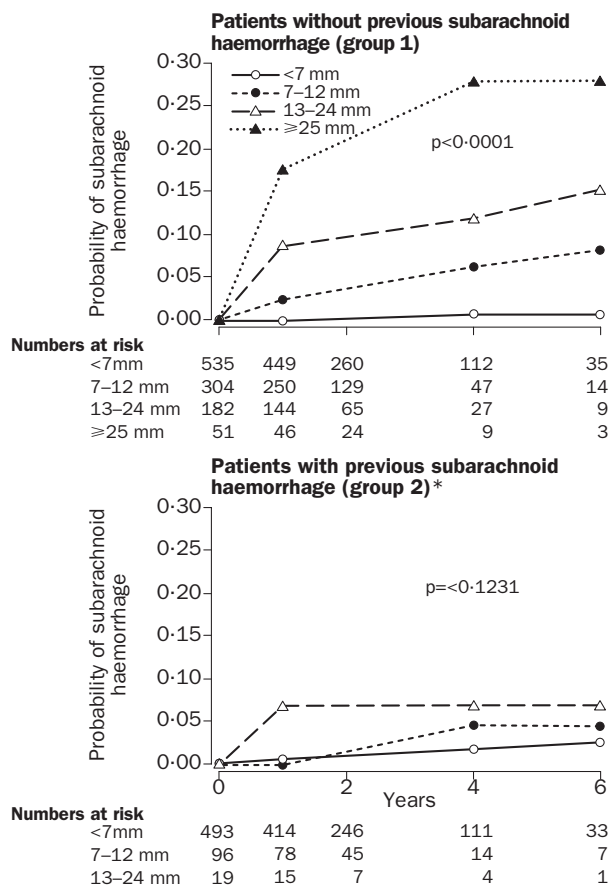


Figure 1: Probability of subarachnoid haemorrhage over time for patients who did not have surgery

\*Data not shown for ≥25 mm group because of small sample size.

30 days and at 1 year. Morbidity and mortality related to surgery or endovascular events 1 year after treatment were calculated with the use of logistic regression and data from the 1 year assessment. Further details of the methods used in this study are available elsewhere.<sup>14</sup>

#### Role of the funding source

The sponsors of the study had no direct role in study design, data collection, data analysis, data interpretation, or writing of the report.

#### Results

Between December, 1991, and December, 1998, 4060 patients were enrolled from 61 centres in the USA, Canada, and Europe. 2035 (50%) patients were identified before 1996; however, the accrual of cases was greatest in 1997 and 1998 when 1775 (43%) joined the study.

Table 1 shows the baseline characteristics of patients in the unoperated and operated cohorts. Conditions that led to the diagnosis of unruptured intracranial aneurysms did not differ substantially in the unoperated and operated cohorts (table 2), although operated patients were more likely to have aneurysmal symptoms and headaches, and

less likely to have subarachnoid haemorrhage from a separate aneurysm. Furthermore, treated patients were more likely to have had aneurysms detected by MRI.

#### Natural history

1692 patients with 2686 aneurysms (1077 patients in group 1 and 615 in group 2) had conservative management of their condition—that is, they did not have surgery or endovascular treatment. In this group, mean follow up was 4.1 years (SD 2.00), with 6544 patient-years of follow-up. Patients were removed from follow-up if they had treatment (410 had surgery and 124 had endovascular treatment), as were those who died (193 patients). Analysis of data from patients who were censored because of treatment showed no pattern according to aneurysmal size, location, or clinical symptoms. Four patients were lost to follow-up after assessment and entry into the study.

Table 1 shows the distribution of unruptured intracranial aneurysms by size and location (parent artery). Overall, aneurysmal signs other than rupture (eg, cranial nerve palsies) were present in 11% of untreated patients, 16% of those who had a surgical procedure, and in 34% of participants who had an endovascular procedure.

Putative risk factors for prediction of a rupture of an unruptured intracranial aneurysm did not differ greatly in the operated and unoperated cohorts at baseline (table 3).

51 patients (3%) in the unoperated cohort had a confirmed aneurysmal rupture during follow-up; in 49 of these, the rupture occurred within 5 years of diagnosis. One additional patient who had a subarachnoid haemorrhage 4 years after diagnosis had a coexisting large fusiform aneurysm that caused a mass effect. Data from the 36 patients who had both an aneurysm and another potential source of subarachnoid haemorrhage were not included in the primary analysis of endpoints. In group 1 patients, only two of the 41 ruptures were in patients with aneurysms less than 7 mm in diameter, but five ruptures were noted in patients with aneurysms 7–9 mm in diameter. By contrast, in group 2 patients, eight ruptures were in aneurysms less than 10 mm in diameter, seven were 2–6 mm, and one was 7–9 mm.

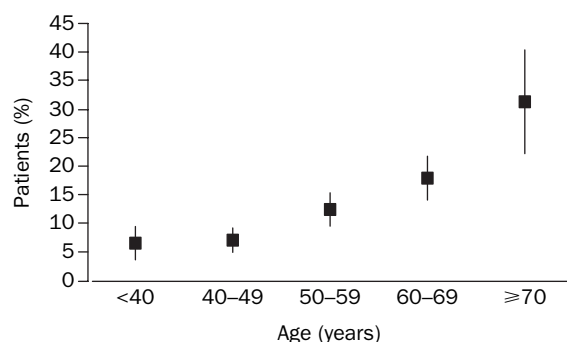
Larger aneurysmal size was associated with a greater risk of rupture in group 1 patients who did not have surgery, but not in group 2 patients, although the number of large aneurysms in group 2 was small. Figure 1 shows rupture rates over time according to aneurysm size and patient groups. Patients in group 2 with unruptured intracranial aneurysms less than 7 mm had higher rupture rates than did those in group 1 ( $p < 0.0001$ ). Otherwise, rupture rates for patients who did not have surgery did not differ between group 1 and group 2.

Data from groups 1 and 2 were combined for the purpose of calculating predictors of future rupture by site and size of unruptured aneurysm, apart from those for people with aneurysms greater than 7 mm in diameter. The running average for successive 3 mm size categories showed optimum cutpoints at diameters less than 7 mm, 7–12 mm, 13–24 mm, and 25 mm or larger. Three locations of aneurysms were associated with higher or

	<7 mm		7-12 mm	13-24 mm	≥25 mm
	Group 1	Group 2			
Cavernous carotid artery (n=210)	0	0	0	3.0%	6.4%
AC/MC/IC (n=1037)	0	1.5%	2.6%	14.5%	40%
Post-P comm (n=445)	2.5%	3.4%	14.5%	18.4%	50%

AC=anterior communicating or anterior cerebral artery. IC=internal carotid artery (not cavernous carotid artery). MC=middle cerebral artery. Post-P comm=vertebrobasilar, posterior cerebral arterial system, or the posterior communicating artery.

Table 4: 5-year cumulative rupture rates according to size and location of unruptured aneurysm



**Figure 2: Poor outcome at 1 year in the surgical cohort by age**  
Poor outcome is death, a Rankin score between 3 and 5, or impaired cognitive status. Bars show 95% CI.

lower rupture rates (table 4), and were therefore used in models to predict rupture.

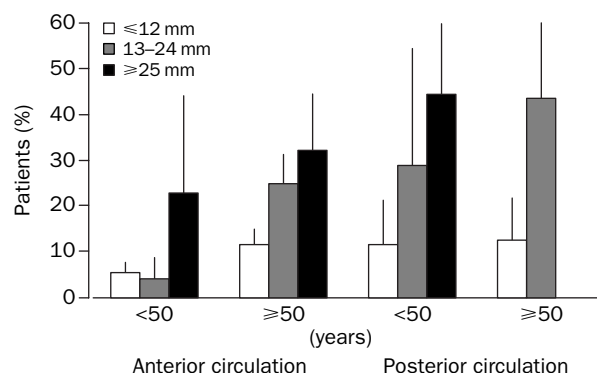
Table 4 shows 5-year cumulative haemorrhage rates by aneurysm site (parent artery), size, and group (for aneurysms <7 mm). About 90% of all unruptured aneurysms were in the anterior circulation for the combined cohort (ie, groups 1 and 2).

A multivariate analysis was done with the proportional hazards methods. The overall model was significant according to the likelihood-ratio test ( $p < 0.0001$ ). Predictors of haemorrhage included aneurysmal size (7–12 mm maximum diameter, relative risk [RR] 3.3 [95% CI 1.3–8.2],  $p = 0.01$ ; 12 mm diameter, 17.0 [8.0–36.1],  $p < 0.0001$ ) and three locations (tip of basilar artery 2.3 [1.1–4.8],  $p = 0.025$ ; cavernous artery 0.15 [0.04–0.64],  $p = 0.01$ ; and posterior communicating artery 2.1 [1.1–4.2],  $p = 0.02$ ) with internal carotid artery aneurysms as the reference group. The effect of patients' ages was not significant when included in the multivariate model (1.007, [0.98–1.03],  $p = 0.56$ ).

The 5-year mortality rate, calculated with the Kaplan-Meier method, was 12.7% (11.7–13.7). In the 51 patients who had unruptured aneurysms at baseline, but with subsequent haemorrhage, 33 (65%) died. Of the 193 patients who died during the follow-up period, 52 died of intracranial haemorrhage, 44 of cancer, 14 of myocardial infarction, 16 of respiratory disease, 5 had cerebral infarction, 7 had congestive heart failure, 44 died of other causes, and 11 deaths were of unknown cause.

### Surgical and endovascular treatment

Of the 4060 patients who had surgery planned, 1917 underwent open surgical repair of their unruptured



**Figure 3: Poor surgical outcomes at 1 year by age, site, and size of aneurysm**

Poor outcome is death, a Rankin score between 3 and 5, or impaired cognitive status. Bars show 95% CI.

aneurysms; 451 patients had endovascular repair. Within these two groups of people who had operations, 264 had more than one procedure, and their treatment group was defined by the first procedure they had had. Mean follow-up was 4.0 years (SD 1.99) for patients who had open surgery and 3.7 years (1.85) for those who had endovascular procedures. Six surgical patients were lost to follow-up after they left hospital. Four of these patients had a Rankin score at discharge of 1, and two had a score of 2. One patient who had an endovascular intervention was lost to follow-up but had a Rankin score of 2 at discharge.

Demographic and clinical characteristics of patients who had surgery or endovascular repair are shown in tables 1, 2, and 3. Mean age was higher in the endovascular group, as were the mean size of aneurysm treated, the proportion of cavernous carotid aneurysms, and basilar tip aneurysms.

Various risk factors were assessed as potential predictors of surgical and endovascular outcome. For patients who had craniotomy, results of multivariate analysis showed that age was a strong predictor of outcome (figure 2) ( $\geq 50$  years RR 2.4 [1.7–3.3],  $p < 0.0001$ ). Other variables that were predictive of poor surgical outcome were a diameter greater than 12 mm (2.6 [1.8–3.8],  $p < 0.0001$ ); location in the posterior circulation (1.6, [1.1–2.4],  $p = 0.025$ ); previous ischaemic cerebrovascular disease (1.90 [1.1–3.02],  $p = 0.01$ ); and aneurysmal symptoms other than rupture (1.59 [1.2–2.4],  $p = 0.004$ ). For the endovascular cohort, results of multivariate analysis showed that poor outcome was

	Open surgical		Endovascular	
	Group 1 (n=1591)	Group 2 (n=326)	Group 1 (n=409)	Group 2 (n=42)
<b>At 30 days</b>				
Surgery-related death	28 (1.8%)	1 (0.3%)	8 (2.0%)	0
Disability				
Rankin score of 3–5 only	48 (3.0%)	7 (2.1%)	9 (2.2%)	1 (2.4%)
Impaired cognitive status only	68 (4.3%)	21 (6.4%)	13 (3.2%)	2 (4.8%)
Rankin score of 3–5 and impaired cognitive status	74 (4.7%)	7 (2.1%)	8 (2.0%)	0 (0.0%)
Overall morbidity and mortality for all patients	218 (13.7%)	36 (11.0%)	38 (9.3%)	3 (7.1%)
<b>At 1 year</b>				
Surgery-related death	43 (2.7%)	2 (0.6%)	14 (3.4%)	0
Disability				
Rankin score of 3–5 only	22 (1.4%)	3 (0.9%)	4 (1.0%)	0
Impaired cognitive status only	87 (5.5%)	23 (7.1%)	13 (3.2%)	3 (7.1%)
Both Rankin score of 3–5 and impaired cognitive status	48 (3.0%)	5 (1.5%)	9 (2.2%)	0 (0.0%)
Overall morbidity and mortality* for all patients	200 (12.6%)	33 (10.1%)	40 (9.8%)	3 (7.1%)

\*Overall morbidity and mortality includes death, and one of both Rankin score 3–5 and impaired cognitive status.

Table 5: Outcome 30 days and 1 year after surgery

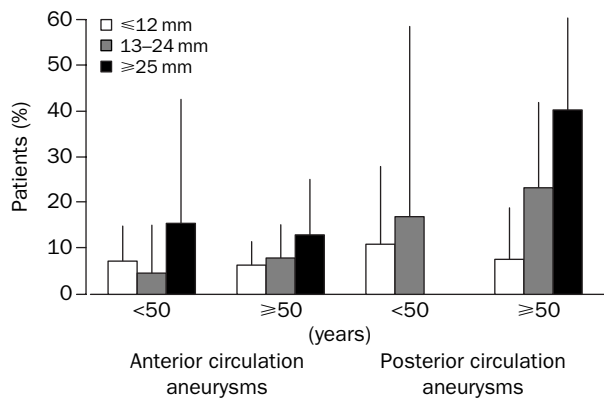


Figure 4: **Poor endovascular outcomes at 1 year by age, site, and size of aneurysm**

Poor outcome is death, a Rankin score between 3 and 5, or impaired cognitive status. Bars show 95% CI.

associated with an aneurysm diameter greater than 12 mm (2.4 [1.0–5.9],  $p=0.03$ ), and location in the posterior circulation (2.25 [1.1–4.4],  $p=0.02$ ).

Table 5 shows morbidity and mortality rates at 30 days and at 1 year for the surgical and endovascular cohorts. In the surgical cohort, rupture during surgery was reported in 116 (6%) patients, intracranial haemorrhage in 78 (4%), and cerebral infarction in 208 (11%). Within the endovascular cohort, perioperative haemorrhage was noted in ten (2%) patients and cerebral infarction in 26 (5%). Within the endovascular cohort, aneurysmal obliteration was judged to be complete in 231 (51%) patients and partly successful in 95 (21%), whereas in 104 (23%) patients, there was no obliteration and in 21 (5%) the status was unknown. For endovascular coiling specifically, obliteration was complete in 55% of patients and incomplete in 91 (24%); in 67 (18%) there was no obliteration and in 12 (3%) the status was unknown.

Figures 3 and 4 show 1-year surgical and endovascular morbidity and mortality rates according to the interactions of patients' age, and aneurysmal size and location. Because of a small sample size, some of the endovascular cohort analyses were associated with wider confidence intervals than were those for the open surgical cohort.

## Discussion

The idea that the natural history of unruptured intracranial aneurysms cannot be extrapolated from evaluation of patients with ruptured aneurysms is reinforced by the natural history data from this study. These data also indicate that aneurysm size (especially in patients who have not had previous subarachnoid haemorrhage) and location have a significant role in determining the risk of future rupture. Early rupture rates in the prospective group were higher than in the previously published retrospective group,<sup>1</sup> but the trends toward higher rates were not significant when compared with the overall retrospective rupture rates. Compared with rupture rates in the retrospective cohort, rupture rates were higher in patients in group 1 of the prospective cohort who had unruptured aneurysms at least 7 mm in diameter, especially for aneurysms 7–9 mm in diameter.

In patients with unruptured intracranial aneurysms of less than 7 mm in diameter who have not had a previous subarachnoid haemorrhage, the rupture rate is low (about 0.1% per year), and accordingly, it would be difficult to improve on the natural history of these lesions. These results do not show that family history of rupture

increases the risk in this group. Of note is that in the cohort of group 1 patients with small aneurysms, very few had symptoms, especially not acute or changing symptoms. These types of symptoms, although rare, might constitute an exception to the broader concept of a benign natural history.

In group 1 patients with unruptured aneurysms of diameter 7 mm or more and in all group 2 patients, the 5-year cumulative rupture rates were higher but were often equalled or exceeded by risks associated with surgical or endovascular repair of comparable lesions. To compare site, size, and group specific risks of the natural history with site, size, and age-specific risks of repair for each patient is important. For example, some of the greatest benefit from open surgery would be for patients younger than 50 years with unruptured aneurysms of the posterior communicating artery that are 7–24 mm in diameter.

Total morbidity and mortality rates at 1 year in patients with open surgical repair were 12.6% for group 1 and 10.1% for group 2; these rates are better than those reported in phase 1 of the ISUIA (15.7% for group 1 and 13.1% for group 2).<sup>1</sup> Patients' age is an important factor in overall surgical outcome, with a substantial increase in risk for those about 50 years and older, which rises substantially after age 60–70 years. Other predictors of poor surgical outcome include large aneurysmal size, location in the posterior circulation (particularly basilar tip), history of ischaemic cerebrovascular disease, and presence of aneurysmal symptoms other than rupture.

In many situations, a high-risk natural history is associated with a high surgical risk. For instance, a 30 mm unruptured intracranial aneurysm at the tip of the basilar artery would have a 5-year rupture risk of about 50–60% (about 40–45% risk of death or severe disability) and an operative risk of death or severe disability in the same range. In such a situation, choices about treatment may in part be based on the decision of a patient and their physician about whether risk is preferable immediately or over time; the decision might also be strongly influenced by the patient's age, comorbidities, and aneurysmal mass effect.

Characteristics of patients in the endovascular cohort differed greatly from those in the surgical group, and hence a direct comparison of rates of morbidity and mortality between these groups is not possible. The initial morbidity and mortality rates of 9.1% and 9.5% in the endovascular group might be relative overestimates because, compared with the surgery group, it had older patients with larger unruptured aneurysms, and a higher proportion of aneurysms in the posterior circulation. Nevertheless, endovascular morbidity and mortality seem to be less dependent on a patient's age, indicating that this procedure might have advantages for older patients. The initial obliteration rates of 55% in patients who had endovascular coiling and 50% in all endovascular patients also emphasise the need for an assessment based not only on immediate morbidity and mortality but also on long-term outcome and durability of treatment over several years. These results might prove highly dependent on aneurysm characteristics such as size, neck-dome ratio, and the presence of an intraluminal thrombus.

From a randomised trial comparing surgical clipping and endovascular coiling in 2143 patients with ruptured intracranial aneurysms, the International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group<sup>15</sup> reported that 23.7% of patients allocated to endovascular treatment were dependent or dead at 1 year compared with 30.6% in the open surgery group. However, these results cannot be easily extrapolated to patients with unruptured intracranial aneurysms.

Unlike previous studies of unruptured intracranial aneurysms, including ISUIA,<sup>1</sup> this study provides natural history data from prospectively identified patients, thereby eliminating several potential selection biases related to retrospective patient identification, including retrospective records review and availability of hard copy arteriograms. The ascertainment of data for risk factors, including family history and lifestyle, was also enhanced.

Potential limitations of this study include the non-randomised nature of the unoperated, surgical and endovascular cohorts, which led to asymmetries within groups; follow-up less than 5 years in over half the patients studied; and the relatively small size of the endovascular cohort compared with the surgical cohort. Continued follow-up of the entire prospective cohort is planned to address the issue of long-term rupture risk and durability of treatment.

Many factors are involved in the decision about management of patients with unruptured intracranial aneurysms. The lowest-risk natural history group includes asymptomatic patients in group 1 with unruptured aneurysms less than 7 mm in diameter in the anterior circulation. Asymptomatic patients younger than 50 years with unruptured aneurysms that are 24 mm or less in diameter in the anterior circulation have the lowest rates of surgical morbidity and mortality—5–6% at 1 year. Patients with no history of aneurysmal symptoms other than rupture are also more likely to have a good surgical outcome. A patient's age is especially important because, although it does not affect rupture rates, it has a substantial effect on surgical morbidity and mortality. Morbidity and mortality associated with endovascular procedures might be less dependent on age than surgical morbidity and mortality. Although endovascular procedures might be associated with less immediate risk, long-term risk and durability of treatment is not known and data from prolonged follow-up of treated patients are needed.

#### Contributors

All members of the steering committee participated in study design, data collection, data analysis, interpretation of results, and writing of the manuscript.

#### Conflict of interest statement

None declared.

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#### International Study of Unruptured Intracranial Aneurysms

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