Durability of endovascular treatment for intracranial aneurysms
Ferns, S.P.

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Late reopening of adequately coiled intracranial aneurysms

frequency and risk factors in 400 patients with 440 aneurysms

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ABSTRACT

Background and purpose
In aneurysms that are adequately occluded 6 months after coiling, the risk of late reopening is largely unknown. We assessed the occurrence of late aneurysm reopening and possible risk factors.

Methods
From January 1995- June 2005, 1808 intracranial aneurysms were coiled in 1675 patients in 7 medical centers. At 6 months, 1066 aneurysms in 971 patients were adequately occluded. At mean 6.0 years after coiling, of the 971 patients, 400 patients with 440 aneurysms underwent 3 Tesla MRA to assess the occlusion status of the aneurysms. Proportions and corresponding 95% confidence intervals (CI) of aneurysm reopening and retreatment were calculated. Risk factors for late reopening were assessed by univariable and multivariable logistic regression analysis, including patient gender, rupture status of aneurysms, aneurysm size ≥10 mm and aneurysm location.

Results
In 11 of 400 patients (2.8%, 95% CI: 1.4- 4.9%) with 440 aneurysms (2.5%, 95% CI: 1.0-4.0%) late reopening had occurred; 3 reopened aneurysms were retreated (0.7%, 95% CI: 0.2- 1.5%). Independent predictors for late reopening were aneurysm size ≥10 mm (Odds Ratio (OR) 4.7, 95% CI: 1.3- 16.3), and location on basilar tip (OR 3.9, 95% CI: 1.1- 14.6). There were no late reopenings in 143 anterior cerebral artery aneurysms.

Conclusions
In patients with aneurysms that are adequately occluded at 6 months, the yield of long-term MRA follow-up for detection of reopened aneurysms that need retreatment is very low. For these patients, extended imaging follow-up in the initial 5-10 years after coiling is generally unnecessary. Longer follow-up may be considered in potential higher-risk patients, such as patients with large or basilar tip aneurysms.
INTRODUCTION

Endovascular coiling has become an established treatment for intracranial aneurysms. A shortcoming of coiling is the possibility of aneurysm reopening over time due to coil compaction, aneurysm growth, coil migration into intraluminal thrombus or resolution of intraluminal thrombus. Reopening occurs in approximately 20% of coiled aneurysms, and about half of reopened aneurysms are retreated. Currently, it is unknown for how long and how often coiled aneurysms need to be followed and whether certain subgroups carry a higher or lower risk for reopening.

Established risk factors for aneurysm reopening are large aneurysm size and low coil packing attenuation. Longer follow-up duration as a risk factor for reopening is under debate. Some studies reported more first-time aneurysm reopenings with longer follow-up and prolonged imaging follow-up has been recommended. However, interpretation of these studies is impeded by a wide variety in time intervals of first follow-up angiography. Reopenings that were detected on first follow up angiography some years after coiling, may have had developed much earlier. Longer follow-up duration was not associated with more aneurysm reopenings in a systematic review and in studies with fixed follow-up intervals.

In a large multicenter patient cohort, we determined the risk of late aneurysm reopening in aneurysms with adequate occlusion at 6 months angiographic follow-up and assessed possible risk factors.

METHODS

Patients

Institutional Review Boards of the participating medical centers (St. Elisabeth Ziekenhuis Tilburg, University Medical Center Utrecht, Academic Medical Center Amsterdam, Leiden University Medical Center, VU Medical Center Amsterdam, Slotervaart Ziekenhuis Amsterdam, and Maastricht University Medical Center, all in the Netherlands) approved the study protocol. Participants provided written informed consent.

From the databases of the centers, we retrieved all patients with a ruptured or unruptured intracranial aneurysm coiled since January 1995 and had adequate aneurysm occlusion (complete occlusion or only a small neck remnant) at 6 months angiographic follow-up according to occlusion status recorded in the databases and radiological reports. Inclusion criteria were: follow-up duration >4.5 years after coiling,
Figure 1. Flow chart showing patient and aneurysm selection.
current age between 18 and 70 years, living independently (Glasgow Outcome Scale 4 and 5)9 and no contra-indications for Magnetic Resonance Imaging at 3 Tesla (3T MR). We aimed to include 400 patients with >4.5 years of MRA follow-up in the study; the end date of the selection period was determined accordingly. We started with the patients with the longest follow-up and continued including patients until the target number of 400 was reached.

We contacted the general practitioners of all eligible patients to find out if the patient was still alive. If a patient had died, we retrieved the date and cause of death. The patients who were still alive received an invitation letter to participate in this long-term Magnetic Resonance Angiography (MRA) follow-up study with background information. Patients who did not respond to the invitation letter were contacted by phone. Participants were scanned on similar 3T MR systems in 2 of the participating centers.

**MR imaging follow-up protocol**

MR imaging examinations were performed on 3T systems (Intera R10; Philips Healthcare, Best, The Netherlands) by using the sensitivity encoding (SENSE) phased-array head coil (MR Imaging Devices, Gainesville, FL, USA). MR imaging protocol included axial T2-weighted fast spin echo and multiple overlapping thin slab acquisition 3D time-of-flight (MOTSA 3D-TOF) MRA sequences. Detailed descriptions of the imaging parameters have been described previously.10 Images were processed into maximum intensity projections and volume rendered 3D images of the circle of Willis. Total MR imaging examination time was 20 minutes. This 3T MRA protocol for follow-up of coiled intracranial aneurysms has been validated in a previous study.11

**MR imaging evaluation**

MRI and MRA images were evaluated by 2 experienced neuroradiologists independently in 3 centers. Discrepancies were resolved in consensus. Aneurysm occlusion status was dichotomized as adequate or incomplete. In incompletely occluded aneurysms, residual aneurysm lumen was measured in 2 directions. Presence of intraluminal thrombus was assessed on axial T2-weighted images. For aneurysms that were considered incompletely occluded on follow-up MRA, images were compared to angiographic follow-up at 6 months to confirm or refute reopening, and to make a clinical advice on retreatment and extended imaging or no follow-up.
**Statistical analysis**

The first 104 included patients were described previously.\(^\text{10}\) We extended this patient cohort to obtain more reliable data and to assess possible risk factors for late aneurysm reopening.

Proportions with 95% confidence intervals (CI) were calculated for aneurysms with reopening and for reopened aneurysms that were retreated. Patient- and aneurysm characteristics of 400 participants in this study were compared to 571 non-participants with adequate aneurysm occlusion at 6 months angiographic follow-up. Patients with aneurysm reopening were compared to patients without aneurysm reopening. The sample t-test was used for comparison of means (P≤0.05 was considered statistically significant) and odds ratios (OR) with 95% CI were calculated for binary outcome measures; patient gender, rupture status of aneurysms, aneurysm size ≥ 10 mm, posterior circulation aneurysms and basilar tip aneurysms. Subsequently, risk factors with a p-value ≤ 0.10 were included in a multivariate logistic regression model. A backward selection strategy was used and odds ratios with 95% CI were calculated.

We calculated inter-observer agreement of the dichotomized scores (adequate and incomplete occlusion) per patient in percentages.

**RESULTS**

**Baseline patient and aneurysm characteristics**

Four hundred patients with 440 coiled aneurysms were included, after selecting and inviting patients treated between January 1995 and June 2005. In this time window, 1808 intracranial aneurysms in 1675 patients were treated by coiling in the 7 participating centers in the Netherlands. Of 1675 patients, 1287 with 1412 aneurysms had 6 months follow-up angiography and 1066 (75%) aneurysms in 971 patients were adequately occluded at this first angiographic follow-up. Of 971 eligible patients with 1066 aneurysms, 157 (16%) could not be traced, and 274 could not be included for a variety of reasons (Figure 1). We invited 540 patients to participate in the study to reach the target of 400 included patients, thus, 140 declined (participation grade 74%). Mean follow-up duration was 6.0 years (median 5.0, range 4.5-12.9 years).

Comparison of patient- and aneurysm characteristics of the 400 included patients (Table 1) with 571 patients that did not participate in the study resulted in a significant lower age (mean age 54.5 versus 57.1 years, p<0.001), due to the inclusion criterion of “current age 18-70 years”. All other variables were comparable between participants and non-participants.
Table 1. Patient- and aneurysm characteristics of all participants in long-term MRA follow-up and of patients with aneurysm reopening

<table>
<thead>
<tr>
<th></th>
<th>400 patients/440 aneurysms with long-term MRA follow-up</th>
<th>11 patients/11 aneurysms with aneurysm reopening</th>
<th>OR (95%CI), p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>276 (69%)</td>
<td>10 (91%)</td>
<td>4.66 (0.59-36.82), 0.14</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>54.5</td>
<td>52.3</td>
<td>-</td>
</tr>
<tr>
<td>median, range</td>
<td>55, 23-70</td>
<td>54, 27-66</td>
<td>-</td>
</tr>
<tr>
<td>Ruptured aneurysms</td>
<td>344 (78%)</td>
<td>9 (75%)</td>
<td>1.26 (0.27-5.94), 0.77</td>
</tr>
<tr>
<td>Mean size (mm)</td>
<td>6.5</td>
<td>8.8</td>
<td>-</td>
</tr>
<tr>
<td>median, range</td>
<td>6.0, 2-20</td>
<td>7.5, 3-20</td>
<td>-</td>
</tr>
<tr>
<td>Size ≥10 mm</td>
<td>66 (15%)</td>
<td>5 (45%)*</td>
<td>5.13 (1.52-17.32), 0.01*</td>
</tr>
<tr>
<td>Intraluminal thrombus</td>
<td>4 (1%)</td>
<td>1 (8%)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Aneurysm location**

|                          | 327 (74%)                                                | 6 (55%)                                           | -             |
| Anterior circulation     |                                                          |                                                   |               |
| ACA                      | 143                                                      | 0                                                 | -             |
| MCA                      | 44                                                       | 2                                                 | -             |
| ICA                      | 140                                                      | 4                                                 | -             |
| Posterior circulation    | 113 (26%)                                                | 5 (45%) †                                         | 2.51 (0.75-8.38), 0.14 |
| Basilar tip              | 61                                                       | 4 †                                               | 3.73 (1.06-13.14), 0.04† |


* For calculation of OR for aneurysm reopening of aneurysms ≥10 mm, aneurysms <10 mm were used as reference group.

† For calculation of OR for aneurysm reopening of posterior circulation aneurysms, anterior circulation aneurysms were used as reference group. For calculation of OR for aneurysm reopening of basilar tip aneurysms, aneurysms on all other locations were used as reference group.

‡ Statistically significant
Aneurysm reopening on long-term follow-up MRA

There was agreement between observers in occlusion status of the aneurysms in 421 of 440 aneurysms (95.7%). Late reopening occurred in 11 of 400 patients (2.8%, 95% CI 1.4-4.9%) with 440 aneurysms (2.5%, 95% CI 1.0-4.0%). Characteristics of patients and aneurysms with reopening are displayed in Table 2. Three of 440 aneurysms were additionally treated with coils (0.7%, 95% CI 0.2-1.5%); an example is given in Figure 2. One reopened and retreated aneurysm had an intraluminal thrombus at initial presentation that had resolved at long-term follow-up. In 5 aneurysms retreatment was thought to be not indicated in the clinical context of the patient (reopening was disc-like in 2 aneurysms, too small to retreat in 2, and 1 patient with reopening had severe co-morbidity, and was unfit for a procedure). Two patients with aneurysm reopening declined retreatment, and in 1 aneurysm, retreatment was considered not possible because of unfavorable morphology (Figure 3).

Risk factors for late aneurysm reopening

Risk factors for late aneurysm reopening are summarized in Table 1. In uni- and multivariable regression analysis, 2 factors were identified as both dependent and independent risk factors for late reopening; aneurysm size $\geq 10$ mm (OR 4.7, 95% CI 1.3-16.3, p=0.016) and location on the basilar tip (OR 3.9, 95% CI 1.1-14.6, p=0.042).
## Table 2. Details of patients and aneurysms with late reopening

<table>
<thead>
<tr>
<th>No</th>
<th>M/F</th>
<th>Age</th>
<th>Aneurysm location</th>
<th>Size (mm)</th>
<th>Previous rupture</th>
<th>Size reopening (mm)</th>
<th>Retreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>61</td>
<td>MCA</td>
<td>3</td>
<td>Y</td>
<td>2x1</td>
<td>N*</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>54</td>
<td>Basilar tip</td>
<td>5</td>
<td>Y</td>
<td>3x2</td>
<td>N*</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>49</td>
<td>Basilar tip</td>
<td>10</td>
<td>Y</td>
<td>5x2</td>
<td>N*</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>66</td>
<td>MCA</td>
<td>20</td>
<td>N</td>
<td>6x3</td>
<td>Y</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>63</td>
<td>PcomA</td>
<td>7</td>
<td>Y</td>
<td>5x5</td>
<td>Y</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>59</td>
<td>ICA tip</td>
<td>12</td>
<td>Y</td>
<td>8x7</td>
<td>N†</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>49</td>
<td>Basilar tip</td>
<td>12</td>
<td>Y</td>
<td>8x3</td>
<td>N*</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>27</td>
<td>ICA tip</td>
<td>6</td>
<td>N</td>
<td>3x3</td>
<td>Y</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>42</td>
<td>PcomA</td>
<td>5</td>
<td>Y</td>
<td>4x3</td>
<td>N§</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>61</td>
<td>SCA</td>
<td>10</td>
<td>Y</td>
<td>9x7</td>
<td>N§</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>45</td>
<td>Basilar tip</td>
<td>7</td>
<td>Y</td>
<td>1x2</td>
<td>N*</td>
</tr>
</tbody>
</table>

MCA: Middle Cerebral Artery, PcomA: Posterior Communicating Artery, ICA tip: Internal Carotid Artery tip, SCA: Superior Cerebellar Artery, Y: yes, N: no

* Retreatment not judged indicated by multidisciplinary team
† Patient not retreated because of co-morbidity
‡ Patient not retreated because of unfavorable morphology of the aneurysm remnant
§ Patient refused retreatment
Figure 2. 27-year-old woman with late reopening and retreatment of unruptured left internal carotid artery tip aneurysm.
A; Angiogram at presentation shows a 6-mm internal carotid artery tip aneurysm. B; Adequate aneurysm occlusion directly after coiling. C; Stable complete occlusion at 6-month follow-up angiogram. D; Volume Rendering image of MRA 4.5 years after coiling shows incomplete aneurysm occlusion with a remnant of 3x3 mm. E; Angiogram confirms incomplete occlusion of the aneurysm. F; Complete occlusion after additional coiling.

Figure 3. 49-year-old woman with late reopening of a ruptured 12-mm basilar artery tip aneurysm, not retreated due to unfavorable morphology.
A; Angiogram directly after coiling shows adequate aneurysm occlusion. B; Small neck remnant on the 6 months follow-up angiogram. C; MRA 4.7 years after coiling shows aneurysm reopening of 3x8 mm at the base of the aneurysm. D; Angiogram 6 years after coiling shows growth of the aneurysm remnant to 5x9 mm. Because of unfavorable vessel geometry, additional coiling was not performed.
DISCUSSION

Our study shows that the vast majority of coiled intracranial aneurysms that are adequately occluded at six months follow-up angiography remain adequately occluded during the following 5 years. First time reopenings long after coiling only occasionally occurred and most reopened aneurysms were not retreated for a variety of reasons. Our results indicate that for the large subgroup of coiled aneurysms with adequate occlusion at 6 months, the yield of long-term MRA is very low.

Independent risk factors for late aneurysm reopening were aneurysm size ≥10 mm and location on the basilar tip, consistent with previous studies concerning both early (within the first 6 months) and late reopening. Although prevalence of aneurysms with intraluminal thrombus on follow-up imaging in our study was very small, one aneurysm reopening was caused by a resolved intraluminal thrombus. Because MR imaging was not performed in all centers at the time of 6 months follow-up, we cannot assess the predictive value for reopening of coiled aneurysms with intraluminal thrombus. The small proportion in our study population with thrombus at follow-up may be explained by instances of reopening at six months follow-up, which made these patients ineligible for the current study. It has been shown previously that partially thrombosed aneurysms may continue to grow after coiling, even after stability for some years. We found a lower risk of late reopening for anterior cerebral artery aneurysms, of which most are located on the anterior communicating artery. A possible explanation is the selection bias; anterior circulation aneurysms with unfavorable anatomy for coiling can mostly be clipped while surgery for basilar artery aneurysms is rarely an alternative.

Presumably the chance of recurrent hemorrhage in adequately coiled aneurysms at 6 months is very low because the late reopening rate is so low. This presumption has been confirmed in previous studies that focused on the recurrent hemorrhage rate in a comparable subgroup of patients with adequately coiled ruptured aneurysms after 6 months. In those studies, the incidence of recurrent SAH after adequate coiling was significantly lower than after clipping. In a long-term follow-up study of ISAT, recurrent hemorrhage after coiling of aneurysms without distinction of adequate or incomplete occlusion was higher compared to clipping, although this did not reach statistical significance.

Apart from the risk of aneurysm reopening, a concern in patients with treated aneurysms is the frequent presence of small untreated aneurysms and the risk to
develop de novo aneurysms over time. Imaging follow-up may be indicated to timely detect new aneurysms and growth of additional untreated aneurysms. The results of previous large follow-up studies addressing these issues indicate that in the first 5 years after coiling (and probably also in the first 10 years), both the risk of de novo aneurysm formation and the risk of growth of existing untreated aneurysms is very low and the risk of SAH from such aneurysms is extremely low.\textsuperscript{8,19,20}

Our study has several limitations. First, 16\% of patients potentially eligible for our study could not be contacted. Most of these patients did have clinical and imaging follow-up beyond the 6-month interval. We have no reason to believe that our sample was biased, because patient- and aneurysm characteristics of participating patients were comparable to non-participants with adequate aneurysm occlusion at 6 months. Most patients we lost were treated very early in our inclusion period, and had moved out of the region during the long follow-up interval. We have tried to contact general practitioners of these patients, and we found no clues for death or dependence of any of the patients from SAH. Second, although our study was prospective in design, patients had no fixed follow-up interval; we retrieved all eligible coiled patients from the participating centers in a large time window from 4.5 years up to 13 years. Therefore, we could only calculate proportions in a wide time interval. Third, the inclusion criterion ‘adequate aneurysm occlusion’ is to some extent a subjective observation, especially for aneurysms with larger neck-remnants. The dichotomization between adequately occluded aneurysms and incompletely occluded aneurysms was chosen to minimize inclusion bias.\textsuperscript{21} Only aneurysms with incomplete occlusion at 6 months were excluded. Eligibility for this study was based on the judgment of the treating multi-disciplinary team at the time of initial presentation.

Our study implies that the first imaging follow-up at 6 months is a crucial point in time: when the coiled aneurysm is adequately occluded, the patient may be considered cured. However, in the clinical context of the individual patient with an adequately occluded aneurysm at 6 months, extended imaging follow-up may be considered in patients with aneurysms ≥10 mm, with aneurysms located on the basilar tip and with partially thrombosed aneurysms. Other factors may also play a role in decision making, such as young patient age, the presence of multiple aneurysms or familiar aneurysms.

Offering very late follow-up imaging may have a two-sided effect in patients fearing aneurysm reopening or a new aneurysm: It may either increase quality of life when no such findings are present or it may have a negative impact when aneurysm reopenings or new aneurysms are detected that remain untreated.\textsuperscript{22}
CONCLUSIONS

Prolonged imaging follow-up within the first 5-10 years after coiling does not seem beneficial in general in patients with aneurysms that are adequately occluded at 6 months, in terms of detecting reopened aneurysms that need retreatment. Whether patients might benefit from screening beyond the 5- to 10-year interval is not yet clarified.
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