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Risk of Rupture of Small Anterior Communicating Artery Aneurysms Is Similar to Posterior Circulation Aneurysms

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Background and Purpose—According to the International Study of Unruptured Intracranial Aneurysms (ISUIA), anterior circulation (AC) aneurysms of <7 mm in diameter have a minimal risk of rupture. It is general experience, however, that anterior communicating artery (AcoA) aneurysms are frequent and mostly rupture at <7 mm. The aim of the study was to assess whether AcoA aneurysms behave differently from other AC aneurysms.

Methods—Information about 932 patients newly diagnosed with intracranial aneurysms between November 1, 2006, and March 31, 2012, including aneurysm status at diagnosis, its location, size, and risk factors, was collected during the multicenter @neurIST project. For each location or location and size subgroup, the odds ratio (OR) of aneurysms being ruptured at diagnosis was calculated.

Results—The OR for aneurysms to be discovered ruptured was significantly higher for AcoA (OR, 3.5 [95% confidence interval, 2.6–4.5]) and posterior circulation (OR, 2.6 [95% confidence interval, 2.1–3.3]) than for AC excluding AcoA (OR, 0.5 [95% confidence interval, 0.4–0.6]). Although a threshold of 7 mm has been suggested by ISUIA as a threshold for aggressive treatment, AcoA aneurysms <7 mm were more frequently found ruptured (OR, 2.0 [95% confidence interval, 1.3–3.0]) than AC aneurysms of 7 to 12 mm diameter as defined in ISUIA.

Conclusions—We found that AC aneurysms are not a homogenous group. Aneurysms between 4 and 7 mm located in AcoA or distal anterior cerebral artery present similar rupture odds to posterior circulation aneurysms. Intervention should be recommended for this high-risk lesion group. **(*Stroke*. 2013;44:3018-3026.)**

Key Words: intracranial aneurysm ■ registries ■ risk factors ■ SAH ■ subarachnoid hemorrhage

The management of patients with unruptured cerebral aneurysms (UA) remains controversial because of their uncertain natural history. Although estimates of the prevalence of intracranial aneurysms range from 0.5% to 6% on radiological and autopsy studies, the incidence of aneurismal subarachnoid hemorrhage (SAH) is 10/100.000 per year in the United States, leading to the conclusion that the majority of UAs do not rupture.[1,2] The average risk of rupture of a UA is estimated to be between 1% and 2% per year.[3,4] The International Study of Unruptured Intracranial Aneurysms (ISUIA) reported on a retrospective and prospective multicenter study in 1998 and 2003.[5,6] In the latter, they observed that aneurysm location, size, and previous SAH were risk factors for rupture, with posterior circulation (PC) aneuryms collectively (including posterior communicating artery [PcoA] aneurysms) and aneurysms >7 mm located in the anterior circulation (AC) rupturing with at rates high enough to justify intervention. This observation seems to contradict the clinical perception that patients

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*A list of collaborators from the @neurIST Investigators is given in the Appendix.

Preliminary findings from this study have been presented as a digital poster at the Annual Meeting of the Congress of Neurological Surgeons, San Francisco, CA, October 16–21, 2010 (http://w3.cns.org/dp/2010CNS/38.pdf) and as an oral presentation at the 62nd annual meeting of the German Society of Neurosurgery (DGNC), Hamburg, Germany, May 7–11, 2011.

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commonly present with ruptured small aneurysms. Moreover, aneurysm locations were segregated only as being either AC or PC for risk assessment, raising concerns that the effects of pathophysiological mechanisms specific to individual arteries were combined reducing sensitivity to location as a risk factor. Work has since been published demonstrating the importance of aneurysm location, along with criteria such as patients' age, sex, ethnicity, and aneurysm morphology (size and shape) as risk factors for rupture. Recently, the Unruptured Cerebral Aneurysm Study of Japan (UCAS Japan) reported an annual rupture rate for UAs of 0.95%.[7] It also found that aneurysms >7 mm in general, smaller aneurysms of the anterior communicating artery (AcoA) or internal carotid-PcoA, and aneurysms having a daughter sac were associated with increased rupture risk.

The aim of the present study was to assess whether AcoA aneurysms behave differently from other AC aneurysms. Furthermore, we provide a detailed comparison with previous studies of the risk factors for aneurysm rupture, and in doing so examine whether simply dividing UAs into anterior or PC locations along with aneurysm size, as proposed by ISUIA, remains adequate for rupture risk analysis.

Methods

As part of the European Union's Sixth Framework Program Information Society Technologies priority, an information platform was designed, developed, and implemented by a group of clinical centers, universities, and companies from across Europe. Its purpose was to integrate complete biomedical information for the management of cerebral aneurysms. The system was used in the collection of the clinical data on aneurysm patients from multiple centers as described below.

Patients

Between November 1, 2006, and March 31, 2012, a total of 932 patients diagnosed with intracranial aneurysms were enrolled at 7 European clinical centers (Royal Hallamshire Hospital, Sheffield, United Kingdom; John Radcliffe Hospital, Oxford, United Kingdom; Erasmus Medical Center Rotterdam, The Netherlands; University Hospital of Geneva, Switzerland; University Hospital of Barcelona, Spain; General Hospital of Catalonia, Spain; University Hospital of Pecs, Hungary) using the platform. The data collection protocol was approved by individual local ethics committees, and written consent obtained from patients or where appropriate, next of kin, in all cases.

All clinical centers were made aware of the importance of consecutive recruitment from an identifiable catchment area but only 1 was able to verify and guarantee consecutive recruitment from a stable population. The University Hospital of Geneva embedded the data collection tool (@neuQuest) in the hospital's electronic information system and trained neurosurgical medical staff to use the platform as the basis of the electronic medical record. Regular checks were performed to ensure consistency between the administrative and medical databases. Thus, prospective and consecutive recruitment of all patients with a newly diagnosed intracranial aneurysm and known to be resident within this referral area was ensured, and the referral area did not vary during the course of data collection.

For analysis, the data were separated into 2 groups:

The Total @neurIST Cohort (TC), including all the cases of diagnosed intracranial aneurysm recruited prospectively or retrospectively by the 7 participating clinical centers. In the TC, 651 (70%) patients were recruited prospectively, and 281 (30%) patients were recruited retrospectively, for a total of 932 patients, of which 343 (36.8%) patients had no history of SAH and 589 (63.2%) patients had a SAH.

The Consecutive Cohort (CC), a subset of the TC, including cases prospectively and consecutively diagnosed with ≥1 saccular intracranial aneurysm, living within the hospital's recruitment area. Two patients were excluded from the analysis because they refused to give consent to participate (0.6%). The CC consisted of 404 patients; 194 (48%) patients without history of SAH and 210 (52%) patients recruited after SAH. Of the patients without SAH, 174 (89.7%) patients had incidentally discovered aneurysm(s) and 20 (10.3%) patients had symptomatic aneurysms causing cranial nerve palsy or focal strokes from upstream thrombosis.

Aneurysms and Clinical Information

For all recruited patients, data were collected relating to aneurysm location, characteristics, clinical history, and risk factors, some particulars of which are as follows.

Neurovascular Nomenclature

Adapted from the ISUIA study, aneurysm locations were defined as follows. The internal carotid artery (ICA), anterior cerebral artery (ACA), AcoA, middle cerebral artery (MCA), vertebral artery, basilar artery, and posterior cerebral artery were considered as parent vessels. In accordance with most neurovascular publications, we defined each parent artery segment as starting proximal to the origin of a branch and finishing proximal to the next branch artery. Each parent artery segment was then given the name of the branch that departs from that segment. The following branches were taken into consideration: ophthalmic artery, PcoA anterior choroidal artery, pericallosal artery, posterior inferior cerebellar artery, and anterior inferior cerebellar artery, and superior cerebellar artery (Figure 1A).

For bifurcations, the segments were defined as per Rhoton,[8] starting where the walls diverge and finishing at the cross-sections perpendicular to the flow within the daughter vessels where the projection of the parent vessel wall crosses the medial wall of the daughter vessel (see Figure 1B).

Risk Factors of Aneurysm Rupture and SAH

Risk factors considered in the study were those previously described for aneurysm rupture, including presence of an unruptured symptomatic aneurysms (relative risk [RR], 8.2 [95% confidence interval {CI}, 3.9–17.0]), aneurysms >10 mm (RR, 5.5 [95% CI, 3.3–9.5]), location in the PC (RR, 4.1 [95% CI, 1.5–11.0]), and female sex (RR, 2.1 [95% CI, 1.1–3.9]).[9–15]

We also included those additional factors identified by a systematic Cochrane literature review of reviews[16] as having significant RR associated with SAH in the general population, including positive family history (RR, 4.0 [95% CI, 2.7–6]), smoking (RR, 2.4 [95% CI, 1.8–3.4]), alcohol consumption of >150 g/wk (RR, 2.1 [95% CI, 1.5–2.8]), hypertension (RR, 2 [95% CI, 1.5–2.7]).

The @neurIST system was designed to serve the clinical management of patients with aneurysms. The data collected therefore included the above parameters as well as the patient's presenting history, symptoms, and signs, and details of any treatments and their follow-up. These records, coupled with angiographic imaging (eg, computed tomography angiogram, magnetic resonance angiogram, digital subtraction angiogram, digital rotational angiogram) and neurovascular morphological measurements and characterizations, were collated using elements (@neuQuest, @neuFuse, @neuInfo) of the purpose built information platform, developed during the course of the project. Prospective and retrospective clinical data were collected and the subject's residency could be determined from within the database.

Statistical Analysis

It has been postulated that the process leading to an aneurysmal SAH depends first on the formation of ≥1 aneurysm and, subsequently, the rupture of the aneurysm wall; our study is designed to estimate the latter risk.

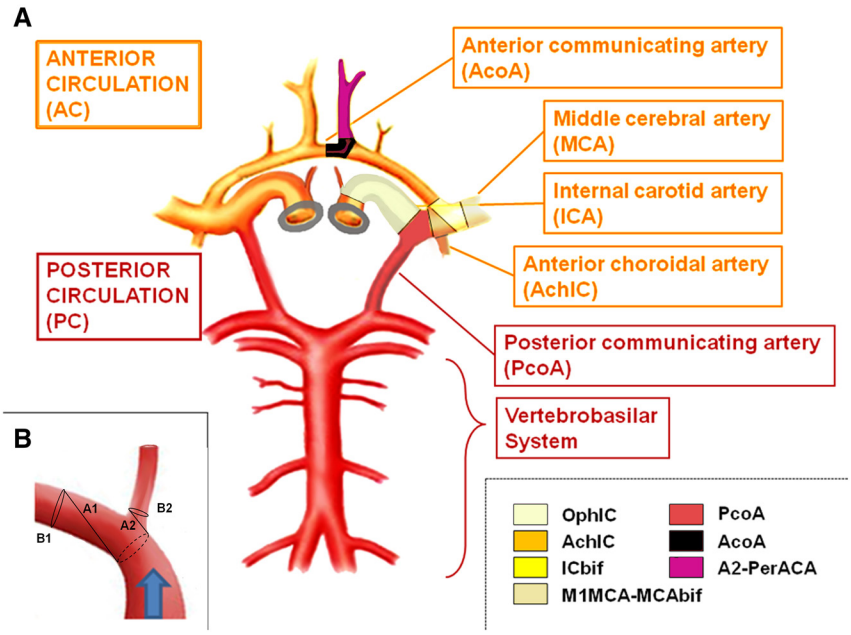

Figure 1. Left, Basis for attributing aneurysm locations according to the International Study of Unruptured Intracranial Aneurysms (ISUIA). Aneurysms of the internal carotid artery (ICA), middle cerebral artery (MCA), and anterior cerebral artery (ACA; excluding posterior communicating artery [PcoA]) belong to the anterior circulation (orange), whereas aneurysms of the vertebrobasilar system, PcoA, and PcoA segment of the ICA belong to the posterior circulation (red). Note that there is no subdivision in ISUIA between ACA and anterior communicating artery (AcoA). **Right**, Refined subdivision of neurovasculature as applied in this study: each parent vessel segment starts proximal to the origin of the branch and finishes proximal to the next branch and takes the name of the branch departing from the segment. Inset, As defined by Rhoton,[8] a bifurcation begins where the walls diverge (dotted line) and ends on the cross-sections perpendicular to the flow (lines B1 and B2) located in the daughter vessels where the projection of the parent vessel wall (lines A1 and A2) cross the medial wall of the daughter vessel. AC indicates anterior circulation; AchIC, anterior choroidal artery segment of the ICA; and PC, posterior circulation.

The above data collection allowed us to count and compare the occurrence of newly diagnosed ruptured and unruptured aneurysms in each vessel segment. To evaluate the risk of rupture of an aneurysm located in a particular vessel segment, the odds of aneurysms being discovered ruptured versus being discovered unruptured was calculated for each vessel segment.

The role of size in AcoA aneurysm rupture was further compared with MCA aneurysms using groups composed of aneurysms with maximum dome sizes in the following ranges: 0 to 4, 4 to 7, 7 to 12, 12 to 25, and >25 mm. Again, the odds of aneurysms being discovered ruptured were calculated for comparison between AcoA and MCA locations.

To compare our observations with those reported in ISUIA, the TC data were analyzed for size and location effects, as per the categorizations used in the ISUIA report. This involved dividing the aneurysms by size into 2 groups: aneurysms of <7 mm in diameter and those between 7 and 12 mm, and then subdividing both groups by location. Observations on larger aneurysms groups are not reported because the rupture risk is known to be high and statistical robustness is low because of their relative rarity and limited population studied. In keeping with the ISUIA categorization, the PC group was composed of aneurysms located in the vertebrobasilar system, basilar tip, posterior cerebral artery, and PcoA segment of the ICA. The AC was formed by pooling all aneurysms located on the ICA (excluding PcoA), ACA (including AcoA), and MCA (ACA+ICA+MCA). To assess the place of AcoA aneurysms relative to this categorization system, subcomponents of the AC (namely the MCA-ICA, the ACA, and AcoA) were also considered separately. The 5-year cumulative rupture risk of 2.6%, calculated by ISUIA for AC aneurysms between 7 and 12 mm, was taken as point of reference. The latter group was used as reference to calculated odds ratios (ORs).

To verify that the TC and CC were consistent, the risk factors and clinical characteristics of the cohorts were compared with each other and, to the extent possible, the same comparisons were made to the results in a 2002 report by Weir et al.[14] Limited to UA patients with no previous history of SAH, similar comparisons were made between the @neurIST TC, Weir et al[14] 2002, the ISUIA cohorts, and the 2012 UCAS report. For this, frequencies were calculated on a per patient basis and, for completeness, we also calculated per aneurysm statistics. The purpose of these comparisons was to identify differences between the cohorts that could affect the conclusions drawn from the observations either attributable to selection bias or to general changes in the population over time.

Case categorization and information extraction were performed using the @neuBrowser tool developed in the course of the @neurIST project. Statistics were produced using SPSS version 15.0 software (SPSS: IBM, NY) or MedCalc software (MedCalc software, Belgium), whichever was considered to be the most practical. Results for continuous variables are reported as mean±SD. The test of significance for mean differences was assessed using Student *t* test (significance level $P<0.05$). Odd ratios are reported with a 95% CI. Significance of differences in proportions was assessed by means of Fisher exact tests.

Results

Summaries of patient demographics, clinical histories, and risk factors obtained for the 2 @neurIST cohorts and their comparisons are given in the Table. In both the TC and CC, there was a ratio of ≈3 females for every male (Table). The average maximal unruptured aneurysm diameter was significantly higher in the TC than in the CC (6.35±4.8 versus 5.51±4.23 mm; $P<0.05$). However, there was a higher proportion of small (2–7 mm) aneurysms (63.9% versus 52.8%; $P<0.05$) and a significantly lower proportion of large (13–24 mm) aneurysms (6.3% versus 12.2%; $P<0.05$) reported in the CC (Table I in the online-only Data Supplement). The proportion of symptomatic patients was significantly smaller in the CC (9% versus 16.9%; $P<0.05$). Both cohort populations were, however, comparable for all other variables studied (Table; Table I in the online-only Data Supplement).

Location and Size Dependence of Aneurysms and Rupture

AcoA was the vessel segment most commonly bearing a ruptured aneurysm (n=162), followed by the PcoA (n=121) and MCA bifurcation (n=72). The occurrence of SAH secondary

Table. Baseline Characteristics of Patients and Aneurysms for Cohorts

	Weir et al[14] (n=507)	Consecutive Cohort (n=404)	Total @neurist Cohort (n=932)	*P* Value*	*P* Value†
Period of recruitment	1967–1987	2007–2012	2007–2012		
Baseline characteristics of patients					
Age, mean (SD)	47 (NA)	55.3 (14.11)	55.02 (13.24)	NA	NS
Sex ratio (% of female)	318/189 (62.7)	298/106 (74)	663/269 (71)	<0.005	NS
Ratio of multiple aneurysms (% of cases with multiple lesions)	111/396 (21.9)	134/270 (33)	278/654 (30)	<0.005	NS
Percentage of patients with SAH	86	53	63	<0.001	<0.001
Number of aneurysms		621	1347		
Max aneurysm diameter, mm; mean (SD)	9.7 (0.3 se)	6.2 (7.35)	6.76 (11.39)	<0.001	NS
Baseline characteristics of aneurysms					
Size of aneurysm, number of patients (%)					
0–1.9 mm		8 (2.0)	13 (1.4)		NS
2–6.9 mm	155 (38.5)	239 (59.2)	490 (52.6)	<0.001	<0.05
7–12 mm	144 (36.0)	117 (29.0)	316 (33.9)	NS	NS
13–24 mm	73 (18.0)	33 (8.2)	95 (10.2)	<0.001	NS
>24 mm	30 (7.5)	7 (1.7)	18 (1.9)	<0.001	NS
Location of aneurysm, number of patients (%)					
Cavernous part of carotid artery	18 (3.5)	26 (6)	50 (5)	NS	NS
Internal carotid artery	53 (10.4)	109 (27)	218 (23)	<0.001	NS
Anterior communicating or anterior cerebral artery	158 (31.2)	141 (35)	308 (33)	NS	NS
Middle cerebral artery	158 (31.2)	137 (34)	386 (31)	NS	NS
Posterior communicating artery	88 (17.4)	65 (16)	186 (20)	NS	NS
Vertebrobasilar system (other than basilar tip)	10 (2)	33 (8)	74 (8)	<0.001	NS
Tip of basilar artery	22 (4.3)	30 (7)	79 (8)	<0.005	NS

NA indicates not applicable; NS, not significant; SAH, subarachnoid hemorrhage; and se, standard error.
**P* value comparing @neurIST Total Cohort (TC) with Weir et al.[14]
†*P* value between @neurIST cohorts.

to the rupture of aneurysms was more frequent in the AcoA and in the PcoA than in the MCA bifurcation (RR, 2.25 [95% CI, 1.7–3.0] and RR, 1.7 [95% CI, 1.2–2.25], respectively).

Figure 2 shows a forest plot reporting the ORs of aneurysms discovered ruptured or unruptured at each anatomic location (regardless of aneurysm size) in the TC. ORs to the right of the reference line (OR=1) reflect a higher than average proportion of aneurysms being ruptured at discovery. AcoA aneurysms had the highest OR (TC: 4.3 [95% CI, 2.8–6.5]; CC: 2.1 [95% CI, 1.4–3.2]) for rupture followed in order by basilar tip, A2 and pericallosal, and PcoA and posterior inferior cerebellar artery aneurysms. In contrast, aneurysms located in the ophthalmic segment of the ICA had the lowest OR for rupture. Observations were similar when analyzing the CC (Figure I in the online-only Data Supplement).

For different size subgroups, the odds of discovering ruptured AcoA aneurysms relative to that of similarly sized MCA aneurysms are compared in Figure 3. The OR for ruptured AcoA aneurysms was the highest in the size group 4 to 7 mm (OR, 8.3 [95% CI, 4.4–16]; $P<0.001$). At larger diameters, the differences decreased as the corresponding proportion of ruptured MCA aneurysms increased; at >12 mm diameter, no conclusions were drawn in light of the small sample size.

Reflecting the ISUIA classification of aneurysms by location (AC or PC) and size (<7 mm, 7–12 mm, or >12 mm in diameter), the incidences and ORs for ruptures of the subgroups are compared in Figure 4 (aneurysms >12 mm excluded). Also shown are the behaviors of separable AC components, broken down as AcoA, ACA (including A1, AcoA, A2, PerA, and Distal ACA aneurysms), or MCA+ICA aneurysms. The OR of ruptured AC aneurysms of <7 mm in size showed fewer ruptured aneurysms than the reference group, suggesting their rupture risk could be ≤2.6% per 5 years. In contrast, aneurysms

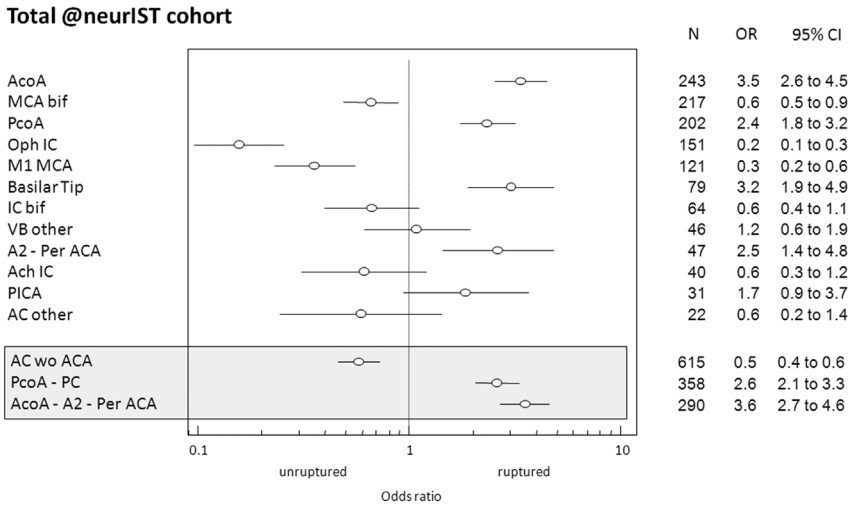

Figure 2. Odds ratios of aneurysms discovered ruptured vs unruptured for each location compared with all other aneurysms included in the cohort. N is the number of aneurysms observed for each location or location cluster. AC indicates anterior circulation; AchIC, anterior choroidal artery segment of the ICA; AcoA, anterior communicating artery; CI, confidence interval; IC bif, ICA bifurcation; MCA, middle cerebral artery; Oph IC, ophtalmic segment of the ICA; OR, odds ratio; PcoA, posterior communicating artery; Per ACA, pericallosal segment of the ACA; PICA, posterior inferior cerebellar artery; and VB other, other location within the vertebrobasilar system.

located in the PC showed a trend to higher ORs (1.29 [95% CI, 0.9–1.9]). These observations are in accordance with the ISUIA observations. We found however, that aneurysms of <7 mm in size in ACA locations in general, and AcoA aneurysms in particular, were more likely to be ruptured at presentation than other AC aneurysms, and that they showed ORs similar to PC lesions (ACA: 1.58 [95% CI, 1.10–2.30]; AcoA: 2.0 [95% CI, 1.31–3.03]). Interestingly, the OR for ruptured aneurysms <4 mm in the AcoA was smaller, although not significantly so, than the reference group (OR, 0.547 [95% CI, 0.279–1.073]). When separated from the AC aneurysms, a low OR for rupture of ICA+MCA became apparent even at diameters up to 12 mm (0.26 [95% CI, 0.18–0.37] for aneurysms <7 mm and 0.61 [95% CI, 0.39–0.95] for aneurysms between 7 and 12 mm; Figure 4).

Comparison With Previous Studies

Included in the Table, along with the details of the @neurIST cohorts, are summary data from Weir et al[14] 2002. A similar summary and analysis, limited to patients with UA at the time of recruitment, is given in Table I in the online-only Data Supplement. Because our interest here is in possible differences in bias between studies, or changes in the patient populations over time, below, we focus primarily on describing the points where significant differences were observed. Care has been taken to compare population of patients recruited according to the same criteria between studies. @neurIST cohorts are compared with Weir et al,[14] whereas population of patients recruited with unruptured aneurysms and no history of SAH are compared with ISUIA and UCAS, and the subpopulation of patients recruited with unruptured aneurysms in Weir et al.[14]

Demographics, Signs, and Symptoms

The TC was populated with older patients, more females, more patients with multiple aneurysms, and fewer patients that had SAH than reported in Weir et al[14] (Table).

The patients with unruptured aneurysms in the TC and ISUIA populations were similar in age (56±13.1 versus 55±13.1 years), whereas those in UCAS were older (65±10.4 years) and those in Weir et al[14] were younger (46 years). Fewer

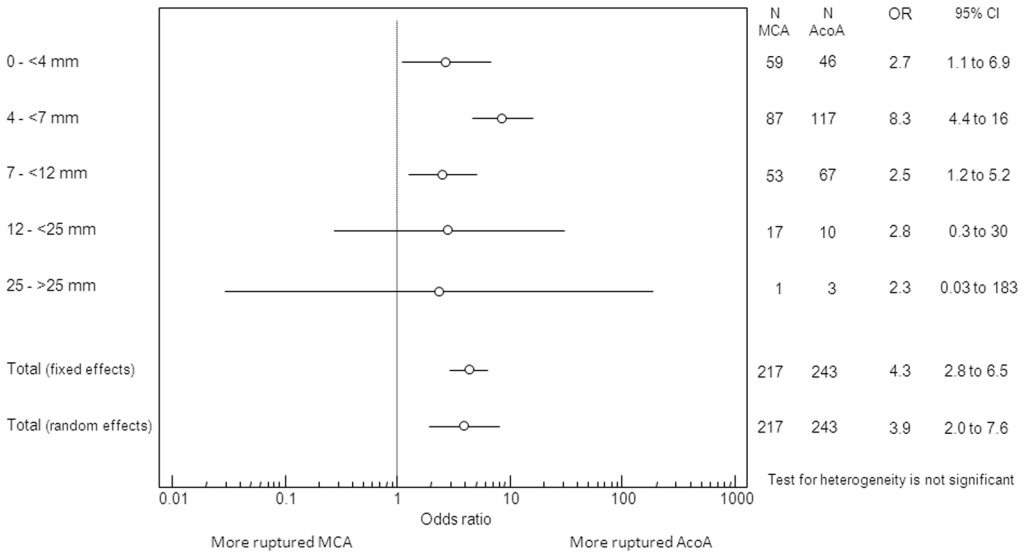

Figure 3. Odds ratios of anterior communicating artery (AcoA) aneurysms being discovered ruptured vs unruptured relative to those of the middle cerebral artery (MCA) stratified by size. CI indicates confidence interval; and OR, odds ratio.

	<7mm			7-12mm		
	ruptured/total	OR	95%CI	ruptured/total	OR	95%CI
ACA+MCA+ICA	209/649	0.54	0.39 to 0.74	**99/211**	**Reference**	
ICA+MCA	78/424	0.26	0.18 to 0.37	46/132	0.61	0.39 to 0.95
ACA	131/225	1.58	1.10 to 2.30	53/79	2.31	1.34 to 4.00
AcoA	104/163	2.00	1.31 to 3.03	46/67	2.47	1.38 to 4.44
PC	107/201	1.29	0.87 to 1.90	76/113	2.32	1.44 to 3.74

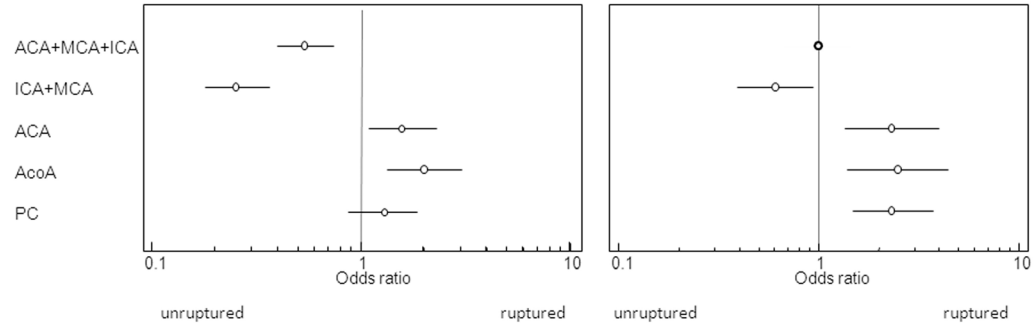

Figure 4. Odds of aneurysms discovered ruptured vs unruptured for groups clustered according to location and size compared with a reference group defined as aneurysms between 7 and 12 mm located in the anterior circulation aneurysm as defined by the International Study of Unruptured Intracranial Aneurysms, and for subsets of the anterior circulation. ACA indicates anterior cerebral artery; AcoA, anterior communicating artery; CI, confidence interval; ICA, internal carotid artery; MCA, middle cerebral artery; OR, odds ratio; and PC, posterior circulation.

of the @neurIST patients with unruptured aneurysms had multiple aneurysms or a family history of aneurysms than those in ISUIA. @neurIST patients had lower levels of alcohol and tobacco consumption and a trend toward fewer patients using stimulants as compared with ISUIA (Table I in the online-only Data Supplement).

Relative to ISUIA, the comparable patient group in UCAS was older, and contained more males, whereas fewer patients were smokers, had multiple aneurysms, were symptomatic, or had a family history of SAH (Table IV in the online-only Data Supplement).

Ruptured Versus Unruptured

The population of patients with unruptured intracranial aneurysms (UA) corresponded to 37% of all cases recruited to the @neurIST (47% in the CC). This clearly contrasts with the observation made between 1967 and 1987 reported by Weir in 2002 wherein only 14% of patients were found to have UAs.

Location

@neurIST contained significantly more patients with internal carotid aneurysms than reported by Weir et al[14] (CC: 27%, TC: 23%, Weir: 10.4%; $P<0.001$). Patients with PC aneurysms (vertebrobasilar and basilar tip) were also more frequent in @neurIST than in Weir et al (16% versus 6.3%; $P<0.01$; Table).

Limited to patients with UAs, internal carotid aneurysms were significantly more represented in the @neurIST cohorts than in ISUIA and Weir et al[14] (patient-based counting, respectively 35% versus 22.9% and 13.9%; $P<0.01$; Table I in the online-only Data Supplement). Comparing the distribution of aneurysms by location, aneurysms located in the ICA were significantly more frequent in @neurIST than in UCAS (aneurysm-based counting: 29% versus 19%; $P<0.001$); in contrast, aneurysms located in PcoA were significantly less frequent in @neurIST (11.9% versus 16.5%; $P<0.05$; Table III in the online-only Data Supplement). This latter observation may be attributable to differences in classifying aneurysms between the PcoA and the anterior choroidal artery segment of the ICA.

Unruptured AcoA aneurysms also formed a much greater fraction of the observed patients with aneurysms in the @neurIST cohort than those in Weir et al[14] and ISUIA (24% versus 13.9% and 10.3%, respectively; $P<0.001$; Table I in the online-only Data Supplement). Comparing @neurIST and UCAS cohorts, a similar representation of unruptured AcoA aneurysm was observed (Table III in the online-only Data Supplement).

The pattern of aneurysm distribution varied slightly between @neurIST centers. Centers where neurosurgeons were less involved in the project reported fewer MCA and pericallosal segment of the ACA aneurysms ($P<0.001$) and proportionally more PcoA, basilar artery, and M1 aneurysms ($P<0.001$).

Size

The average aneurysm size was similar between UCAS and @neurIST CC (Table I in the online-only Data Supplement), with progressively larger average aneurysm sizes being seen in the @neurIST TC, ISUIA, and Weir et al[14] studies.

However, concerning the distribution of aneurysm sizes, the @neurIST TC was close to that of Weir et al,[14] whereas the distribution for the @neurIST CC was closer to that of ISUIA, with the former pairing having slightly fewer small and more midsized aneurysms relative to the latter pairing. UCAS was populated with significantly more patients with aneurysms <7 mm than ISUIA, TC, and CC (78.4% versus 62%, 53.4%, 65.2% respectively; $P<0.01$; Table II in the online-only Data Supplement).

Discussion

This study was designed to evaluate AcoA aneurysm rupture risk relative to the anterior and PC location and size groupings used in ISUIA. Our motivation was the common perception that the behavior of AcoA aneurysms is not that suggested

by the ISUIA results. Consistent with ISUIA, we found that aneurysms <7 mm in size and located in the AC (as defined in ISUIA) were less likely to be discovered ruptured than aneurysms in other locations or of larger size. More importantly, however, our results also provide statistical evidence that AcoA aneurysms rupture with smaller diameters than MCA aneurysms and, that generally, AcoA aneurysms rupture at least as frequently as those of the PC, in contrast to those in other AC locations. Furthermore, our data indicate that risk of rupture of aneurysms of <7 mm located in the internal carotid or MCA is low relative to the PC and AcoA, but not negligible. Thus, the AC as defined by ISUIA should not be considered homogeneous for aneurysm rupture, and we suggest that because of unknown factors (ie, embryogenesis or blood flow coherence), both AcoA and PcoA be considered with the PC for risk stratification.

The distinct rupture risk of AcoA aneurysms seen in the present study has important implications for our understanding of the ISUIA and UCAS studies. As mentioned by the authors of ISUIA, "the potential limitations of the study include the nonrandomised nature of the unoperated, surgical and endovascular cohorts, which led to asymmetries within groups;…" We think that the implications of this possible recruitment bias have not been fully appreciated by the medical community. The assignment of patients to one of the 2 ISUIA cohorts (treated or not treated) was "based on whether surgical or endovascular treatment of ≥1 unruptured intracranial aneurysm was planned on clinical grounds at the time the patient was first seen at the ISUIA center." Although the study coordinators took steps to minimize bias, there is no description or discussion of how consecutive the recruitment was. It may have been for various unstated reasons, for example, a reputation to rupture at small diameters or surgical accessibility, that more patients with unruptured AcoA aneurysms were treated and not observed in ISUIA. This may explain why patients with AcoA aneurysms represented only 13.5% of patients enrolled, as opposed to 24% in @neurIST, and why 10.3% were followed up without surgery. Other possible reasons for this difference include the following: (1) increased opportunities and improved quality of cerebral imaging, leading to more patients being diagnosed with incidental aneurysms, (2) a decrease in the incidence of rupture of existing aneurysms, resulting in an increase of the prevalence of unruptured lesions, (3) an aging population that may increase the prevalence of aneurysms, and (4) changes in an environmental risk factor such as increased prohibition of smoking in public areas. These factors apart, patients in ISUIA with ICA and AcoA aneurysms were significantly more frequently assigned to treatment than those with PcoA aneurysms. All together, our observations suggest that the AcoA location was under-represented in the ISUIA study, and that the particular behavior of lesions in that location could not be distinguished from lesions in other AC sites. This conclusion is supported by our finding that when all AC aneurysms are included in 1 single group, the increased rupture risk associated of AcoA aneurysms is masked (Figure 4).

Based on these considerations, we emphasize that the observation in ISUIA of a negligible rupture risk for AC aneurysms <7 mm in size is only applicable in the situation where expert clinicians had considered observation as an acceptable alternative to treatment.

In order that our data be valid as a basis for the above comparison of our patient group with ISUIA, we sought to reduce case-selection bias as much as possible through a multicenter, population-based study (transversal study). Patients were recruited prospectively and consecutively in one of the clinical centers, and an audit was performed to verify that cases were not missed. All the other centers attempted to achieve these aims but were not able to provide checks that all cases were captured, and hence completeness in these sites is not guaranteed. To estimate and identify potential biases, a number of characteristics of patients and aneurysms reported when the lesion was initially discovered were examined between the @neurIST cohorts. We observed that the proportion of incidentally discovered aneurysms in @neurIST was significantly higher than in historical reports but also that this trend was more pronounced in the CC where all aneurysms identified within the clinical center were captured. However, the proportion of patients with known risk factors (familial history, symptomatic, multiple aneurysms) was lower. These observations suggest that selection biases are progressively attenuated because of the increased use and quality of head imaging. Despite differences in recruited populations, similar results were obtained in the 2 @neurIST cohorts and when analyzing separately cohorts recruited in each center.

All the studies of intracranial aneuryms, including the present, are affected by ≥2 limitations. First, the recruitment population can be naturally defined by the established, stable activity of the centers involved, but this is a difficult quantity to determine accurately. Furthermore, costs and ethical issues preclude screening for intracranial aneurysms in a randomly selected population. In consequence, we are not able to report absolute incidence, but rather must consider the odd ratios of aneurysm rupture associated with a condition in the fraction of the recruited population affected or not by the studied risk factor. Therefore, it can be assumed that the OR for rupture was overestimated because of undiagnosed unruptured aneurysms mentioned above. In counterpoint, the loss of information on patients with lethal hemorrhage and dying before being brought to medical attention and the impact on natural history in treated cases would lead to an underestimation of the OR. The validity of our observation may therefore be affected by the selection of a population where the distribution of unruptured aneurysms according to location and size does not match the distribution in the overall population.

When analyzing the odds of aneurysm rupture by location, the AcoA location was the most frequent site of aneurysm rupture followed by PcoA and MCA bifurcation in both the consecutive and TC. To determine whether the observed high frequency of ruptured aneurysms is associated with a higher prevalence of aneurysm or a higher risk of aneurysm rupture, the prevalence of aneurysm by location and size groups was estimated from the population of patients diagnosed with unruptured aneurysms We could not identify factors that could explain why unruptured aneurysms in the AcoA should be underdiagnosed as compared with other locations. As for aneurysms located in the IC (close to bone structures),

the incidence of unruptured aneurysms diagnosed increased between older and more recent studies.

Concerning risk associated with size, we made the assumption that if aneurysm rupture modifies the size or the morphology, it would happen regardless of location. Therefore, we decided to highlight the risk of rupture associated with aneurysm size by comparing AcoA with MCA, both locations sharing high anatomic similarities. Aneurysms between 4 and 7 mm in the AcoA were significantly more frequently observed ruptured than similar size aneurysms in the MCA location. This observation also held when the AcoA location was compared with other AC locations.

It has been debated whether the risk of rupture of an UA can or cannot be extrapolated from size or morphology observations of ruptured aneurysms as these features may be modified by the rupture itself.[17,18] The Small Unruptured Intracranial Aneurysm Verification (SUAVe) study has demonstrated the different characteristics of aneuryms relative to their growth and rupture. Different types of aneurysm evolution have been described, from rapid aneurysm development and rupture at small sizes within days or months, to slower growing aneurysms with rupture occurring after years or remaining rupture free for decades. Based on a single evaluation at the time of diagnosis, our work is unsuited to answering questions of how aneurysms grow and what rupture rate to expect. Recently, the UCAS Japan reported results of a longitudinal follow-up study of patients enrolled from January 2001 through April 2004 and follow-up until April 2010. A total of 5720 patients with 6697 aneurysms were studied; of which, 3050 aneurysms were treated during follow-up, and 3647 aneurysms were left for observation. A total of 11 660 aneurysm-years were recorded with 111 aneurysm ruptures. The overall annual rupture rate in the untreated population of patients in Japan was estimated at 0.95% (95% CI, 0.79–1.15). The authors report that compared with MCA aneurysms, lesions located in the AcoA or in the PcoA are more likely to rupture with hazard ratio of 1.90 (95% CI, 1.12–3.21) and 2.02 (95% CI, 1.13–3.58), respectively. As stated by the UCAS authors, however, this type of study can never be entirely free of case-selection bias. A significant proportion of small aneurysms were treated, and the characteristics of these aneurysms were different from the studied group. Therefore, it is difficult to extrapolate the observed rupture rate to the general population of incidentally discovered aneurysms. It would be extremely interesting to compare the OR and the rate of rupture for aneurysms stratified in identical location and size groups for both @neurIST and UCAS. @neurIST continues to record rupture or treatment of unruptured aneurysms in the CC cohort to provide longitudinal data on top of the transversal information reported herein. We may then extrapolate rupture rates in the clinically pertinent population by comparing ORs with homogenous aneurysm groups with known rupture rates and be able to propose estimates.

Currently, most studies apply multiple univariate analyses in evaluating rupture risk but these may be inadequate because, as illustrated by our results, location, size, and many other factors may influence aneurysm behavior, such as sex, smoking, alcohol consumption, and hypertension. New tools are being developed to assess the risk of rupture using genetics, transcriptomics, morphodynamic evaluation, and simulations, and new treatments are being explored. This progress puts ever greater demands on the scale of aneurysm studies required for adequate and appropriate statistical analyses to be performed. The only way to achieve this is through wider multicentric collaboration and rigorous patient documentation practices. Further projects need to be launched to integrate all this information and help clinicians provide individualized recommendations to patients and the general population.

Conclusions

AcoA aneurysms with a size between 4 and 7 mm have a higher risk of rupture than was inferred from the ISUIA observations. We recommend that in the absence of complicating comorbidities, unruptured AcoA aneurysms >4 mm should be treated. Small aneurysms of <7 mm located in the internal carotid or middle cerebral arteries were seen to present lower risk of rupture. We recommend following these aneurysms with regular imaging.

Appendix

Collaborators From the @neurIST Investigators

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Supplementary Table I

Cohort	ISUIA no surgery (n=1692)	ref	Weir et al unruptured (n=170)	p	UCAS Not Surg (n=3647)	p	Consecutive C. noSAH (N=191)	p	Total @neurist C. no SAH (N=343)	p	p*
Period of recruitment	1991-1998		1967-1987		2001-2004		2007-2012		2007-2012		
Baseline characteristics of patients											
Age (mean [SD])	55.2 [13.1]		46[NA]	NA	65.0 [10.4]	<0.0001	57.35 [14.09]	0.03	56.67 [13.09]	NS	NS
Gender ratio (% of female)	1261/431 (74.5%)		124/46 (72.9%)	NS	2480/1167 (68%)	<0.0001	148/43 (77%)	NS	262/81 (76%)	NS	NS
ratio of multiple aneurysms (% cases with multiple lesions)	679/1013 (40.3%)		NA	NA	1003/2641 (27.5%)	<0.0001	59/132 (31%)	<0.05	96/247 (28%)	<0.001	NS
symptomatic patients	186/1506 [11%]		9%	NA	171/5720 [3%]	<0.0001	18/173 [9.4%]	NS	58/285 [16.9%]	<0.01	<0.05
number of aneurysms	2686		NA		6697		291		493		
Max aneurysm diameter (mm) (mean [SD])	7.4 [6.9]		7.76 [0.68"se"]	NS	5.3[3.3]	<0.0001	5.51 [4.23]	<0.001	6.35 [4.8]	<0.005	<0.05
Baseline characteristics of aneurysms											
Size of aneurysm (number of patients [%])											
0-1.9mm							4 [2.1%]	NA	4 [1.2%]	NA	NS
2-6.9mm	1049 [62%]		79 [55%]	NS			122 [63.9%]	NS	181 [52.8%]	<0.005	<0.05
7-12mm	390 [23%]		40 [28%]	NS			50 [26.2%]	NS	108 [31.5%]	<0.005	NS
13-24	198 [12%]		15 [11%]	NS			12 [6.3%]	<0.05	42 [12.2%]	NS	<0.05
>24mm	55 [3%]		9 [6%]	NS			3 [1.6%]	NS	8 [2.3%]	NS	NS
Location of aneurysm (number of patients [%] number of aneurysms [%])											
Cavernous part of carotid artery	210 [12.4%]		18 [10.6%]	NS			22 [12%]	25[3%] NS	37 [11%]	42[3%] NS	NS
Internal carotid artery	387 [22.9%]		22 [13.9%]	<0.01			68 [36%]	81[28%] <0.0005	121 [35%]	144[29%] <0.0001	NS
Anterior communicating or anterior cerebral artery	175 [10.3%]		22 [13.9%]	NS			58 [30%]	61[21%] <0.0001	82 [24%]	87[18%] <0.0001	NS
Middle cerebral artery	475 [28.1%]		61 [35.9%]	<0.05			65 [34%]	82[28%] NS	114 [33%]	139[28%] NS	NS
Posterior communicating artery	246 [14.5%]		37 [21.8%]	<0.05			18 [9%]	19[6%] NS	39 [11%]	41[8%] NS	NS
Vertebrobasilar system (other than basilar tip)	87 [5.1%]		5 [2.9%]	NS			15 [8%]	15[5%] NS	21 [6%]	21[4%] NS	NS
Tip of basilar artery	112 [6.6%]		5 [2.9%]	NS			8 [4%]	8[3%] NS	19 [6%]	19[4%] NS	NS

NS: non significant
NA: not available
p: p-value compared to ISUIA
p*: p-value comparing both @neurIST cohorts

Supplementary Table II

	UCAS						@neurIST					
Cohort	Total UCAS cohort		Not Surgically Treated before Rupture		Surgically Treated before Rupture		Consecutive cohort No SAH			Total cohort No SAH		
	(N = 6697)		(N = 3647)		(N = 3050)		(N=187)	p	p*	(N=339)	p	p*
maximal aneurysm size												
≥7 mm	1711 [25.5]		786 [21.6]		925 [30.3]		65 [34.8]	<0.01	<0.0001	158 [46.6]	<0.0001	<0.0001
3-4 mm	3132 [46.8]	4986 [74.5]	2000 [54.8]	2861 [78.4]	1132 [37.1]	2125 [69.7]	122 [65.2]	<0.01	<0.0001	181 [53.4]	<0.0001	<0.0001
5-6 mm	1854 [27.7]		861 [23.6]		993 [32.6]							

p = compared to Total UCAS cohort

p*= compared to Not Surgically Treated before Rupture group from UCAS

Supplementary Table III

	UCAS						@neurIST							
	Total		Not surgically treated before rupture		Surgically treated before rupture		Consecutive cohort no SAH				Total @neurIST C. no SAH			
		%		%		%		%	p	p*		%	p	p*
Middle cerebral artery	2425	**36.2**	1210	**33.2**	1215	**39.8**	82	**31**	NS	NS	139	**31**	<0.05	NS
Anterior communicating artery	1037	**15.5**	530	**14.5**	507	**16.6**	47	**18**	NS	NS	63	**14**	NS	NS
Internal carotid artery	1245	**18.6**	696	**19.1**	549	**18**	77	**29**	<0.001	<0.001	131	**29**	<0.001	<0.001
Internal carotid–posterior communicating artery	1037	**15.5**	602	**16.5**	435	**14.3**	23	**9**	<0.005	<0.001	54	**12**	<0.05	<0.05
Basilar tip and basilar–superior cerebellar artery	445	**6.6**	327	**9**	118	**3.9**	13	**5**	NS	<0.05	25	**6**	NS	<0.05
Vertebral artery–posterior inferior cerebellar artery and vertebrobasilar junction	123	**1.8**	80	**2.2**	43	**1.4**	8	**3**	NS	NS	13	**3**	NS	NS
Other	385	**5.7**	202	**5.5**	183	**6**	16	**6**	NS	NS	27	**6**	NS	NS
Total	6697		3647		3050		266				452			

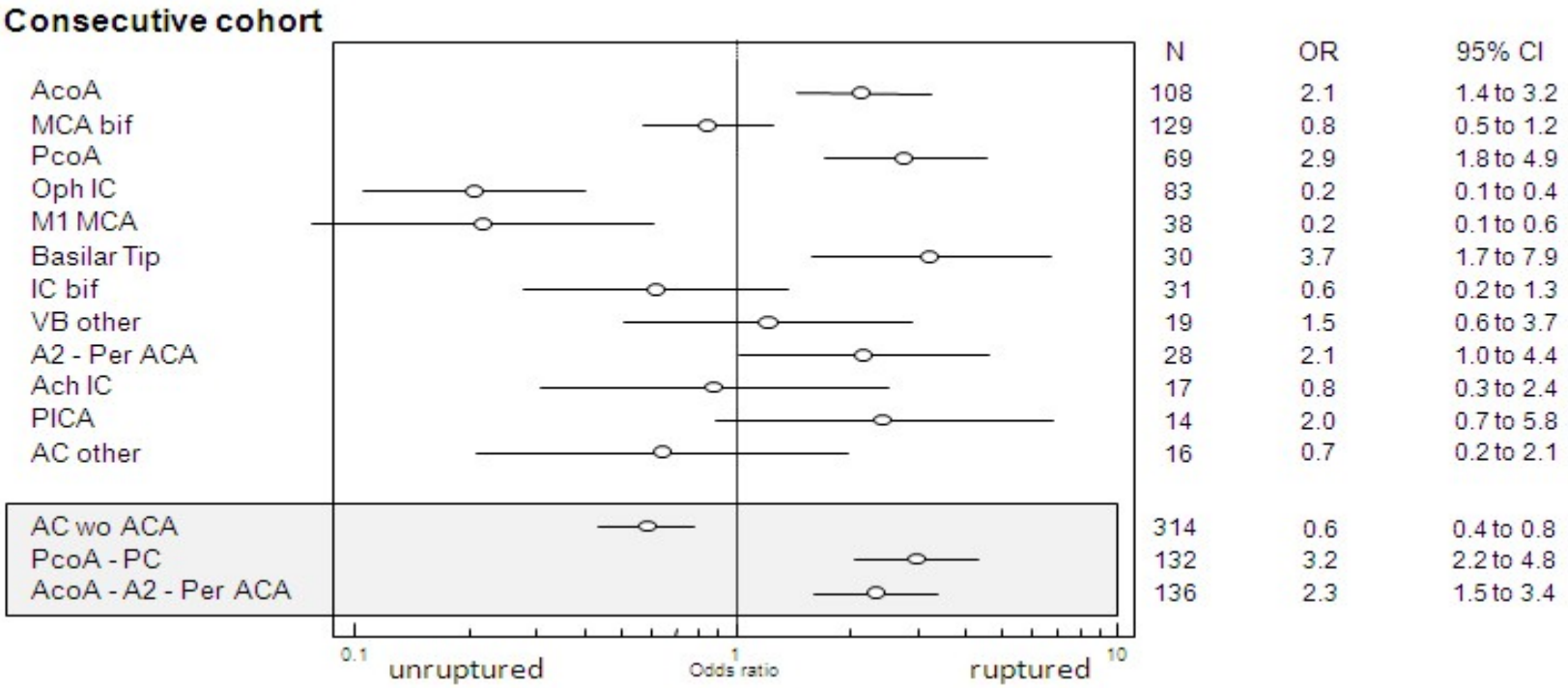
p = probability their is a difference compared to UCAS total

p*= probability their is a difference compared to UCAS Not surgical group

Supplementary Table IV

Cohort	ISUIA no surgery (n=1692)	*ref*	UCAS Not Surg (n=3647)	*p*	Consecutive C. noSAH (N=191)	*p*	Total @neurist C. no SAH (N=343)	*p*	*p**	Consecutive cohort (N=404)	*p*	Total @neurist cohort (N=932)	*p*	*p**
Medical History														
Hypertension	732 (43·6%)		1665 (45.6%)	NS	68 (35.6%)	<0.05	144(42.0%)	NS	NS	110 (27.2 %)	<0.001	320 (34.3 %)	<0.001	<0.01
Hypertension therapy	637 (37·8%)				60 (31.4%)	NS	126(36.7%)	NS	NS	88 (21.7 %)	<0.001	258 (27.7 %)	<0.001	<0.001
Valvular disease	37 (2·2%)				3/158 (1.9%)	NS	4/305(1.3 %)	NS	NS	3 (1 %)	NS	8 (1 %)	<0.05	NS
Family History														
Aneurysms	276 (18·4%)		416 (11.4%)	<0.0001	15 (7.9%)	<0.005	45 (13.1%)	NS	NS	22 (5.4%)	<0.001	88 (9.4 %)	<0.001	NS
Behavioural history														
Alcohol (>5 drinks per week)	502 (30·2%)				29 (15.2%)	<0.0001	54 (15.7%)	<0.0001	NS	58 (14.4 %)	<0.001	175 (18.7 %)	<0.001	NS
Current smoker	693 (41·1%)		551 (15%)	<0.0001	54 (28.3%)	<0.001	92 (26.8%)	<0.0001	NS	98 (24.2 %)	<0.001	258 (28 %)	<0.001	NS
Former smoker	602 (35·7%)				30 (15.7%)	<0.0001	78 (22.7%)	<0.0001	NS	57 (14.1 %)	<0.001	204 (22 %)	<0.001	<0.001
Use of stimulants	79 (4·7%)				5 (2.6%)	NS	10 (2.9%)	NS	NS	6 [1.5%]	<0.005	12 (1.3 %)	<0.0001	NS
Associated disorders														
Coarctation of aorta	9 (0·5%)				2 (0.9%)	NS	3 (0.9%)	NS	NS	3 (0.7%)	NS	4 (0.4%)	NS	NS
Polycystic kidney disease	25 (1·6%)		11 (0.3%)	<0.0001	7 (3.6%)	NS	10 (3%)	<0.05	NS	8 (1.8%)	NS	12(1.3%)	NS	NS
Arteriovenous malformation	34 (2·0%)				2 (0.9%)	NS	3 (0.9%)	NS	NS	3 (0.7%)	<0.06	7 (0.7%)	<0.01	NS
Ehlers-Danlos syndrome	0 (0%)				1 (0.5%)	NS	1(0.3%)	NS	NS	1 (0%)	NS	1(0.1%)	NS	NS
Neurofibromatosis	0 (0%)				0 (0%)	NS	0 (0%)	NS	NS	0 (0%)	NS	1 (0.1%)	NS	NS
Tuberous sclerosis	0 (0%)				0 (0%)	NS	0 (0%)	NS	NS	0 (0%)	NS	0 (0%)	NS	NS
Moyamoya disease	0 (0%)				0 (0%)	NS	1 (0.3%)	NS	NS	1 (0.2%)	NS	2 (0.2%)	NS	NS
Hypocoagulable state	6 (0·4%)				0 (0%)	NS	2 (0.6%)	NS	NS	0 (0%)	NS	3 (0.3%)	NS	NS
Fibromuscular disease	14 (0·9%)				0 (0%)	NS	0 (0%)	NS	NS	0 (0%)	NS	2 (0.2%)	NS	NS

Supplementary Figure I



Supplemantal Table and Figure Legends

Supplementary table I:
Base line characteristics of patients and aneurysms for cohorts of cases with unruptured aneurysms.

Supplementary table II:
Distribution of aneurysms by size in UCAS and @neurIST no SAH cohorts.

Supplementary table III:
Distribution of aneurysms by location in UCAS and @neurIST no SAH cohorts.

Supplementary table IV:
Medical, family and behavioural history and associated disorders characteristics for all cohorts.

Supplementary figure I:

Odds of aneurysms discovered rupture versus unruptured for each location compared to the odds of all other aneurysms included in the consecutive cohort (CC). N is the number of aneurysms observed for each location or location cluster.