Factors Associated with Subsequent Subarachnoid Hemorrhages in Patients with Multiple Intracranial Aneurysms

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■ BACKGROUND: **Detection of multiple intracranial aneurysms (MIAs) in patients with aneurysmal subarachnoid hemorrhage (aSAH) is common and the optimal management of the additional unruptured intracranial aneurysms (UIA) is often a matter of debate. We calculate the incidence and the factors associated with subsequent aSAHs from untreated additional aneurysms in a single-center group of patients with aSAH and MIAs.**

■ METHODS: **Charts of patients with MIAs admitted to our neurosurgery department for aSAH between January 2000 and March 2020 were retrospectively reviewed. Incidence rate and factors associated with subsequent aSAHs were calculated with univariable and multivariable analyses.**

■ RESULTS: **Of the unruptured aneurysms, 50% were preventively treated. During a median follow-up of 3 years, 20 of 174 patients (11.5%) presented with a second aSAH. Incidence of rupture of an additional untreated aneurysm was 18.05 per 1000 person/years (confidence interval, 10.69–30.47). Rupture incidence of an additional aneurysm located in the anterior circulation was 32.70 per 1000 person/years and 40.73 per 1000 person/years in the posterior circulation. Presence of untreated mirror and de novo aneurysms increased the risk of overall subsequent aSAHs by 16.9-fold and 7.6-fold, respectively. Most untreated additional aneurysms causing a subsequent aSAH were smaller than 7 mm (73.3%), with middle cerebral artery being the most frequent location (40.0%).**

■ CONCLUSIONS: **Incidence of subsequent aSAHs is high in patients with aSAH-MIA. Untreated mirror and de novo aneurysms are associated with higher rupture risk. Longer follow-up and prophylactic treatment of asymptomatic aneurysms at higher rupture risk are recommended to prevent the significant poor outcome of subsequent aSAHs.**

INTRODUCTION

The incidence of aneurysmal subarachnoid hemorrhage (aSAH) is 9 per 100,000 patients/year and it accounts for high mortality and severe permanent disability. With the advances in neuroimaging, the detection of asymptomatic additional intracranial aneurysms (IAs) other than the ruptured ones has increased.[1] About 15%–22% of patients with unruptured IAs (UIAs) and 20%–33% of patients with aSAH present with multiple IAs (MIAs), with a predisposition for female sex.[2-9] In patients with aSAH size and location of the ruptured aneurysm (at the basilar terminus and middle cerebral artery [MCA]) is correlated with a higher possibility of finding bystander aneurysms.[7] Other reported factors associated with the presence of MIAs are

Key words
- Aneurysm
- Intracranial aneurysm
- Risk factor
- Rupture
- Subarachnoid hemorrhage

Abbreviations and Acronyms
aSAH: aneurysmal subarachnoid hemorrhage
CT: Computed tomography
CTA: Computed tomography angiography
DSA: Digital subtraction angiography
IA: Intracranial aneurysm
MCA: Middle cerebral artery
MIA: Multiple intracranial aneurysms
MRA: Magnetic resonance angiography
MRI: Magnetic resonance imaging
mRS: modified Rankin Scale
SIA: Single intracranial aneurysm
UIA: Unruptured intracranial aneurysm

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age >40 years, arterial hypertension, smoking, and familiar history positive for IAs.[9]

Managing additional asymptomatic aneurysms in patients with previous aSAH (aSAH-MIA) is often challenging because of the potential treatment risks. Few studies have directly addressed this topic. It has recently been shown that patients with aSAH-MIA have a higher short-term morbidity than do patients with a single IA (SIA).[8] Furthermore, a second aSAH is known to carry higher mortality and morbidity than the first aSAH (71% death rate and 29% chance of severe neurologic deficits in the surviving patients or 11% of the total patients).[10] Risk-calculating tools for the management of UIAs are not specifically validated for the aSAH-MIA group, in particular for the rerupture rate. The PHASES scoring system attributes only 1 additional point out of 32 to the calculation of the 5-year rupture risk to patients with previous aSAH. We wonder whether this value truly reflects the real incidence of rupture of other IAs.[11] Moreover, some of the included studies had important selection bias, which affected the calculation of the total rupture rate, also as a result of the preventive treatment of some patients developing symptoms or presenting increase of aneurysm size.[12,13]

This study aims to calculate the incidence rate and identify factors associated with subsequent aSAHs from not prophylactically treated unruptured aneurysms in these patients.

METHODS

Medical records of patients admitted for aSAH to the Department of Neurosurgery, Radboud University Medical Center, Nijmegen, the Netherlands between January 2000 and March 2020 were retrospectively reviewed. The study was conducted according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for transparent reporting.[14]

Patients with ≥1 intradural saccular aneurysm other than the ruptured one were included in the analysis. Extradural, dissecting, mycotic, and traumatic aneurysms and aneurysms related to arteriovenous malformations were excluded.

We collected known risk factors for rupture of IA. Patients' demographic characteristics (age at time of first aSAH, sex, and ethnicity), relevant past medical history (hypertension, hyperlipidemia, diabetes mellitus, collagen diseases, and polycystic kidney disease), habits (smoking, drug or alcohol abuse, and use of antiestrogenic drugs), and family history of aSAH were collected. For each patient, the date of aSAH, clinical grade on arrival (World Federation of Neurosurgical Societies grading system), Fisher grade on initial computed tomography (CT) scan, location, size, morphology of the ruptured aneurysm, date, and type of treatment were also noted. The subarachnoid hemorrhage pattern on the admission head CT or brain magnetic resonance imaging (MRI); the aneurysm morphology, location, and size on the vessel imaging (digital subtraction angiography [DSA], CT angiography [CTA] or magnetic resonance angiography [MRA]); and/or the direct inspection during clipping were used to determine the ruptured aneurysm in this group of patients with MIAs. Height, width, transverse diameter, and neck size were noted and the fundus/neck ratio was calculated for each aneurysm. Number, location, size, morphology of additional aneurysms, eventual timing and type of treatment, presence of remnants or recanalization of the treated aneurysms, aneurysm growth, growth of de novo aneurysms not previously detected, clinical outcome, and follow-up length were also collected.

The primary end point was the occurrence of subsequent aSAHs as a result of the rupture of another previously asymptomatic aneurysm or of the previously ruptured aneurysm. The secondary end point was the clinical outcome between the group of patients with a single aSAH versus the group of patients with multiple aSAHs from multiple previously untreated MIAs. The modified PHASES score was calculated for each additional aneurysm causing subsequent aSAHs.

Treatment Methods

All patients were treated by the local hybrid vascular neurosurgeons, fully trained in surgical clipping and endovascular treatment of IAs. The treated aneurysm (or one of the treated aneurysms) at the time of the initial aSAH was the ruptured lesion based on the subarachnoid hemorrhage pattern on the admission head CT or brain MRI; the aneurysm morphology, location, and size on the vessels imaging (DSA, CTA, or MRA); and/or the direct inspection during clipping. As per our protocol, after discharge, patients undergoing coiling were followed up with postoperative DSA at 6 months and then yearly MRA until 2009. Since 2010, patients have been followed up with postoperative MRA at 6 months and then yearly MRA. Patients who underwent clipping were assessed with postoperative CTA or DSA and then yearly MRA or CTA in case of other untreated aneurysms. Imaging was repeated or anticipated in cases of evidence of aneurysm growth or increase in size of aneurysm remnants. Additional unruptured aneurysms with high rupture risk (PHASES score) or evidence of growth at follow-up were prophylactically treated because of the calculated high rupture risk.

Statistical Analysis

Stata statistical software release 14 (StataCorp LLC, College Station, Texas, USA) was used for statistical analysis. The incidence of subsequent aSAHs was calculated for the overall population of patients with ≥1 untreated additional aneurysm and by relevant subgroups, such as the rupture of a previously ruptured or additional aneurysm, the total number of IAs per patient, the percentage of the treated IAs per patient, the location of the aneurysm (anterior or posterior circulation), by comparing the largest additional aneurysm in the group of patients with 1 aSAH and the ruptured aneurysm causing the second aSAH in the group of patients with subsequent aSAHs. Missing data were handled with a pairwise deletion approach. Patients without information on follow-up length were excluded from the incidence rate calculation. Only a total of 2 events (aSAHs) were considered in patients presenting with >2 aSAHs from the rupture of >2 different aneurysms.

Univariable analysis was performed to calculate the incidence and identify factors associated with subsequent aSAHs. Categorical data were compared using a Pearson χ^2 test. Continuous data were compared using an independent t test. P values <0.05 were considered statistically significant. Variables of factors related to subsequent aneurysmal rupture with a P value <0.3 were included in a multivariable Cox regression analysis model for backward elimination procedure.

RESULTS

Patient Population

Patients' demographic, clinical, and radiologic characteristics are summarized in Table 1.

A total of 174 consecutive patients with aSAH-MIA were admitted. During follow-up, 20 patients presented with a second aSAH, and 2 patients returned with a third aSAH, for a total of 22 subsequent aSAHs.

Characteristics of IAs

Number, location, size, and shape of IAs are presented in Supplementary Table 1.

The group of 154 patients with single aSAH had a total of 382 aneurysms.

Of 228 unruptured aneurysms from this group, 126 were preventively treated because of the anatomic proximity to the initially treated aneurysm, because of concerning features (irregular or multilobular shape or PHASES score $\geq$4), or because of evidence of growth (6 aneurysms), suggesting high rupture risk. The average size of the new growth was 3.4 mm (range, 2.0–8.0 mm) in 14 months (range, 8–25 months).

In the group of 20 patients with subsequent aSAHs, 14 patients presented with a second aSAH from a previously untreated aneurysm and 6 from a previously ruptured and treated aneurysm. In addition, 2 patients from this group also presented with a third aSAH, one from a previously untreated aneurysm and one from a previously preventively treated aneurysm (for a total of 14 + 6 + 2 = 22 subsequent aSAHs). In this group, there were in total 35 ruptured aneurysms (20 initially ruptured aneurysms at the first aSAH, 14 previously asymptomatic aneurysms that ruptured at the time of the second aSAH, and 1 previously asymptomatic aneurysms that ruptured at the time of the third aSAH) and 17 unruptured aneurysms.

Aneurysm Treatment and Follow-Up

The aneurysm treatment strategy is summarized in Figure 1 and Supplementary Table 2.

About half of the total unruptured aneurysms (55.3% from the group with single aSAH and 44.4% from the group with multiple aSAHs) were preventively treated based on the calculated rupture risk or the evidence of growth at follow-up. Mean interval from aSAH to the first treatment of an additional unruptured aneurysm was 16.2 months. There was believed to be no indication to treat the other aneurysms based on the calculated low rupture risk (PHASES score).

The overall percentage of treated and untreated aneurysms and treatment modality was comparable between the 2 groups: 73.3% of the total number of aneurysms were treated in the group of patients with a single aSAH and 80.7% of the aneurysms in the group of patients with subsequent aSAHs. Of the aneurysms, 75.7% were treated endovascularly and 24.3% surgically. Nine living patients with an additional untreated aneurysm were lost at follow-up (5.8% of the total population; 2.1% of the total number of IAs).

The percentage of treated aneurysm recanalizations, coil impactions, and neck remnants was higher in the group presenting with subsequent aSAHs compared with the group with single aSAH (27.9% and 22.5%, respectively).

Table 1. Demographic, Radiologic, and Clinical Characteristics of Patients with Aneurysmal Subarachnoid Hemorrhage and Multiple Intracranial Aneurysms with Single and Subsequent Aneurysmal Subarachnoid Hemorrhages

Characteristics	Total	Single aSAH	Multiple aSAHs
Number of patients	174	154	20
Female, n (%)	134 (77)	116 (75.3)	18 (90)
Age (years), mean ± standard deviation	54.3 ± 11.5	54.7 ± 9.2	54.3 ± 11.9
Finnish or Japanese ethnicity (%)	0.0	0.0	0.0
Hypertension (%)	28.2	28.6	25.0
Smokers (%)	22.4	22.7	20.0
Alcohol abuse (%)	6.9	7.8	5.0
Hyperlipidemia (%)	6.3	4.5	20.0
Familiar history of aSAH (%)	2.9	1.9	10.0
Fisher grade (%)			
Unknown	14.0	6.5	21.4
2	19.9	20.8	19.0
3	8.6	12.3	4.8
4	57.6	60.4	54.7
World Federation of Neurosurgical Societies grade (%)			
Unknown	11.8	4.5	19.0
I	23.2	27.3	19.0
II	14.8	20.1	9.5
III	8.9	5.8	11.9
IV	22.5	26.0	19.0
V	18.8	16.2	21.4

aSAH, aneurysmal subarachnoid hemorrhage.

Among the 7 patients who presented with a rerupture of a previously treated aneurysm, 1 was initially treated elsewhere and presented with a second aSAH 62 months after the first event and 3 patients rebled acutely or semiacutely within 1 month of the initial treatment (1, 3, and 30 days postoperatively, respectively). Furthermore, 1 patient rebled 13 months after the first treatment during follow-up for a known aneurysm neck remnant <7 mm, and 2 patients presented with a rebleed as result of the growth of a known aneurysm remnant at 36 and 104 months, respectively.

The mean time interval between 2 aSAHs in the same patient was 70.6 months (5.9 years).

Incidence of Subsequent aSAHs

The overall incidence rate of having subsequent aSAHs was 27.01 per 1000 person/years (95% confidence interval, 17.65–41.51). The incidence rate of rupture of a previously untreated additional aneurysm was 18.05 per 1000 person/years (confidence interval, 10.69–30.47).

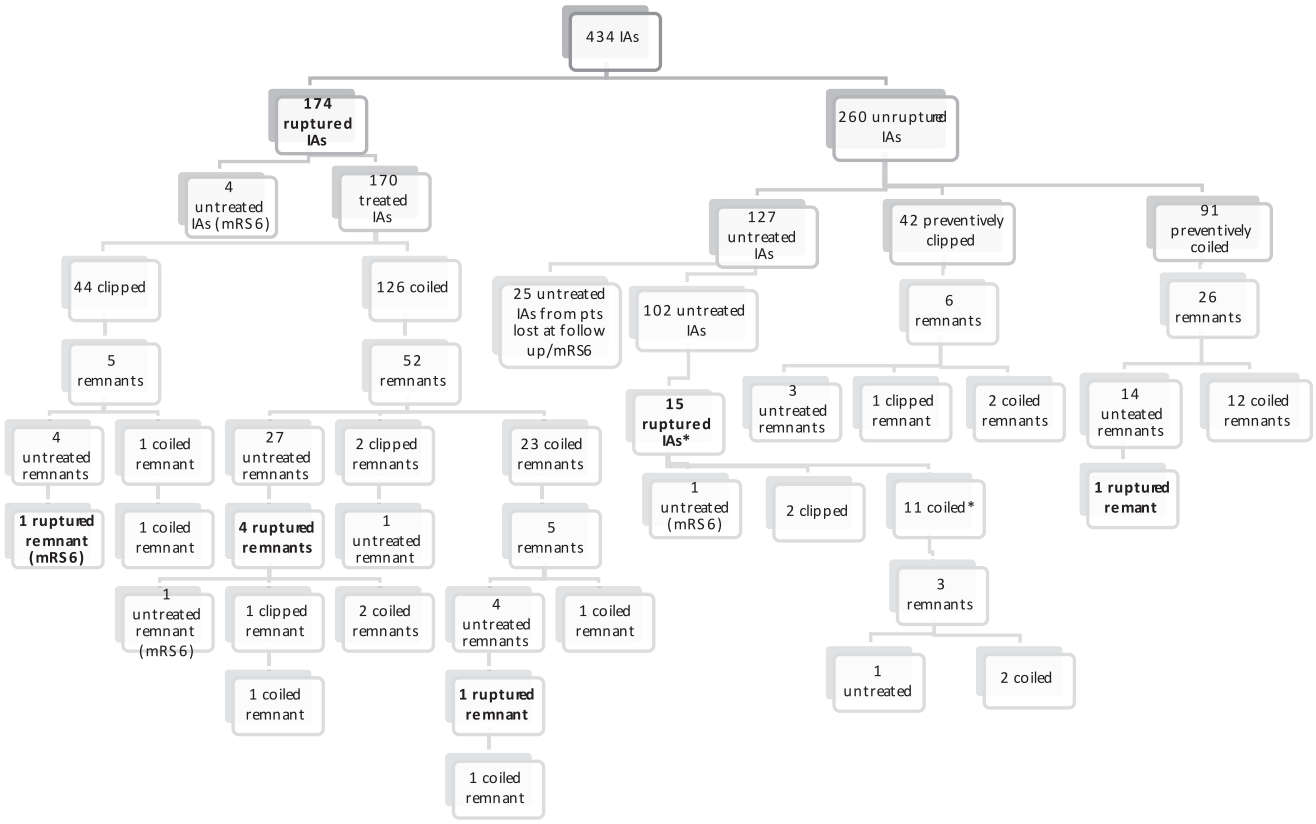

Figure 1. Treatment strategy and rupture events for the multiple intracranial aneurysms (IAs) in the presented case series. * one patient from this group presented with rupture of 3 different aneurysms. mRS, modified Rankin Scale; pts, patients.

For aneurysms located in the anterior circulation, incidence of rupture of a previously untreated additional aneurysm was 32.70 per 1000 person/years, whereas it was 40.73 per 1000 person/years for aneurysms located in the posterior circulation (Table 2).

Univariable and Multivariable Analysis

Hyperlipidemia ($P = 0.001$) was significantly related to the occurrence of subsequent aSAHs at univariable analysis (Table 3). Presence of untreated mirror and de novo aneurysms increased the overall risk of subsequent aSAHs by 16.9-fold and 7.6-fold, respectively, and the risk of rupture of additional previously asymptomatic aneurysms by 115.6-fold and 123.4-fold, respectively (Tables 3 and 4). Variables associated with subsequent aSAH from the rupture of a previously ruptured aneurysm are summarized in Supplementary Table 5.

Characteristics of Ruptured Aneurysms in Patients with Subsequent aSAHs

The characteristics of all 15 previously untreated aneurysms that caused a subsequent aSAH are reported in Table 5. All aneurysms were saccular and most (73.3%) were small (<7 mm). The MCA was the most frequent site of subsequent aSAHs from an additional previously untreated aneurysm (40.0%) and 26.7% of the subsequent aSAHs were caused by the rupture of a mirror aneurysm.

The characteristics of all ruptured aneurysms in patients with subsequent aSAHs (previously treated and previously untreated) are summarized in Supplementary Table 3.

Clinical Outcome

The percentage of patients with no to moderate disability but overall functional independence (modified Rankin Scale [mRS] score 0–3) was higher in the single aSAH group than in the group with a second or a third aSAH (79.2% vs. 60.0% vs. 50.0%, respectively). The mortality in the group of patients with 2 aSAHs was higher than in the group of patients with a single aSAH (40.0% vs. 15.6%, respectively). The overall mortality increased in cases of a third aSAH compared (100%) with a single aSAH (40.0%) (Figure 2 and Supplementary Table 4).

Likewise, the percentage of patients with no to moderate disability but overall functional independence (mRS score 0–3) was higher in the group of patients whose UIAs were all preventively treated compared with the group in whom some IAs were left untreated (95.1% vs. 57.0%, respectively). The mortality in the group of patients with some IAs left untreated was significantly higher than in the group of patients in whom all IAs were treated (30.0% vs. 1.2%, respectively) (Table 6).

DISCUSSION

General risk of primary IA rupture is known to be related to patient factors such as age, female sex, hyperlipidemia, hypertension, smoking, and alcohol, and to aneurysm characteristics such as size >7 mm, perpendicular height, and location (with the anterior communicating artery being the most common site).[15-18] However, few studies have investigated the aneurysmal rupture risk and risk of rebleeding in patients with MIAs.

Cong et al.[19] found no statistically significant difference in the rebleeding risk between aSAH patients with MIAs or with SIA. On the other hand, Solanki et al.[20] reported the presence of MIAs as a risk factor for rebleeding in patients with aSAH-MIA not undergoing treatment of the symptomatic aneurysm. However, only 1% of the rebleeding was caused by the rupture of a previously asymptomatic aneurysm. Suzuki et al.[18] also noticed a higher rupture risk in patients with MIAs than in patients with SIA without previous aSAH.

In our series of 174 patients, we recorded 22 further aSAHs after the initial aSAH, with 70.6 months average interval between 2 events in the same patient. The overall incidence rate of a second aSAH was 27.01 per 1000 person/years. The incidence rate of rupture of an additional aneurysm was 18.05 per 1000 person/years. Taking into account the selection bias within this patient group, although more than half of the patients with asymptomatic additional aneurysms underwent preventive treatment, this is a relatively high rupture rate. The calculated 5-year rupture risk according to the PHASES score in the group of patients who presented with multiple aSAHs in our series of patients with aSAH-MIA ranged from to 0.4% to 17.8% (**Table 5** and **Supplementary Table 6**). This evidence might imply that the PHASES score is not suitable to use in the aSAH-MIA group.

Reported patient-related risk factors for aSAH in patients with MIAs do not differ from those for SIA. Suzuki et al.[18] found a higher incidence of ruptured aneurysms in younger patients with aSAH-MIA. We reported no significant age difference in the 2 cohorts of patients.

In their series of 97 patients with anterior circulation MIAs (58 ruptured, 39 unruptured), Jiang et al.[21] found that females have higher incidences of MIAs and aSAH, but there was no difference with males in the rupture rate for MIAs. These investigators also found that current smokers and patients with medically uncontrolled hypertension were more likely to have aneurysmal rupture. Likewise, most patients in our series were female; however, the female/male ratio increased by almost 3-fold in the group with subsequent aSAHs. Hyperlipidemia was significantly related to the occurrence of subsequent aSAHs ($P = 0.001$).

Several aneurysm-related rupture risk factors are described for patients with MIA, who, according to Suzuki et al.,[18] have a higher absolute rupture risk compared with patients with UIA. When analyzing the cohort of patients with MIAs from the UCAS study, Shojima et al.[22] reported that the largest aneurysm is more likely to rupture among coexisting aneurysms. Conversely, Suzuki et al.[18] found a higher rupture risk in small UIAs (<10 mm), located at a bifurcation, larger length, and lower pressure loss coefficient in patients with aSAH-MIA. Ruptured aneurysms in Jiang et al.'s series of patients with MIA were more likely to be located on the communicating segment of the internal carotid and the anterior communicating artery, to be mirror aneurysms, and to present with blebs.[21]

Table 2. Ruptured Incidence Rate of Subsequent Aneurysmal Subarachnoid Hemorrhages as a Result of the Rerupture of a Previously Ruptured Aneurysm or the Rupture of Untreated Additional Aneurysms in Patients with ≥1 Untreated Additional Aneurysm

Group	Number of Events	Incidence Rate* (95% Confidence Interval)
Overall (N = 167)	21	27.01 (17.65–41.51)
Ruptured aneurysm		
Previously ruptured and treated	7	9.02 (4.30–18.93)
Additional, previously untreated	14	18.05 (10.69–30.47)
Total number of IAs		
Rerupture of previously ruptured aneurysm (number of patients)		
Patients with 2 IAs (n = 104)	6	15.54 (6.98–34.59)
Patients with 3 IAs (n = 43)	0	—
Patients with ≥4 IAs (n = 19)	1	8.64 (1.22–61.33)
Rupture of additional aneurysm (number of patients)		
Patients with 2 IAs (n = 104)	5	12.95 (5.39–3.11)
Patients with 3 IAs (n = 43)	8	29.20 (14.60–58.39)
Patients with ≥4 IAs (n = 19)	1	8.64 (1.22–61.33)
Percentage of treated aneurysms		
Rerupture of previously ruptured aneurysm		
>40% (n = 14)	0	—
40%–59% (n = 49)	2	10.89 (2.72–43.55)
60%–79% (n = 22)	1	6.32 (0.89–44.88)
≥80% (n = 81)	4	9.62 (3.61–25.64)
Rupture of additional aneurysm		
>40% (n = 14)	1	54.51 (7.68–386.99)
40%–59% (n = 49)	3	16.34 (5.27–50.65)
60%–79% (n = 22)	5	31.61 (13.16–75.95)
≥80% (n = 81)	5	12.03 (5.01–28.90)
Ruptured aneurysm location		
Rerupture of previously ruptured aneurysm		
Anterior circulation (n = 54)	3	12.26 (3.95–38.02)
Posterior circulation (n = 37)	4	27.15 (10.19–72.35)
Rupture of additional aneurysm		
Anterior circulation (n = 54)	8	32.70 (16.35–65.38)
Posterior circulation (n = 37)	6	40.73 (18.30–90.66)

IA, intracranial aneurysm.
*Per 1000 person-years.

Table 3. Variables Associated with Overall Subsequent Aneurysmal Subarachnoid Hemorrhages in Univariable and Multivariable Analysis

	Univariable			Multivariable	
Variable	**Pearson χ^2**	**Mean Difference (95% CI)**	***P***	**Hazard Ratio (95% CI)**	***P***
Sex (female)	2.32	—	0.128	0.16 (0.02—1.3)	0.08
Age at first aSAH	—	2.63 (—5.73 to 4.66)	0.838	—	—
Hypertension	0.33	—	0.567	—	—
Smokers	0.23	—	0.631	—	—
Alcohol abuse	0.40	—	0.528	—	—
Hyperlipidemia	14.54	—	0.001	0.74 (0.22—2.49)	0.627
Familiar history of aSAH	3.56	—	0.059	2.08 (0.46—9.44)	0.326
Total number of aneurysms	—	—0.11 (—0.44 to 0.22)	0.515	—	—
Number of untreated aneurysms	—	—0.03 (—0.36 to 0.31)	0.878	—	—
Total nr. of mirror aneurysms	—	—0.10 (—0.30 to 0.09)	0.289	1.09 (0.31—3.88)	0.897
Number of untreated mirror aneurysms	—	—0.14 (—0.29 to 0.02)	0.083	16.88 (4.46—63.96)	0.001
Total number of de novo aneurysms	—	—0.06 (—0.18 to 0.06)	0.343	—	—
Number of untreated de novo aneurysms	—	—0.09 (—0.22 to 0.04)	0.162	7.62 (1.63—35.60)	0.010

CI, confidence interval; aSAH, aneurysmal subarachnoid hemorrhage.

Unlike in previous reports, most ruptured aneurysms in our series were <7 mm at the time of the second or third aSAH (73.3%). This finding can be explained by the fact that the preventive treatment of asymptomatic aneurysms with high ruptured risk might have excluded larger aneurysms from the analysis. Four patients in our series presented with a subsequent aSAH from the rupture of a known untreated aneurysm <7 mm. Preventive treatment was not offered in these cases because of the patient's

Table 4. Variables Associated with the Rupture of a Previously Asymptomatic Additional Aneurysm in Univariable and Multivariable Analysis

	Univariable			Multivariable	
Variable	**Pearson χ^2**	**Mean Difference (95% CI)**	***P***	**Hazard Ratio (95% CI)**	***P***
Sex (female)	1.90	—	0.168	0.00 (0.00—7.77E^{+167})	0.952
Age at first aSAH	—	—0.53 (—6.88 to 5.83)	0.871	—	—
Hypertension	0.01	—	0.960	—	—
Smokers	0.06	—	0.936	—	—
Alcohol abuse	1.32	—	0.250	0.00 (0.00—0.00)	0.984
Hyperlipidemia	9.89	—	0.002	0.37 (0.07—2.11)	0.263
Familiar history of aSAH	1.01	—	0.316	—	—
Total number of aneurysms	—	—0.31 (—0.72 to 0.09)	0.130	0.96 (0.39—2.35)	0.929
Number of untreated aneurysms	—	—0.21 (—0.62 to 0.20)	0.307	—	—
Total number of mirror aneurysms	—	—0.19 (—0.48 to 0.10)	0.187	0.47 (0.05—4.95)	0.531
Number of untreated mirror aneurysms	—	—0.21 (—0.46 to 0.03)	0.082	115.60 (5.85—2285.32)	0.002
Total number of de novo aneurysms	—	0.07 (—0.18 to 0.12)	0.579	—	—
Number of untreated de novo aneurysms	—	—0.07 (—0.23 to 0.08)	0.336	123.42 (4.24—3591.88)	0.005

CI, confidence interval; aSAH, aneurysmal subarachnoid hemorrhage.

Table 5. Characteristics and Size of Additional Previously Untreated Aneurysms Causing Subsequent Aneurysmal Subarachnoid Hemorrhages, Time Between Two Aneurysmal Subarachnoid Hemorrhages, Total Follow-Up (months), Calculated Rupture Risk, and Patients' Modified Rankin Scale Score

Aneurysm													
		Size (mm)											
Location	Shape	Size*	Size (Height × Width × Transverse)	Neck	F:N ratio	Mirror	De Novo	Growth	Time Between Aneurysmal Subarachnoid Hemorrhages	Follow-Up	PHASES Score	5-Year Rupture Risk	Modified Rankin Scale Score
MCA	Saccular	S	6.0 × 5.0 × 5.0	2.5	2.4	Yes	No	No	0.5	0.5	4	0.9	6
MCA	Saccular	S	8.9 × 12.7 × 9.4	5.8	3.6	No	No	No	134	144	8	3.2	0
RICA	Saccular	S	5.0 × 5.0 × 4.0	2.0	2.5	Yes	No	No	24	88	1	0.4	1
SCA	Saccular	S	1.9 × 1.9 × 2.9	1.6	1.8	No	No	No	88	199	5	1.3	1
MCA	Saccular	L	15.0 × 11.0 × 10.0	3.0	5.0	No	No	No	96	228	9	4.3	4
ACom	Saccular wide neck	S	1.1 × 1.0 × 0.6	4.0	0.3	No	No	No	3	48	6	1.7	2
MCA	Saccular	S	4.0 × 3.0 × 2.0	1.5	2.7	No	No	No	6	6	3	0.7	6
PCA	Saccular	S	5.0 × 2.0 × 2.0	2.0	2.5	No	No	Yes	53	29	4	0.9	1
PICA	Saccular	S	4.0 × 4.0 × 3.0	1.0	4.0	Yes	No	No	216	216	5	1.3	6
PCA	Saccular	S	5.0 × 3.5 × 5.0	2.0	2.5	No	Yes	No	50	50	5	1.3	6
Basilar artery	Saccular	L	18.0 × 13.0 × 12.0	6.0	3.0	No	No	Yes	48	48	12	17.8	6
ACom	Saccular bilobed	S	4.1 × 3.8 × 3.8	2.7	1.5	No	No	No	1	13	5	1.3	3
Basilar artery	Saccular	S	3.0 × 3.0 × 2.0	2.0	1.5	No	No	No	27	36	5	1.3	2
Basilar artery	Saccular	M	13.0 × 13.0 × 8.0	6.0	2.2	No	No	No	209	247	12	17.8	2
MCA	Saccular	L	24.0 × 18.0 × 14.0	6.0	4.0	Yes	No	No	4	4	12	17.8	6

MCA, middle cerebral artery; RICA, right internal carotid artery; SCA, superior cerebellar artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; ACom, anterior communicating artery.
*S, small (<7 mm); M, medium (<15 mm); L, large (15–25 mm).

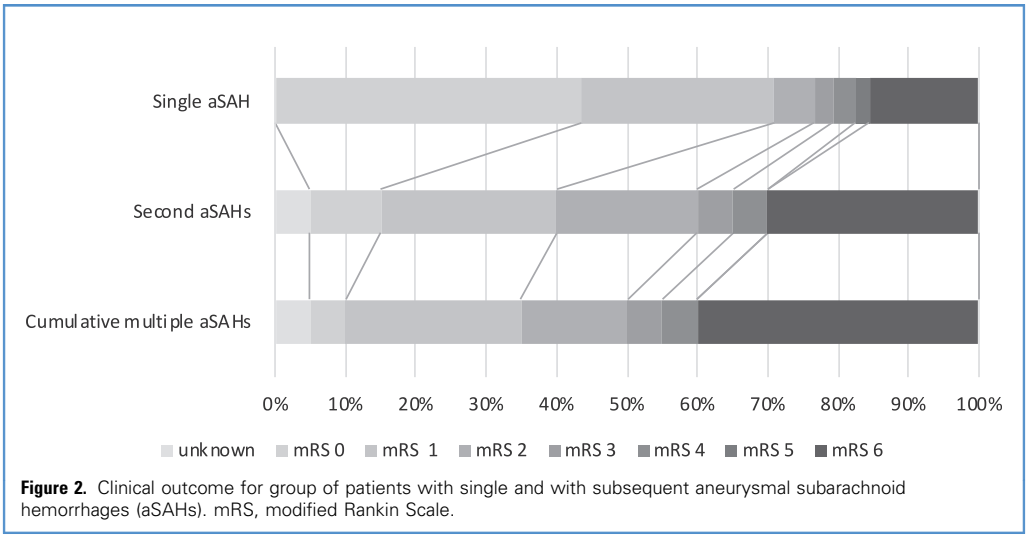

Figure 2. Clinical outcome for group of patients with single and with subsequent aneurysmal subarachnoid hemorrhages (aSAHs). mRS, modified Rankin Scale.

poor clinical status or their refusal, despite the high rupture risk. The incidence of subsequent aSAHs caused by the rupture of a previously asymptomatic posterior circulation aneurysm was higher than in the anterior circulation (40.73 and 32.70 per 1000 person/years, respectively).

The presence of untreated mirror and de novo aneurysms increased the overall risk of subsequent aSAHs by 16.9-fold and 7.6-fold, respectively. Furthermore, the risk of rupture of additional previously asymptomatic aneurysms was 115.6-fold higher in the presence of untreated mirror aneurysms and 123.4-fold higher in the presence of a de novo aneurysm. Overall, the MCA was the most frequent site of subsequent aSAHs from an additional previously untreated aneurysm (26.7%).

Table 6. Clinical Outcome for the Group of Patients with all Intracranial Aneurysms Prophylactically Treated and the Group of Patients with ≥1 Untreated Intracranial Aneurysm

Modified Rankin Scale Score	All IAs Treated (%)	Not all IAs Treated (%)
Unknown	3.6	2.2
0	54.2	25.8
1	28.9	25.8
2	8.4	3.2
3	3.6	2.2
4	0	5.4
5	0	3.2
6	1.2	30.1
0–3	95.1	57.0
4–5	0	8.6

IA, intracranial aneurysm.

To date, the optimal management of additional asymptomatic aneurysms in patients with aSAH-MIA is still a matter of debate, taking into account the risks of treatment versus the natural course of this disease. Huang et al.[23] stated that long-term radiologic surveillance for asymptomatic IAs in patients without previous aSAH is recommended also in the elderly (≥65 years) in the presence of MIAs because of the potential of aneurysm growth. Aneurysm growth rate over time in patients with incidental findings of MIAs has been shown to be 2.43-fold more likely than in patients with single UIAs, with smoking and hypothyroidism having a stronger effect on the growth rate especially for large UIAs (≥7 mm).[24] Brinjikji et al.[25] confirmed that aneurysm size, smoking status, PHASES score, and ELAPSS (Earlier Subarachnoid Hemorrhage, Location of Aneurysm, Age >60 Years, Population, Size of Aneurysm, Shape of Aneurysm) score are associated with aneurysm growth in patients with aSAH-MIA.[26] In a recent literature meta-analysis including 7208 patients with MIA,[27] 13.1% patients reported aneurysmal growth at follow-up, with aneurysm size and smoking as independent risk factors, whereas previous aSAH had a negative effect on aneurysmal growth. Two of the 15 previously untreated aneurysms in our series were found to be larger at the moment of the subsequent aSAH. Furthermore, the presence of MIAs has also been identified among the clinical and anatomic risk factors for the formation of de novo aneurysms together with female sex, age <40 years, family history of aSAH, smoking history, and internal carotid as the initial site, independently from a previous aSAH. Longer radiologic follow-up has been recommended for these patients.[28]

In our series, the group of patients with >1 aSAHs presented with a higher recanalization rate or regrowth of the treated aneurysm than did patients in the group with a single aSAH (27.9% and 22.5%, respectively). Moreover, 7 patients (4%) presented with a rebleed from a previously ruptured aneurysm and 1 patient (0.6%) had a rupture of a de novo aneurysm that was found close to a previously treated ruptured aneurysm. Our analysis was performed in a stable and representative population,

with only 5.8% of the living patients lost at follow-up (2.1% of the total number of IAs).

This result confirms the importance of long clinical and radiologic follow-up for these patients, who, in our opinion, represent a particular subgroup of patients with IAs because of the intrinsic higher rupture risk of the additional aneurysms.

Regarding preventive treatment of asymptomatic IAs, in a recent study, Lawson et al.[29] evaluated cost-benefits of treating UIAs in patients without previous aSAH over the natural bleeding risk, suggesting clipping for patients between 61 and 69 years and coiling for patients between 70 and 79 years of age. According to the findings of Lawson et al.,[29] any treatment beyond this age limit should be carefully considered because of the extremely poor outcome of the treated patients.[29] On the other hand, it has been also shown that short-term morbidity after aSAH in patients with MIAs is higher than in patients with SIAs, although this excess morbidity does not worsen the functional outcome or lower overall survival.[8]

The clinical outcome significantly differed between the group of patients presenting with a single aSAH versus subsequent aSAH. The percentage of patients with no to moderate disability but overall functional independence (mRS score 0–3) was consistently lower after a second or third aSAH (79.2% after the first aSAH vs. 60.0% and 50.0%, respectively). Likewise, the mortality in the group of patients with 2 aSAHs was significantly higher than in the group of patients with a single aSAH (40.0% vs. 15.6%, respectively) and the overall mortality evidently increased, reaching 100% of the cases with a third aSAH.

The percentage of patients with no to moderate disability but overall functional independence (mRS score 0–3) was substantially higher in the group of patients whose UIAs were all preventively treated compared with the group in whom some IAs were left untreated (95.1% vs. 57.0%, respectively). We believe that the extremely high morbidity and mortality rate of multiple aSAHs outweighs the potential risks of a preventive treatment of selected asymptomatic aneurysms in these patients. Future studies are needed to provide stronger evidence in the decision-making process for the preventive treatment of additional IAs for this group of patients.

Study Limitations

The limitations of this study include its retrospective and nonrandomized design. The sample size is small and confined to 1 center. Another limiting factor to consider is how preventive treatment of about half of the asymptomatic additional aneurysms might have changed the natural history of the disease and affected our results, thus reducing the real incidence of subsequent aSAHs. Likewise, although on one hand, an increased rupture risk of bystander aneurysms because of hemodynamic changes after treatment of proximal aneurysms has been formulated in some studies, the treatment of additional asymptomatic aneurysms biased the results of most reported case series of patients with aSAH-MIA.[30] Future prospective randomized trials are needed to validate the preventive treatment of additional unruptured aneurysms at high risk of rupture in patients with aSAH-MIA.

CONCLUSIONS

Patients with aSAH-MIA are a particular group of patients with a consistent risk of subsequent aSAHs from the rupture of the additional untreated aneurysms. Hyperlipidemia, presence of untreated mirror, and de novo aneurysms are significantly correlated to higher likelihood of presenting subsequent aSAHs. Longer follow-up and preventive treatment of asymptomatic aneurysms with high rupture risk are justified by the lower disability rate than in patients with additional aneurysms left untreated and are advisable to reduce the high mortality of subsequent aSAHs.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Luigi Rigante: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization. **Hieronymus D. Boogaarts:** Supervision, Project administration. **Ronald H.M.A. Bartels:** Supervision, Project administration. **Priya Vart:** Formal analysis, Software, Validation. **Rene Aquarius:** Methodology, Writing – review & editing, Project administration. **J. André Grotenhuis:** Supervision. **Walid Moudrous:** Resources. **Anthonius M. De Korte:** Writing – review & editing. **Joost de Vries:** Supervision, Conceptualization, Methodology, Validation, Writing – review & editing, Project administration.

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SUPPLEMENTARY DATA

Supplementary Table 1. Number of Patients with Single and Subsequent Aneurysmal Subarachnoid Hemorrhages, Total Number of Aneurysms, Number of Mirror and De Novo Aneurysms, and Number, Location, and Size of Ruptured Intracranial Aneurysms

Group	Total	Single aSAH	Subsequent aSAHs
Number of patients	174	154	20
Total number of aneurysms	434	382	52
Total number of ruptured aneurysms	189	154	35
Total number of unruptured aneurysms	245	228	17
Patient with 2 IAs (%)	111	100	10
Patient with 3 IAs (%)	44	37	8
Patient with 4 IAs (%)	17	15	2
Patient with 5 IAs (%)	1	1	0
Patient with 6 IAs (%)	1	1	0
Total number of mirror aneurysms	32	26	6
Total number of ruptured mirror aneurysms	22	19	3
MCA	30	17	3
PCom	7	7	0
Pericallosal artery	2	2	0
PICA	2	0	2
ICA	1	0	1
De novo aneurysms	7	5	2
Total number of ruptured de novo aneurysms	1	0	1
Ruptured aneurysms	189	154	35
ACom	45	39	6
MCA	47	36	11
PCom	39	34	5
BA	21	16	5
PICA	13	10	3
ICA	7	5	2
Ophthalmic ICA (C6)	5	4	1
A2—A3	6	6	0
VA	3	3	0
SCA	4	3	1
PCA	1	1	1
Size ruptured unknown	16	11	5
Size ruptured <7 mm	96	79	18
Size ruptured 7—9.9 mm	41	38	3
Size ruptured 10—19.9 mm	35	28	7
Size ruptured >19.9 mm	3	1	2

aSAH, aneurysmal subarachnoid hemorrhage; IA, intracranial aneurysm; MCA, middle cerebral artery; PCom, posterior communicating artery; PICA, posterior inferior cerebellar artery; ICA, internal carotid artery; ACom, anterior communicating artery; BA, basilar artery; VA, verterbral artery; SCA, superior cerebellar artery; PCA, posterior cerebral artery.

Supplementary Table 2. Total of Treated and Untreated Aneurysms, Number of Untreated Mirror Aneurysms, Total Number of Treated Aneurysms Recanalization, Number of Procedures, Clipping, Endovascular Treatments, Mean Follow-Up Length (months) in the Group of Patients with Single and Subsequent Aneurysmal Subarachnoid Hemorrhages

Group	Total	Single aSAH	Subsequent aSAHs
Total treated aneurysms (% total aneurysms)	322 (74.2)	280 (73.3)	42 (80.7)
Total preventive treatment of unruptured aneurysms (% total unruptured aneurysms)	134 (54.5)	126 (55.3)	8 (44.4)
Total untreated aneurysms (% total aneurysms)	112 (25.8)	102 (26.7)	10 (19.3)
Number of untreated mirror aneurysms	16	12	4
Treated aneurysms remnants/recanalization/growth, number of Events (% treated aneurysms)	75 (23.2)	63 (22.5)	12 (27.9)
Total number of procedures	304	255	49
Clipping, n (%)	74 (24.3)	61 (23.9)	13 (26.5)
Endovascular treatments (%)	230 (75.7)	194 (76.1)	36 (73.5)
Mean follow-up length (months) ± standard deviation	59.8 ± 62.9	53.9 ± 56.7	98.3 ± 85.9

aSAH, aneurysmal subarachnoid hemorrhage.

Supplementary Table 3. Location, Size, Presence of Mirror or De Novo Aneurysm in the Group of Patients with Subsequent Aneurysmal Subarachnoid Hemorrhages

Group	Total SAHs	First SAH	Second or Third SAH from Previously Treated Aneurysm	Second or Third SAH from Previously Untreated Aneurysm	Presence of Mirror Aneurysm	Second SAH from Mirror Aneurysm	Second SAH from De Novo Aneurysm
Total	42	20	7	15	6	6	1
MCA, n (%)	13 (31.0)	6 (30.0)	2 (28.6)	5 (33.3)	3 (50.0)	2 (33.3)	0 (0.0)
ACom, n (%)	7 (16.7)	4 (20.0)	1 (14.3)	2 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)
PCom (%)	6 (14.3)	4 (20.0)	1 (14.3)	1 (6.7)*	0 (0.0)	0 (0.0)	1 (100.0)*
Basilar artery (%)	6 (14.3)	2 (10.0)	1 (14.3)	2 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)
PICA (%)	4 (9.3)	2 (10.0)	1 (14.3)†	1 (6.7)	2 (33.3)	3 (50.0)‡	0 (0.0)
ICA (%)	2 (4.7)	1 (5.0)	0 (0.0)	1 (6.7)	1 (16.7)	1 (16.7)	0 (0.0)
Ophthalmic ICA (C6) (%)	2 (4.7)	1 (5.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SCA (%)	1 (2.3)	0 (0.0)	0 (0.0)	1 (6.7)†	0 (0.0)	0 (0.0)	0 (0.0)
PCA (%)	1 (2.3)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
Size ruptured unknown, n (%)	5 (11.9)	5 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Size ruptured <7 mm, n (%)	20 (47.6)	8 (40.0)	3 (42.9)†	9 (60.0)	5 (83.3)	5 (83.3)†	1 (100.0)*
Size ruptured 7–9.9 mm, n (%)	5 (11.9)	3 (15.0)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Size ruptured 10–19.9 mm, n (%)	9 (21.4)	3 (15.0)	1 (14.3)	4 (26.7)	0 (0.0)	0 (0.0)	0 (0.0)
Size ruptured >19.9 mm, n (%)	3 (7.1)	1 (5.0)	1 (14.3)	1 (6.7)	1 (16.7)	1 (16.7)	0 (0.0)

SAH, subarachnoid hemorrhage; MCA, middle cerebral artery; ACom, anterior communicating artery; PCom, posterior communicating artery; PICA, posterior inferior cerebellar artery; ICA, internal carotid artery; SCA, superior cerebellar artery; PCA, posterior cerebral artery.

*De novo aneurysm.

†1 patient with a third SAH.

‡One of the second aneurysmal subarachnoid hemorrhages from rupture of a mirror aneurysm, which also reruptured, causing a third aneurysmal SAH.

Supplementary Table 4. Clinical Outcome for Group of Patients with Single and with Multiple Aneurysmal Subarachnoid Hemorrhages

Modified Rankin Scale Score	Single aSAH (%)	Second aSAHs (%)	Cumulative Multiple aSAHs(%)
Unknown	0	5.0	5.0
0	43.5	10.0	5.0
1	27.3	25.0	25.0
2	5.8	20.0	15.0
3	2.6	5.0	5.0
4	3.2	5.0	5.0
5	1.9	0	0
6	15.6	30.0	40.0
0—3	79.2	60.0	50.0
4—5	5.1	5.0	5.0

aSAH, aneurysmal subarachnoid hemorrhage.

Supplementary Table 5. Variables Associated with Subsequent Aneurysmal Subarachnoid Hemorrhages Caused by the Rupture of a Previously Ruptured Aneurysm in Univariable and Multivariable Analysis

	Univariable			Multivariable	
Variable	Pearson χ^2	Mean Difference (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Sex (female)	2.30	—	0.632	—	—
Age at first aSAH	—	−1.82 (−10.60 to 6.96)	0.682	—	—
Hypertension	0.67	—	0.414	—	—
Smokers	0.26	—	0.609	—	—
Alcohol abuse	0.40	—	0.528	—	—
Hyperlipidemia	4.78	—	0.029	1.68 (0.29—9.60)	0.561
Familiar history of aSAH	3.46	—	0.063	3.94 (0.46—33.97)	0.212
Total number of aneurysms	—	0.22 (−0.35 to 0.78)	0.449	—	—
Number of untreated aneurysms	—	0.24 (−0.32 to 0.80)	0.401	—	—
Total number of mirror aneurysms	—	0.41 (−0.29 to 0.37)	0.807	—	—
Number of untreated mirror aneurysms	—	0.02 (−0.08 to 0.12)	0.724	—	—
Total number of de novo aneurysms	—	0.04 (−0.16 to 0.25)	0.692	—	—
Number of untreated de novo aneurysms	—	0.01 (−0.07 to 0.09)	0.774	—	—

CI, confidence interval; aSAH, aneurysmal subarachnoid hemorrhage.

Supplementary Table 6. Calculated PHASES Score for the Ruptured Aneurysm Causing a Second or a Third Aneurysmal Subarachnoid Hemorrhage in the Presented Series of Patients with Aneurysmal Subarachnoid Hemorrhage and Multiple Intracranial Aneurysms

Patient	Age at SAH	Ethnicity	Hypertension	Earlier SAH	Size Aneurysm Second SAH	Site Aneurysm Second SAH	PHASES Score Aneurysm Second SAH	5-Year Rupture Risk (%)	Time Between First and Second SAH (months)	Site Aneurysm Third SAH	Site Aneurysm Third SAH	PHASES Score Aneurysm Third SAH	5-Year Rupture Risk (%)	Time from First to Third SAH (months)
1	0	0	1	1	0	2	4	0.9	0.5					
2	0	0	0	1	1	6	8	3.2	134					
3	0	0	0	1	0	0	1	0.4	24	0	4	5	1.3	88
4	0	0	0	1	6	2	9	4.3	96					
5	0	0	1	1	0	4	6	1.7	3					
6	0	0	0	1	0	2	3	0.7	6					
7	0	0	0	1	0	4	4	0.9	0.5					
8	0	0	0	1	0	4	5	1,3	0.3					
9	0	0	0	1	0	4	5	1.3	216	0	4	5	1.3	217
10	0	0	0	1	Unknown	4	7?	2.4?	0.2					
11	0	0	0	1	0	4	5	1.3	62					
12	0	0	0	1	0	4	5	1.3	50					
13	0	0	0	1	0	6	7	2.4	36					
14	0	0	1	1	10	2	14	17.8	0					
15	0	0	0	1	3?	4	7?	2.4?	92					
16	1	0	0	1	6	4	12	17.8	48					
17	0	0	0	1	0	4	5	1.3	1					
18	0	0	0	1	0	4	5	1.3	27					
19	0	0	1	1	6	4	12	17.8	209					
20	0	0	1	1	10	2	14	17.8	4					

?, estimated value.