Late Reopening of Adequately Coiled Intracranial Aneurysms
Frequency and Risk Factors in 400 Patients With 440 Aneurysms
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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 to June 2005, 1808 intracranial aneurysms were coiled in 1675 patients at 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 magnetic resonance angiography to assess occlusion status of the aneurysms. Proportions and corresponding 95% CI of aneurysm reopening and retreatment were calculated. Risk factors for late reopening were assessed by univariate and multivariate logistic regression analysis, and included patient sex, 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 (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 the 143 anterior cerebral artery aneurysms.

Conclusions—For the vast majority of adequately occluded intracranial aneurysms 6 months after coiling (those <10 mm and not located on basilar tip), prolonged imaging follow-up within the first 5 to 10 years after coiling does not seem beneficial 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 clear. (Stroke. 2011;42:1331-1337.)

Key Words: intracranial aneurysm ■ radiology ■ interventional ■ coiling ■ follow-up ■ MRA

Endovascular coiling has become an established treatment for intracranial aneurysms.1,2 A shortcoming of coiling is the possibility of aneurysm reopening over time caused by 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.3 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.4,5 It is debated whether longer follow-up duration is a risk factor for reopening. Some studies report more first-time aneurysm reopenings with longer follow-up and so prolonged imaging follow-up has been recommended.5,6 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.3,7,8

In a large multicenter patient cohort, we determined the risk of late aneurysm reopening in aneurysms with adequate

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occlusion at 6 months angiographic follow-up and assessed possible risk factors.

Materials and 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 are 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 who had adequate aneurysm occlusion (complete occlusion or only a small neck remnant) at 6 months angiographic follow-up; this was determined by to occlusion status as recorded in the databases and radiological reports. Inclusion criteria were: follow-up duration >4.5 years after coiling, current age between 18 and 70 years, living independently (Glasgow Outcome Scale 4 and 5), and no contraindications for magnetic resonance imaging at 3 Tesla (3T MR). The upper age limit of 70 years was chosen because it is unclear if we would subject a patient over 70 years of age to retreatment if an aneurysm reopening was found. First, because there is an increased risk of treatment complications in these patients, and second, the anticipated annual risk of rupture from an aneurysm reopening is low. We aimed to include 400 patients with >4.5 years of magnetic resonance angiography (MRA) follow-up in the study; the end date of the selection period was determined accordingly. We started with 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 whether 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 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) by using the sensitivity encoding phased-array head coil (MR Imaging Devices). 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. Details of the imaging parameters have been described previously. 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.

MR Imaging Evaluation

MR imaging and MRA images were evaluated by 2 experienced neuroradiologists independently in 3 centers. Discrepancies were resolved in consensus. Reopening was defined as flow on MRA at the base of the aneurysm, either caused by compaction of the coil mesh or by aneurysm growth.

All MRA studies were scored with the Raymond-Roy classification system and were dichotomized between adequately occluded aneurysms (Raymond classification I and II) and incomplete occluded aneurysms (Raymond classification III) for optimal interobserver agreement. In incompletely occluded aneurysms, residual aneurysm lumen was measured in 2 directions. In the case of new aneurysm formation at the site of the coiled aneurysm, it was not considered a recurrence, but rather a de novo aneurysm. 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 decision about retreatment and extended imaging, or not to follow-up.

Statistical Analysis

The first 104 included patients were described previously. We extended this patient cohort to obtain data that are more reliable and to assess possible risk factors for late aneurysm reopening.

Proportions with 95% 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 with 571 nonparticipants with adequate aneurysm occlusion at 6 months angiographic follow-up. Patients with aneurysm reopening were compared with patients without aneurysm reopening. The sample t test was used for comparison of means (P≤0.05 was considered statistically significant) and ORs with 95% CI were calculated for binary outcome measures: patient sex, rupture status of aneurysms, aneurysm size≥10 mm, posterior circulation aneurysms, and basilar tip aneurysms. Subsequently, risk factors with a probability value ≤0.10 were included in a multivariate logistic regression model. A backward selection strategy was used and ORs with 95% CI were calculated.

We calculated interobserver 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 at the 7 participating centers in the Netherlands. Of 1675 patients, 1287 patients with 1412 aneurysms had 6 months follow-up angiography, and 1066 (75%) aneurysms in 971 patients were adequately occluded at this first follow-up. Of 971 eligible patients with 1066 aneurysms, 157 patients (16%) could not be traced, and 274 patients 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 patients declined (participation grade, 74%).

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 significantly lower age (mean, 54.5 versus 57.1 years, P<0.001), because of the inclusion criterion of “current age 18 to 70 years.” All other variables were comparable between participants and nonparticipants.

Aneurysm Reopening on Long-Term Follow-Up MRA

Mean duration of follow-up was 6.0 years (median, 5.0 years; range, 4.5–12.9 years). 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 contraindicated 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 comorbidity, and was unfit for a procedure). Two patients with aneurysm reopening declined retreatment, and in 1 aneurysm, retreatment was not considered possible because of unfavorable morphology (Figure 3).

Figure 1. Flow chart showing patient and aneurysm selection.

### Risk Factors for Late Aneurysm Reopening
Risk factors for late aneurysm reopening are summarized in Table 1. In uni- and multivariate regression analysis, 2 factors were identified as both dependent and independent risk factors for late reopening; these were aneurysm size ≥10 mm (multivariate analysis: 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).

### Discussion
Our study shows that the vast majority of coiled intracranial aneurysms that are adequately occluded at 6 months follow-up angiography remain adequately occluded during the following 5 years. First-time reopenings occurring long after coiling were only occasional, 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. We found that aneurysm rupture was not a predictor for late aneurysm recurrence. Other studies have found ruptured aneurysms to result in higher risk for both early and late recurrence. It is possible that the rupture of an aneurysm causes temporary instability related to resolving hematoma around the aneurysm, which can cause early recurrence, and that this instability is dissolved within 6 months.

We found a lower risk of late reopening for anterior cerebral artery aneurysms, which are most often 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. We could not find data on long-term follow-up of aneurysms that were adequately occluded at time of treatment and at 6 months follow-up for balloon- or stent-assisted coiling. Although unlikely, these aneurysms may have a different course during follow-up than did the aneurysms of our series.
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 subarachnoid hemorrhage after adequate coiling was significantly lower than after clipping.\textsuperscript{18,19} In a long-term follow-up study of the International Subarachnoid Aneurysm Trial, recurrent hemorrhage after coiling of aneurysms without distinction of adequate or incomplete occlusion was higher compared with after clipping, although this did not reach statistical significance.\textsuperscript{10} Neck size might also be a determinant of reopening, but because a neck size measurement at time of treatment was lacking for many patients, we could not include this factor as determinant in our analysis.

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 detect new aneurysms and growth of additional untreated aneurysms in a timely fashion. The results of previous large follow-up studies addressing these issues, however, 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; also, the risk of subarachnoid hemorrhage from such aneurysms is extremely low.\textsuperscript{8,20,21}

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 those of nonparticipants with adequate aneurysm occlusion at 6 months. Most patients with whom we lost contact 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 after clipping.\textsuperscript{18,19}

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>Characteristic</th>
<th>400 Patients/440 Aneurysms With Long-Term MRA Follow-Up</th>
<th>11 Patients/11 Aneurysms With Aneurysm Reopening</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>Mean N % Median Range</td>
<td>Mean N % Median Range</td>
<td>4.66</td>
<td>0.59–36.82</td>
<td>0.14</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>54.5 55 23–70</td>
<td>52.3 54 27–66</td>
<td>1.26</td>
<td>0.27–5.94</td>
<td>0.77</td>
</tr>
<tr>
<td>Ruptured aneurysms</td>
<td>344 78</td>
<td>9 75</td>
<td>8.8 7.5 3–20</td>
<td>5.13</td>
<td>1.52–17.32</td>
</tr>
<tr>
<td>Mean size (mm)</td>
<td>6.5 6.0 2–20</td>
<td>6 55</td>
<td>6.5 6.0 2–20</td>
<td>2.51</td>
<td>0.75–8.38</td>
</tr>
<tr>
<td>Size &gt;10 mm</td>
<td>66 15</td>
<td>5 45</td>
<td>3.73</td>
<td>1.06–13.14</td>
<td>0.04†</td>
</tr>
<tr>
<td>Aneurysm location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>327 74</td>
<td>6 55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>143</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>44</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>140</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>113 26</td>
<td>5 45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basilar tip</td>
<td>61</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MRA indicates magnetic resonance angiography; OR, odds ratio; ACA, anterior cerebral artery; MCA, middle cerebral artery; ICA, internal carotid artery; . . ., not calculated.

*For calculation of OR for aneurysm reopening of aneurysms >10 mm, aneurysms <10 mm were used as reference group.
†Statistically significant.
‡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.

Table 2. Details of Patients and Aneurysms With Late Reopening

<table>
<thead>
<tr>
<th>No.</th>
<th>M/F</th>
<th>Age (Years)</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>2×1</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>3×2</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>5×2</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>6×3</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>5×5</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>8×7</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>8×3</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>3×3</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>4×3</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>9×7</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>1×2</td>
<td>N*</td>
</tr>
</tbody>
</table>

MCA indicates middle cerebral artery; PcomA, posterior communicating artery; ICA, internal carotid artery; 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.
from subarachnoid hemorrhage. 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 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 (both completely occluded aneurysms and aneurysms with a small neck remnant) and incompletely occluded aneurysms was chosen to minimize inclusion bias. Only aneurysms with incomplete occlusion at 6 months were excluded. Eligibility for this study

Figure 2. A 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, Directly after coiling adequate aneurysm occlusion. 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 reopening of 3×3 mm. E, Angiogram confirms incomplete occlusion of the aneurysm. F, Complete occlusion after additional coiling.

Figure 3. A 49-year-old woman with late reopening of a ruptured 12-mm basilar artery tip aneurysm, not retreated because of unfavorable morphology. A, Angiogram directly after coiling shows adequate aneurysm occlusion. B, Small neck remnant on the 6-month follow-up angiogram. C, MRA 4.7 years after coiling shows aneurysm reopening of 3×8 mm at the base of the aneurysm. D, Angiogram 6 years after coiling shows growth of the aneurysm remnant to 5×9 mm. Because of unfavorable vessel geometry, additional coiling was not performed.
was based on the radiological report of 6 months follow-up digital subtraction angiography.

Our study implies that the first imaging follow-up at 6 months is a crucial point in time; when the coiled aneurysm (<10 mm and not located on the basilar tip) is adequately occluded, it is very likely it will remain stable over time. This is especially true for aneurysms <10 mm and aneurysms not located on the basilar tip, which are the vast majority of coiled aneurysms. 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 the presence of familiar aneurysms.

Offering very late follow-up imaging may have a dual 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.

In conclusion, for the vast majority of adequately occluded intracranial aneurysms 6 months after coiling (those <10 mm and not located on basilar tip), prolonged imaging follow-up within the first 5 to 10 years after coiling does not seem beneficial 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 clear.

Appendix

LOTUS Study Group (Alphabetical Order)

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