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RESEARCH PAPER

Unruptured intracranial aneurysm follow-up and treatment after morphological change is safe: observational study and systematic review

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ABSTRACT

Background The management of small unruptured incidentally discovered intracranial aneurysms (SUIAs) is still controversial. The aim of this study is to assess the safety of a management protocol of SUIAs, where selected cases with SUIAs are observed and secured only if signs of instability (growth) are documented.

Methods A prospective consecutive cohort of 292 patients (2006–2014) and 368 SUIAs (anterior circulation aneurysms (ACs) smaller than 7 mm and posterior circulation aneurysms smaller than 4 mm without previous subarachnoid haemorrhage) was observed (mean follow-up time of 3.2 years and 1177.6 aneurysm years). Factors associated with aneurysm growth were systematically reviewed from the literature.

Results The aneurysm growth probability was 2.6 ±0.1% per year. The rate of unexpected aneurysm rupture before treatment was 0.24% per year (95% CI 0.17% to 2.40%). The calculated rate of aneurysm rupture after growth was 6.3% per aneurysm-year (95% CI 1% to 22%). Aneurysms located in the posterior circulation and aneurysms with lobulation were more likely to grow. Females or patients suffering hypertension were more likely to have an aneurysm growing. The probability of aneurysms growth increased with the size of the dome and was proportional to the number of aneurysms diagnosed in a patient.

Conclusions It is safe to observe patients diagnosed with SUIAs using periodic imaging. Intervention to secure the aneurysm should be performed after growth is observed.

INTRODUCTION

Improved and more widely accessible non-invasive intracranial imaging techniques have led to an increased proportion of incidentally discovered small unruptured intracranial aneurysms (SUIAs) during the past few decades.[1 2] Generally, the overall prevalence of unruptured intracranial aneurysms (UIAs) is estimated between 2% and 4% in the general population, while the incidence of subarachnoid haemorrhage (SAH) is reported to vary between 3 and 23 per 100 000 people per year.[3 4] The management strategy for completely asymptomatic SUIAs remains a matter of controversy. Balancing the risks and benefits between conservative follow-up and early preventive interventions, either endovascular or surgical, is therefore of paramount importance. Past and current studies are reporting that aneurysms may be classified with a high or low rupture risk on the basis of their location and size.[4–11] In selected groups, the risk of rupture may be <1% per year.[5–8] Those risks associated with the natural history have to be balanced with well-known treatment-related mortality and morbidity to secure an UIA, as the overall treatment-associated mortality and morbidity ranges between 0.5–0.7% and 3–17%, respectively.[12 13] Additionally, the impact of any management strategy on Health-Related Quality of Life (HRQoL) or cognition remains poorly investigated.[13]

According to the model of intracranial aneurysms (IAs) natural course proposed by Yonekura *et al*,[14] aneurysms may: (1) rupture immediately after aneurysm formation, (2) form and grow before rupture or (3) remain stable for a long time after formation. Therefore, the authors suggest the hypothesis that aneurysm growth could be used as a surrogate marker of increased risk of rupture. The primary goal of this study is to assess the aneurysm behaviour and safety of a management protocol of SUIAs based on an initial selection of cases to be followed-up, proceeding to an intervention to secure the aneurysm, when morphological changes are observed on cerebrovascular imaging.

METHODS

Study design

This study is an analysis of prospectively collected data from patients recruited in the @neurIST project at the Geneva University Hospital (HUG).[15] All patients diagnosed with IAs with an indication to be followed-up between 1 November 2006 and 1 April 2014 were invited to participate. Four patients refused to consent and were therefore not included. A prior authorisation was requested from a next of kin when patients were unable to give consent. Subsequently, a formal consent was obtained from the patient himself or from a next of kin, if the patient remained unable to give consent or had died. Investigators recorded data according to the @neurIST protocol.[1 15] The study has been approved by the local ethics committee (Geneva CCER 07-056).

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Patients

Patients were eligible for follow-up in the absence of symptoms induced by the aneurysm and in the absence of major risk factors (positive familial history, polycystic kidney disease (PKD), uncontrolled hypertension, heavy smokers (≥20 cigarettes per day) with no intention to stop) and diagnosed with one or more: (1) anterior circulation aneurysms (ACs) smaller than 7 mm,[6 11] (2) internal carotid artery intracavernous segment aneurysms (Cav ICs) of any size and (3) posterior circulation aneurysms (PCs) smaller than 4 mm (as defined in ISUIA,[11] aneurysms located in the posterior communicating artery segment of the internal carotid artery (PcoAs) are classified as PCs).

Data collection

Baseline characteristics were collected for all recruited patients, including patient history, risk factors for IAs development and rupture, as well as the number of aneurysms, location and morphological description. Alterations of modifiable risk factors and radiological evolution of each aneurysm were recorded. The first cerebrovascular image showing a SUIA was defined as day 0 for follow-up (FU). Follow-up data on the patient's clinical status, risk factors and imaging were recorded through direct interviews at 6 months and 1, 2 and 5 years and thereafter every 5 years. The follow-up was stopped after treatment for one of the following reasons: (1) aneurysm growth, (2) aneurysm rupture, (3) patients requested treatment or (4) patient's death. Clinical status of patients was reported using the modified Rankin Scale (mRS), the Mini-Mental State Examination (MMSE), the National Institute of Health (NIH) Stroke Score (NIHSS) and the presence or absence of cranial nerve deficits. Furthermore, the initial symptom that triggered investigation and head imaging was documented. Recorded risk factors included positive family history, smoking (if more than 100 cigarettes in a life time), alcohol consumption of more than 150 g per week, caffeine (cups per day), hypercholesterolaemia, hypertension (systolic >140/90 mm Hg), oral contraception and presence of a predisposing genetic condition (PKD, Ehlers-Danlos syndrome, Marfan syndrome, fibromuscular dysplasia or moyamoya syndrome or disease).[9–11 16–18]

The diagnosis of IAs was based on images obtained from MR angiogram, high-resolution three-dimensional (3D) CT angiogram (CTA), digital subtraction angiography (DSA) or conventional digital rotation angiography (3D-DRA). The aneurysm morphology was classified either as saccular on bifurcation, saccular sidewall or fusiform. Neck and dome sizes (in mm), maximal diameter and diameter perpendicular to the neck-to-dome line were measured and recorded. The presence of submillimetric irregularities (roughness), single or multiple blebs or lobules, intra-aneurysmal thrombus, wall calcification and the spatial relationship to perforator arteries were documented. Imaging was performed before each follow-up and carefully examined searching for new lesions or morphological changes of known aneurysms according to the criteria defined by Backes *et al*.[19] Imaging consisted most frequently of MRI including time of flight (TOF) sequences, and also contrast injected high-resolution CT scan (CTA) or conventional DSA and 3D-DRA. Imaging studies were reviewed by two independent clinicians as part of clinical routine (1 vascular neuroradiologist and 1 vascular neurosurgeon) viewing orthogonal maximum intensity projection (MIP) as well as 3D volume rendering reconstructions using Osirix V.7.5 software (Osirix, Pixmeo, Geneva, Switzerland).

Location of aneurysms was reported according to the @neurIST nomenclature.[1] The internal carotid (IC), anterior cerebral artery (ACA), middle cerebral artery (MCA), vertebral artery (VA), basilar artery (BA) and posterior cerebral artery are parent vessels divided into segments delimited by departing branches. The ophthalmic artery (Oph IC), PcoA, anterior choroidal artery (Ach IC), anterior communicating artery (AcoA), pericallosal artery (Per ACA), posterior inferior cerebellar artery (PICA), anterior inferior cerebellar artery and superior cerebellar artery are branches delimiting the parent vessel segments. Bifurcations are defined according to Rhoton,[20] starting where the walls diverge and finishing at the cross-sections perpendicular to the flow within the daughter vessel, where the projection of the parent vessel wall crosses the medial wall of the daughter vessel.

Data were collected and analysed per patient and aneurysm. Cases were grouped in two categories: (A) patients with 'stable' aneurysms or (B) patients with 'unstable' aneurysms. Patients with stable aneurysms are patients continuing observation according to the protocol. Correspondingly, patients with unstable aneurysms were treated by an intervention to secure the aneurysm because of (1) aneurysm growth, (2) aneurysm rupture or (3) patients requesting treatment. The fact that a patient requested the lesion to be secured was considered as a sign of aneurysm instability because patients reported a change in headache pattern considered as ill-defined warning symptoms, the most accepted symptom being the so-called 'sentinel headache'.[21]

The primary outcome measure was a subsequent aneurysm treatment or death from aneurysm rupture. The incidence of rupture was assessed per aneurysm rather than per patient. Data were censored at the time of patient's death, surgical or endovascular intervention or at the last follow-up. When a patient underwent a surgical or endovascular intervention, data from the period up to the time of the intervention were included in the analysis of risk of growth and rupture.

Statistical analysis

Statistical analyses were performed using SPSS V.19.0 software (SPSS, IBM, New York, USA) or MedCalc software (MedCalc software, Belgium). Results for continuous variables are reported as mean±SD. Categorical variables are presented as median and quartiles or by absolute and relative frequencies. Differences between groups were tested using the Student's t-test for continuous variables and χ^2 or Mann-Whitney U test for categorical factors. Two-sided p values of <0.05 were considered as threshold for statistical significance. ORs are reported with a 95% CI. Differences in proportions between groups were assessed using the Fisher's exact test.

Systematic review

A review was performed according to the PRISMA 2009 protocol. An unrestricted search using the keywords 'intracranial aneurysm' AND 'aneurysm growth' AND 'associated factors' was performed on 24 May 2015 on: PubMed and Web of Science resulting in a list of 102 references. Twenty-four full-text articles were assessed as eligible after title and abstract examination of all identified references. Data from 12 studies could be included in the quantitative meta-analysis (Bor *et al*,[22] Kubo *et al*,[23] Matsumoto *et al*,[24] Inoue *et al*,[25] Sonobe *et al*,[8] So *et al*,[26] Burns *et al*,[27] Sprengers *et al*,[28] Miyazawa *et al*,[29] Wermer *et al*,[30] Matsubara *et al*[31] and Phan *et al*[32]).

RESULTS

Cohort characteristics

During the study period, 1002 consecutive patients with 1478 IAs were diagnosed. Most patients (581; 58.0%) were diagnosed with UIAs and 421 (42.0%) patients after SAH. According to the institutional management protocol, half of the patients (n=289; 49.7%) with UIAs were treated by securing the aneurysmal sac using endovascular coiling or stenting, surgical clipping or a combination of different techniques. A total of 292 patients (29.1%) with 368 newly diagnosed UIAs were initially followed-up and recruited in the cohort while the remaining served as the cohorts validation group.

Natural course: patients

The 292 patients in the follow-up cohort were observed during an average time of 3.2±2.3 years (range 3 months to 12 years). By 1 April 2014, 31 patients (10.6%) were considered to have unstable lesions and 30 (10.2%) were treated accordingly with 1 patient with ruptured aneurysm dying before treatment. Two patients (0.7%) with a total of three aneurysms died of unrelated causes. Aneurysm growth was observed in 23 patients (7.9%) resulting in the exclusion of 24 unstable aneurysms and 8 aneurysms were lost to follow-up when treated 'en passant'. Two patients (0.7%) suffered an aneurysm rupture during follow-up after growing and while waiting for treatment, scheduled within <6 weeks of the morphological change observation (AcoA and PICA aneurysms). One patient (0.4%) suffered an unexpected rupture triggered by acute cocaine consumption in an ex-cocaine addicted patient (M1MCA aneurysm). Five patients (1.7%) requested a total of five aneurysms to be treated. On 1 April 2014, 259 patients and 325 aneurysms were still followed-up.

Patients with unstable aneurysms had similar basic characteristics as patients with stable aneurysms except suffering more often from hypercholesterolaemia (48% vs 29%; p<0.03) (table 1).

Natural course: aneurysms

During the follow-up period, 30 patients with 31 aneurysms underwent surgical or endovascular repair due to: (1) changed aneurysm morphology (23 patients with 24 aneurysms), (2) ruptured dome (2 patients with 2 aneurysms) and (3) patients requested treatment (5 patients with 5 aneurysms). One additional patient had a ruptured PICA aneurysm but unfortunately died before treatment was possible. The mean time of follow-up for patients that crossed over to treatment/intervention was 2.7 ±2.3 years, while the remaining aneurysms were followed for an average of 3.5±2.4 years. The probability to continue observation decreased linearly over time at a rate of 2.6±0.1% per aneurysm year (linear regression p<0.0001) (figure 1).

The number of growing aneurysms in each location is too small to allow the demonstration of statistically significant signals, but the distribution of OR for growth according to location in this longitudinal study is similar to the distribution of OR for ruptured status at initial diagnosis in our previous transversal study (p<0.05 Spearman's rank correlation).[1] AcoA, PcoA and basilar tip aneurysms showed a higher propensity for growing as compared with aneurysms in other locations and aneurysms located in the Oph IC; MCA bifurcation and IC bifurcation were less likely to change morphology (figure 2; table 2). Aneurysms larger than 4 mm were more likely to grow

Table 1 Patient characteristics for each cohort of patients diagnosed with SUIAs

Patients				
Characteristic	**Total cohort (n=292)**	**Still in follow-up (n=259)**	**Unstable aneurysms (n=31)**	**p Value**
Age, mean-year (±SD)	55.1±15.4	55.6±15.5	51.5±14.5	
Follow-up, mean (±SD)	3.2±2.3	3.5±2.4	2.7±2.3	
Female sex, n (%)	225 (77.1)	199 (76.2)	26 (83.9)	
Symptoms, n (%)				
Headaches	117 (40.1)	104 (39.8)	13 (41.9)	
Screening	65 (22.3)	56 (21.5)	9 (29.0)	
Stroke/TIA	43 (14.7)	40 (15.3)	3 (9.7)	
Prior SAH	17 (5.8)	15 (5.7)	2 (6.5)	
Auditive symptoms	30 (10.3)	27 (10.3)	3 (9.7)	
Visual symptoms	13 (4.5)	12 (4.6)	1 (3.2)	
mRS, n (%)				
0–1	252 (86.3)	228 (87.4)	24 (77.4)	
2–4	40 (13.7)	33 (12.6)	7 (22.6)	
Medical history, n (%)				
Anticoagulation/aggregation	79 (27.1)	63 (24.7)	10 (32.3)	
Hypertension	140 (48.0)	121 (46.4)	19 (61.5)	0.13
Tobacco	154 (52.7)	138 (52.9)	16 (51.6)	
Alcohol	69 (23.6)	62 (23.8)	7 (22.6)	
Caffeine	141 (48.3)	128 (49.0)	13 (41.9)	
Hypercholesterolaemia	91 (31.2)	76 (29.1)	15 (48.4)	**0.029**
Family history	38 (13.0)	35 (13.4)	3 (9.7)	
Other RF	88 (30.1)	77 (29.5)	11 (35.5)	
Multiple aneurysms	93 (31.8)	82 (31.4)	11 (35.5)	
≥3 aneurysms	31 (10.6)	27 (10.3)	4 (12.9)	

Bold values are statistically significant.
Comparison between still in follow-up and unstable cohorts (Fisher exact test).
mRS, modified Rankin Scale; RF, risk factor; SAH, subarachnoid haemorrhage; SUIAs, small unruptured intracranial aneurysms; TIA, transitory ischaemic attack.

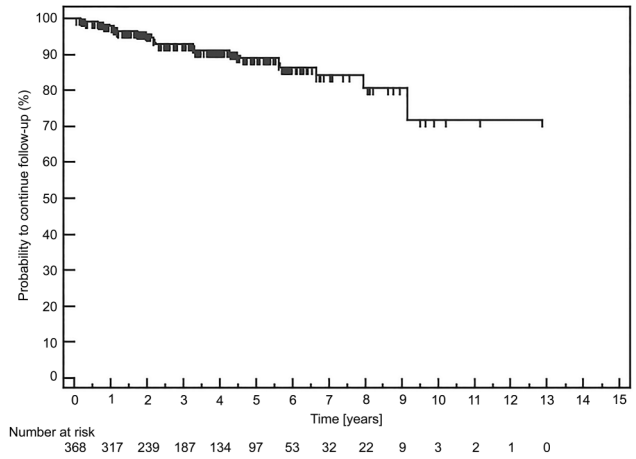

Figure 1 Kaplan-Meier curve showing the declining fraction of patients followed-up untreated over time. Number at risk represent the number of patients still observed after each specific number of years of follow-up.

than smaller aneurysms (OR 4.0, 95% CI 1.9 to 8.3, p<0.001). A small number of lesions were irregular in shape (n=92, 25%). Aneurysm growth seemed to be associated with irregular shape (OR 2.1, 95% CI 1.0 to 4.5, p<0.05).

Three aneurysms ruptured, two after growth (AcoA and PICA) and one after acute cocaine abuse (M1MCA). Two patients (with each a M1MCA and AcoA aneurysms) were treated in emergency and recovered with a discharge mRS of 3 improving to 2 after 1 year. The patient who suffered from a PICA aneurysm rupture died before any intervention could be initiated. During 1177.6 aneurysm-years of follow-up, three aneurysm ruptures were experienced representing an annual risk of 0.24% (95% CI 0.17% to 2.40%) and an annual lethal risk of 0.078% (95% CI 0.01% to 1.5%).

DISCUSSION

The overall risk of bleeding from an incidentally discovered UIA is known to be close to 1.1% per year and seems to be almost constant over a period of 25 years.[33] The risk varies significantly according to the aneurysm location, size and presence of dome irregularities, ethnicity, patient age, presence of hypertension or other comorbidities such as smoking, alcohol consumption or hypercholestrolaemia.[1 5–18 33] Based on the aforementioned observations, aneurysm rupture risk predictive models have been proposed to select cases for intervention/observation.[33–35]

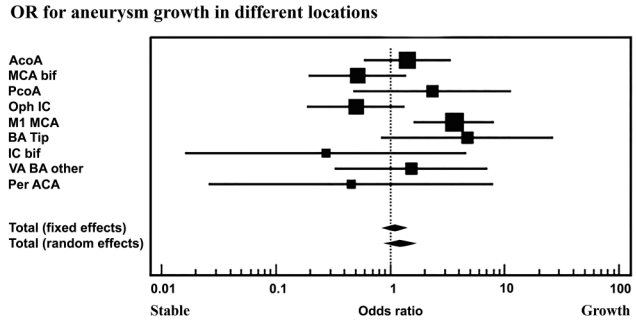

Figure 2 Distribution of ORs for aneurysm growth by location classified by order of frequencies of diagnosis in the overall population. ACA, pericallosal segment of the anterior cerebral artery; AcoA, anterior communicating artery; BA, basilar artery; bif, bifurcation; IC, internal carotid; MCA, middle cerebral artery; M1MCA, the first segment of the middle cerebral artery starting at the carotid bifurcation and finishing just prior to the MCA bifurcation is labelled M1MCA; Oph, ophthalmic artery; PcoAs, posterior communicating arteries; VA, vertebral artery.

The current study assessed the outcome of patients with SUIAs which were not considered initially for invasive aneurysm treatment, respecting the criteria previously mentioned in the methods. Invasive aneurysm treatment was recommended to all patients where a morphological change of the aneurysm was observed. This protocol is compliant with the most recent American Heart Association/American Stroke Association guidelines for the management of UIAs.[36] The results of this study show that the management protocol exposed patients to an extremely low rate of unexpected rupture and lethal risk (annual rupture risk of 0.24% (95% CI 0.17% to 2.40%) and an annual lethal risk of 0.078% (95% CI 0.01% to 1.5%)). Rates that were integrated over 5 years are approximately half the morbidity/mortality rates associated with the interventional treatment of very small IAs (morbidity 2.6%, 95% CI 0.8% to 6.1% and mortality 0%, 95% CI 0.0% to 0.2%).[37]

The UIA probability of growth in this study is of 2.6±0.1% per aneurysm year and is constant over time over the first 10-year period. The systematic review of the literature reveals an estimation of a yearly growth probability of 3.85% (95% CI 3.4% to 4.3%) with a total follow-up of 7799.1 patient-years and 300 growth events observed in 3079 patients and 3855 aneurysms. The higher growth probability is most probably due to the inclusion of aneurysms larger than 7 mm in most previous studies.

The risk associated with aneurysm growth is difficult to assess. Two patients out of 31 cases with unstable IUAs suffered an aneurysm rupture while waiting for treatment (OR 6.3, 95% CI 1% to 22% per aneurysm year). According to Inoue *et al*[25] and Villablanca *et al*,[38] aneurysm growth increases the risk of rupture by a factor 10 and the annual rupture rate for growing UIAs ranges between 2.4% and 18% per patient year. In this cohort, aneurysm rupture risk in the growth group was 1.2% (95% CI 0.7% to 21.2%), which is an order of magnitude higher than the overall FU cohort's rupture risk. Furthermore, in this cohort patients classified as bearing an unstable aneurysm were more frequently suffering of hypercholesterolaemia; aneurysms were frequently larger than 4 mm and more frequently irregular.

The systematic review of the literature also shows that women and patients suffering from hypertension are more at risk of aneurysm growth. Patients with multiple SUIAs are more likely to have one aneurysm that grows but aneurysm multiplicity is not associated with a greater probability for aneurysms to grow. The probability of aneurysm growth increases with aneurysm size and the presence of lobulations. Aneurysms located in the PC are more likely to grow. In contrast, aneurysms in IC are less likely to grow. Surprisingly smoking and alcohol consumption are not associated with aneurysm growth (table 3).

The strength of the study resides in its prospective design, population-based and consecutive recruitment of patients, stratification of cases in groups according to predefined criteria and long-term follow-up with a low dropout rate. The main weakness of the study is that it is a single-centre study with a limited number of events. A systematic literature review was performed to partially overcome the latter limitation. The analysis of predictive factors is extremely difficult because of the bias induced by the selection of patients according to the criteria using those specific factors. It can be expected that using a perfect disease model to select patients will completely eliminate the effect of risk factors on the outcome. A continuous monitoring of the

Table 2 Aneurysms characteristics for each cohort of patients diagnosed with SUIA

Unruptured aneurysms				
Characteristic	**Total cohort (n=368)**	**Still in follow-up (n=325)**	**Unstable aneurysms (n=32)**	**p Value**
Location, n (%)				
AcoA	54 (14.7)	47 (14.2)	6 (18.8)	
MCA bifurcation	82 (22.3)	77 (23.3)	5 (15.6)	
PcoA	10 (2.7)	8 (2.4)	2 (6.2)	
Oph IC	84 (22.8)	79 (23.9)	5 (15.6)	
M1MCA	41 (11.1)	31 (9.4)	7 (21.9)	
BA Tip	6 (1.6)	4 (1.2)	1 (3.1)	
IC bifurcation	15 (4.1)	15 (4.5)	0	
VA and BA other	14 (3.8)	12 (3.6)	1 (3.1)	
Per ACA	9 (2.4)	9 (2.7)	0	
Ach IC	10 (2.7)	8 (2.4)	2 (6.2)	
PICA	5 (1.4)	4 (1.2)	1 (3.1)	
Cav IC	38 (10.3)	36 (10.9)	2 (6.2)	
Largest dimension				
Distribution, n (%)				
<4 mm	230 (62.5)	218 (65.9)	7 (18.9)	
4–6.9 mm	138 (37.5)	113 (34.1)	25 (67.6)	***<0.001***
Other features				
Irregular shape	92 (25)	79 (24.3)	13 (40.6)	**<0.05**
Rough appearance	49 (13.3)	42 (12.7)	7 (21.9)	
Lobulation	43 (11.7)	37 (11.2)	6 (18.5)	
Thrombosed/calcified	5 (1.4)	4 (1.2)	1 (2.7)	

Bold values are statistically significant.
Comparison between still in follow-up and unstable aneurysm cohorts (Fisher exact test).
Ach IC, anterior choroidal artery; AcoA, anterior communicating artery; BA, basilar artery; ICA, internal carotid artery; MCA, middle cerebral artery; Oph IC, ophthalmic artery; PcoA, posterior communicating artery; Per ACA, pericallosal artery; PICA, posterior inferior cerebellar artery; SUIAs, small unruptured intracranial aneurysm; VA, vertebral artery.

Table 3 Meta-analysis of factors suspected to be associated with intracranial aneurysm growth

Factor	Categories	Number of studies	Number of cases	OR	95% CI	p Value
Multiplicity	Multiple aneurysms/single aneurysm					
	On patient basis	**11**	1932	**2.8**	**1.4 to 5.7**	**0.005**
	On aneurysm basis	11	2425	1.5	0.9 to 2.4	0.1
Location	ACA/other location	9	2422	0.9	0.6 to 1.2	0.46
	MCA/other location	9	2422	1.12	0.7 to 1.6	0.6
	IC/other location	**6**	1792	**0.6**	**0.4 to 0.8**	**0.002**
	PC/other location	**9**	2422	**1.6**	**1.1 to 2.2**	**0.013**
Size	**4–7 mm/<4 mm**	**6**	1731	**2.2**	**1.2 to 4.3**	**0.016**
Lobulations	**Lobulation/no lobulation**	**4**	1048	**3.4**	**1.5 to 7.6**	**0.003**
Hypertension	**Hypertensive/none hypertensive**	**10**	2491	**1.6**	**1.1 to 2.4**	**0.02**
Gender	**Female/male**	**13**	3414	**1.4**	**1.03 to 1.8**	**0.03**
Smoking	Smoker/non-smoker	10	2086	1.2	0.9 to 1.6	0.23
Alcohol	Alcohol abuse/no alcohol abuse	3	812	1.2	0.6 to 2.6	0.5

Bold values are statistically significant.
MCA, middle cerebral artery.

yearly growth probability and management of the failure rate in the cohort will be continued and extended by collaborations with other institutions (AneurysmDataBase; http:www.swissneurofoundation.ch) and also periodically reported.

Conclusions

According to the above results, it is safe to observe smaller than 7 mm unruptured saccular ACs (IC and MCA) and lesions smaller than 4 mm located in higher risk regions (eg, AcoA, Pericallosal artery (PerA) CA, PcoA and all other PCs). We recommend monitoring patients with untreated IAs with regular cerebrovascular imaging. Optimal periodicity still needs to be defined. Predictive factors for aneurysm rupture and aneurysm growth are very similar and therefore suggest at least sharing some common mechanisms. In the absence of better indicators, aneurysm growth and changes in patient's symptoms or anxiety are acceptable surrogate markers of an increased risk of future imminent aneurysm rupture.

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Contributors RG contributed to the analysis and interpretation of data, and drafting and revising of the manuscript for intellectual content. OPG participated in the interpretation and revising of the manuscript for intellectual content. JC and GM contributed to the analysis and interpretation of data. FP contributed to the analysis and interpretation of data, and revising of the manuscript for intellectual content. MJ, M-VC, BS, SM, ZK and KS were responsible for the revising of the manuscript for intellectual content. VMP and DR contributed to the conceptualisation of the study, and revising of the manuscript for intellectual content. PB contributed to the design and conceptualisation of the study, analysis and interpretation of the data, and drafting and revising of the manuscript for intellectual content.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Geneva CCER 07-056 (local ethics committee).

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Unruptured intracranial aneurysm follow-up and treatment after morphological change is safe: observational study and systematic review

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