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New Detected Aneurysms on Follow-Up Screening in Patients With Previously Clipped Intracranial Aneurysms Comparison With DSA or CTA at the Time of SAH

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Background and Purpose—Patients with a history of aneurysmal subarachnoid hemorrhage may have aneurysms on screening several years after the hemorrhage. For determining the benefits of follow-up screening, it is important to know whether these aneurysms have developed after the hemorrhage or are visible in retrospect, and if so, whether the size has increased.

Methods—Aneurysms were categorized into de novo aneurysms and aneurysms visible in retrospect (already present) with increased or stable size. We studied aneurysm characteristics for these 3 categories: the relation between aneurysm development or enlargement and duration of follow up and the relation between enlargement and initial size of the aneurysm.

Results—In 87 of 495 patients (17.6%), aneurysms were detected; for 51 of these patients with 62 aneurysms, the original catheter or computed tomographic angiogram was available for comparison. Of the 62 aneurysms, 19 were de novo and 43 were visible in retrospect, 10 with increased size and 33 with stable size. De novo aneurysms were mainly ≤ 5 mm (95%) and located at the middle cerebral artery (63%). For aneurysms visible in retrospect, the most frequent location was the posterior communicating artery (21%). There was no relation between the development of de novo aneurysms or enlargement and the duration of follow-up or between enlargement and the initial size of the aneurysm.

Conclusions—Of aneurysms detected at screening, one third were de novo and two thirds were missed at the time of the initial hemorrhage. One quarter of initially small aneurysms had enlarged during follow-up. (*Stroke*. 2005;36:1753-1758.)

Key Words: aneurysm ■ angiography ■ computed tomography ■ subarachnoid hemorrhage

Patients who have survived an episode of subarachnoid hemorrhage (SAH) and in whom the ruptured and additional aneurysms have been successfully treated by means of surgical clipping or endovascular coiling are at risk for a new episode of SAH later in life. Such new episodes may arise not only from a remnant or regrowth of a previously treated aneurysm but also from new aneurysms at sites that differ from the originally ruptured aneurysm.¹⁻⁴

Screening of new aneurysms might be useful. In the evaluation of the effectiveness of screening, the rate of development of new aneurysms and increase in size of small but already present aneurysms are important variables. Scant data exist on the risk of aneurysm development and aneurysm enlargement over time.⁴⁻⁸ Because large unruptured aneurysms have a higher risk of rupture than small aneurysms,⁸ aneurysms that increase in size probably have a higher risk of rupture than aneurysms that remain stable over time.⁵ When

aneurysms are found on screening several years after the SAH, comparison with the initial catheter angiogram (DSA) or computed tomography angiogram (CTA) made at time of the SAH may reveal whether these aneurysms developed after the SAH or whether these are visible in retrospect on the original angiograms, and if so, whether the aneurysms increased in size.

We screened a large cohort of patients with a previously clipped ruptured aneurysm and compared the findings with the original DSA or CTA at the time of SAH in patients with aneurysms that were detected by screening to obtain information on aneurysm development and enlargement.

Methods

Patients

The study was approved by the ethics committees of the 2 participating University Hospitals (hospital A and B). Informed consent was obtained from all patients.

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*A full listing of members of the ASTRA Study Group is given in the appendix of this article.

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TABLE 1. Characteristics of Study Subjects and Aneurysms

	Aneurysms			
	All	De Novo	Visible in Retrospect, Increased Size	Visible in Retrospect, Same Size
Patients	51	13	10	28
Women, %	32 (63%)	10 (77%)	7 (70%)	15 (54%)
Mean age (at time of screening)	51.7 (range, 30–69)	47.7 (range, 30–66)	53.5 (range, 40–68)	53 (range, 35–69)
Mean follow-up after SAH, y	8.1 (range, 4–14)	8.6 (range, 5–14)	6.9 (range, 4–11)	8.3 (range, 4–14)
Aneurysms	62	19	10	33
Location, %				
Carotid artery		5 (26%)	4 (40%)	18 (55%)
Cavern/siphon*		2	0	5
Ophthalmic		1	0	4
Pcom		2	3	6
Anterior choroid		0	1	1
Carotid bifurcation		0	0	2
MCA		12 (63%)	3 (30%)	7 (21%)
Anterior communicating artery		2 (11%)	2 (20%)	3 (8.8%)
Vertebrobasilar		0	1 (10%)	5 (15%)
Size				
<3 mm		6 (32%)	0	12 (36%)
3–5 mm		12 (63%)	5 (50%)	19 (58%)
5–10 mm		1 (5.3%)	4 (40%)	2 (6.1%)
>10 mm		0	1 (10%)	0

*Cavern/siphon means the cavernous part of the carotid artery and carotid siphon. Other abbreviations are as defined in text.

Patients were derived from a database of all patients with SAH admitted since 1985. Patients were eligible for screening if they had been successfully treated by means of surgical clipping of a ruptured aneurysm between 1985 and 2001 in 1 of the 2 university medical centers. In only 1 of the 1 participating hospitals was it standard clinical practice to perform a DSA postoperatively. Further inclusion criteria were age between 18 and 70 years and independence in daily care. Patients with serious comorbidity that might decrease life expectancy or increase the risks of treatment were excluded. For the present study, patients were included when (1) a new aneurysm was suspected on the screening CTA at a location different from the clip site and (2) the original DSA or CTA at the time of the original SAH was available for review. None of the patients underwent follow-up screening before this follow up screening for study purposes.

Screening

All patients were screened by means of multislice CTA with a Philips Mx8000 LDT (16-slice spiral CT scanner) in hospital A and a Philips Picker Mx8000 (4-slice spiral CT scanner) in hospital B. Multislice CTA allows visualization of fine vascular details, has a high sensitivity and specificity for detection of aneurysms, including very small ones, and has an excellent correlation with DSA concerning aneurysm size.^{9,10}

All CTAs were independently evaluated on a Philips MXView workstation by 2 neuroradiologists at the center where screening was performed. In case of disagreement, a final evaluation was made by consensus. For patients with suspected aneurysms on CTA, a DSA was performed additional to the CTA when the diameter of the largest aneurysm was ≥ 3 mm in diameter. In both hospitals, angiography was performed with an angiographic unit (Intergrity V3000; Philips Medical Systems) with an image intensifier matrix of 1.024×1.024 . Two or 3 projections were acquired of the aneurysm and clip site (lateral, posteroanterior, and/or

oblique). The decision to perform a 3D angiogram was left to the neurointerventional radiologist.

Comparison With Pre- or Postoperative DSA or CTA

The hard copies of the DSA at the time of SAH and the hard copies or digital datasets of the CTA at time of the diagnosis were available from mid-1993. The aneurysms found at screening were compared with this pre- or postoperative DSA and/or CTA regarding presence, size, and shape.

Aneurysm locations were categorized into: (1) internal carotid artery containing the cavernous part of the internal carotid artery/carotid siphon, the origin of the ophthalmic artery, posterior communicating (Pcom) artery, anterior choroidal arteries, and the carotid bifurcation; (2) middle cerebral artery (MCA); (3) anterior cerebral artery including the anterior communicating artery; and (4) vertebrobasilar system.

On the digital dataset of the CTA we were able to measure the size of the aneurysm directly. On DSA and on the hard copies of CTA, we could not perform a direct measurement but instead related the size of the aneurysm to the size of the carotid artery or basilar artery. This proportion was compared with the same proportion on the screening CTA.

Based on the comparison with the pre- or postoperative CTA or DSA, the aneurysms were categorized into (1) de novo aneurysms, which were not present on the preoperative DSA or CTA; (2) aneurysms visible in retrospect with increased size (the aneurysm is retrospectively visible and has enlarged); (3) aneurysms visible in retrospect with stable size.

Data Analysis

We calculated the proportions of de novo aneurysms, aneurysms visible in retrospect with increased size, and aneurysms visible in

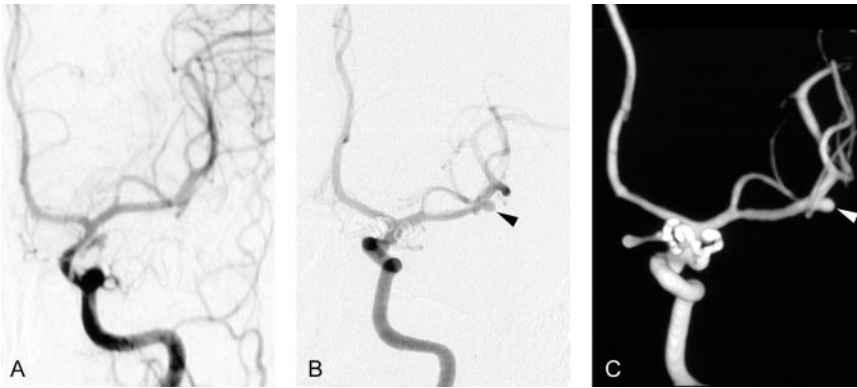


Figure 1. De novo aneurysm on the left MCA bifurcation (arrowhead). A, DSA of 1997, on which no aneurysm can be detected. B, DSA and C, 3D angiogram of 2003, showing an aneurysm on the left MCA.

retrospect with stable size. The size and location of all aneurysms were given for each of these 3 categories. For the aneurysms visible in retrospect with increased size, the increase in size was given.

By means of linear regression analysis, we quantified the association between de novo aneurysm formation and between the growth (increase in mm) of aneurysms visible in retrospect on the 1 hand and the period of follow-up on the other. We also quantified the association between the growth of aneurysms visible in retrospect and the initial size of the aneurysm at the time of SAH.

Results

Of 495 screened patients, 87 (17.6%; 95% confidence interval [CI], 14.2% to 20.1%) had at least 1 aneurysm at a different location than the clip site detected on CTA, of whom 63 underwent additional DSA. For 36 of these 87 patients, including 7 who had been treated after 1993, original films could no longer be retrieved. For 51 patients, the original DSA or CTA at the time of the SAH was available for review. In these 51 patients, 62 aneurysms were detected on screening CTA. None of these aneurysms had been described on the CTA or DSA at the time of the original SAH. The mean age at time of screening was 51.7 years (range, 30 to 69), and 32 patients were women (63%). The mean follow-up time after SAH was 8.1 years (range, 4 to 14). When we reviewed the original DSA or CTA, the aneurysm was not present in 19 instances (31% de novo aneurysms). Ten (16%) aneurysms could retrospectively be detected and had an increased size, and 33 aneurysms (53%) could retrospectively be detected but had remained stable regarding shape and size. The patient and aneurysm characteristics for each of the 3 categories of aneurysms are presented in Table 1. Figures 1 through 3 show examples of a de novo aneurysm (Figure 1), an aneurysm

visible in retrospect with increased size (Figure 2), and an aneurysm of stable size (Figures 2 and 3).

The majority of de novo aneurysms were located on the MCA (12 of 19 [63%]) and were smaller than 5 mm (18 of 19 [95%]). The aneurysms visible in retrospect with increased size were located mainly on the carotid artery (4 of 10 [40%]) with the Pcom as the most common location. Half of these aneurysms were smaller than 5 mm (5 of 10 [50%]) at time of the screening. The aneurysms visible in retrospect with stable size were located mainly on the carotid artery (18 of 33 [55%]), most commonly located at the Pcoms. Almost all of these aneurysms were smaller than 5 mm (31 of 33 [94%]). The initial size of the aneurysm at time of the SAH and the number of follow-up years per patient are represented in Table 2.

The shortest interval for development of a new aneurysm was 5.5 years, and that for growth of an aneurysm visible in retrospect, 4 years. Weighted linear regression did not show a statistically significant linear relation between the development of de novo aneurysms and the period of follow-up ($\beta=0.07$; 95% CI, -0.09 to 0.2) and between growth of aneurysms visible in retrospect and period of follow-up ($\beta=0.1$; 95% CI, -0.5 to 0.7). The value of 0.1 implies that for each more year of follow-up, the size of the aneurysm increased by 0.1 mm. The corresponding 95% CI implies that the data are compatible with a change in size of the aneurysm per follow-up year ranging from a decrease in size of 0.5 mm to an increase in size of 0.7 mm. The smallest initial size of an aneurysm visible in retrospect that increased in size was 2 mm. We found no statistically significant linear relation

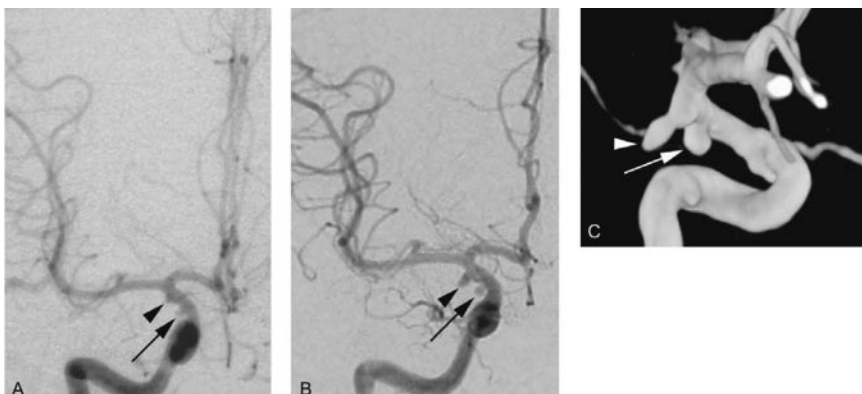


Figure 2. Aneurysms visible in retrospect with increased size and stable size. The anterior choroidal aneurysm (arrowhead) has increased in size. The Pcom aneurysm (arrow) is stable in size. A, DSA in 1996; B, DSA and C, 3D angiogram in 2003.

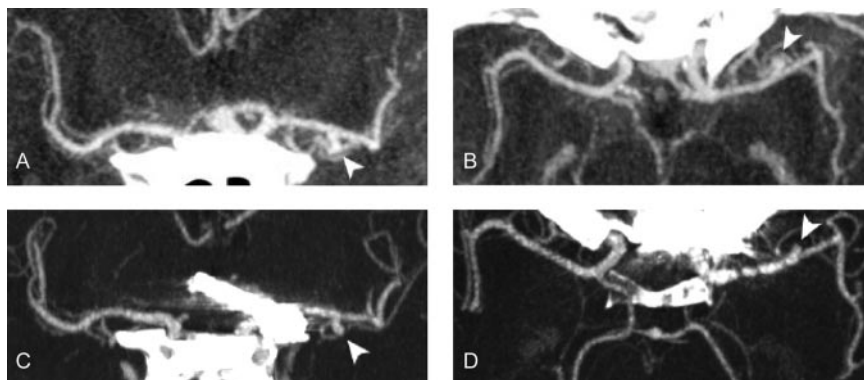


Figure 3. Aneurysms visible in retrospect with stable size: aneurysm on the left MCA (arrowhead); 20-mm slab maximum-intensity projection of single-slice CTA with coronal (A) and axial (B) view in 2000 and multislice CTA coronal (C) and axial (D) views in 2004.

between growth of aneurysms visible in retrospect and the initial size of the aneurysm at the time of the SAH ($\beta=0.0$; 95% CI, -3.0 to 2.9).

Discussion

In the reassessment of aneurysms detected at screening in patients with a previously clipped aneurysm after an SAH, almost one third of the aneurysms were de novo; of the aneurysms visible in retrospect, approximately one quarter increased in size. De novo aneurysms were mainly MCA aneurysms and smaller than 5 mm. Aneurysms visible in retrospect were mostly located at the origin of the Pcom artery. Half of the aneurysms with increased size were larger than 5 mm at the time of screening, and most of the aneurysms with stable size were smaller than 5 mm. Patients with a de novo or enlarged aneurysm were more often women. There was no linear relation between the development of de novo aneurysms and the duration of follow-up and also no linear relation between enlargement of existing aneurysms and the initial size of the aneurysm or duration of follow-up.

Aneurysm site differs between de novo aneurysms and ruptured aneurysms at the initial SAH. The most frequent site of de novo aneurysms is the MCA, whereas the most frequent site of ruptured aneurysms is the anterior communicating artery.¹¹ This preponderance of MCA aneurysms is also present in familial SAH.¹² The predominance of carotid artery aneurysms in patients with an aneurysm visible in retrospect can be explained by the difficulties in visualization (small

aneurysm size, proximity of bone) and interpretation of aneurysms at this location (differentiation of an infundibulum from an aneurysm at the origin of the Pcom can be difficult).¹³ The better image quality with a multislice CT scanner and the double reading of experienced radiologists may explain why during screening more aneurysms were seen than at time of the SAH when a single-slice CTA was assessed by usually only 1 radiologist. Also, the initial DSA was often performed with the catheter in the common carotid artery, not selectively in the internal carotid artery, and also without the possibility of additional 3D angiography. Conventional DSA offers a limited number of projections compared with multislice CTA, in which all possible projections can be obtained.

For the individual patient, it makes no difference whether a new SAH arises from a de novo aneurysm or an already existing (additional) aneurysm. However, differentiating between de novo and growing additional aneurysms is important to understand the pathophysiology of second episodes of SAH, to determine whether screening is more beneficial than reviewing original films, and if so, to calculate the optimal frequency of screening. Because most of the aneurysms detected at screening are additional aneurysms missed at the time of the initial SAH, reviewing the DSA or CTA performed at the time of the SAH may reveal initially undetected additional aneurysms. We have, however, not reviewed the original DSA or CTA performed at the time of the SAH blinded for the results of the screening CTA. We therefore have no data on the yield of reviewing the initial DSA or CTA

TABLE 2. Aneurysm Size on Follow-Up

	Initial Size, mm	Actual Size, mm	Aneurysm Location	Increase, mm	Follow-Up, y
1	2	5×5	MCA	3	11
2	3	6×6	Pericallosal	3	11
3	2.5	4.5×4.5	Carotid (Pcom)	2	11
4	3	5×6	Carotid (choroidal)	3	7
5	3	11×7	Anterior communicating	8	6
6	3	3×5	Carotid (Pcom)	2	6
7	Fusiform	Fusiform with bleb of 3×1.5	Basilar	3 (bleb)	5
8	2.5	3×3	MCA	0.5 (and changed shape)	4
9	2	3×4	Carotid (Pcom)	2	4
10	4	4×5	MCA	1	4

before performing the screening. In only 1 of the 2 participating hospitals was it standard clinical practice to perform a postoperative DSA. This postoperative DSA was usually a selective catheterization of the aneurysm-bearing vessel only, which was well visualized before the treatment as well. Therefore, this postoperative DSA was valuable to detect incompletely clipped aneurysms but of little value in detecting additional aneurysms.

More than three quarters of the patients with de novo aneurysms were women, which is a higher proportion than in our hospital-based series of all patients with SAH admitted to our hospital since 1985, in which 67% of the patients were female.¹⁴ This is in concordance with the finding that female sex is an important risk factor for the growth and development of intracranial aneurysms⁵ and with the finding that new episodes of SAH predominantly occur in women.¹⁶ Our screened population (mean age, 51.7 years at time of screening) was younger than the total hospital-based series of patients with SAH (53 years at the time of SAH) because we did not invite patients older than 70 years of age for screening. Within the subset of relatively young patients invited for screening, those patients who proved to have de novo aneurysms were considerably younger than the study population in general, which is in agreement with the generally young age of patients with recurrent SAH.¹⁵

There was no linear relation between de novo aneurysm formation and the duration of follow-up, although the small number of patients preclude definite conclusion. For the development of de novo aneurysms, rates ranging between 0.84% and 2.2% per year are reported in the literature.^{1,3-5} In these articles, it is assumed that the development of de novo aneurysms is linearly related to time. If we consider the development of de novo aneurysms to be linearly related to time, then the incidence of de novo aneurysms in our study would be 0.67 per year (in 17.6% of patients, an aneurysm was detected that was de novo in 31%, with a mean follow-up period of 8.1 years: $18\% \times 31\% / 8.1 = 0.67$).

Because we did not find de novo aneurysms within the first 5 years after the SAH, the initial years might not be included in determining the rate of development of new aneurysms. Whether the rate of development of new aneurysms beyond a certain time after SAH is linear or not remains uncertain.

There was also no linear relation between enlargement of existing aneurysms and duration of follow-up. Again, the number of enlarged aneurysms is too small to detect a trend. In a long-term follow-up study of unruptured aneurysms, the duration of follow-up was inversely related to aneurysmal growth. This is explained by the frequent rupture of growing aneurysms.⁵

No linear relation was found between enlargement of existing aneurysms and the initial size of the aneurysm. In a series of patients with unruptured aneurysms followed up by means of MRA, enlargement of aneurysms was found only in those larger than 9 mm from the outset.⁶ In our series, the initial size of all but 1 of the enlarged aneurysm was ≥ 3 mm. We cannot confirm the enlargement of initially large aneurysms because large aneurysms had already been detected at the time of SAH. Our data do, however, convincingly show that initially small aneurysms also have a ten-

dency to enlarge over time. Thus, initially small aneurysms with an inconsequential risk of rupture may turn into larger aneurysms with significant risk of rupture.^{5,6}

A clip-induced artifact may cause a problem in evaluation at the clip site. Because we only included aneurysms in a different location than the clip site, this did not interfere with our analysis. However, in exceptional cases the clip artifact was extended and also degraded the image quality of nearby vessels. This might have resulted in false-negative CTAs. We assume that only size and not type (de novo aneurysm or visible in retrospect) of aneurysms determine the chance of missing it. Thus, the proportions of de novo aneurysms and additional aneurysms are not biased by missed aneurysms. The total number of aneurysms in the entire group of patients studied may be larger than we found.

On the basis of the results of the present study, no recommendations can be given regarding screening for new aneurysms in the years after an SAH. We have previously performed a decision analysis on the effectiveness of screening for new aneurysms in patients treated for a ruptured intracranial aneurysm.¹⁶ It was concluded that presently screening cannot be recommended but that sound conclusions about its effectiveness cannot be made because of the scarcity of data on key estimates of this model, such as the incidence of de novo aneurysms. This justifies our study on the incidence of new aneurysms for a large cohort of patients with a long-term follow-up after SAH. Effectiveness and cost-effectiveness of (repeated) screening depend on more than the chance of finding aneurysms and the size and thereby rupture risk of these aneurysms. Also, the risks of treatment, age of the patients (which relates to the expected life years), other demographic factors such as sex, smoking status, hypertension, and the impact of finding but not treating an aneurysm need to be taken into account. Therefore, an extensive decision analysis (eg, a Markov chain model with Monte Carlo simulation) is needed to assess whether screening is beneficial, and if so, at what intervals it should be performed.

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Appendix

Members of the ASTRA (Aneurysm Screening After Surgical Treatment for Ruptured Aneurysms) Study Group are as follows:

Executive Committee:

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