Long-Term Recurrent Subarachnoid Hemorrhage After Adequate Coiling Versus Clipping of Ruptured Intracranial Aneurysms

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Background and Purpose—Coiling is increasingly used as treatment for intracranial aneurysms. Despite its favorable short-term outcome, concerns exist about long-term reopening and inherent risk of recurrent subarachnoid hemorrhage (SAH). We hypothesized a higher risk for recurrent SAH after adequate coiling compared with clipping.

Methods—Patients with ruptured intracranial aneurysms coiled between 1994 and 2002 with adequate (>90%) aneurysm occlusion at 6-month follow-up angiograms were included. We interviewed these patients about new episodes of SAH. By survival analysis, we assessed the cumulative incidence of recurrent SAH after coiling and compared it with the incidence of recurrent SAH in a cohort of 748 patients with clipped aneurysms by calculating age and sex-adjusted hazard ratios.

Results—Of 283 coiled patients with a total follow-up of 1778 patient-years (mean, 6.3 years), one patient had a recurrent SAH (0.4%) and 2 patients had a possible recurrent SAH. For recurrent SAH within the first 8 years after treatment, the cumulative incidence was 0.4% (95% CI, 0.4 to 1.2) after coiling versus 2.6% (95% CI, 1.2 to 4.0) after clipping (hazard ratio, 0.2; 95% CI, 0.03 to 1.6). For possible and confirmed recurrent SAH combined, the cumulative incidence was 0.7% (95% CI, 0.3 to 1.7) after coiling versus 3.0% (95% CI, 1.3 to 4.6) after clipping (hazard ratio, 0.7; 95% CI, 0.2 to 2.3).

Conclusion—Patients with adequately occluded aneurysms by coiling at short-term follow-up are at low risk for recurrent SAH in the long term. Within the first 8 years after treatment, the risk of recurrent SAH is not higher after adequate coiling than after clipping. (Stroke. 2009;40:1758-1763.)

Key Words: epidemiology □ intracranial aneurysm □ subarachnoid hemorrhage

Endovascular treatment of intracranial aneurysms by coiling results in better short-term outcome than clipping in patients with aneurysmal subarachnoid hemorrhage (SAH). An important drawback of coiling is reopening of the aneurysm as a result of coil compaction, growth of a neck remnant, or dissolution of an intraluminal thrombus. Reopening occurs in approximately 20% of coiled aneurysms, predominantly within the first year after coiling, and exposes the patient to the risk for recurrent SAH in the long term. Therefore, most centers perform one or more follow-up angiograms during the initial years after coiling. It is unknown for how long and how often coiled aneurysms need to be followed up and whether certain subgroups carry a higher risk for reopening. In patients with complete or near complete occlusion at 6-month follow-up angiogram, the long-term risk for reopening appears to be low.

The incidence of recurrent SAH after clipping is low with a cumulative incidence of approximately 3% within the initial 10 years after treatment. Recurrent SAH after clipping is caused by rupture of a recurrent aneurysm at the clip site or by rupture of an untreated additional or a de novo aneurysm. Long-term follow-up data on recurrent SAH after coiling are scarce. Because of the concern of late reopening after coiling, we aimed to evaluate whether adequately coiled aneurysms carry a higher risk of recurrent SAH than clipped aneurysms. Therefore, we assessed the cumulative incidence of long-term recurrent SAH in patients with complete or near complete occlusion at 6-month follow-up angiograms after coiling and compared it with the cumulative incidence of long-term recurrent SAH after clipping.

Methods

This study was approved by the Institutional Review Boards of both participating hospitals.

Patients With Coiled Ruptured Aneurysms

In 2 centers in The Netherlands (St. Elisabeth Ziekenhuis Tilburg and UMC Utrecht) with ample experience in endovascular treatment...
of aneurysms, we retrieved from the prospectively collected databases consecutive patients who met the following criteria: (1) admission with aneurysmal SAH between November 1994 and December 2002; (2) selective coil treatment of the ruptured intracranial aneurysm; (3) adequate (>90%) occlusion at 6 months' follow-up after the initial coiling procedure; and (4) age >20 years. Patients with additional untreated aneurysms were not excluded. Patients who were discharged to a nursing home and resided there at 6 months after the SAH were not called back for follow-up angiography and thus were not eligible for the current study.

For those patients who fulfilled the inclusion criteria, we first contacted the general practitioner to inquire if patients were still alive. The medical records of patients who had died during the follow-up period were reviewed to retrieve the exact cause of death. All other patients were contacted by telephone. During a semistructured interview, we asked whether a recurrent SAH had occurred. When no phone number was provided, we sent a short questionnaire by mail.

For all patients, data on age, sex, and site of aneurysms at time of the initial SAH were collected. In case a recurrent SAH or other type of stroke was reported by the patient or the general practitioner, we retrieved data from the hospitals where these patients had been admitted. All brain imaging was reviewed to assess the cause of stroke and to evaluate the degree of occlusion of the coiled aneurysm at the time of recurrent SAH.

In case patients had died suddenly without being admitted, we classified the event as a possible recurrent SAH if no further information was available.

Patients With Clipped Ruptured Aneurysms
The patient retrieval and methods of follow-up of the clipped patients have been described previously. From the database of the UMC Utrecht we retrieved patients with aneurysmal SAH and clipping of the ruptured aneurysm between 1985 and 2001. Patients who were discharged to a nursing home and patients <20 years old were not included. A postoperative angiography was performed in a minority of patients. The decision to perform postoperative angiograms was left to the discretion of the treating neurosurgeon.

Data Analysis
Survival analysis was used to assess the cumulative incidence for recurrent SAH after adequate clipping and after clipping. The follow-up period after coiling started at the 6-month follow-up angiography. In parallel, we used follow-up data starting from 6 months after clipping. We stopped continuing the survival analysis when the cohort no longer exceeded 50 patients.

The incidence rate per 100 000 patient-years with corresponding 95% CIs was calculated for episodes of confirmed recurrent SAH only and for episodes of confirmed and possible recurrent SAH combined. When patients died during follow-up from another cause rather than SAH or were lost to follow-up, they were censored at that time.

We compared the results of the survival analysis for clipped and coiled patients by calculating the age and sex-adjusted hazard ratio with corresponding CI for recurrent SAH after clipping versus clipping by Cox regression analysis.

Results
Patients With Coiled Aneurysms
Between 1994 and 2002, 476 patients admitted with aneurysmal SAH were treated by coiling. Of these 476 patients, 112 (24%) were not followed up by angiography at 6 months: 64 patients (13%) died before follow-up; 21 patients (4%) were admitted to a nursing home; 16 patients (3%) declined follow-up angiography; in 6 elderly patients (1%), follow-up was judged not indicated; 3 patients (0.6%) did not show up for follow-up angiography; and for 2 patients (0.4%), the reason was unknown (Figure 1). Of the 364 patients with follow-up angiography at 6 months, 290 (80%) showed adequate aneurysm occlusion and were eligible for this study. Follow-up data of 283 patients were retrieved. For 7 patients (2%), we could not contact the patient or their general practitioner. The address and phone number of 3 patients was unknown, 2 patients had emigrated, and 2 patients did not respond to phone calls or to the letter. Mean duration of follow-up was 6.3 years (range, 1.0 to 12.2 years) with a total of 1778 patient-years (Table 1). Baseline characteristics of these patients were comparable to those of the excluded 74 patients with incompletely occluded aneurysms at the

Table 1. Baseline Characteristics of Included Patients With Coiled and Clipped Aneurysms

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients With Coiled Aneurysms (n=283)</th>
<th>Patients With Clipped Aneurysms (n=748)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at initial SAH, years ± SD (range)</td>
<td>51.0 ± 11.0 (26–82)</td>
<td>50.4 ± 12.3 (21–84)</td>
</tr>
<tr>
<td>Women, %</td>
<td>201 (71)</td>
<td>499 (67)</td>
</tr>
<tr>
<td>Mean follow-up, years (range)</td>
<td>6.3 (1.0–12.2)</td>
<td>7.6 (0.04–19.5)</td>
</tr>
<tr>
<td>Aneurysm site, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>66 (23)</td>
<td>155 (21)</td>
</tr>
<tr>
<td>ACA</td>
<td>99 (35)</td>
<td>270 (36)</td>
</tr>
<tr>
<td>MCA</td>
<td>18 (6)</td>
<td>133 (18)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>100 (35)</td>
<td>39 (5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>151 (20)</td>
</tr>
</tbody>
</table>

ICA indicates internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery.
6-month angiography. Mean age of patients with incompletely occluded aneurysms was 53 years, 62% were female, and the distribution of aneurysm location was as follows: internal carotid artery, 22%; anterior cerebral artery, 28%; middle cerebral artery, 10%; and posterior circulation, 40%. However, the mean aneurysm size was 8.3 mm for adequately occluded aneurysms and 13.4 mm for incompletely occluded aneurysms.

Patients With Clipped Aneurysms
Of the 930 patients who survived SAH, 154 did not meet the inclusion criteria (17%): 64 patients were admitted to a nursing home after hospitalization; 4 patients were <20 years old; 30 patients were coiled or had received intracranial bypass surgery; and for 26 patients, the aneurysm was left untreated. The remaining 776 patients met the inclusion criteria. Of these patients, 24 (3%) patients were lost to follow-up: 7 patients lived abroad; 2 patients did not respond to the invitation letter; and of 15 patients, the address was unknown, rendering 752 patients with a mean duration of follow-up of 8.0 years (range, 0.2 to 20.1 years) and a total of 6016 patient-years. Because we used follow-up data starting from 6 months after clipping in analogy to coiling, 4 patients with a shorter follow-up duration than 6 months were excluded. One of these 4 patients died from rebleeding within 6 months after clipping. Thus, we included for the analysis 748 clipped patients with a mean duration of follow-up of 7.6 years (range, 0.04 to 19.5 years) and a total of 5661 patient-years.

Baseline characteristics of both patient populations are summarized in Table 1.

Recurrent Episodes of SAH
One of 283 included coiled patients had a recurrent episode of SAH (0.4%; 95% CI, 0% to 2.0%). The incidence rate of recurrent SAH was 57 per 100 000 patient-years (95% CI, 6 to 311 per 100 000) for the first 10 years of follow-up. Recurrent SAH occurred 23 months after clipping of a small basilar tip aneurysm in a 52-year-old man (Figure 2). The aneurysm was adequately occluded by recoiling after the recurrent SAH, but reopened again and was coiled for a third time. This patient survived and was slightly disabled but independent for activities of daily life 7 years after the recurrent SAH.

Of 283 coiled patients, 2 had died suddenly without available imaging. These patients were found dead in bed after 2 and 10 years after coiling. These events were defined as possible recurrent SAH. Combining those 2 patients with the patient with confirmed recurrent SAH, the frequency of recurrent SAH would be 1.1% (95% CI, 0.2% to 3.1%) with an incidence rate of 171 of 100 000 patient-years (95% CI, 31 to 494 per 100 000) within the first 10 years of follow-up. These 3 patients with confirmed or possible recurrent SAH after coiling are summarized in Table 2.

Recurrent SAH after clipping occurred in 17 of 748 patients (2.3%; 95% CI, 1.3% to 3.6%). The incidence rate after clipping was 247 of 100 000 patient-years (95% CI, 118 to 377 per 100 000) for the first 10 years of follow-up. The history of another 2 patients was suggestive of SAH and was classified as possible recurrent SAH. In 4 patients with recurrent SAH, an aneurysm at the clip site was found. In one of these patients also, a second aneurysm at another location was detected. The remaining 13 patients had no aneurysm at the clip site but had developed a de novo aneurysm or had bled from an aneurysm that was not identified at the time of the initial SAH.

Two coiled patients (0.7%) had died from intracerebral hemorrhage originating from the basal ganglia after 6 and 8 years of follow-up. One of these patients had a history of hypertension and had been treated with oral anticoagulation. The second patient had no oral anticoagulation and a history of hypertension was unknown. (CT images of these patients
are shown in supplemental Figures I and II, available online at http://stroke.ahajournals.org.) For both patients, the last follow-up angiography after coiling showed complete occlusion. Within the cohort of clipped patients, 10 instances of intracerebral hemorrhage occurred (1.3%).

Survival Analysis
Survival analysis was performed for the first 8 years, because at 8 years of follow-up, the number of patients in the cohort no longer exceeded 50 coiled patients (Figure 3). The cumulative incidence of confirmed recurrent SAH was 0.4%

### Table 2. Patient and Aneurysm Characteristics of the 3 Patients With Confirmed or Possible Recurrent SAH After Coiling

<table>
<thead>
<tr>
<th>Sex, Age, years</th>
<th>Aneurysm Location and Size</th>
<th>Confirmed/Possible Recurrent SAH</th>
<th>Delay Recurrent SAH After Coiling</th>
<th>Imaging After Recurrent SAH?</th>
<th>Additional Coiling?</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, 52</td>
<td>Basilar tip, 7 mm</td>
<td>Confirmed</td>
<td>23 months</td>
<td>Yes: incomplete occlusion</td>
<td>Yes, twice</td>
<td>Mild disability</td>
</tr>
<tr>
<td>Female, 66</td>
<td>SCA, 15 mm</td>
<td>Possible (found dead in bed)</td>
<td>2 years</td>
<td>No</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>Female, 53</td>
<td>MCA, 12 mm</td>
<td>Possible (found dead in bed)</td>
<td>10 years</td>
<td>No</td>
<td>No</td>
<td>Death</td>
</tr>
</tbody>
</table>

SCA indicates superior cerebellar artery; MCA, middle cerebral artery.
The cumulative incidence of confirmed and possible recurrent SAH was 0.7% (95% CI, 0.3 to 1.7%) after coiling and 3.0% (95% CI, 1.3 to 4.6%) after clipping. The age- and sex-adjusted hazard ratio for recurrent SAH after clipping versus coiling was 0.7 (95% CI, 0.2 to 2.3).

Discussion

In the first 8 years after treatment, the long-term risk of recurrent SAH is small both after clipping and after adequate coiling. For adequately coiled aneurysms, this risk was lower than anticipated and did not exceed the incidence of recurrent SAH after clipping. From our data, however, we cannot conclude that clipping is superior to coiling. Because the incidence of recurrent SAH is small, the corresponding CIs are wide, which leaves some uncertainty regarding the hazard ratio for recurrent SAH after clipping versus coiling.

The selection of patients with adequate occlusion at 6-month follow-up imaging is a likely explanation for the low incidence of recurrent bleeding after clipping. Observational studies have shown that the reopening rate is highest within the first 6 months after coiling and decreases thereafter. Interpretation of these studies is impeded by a variety of time intervals of follow-up angiography, so late-detected reopenings had possibly developed earlier. In a series of 126 patients with fixed angiographic follow-up intervals at 6 and 18 months after coiling, all reopened aneurysms were found at 6-month angiography. As a consequence of early reopening, the majority of recurrent treatment occurs within 10 months after initial coiling. Coiled aneurysms in these patients may form a separate group that behaves differently and that may carry a higher risk of repetitive reopening. Therefore, prolonged follow-up imaging for these aneurysms is recommended. In our study, we excluded this subgroup of patients, so we had presumed a small risk of recurrent SAH.

The distribution of aneurysm sites between coiled and clipped patients showed a larger proportion of aneurysms located in the posterior circulation within the coiled group (Table 1). Although there are hardly any data on the relation between rebleeding risk after treatment and aneurysm site, there is good evidence that unruptured aneurysms in the posterior circulation carry a higher rupture risk than unruptured aneurysms in the anterior circulation. This might imply a higher rebleeding rate for the coiled cohort, which has not been confirmed by our study results. Thus, the absence of a higher rebleeding rate in the coiled group is unlikely to be explained by differences in aneurysm sites between the 2 cohorts.

Despite the concerns regarding late reopening, the incidence of recurrent SAH after coiling was not higher than after clipping. This could be the result of some important differences between the follow-up of coiled and clipped aneurysms. By the end of the coiling procedure, the occlusion status of the aneurysm is known in contrast to clipping. In general, imaging was not performed in our patients immediately after clipping and a residual neck could have remained unnoticed. Another aspect is the presence of additional untreated aneurysms. The majority of the recurrent episodes of SAH after clipping were caused by additional aneurysms that were in retrospect present at the initial SAH or by de novo aneurysms that developed afterward. The awareness of the prevalence and development of multiple aneurysms by clinicians and the fast development of new techniques to detect aneurysms since the introduction of coiling procedures could explain the relatively large number of recurrent SAH from additional and de novo aneurysms in the older cohort of clipped patients. In our study population, 10% of clipped patients had one or more additional aneurysms that were coiled in the same or a repeat procedure. As a result of the small number of episodes of recurrent SAH and insufficient information regarding possible recurrent SAH, we could not assess the proportion of recurrent SAH from coiled aneurysms versus additional untreated aneurysms.

Awaiting the results from a large randomized clinical trial, a few other observational studies have assessed recurrent SAH after coiling, but these studies did not focus on adequately occluded aneurysms at 6 months’ follow-up. A large cohort study with a mean follow-up of 4.0 years, including 295 coiled patients and 706 clipped patients, found a rerupture rate of 3.5% for coiled patients versus 1.3% for clipped patients. This difference was not statistically significant. The rerupture rate of coiled aneurysms was inversely related to the level of aneurysm occlusion after treatment. For completely occluded aneurysms immediately after treatment, the authors found an overall rerupture rate of 1.1%, which corresponds with the rerupture rate we found for confirmed and possible recurrent SAH together. The vast majority of reruptures occurred in the first month after coiling, which is also found in another observational study that focused on early rerupture after coiling. Late rebleeding after coiling appears to occur predominantly in patients without regular follow-up angiography and hence not timely detected reopening or in patients with an untreatable reopening of the coiled aneurysm. These studies indicate that the short-term risk for recurrent SAH after coiling seems to be more important than the long-term risk. This may have significant implications for the follow-up imaging schedules after coiling.

A limitation of our study was the definition of “adequate occlusion,” which meant aneurysm occlusion of more than 90%. This is a partly subjective measure depending on the interpretation of the radiologist. As a consequence, aneurysms with a little lower occlusion grade than 90% could have been included and, conversely, aneurysms with a little higher occlusion grade than 90% could have been excluded. We tended to include cases with an uncertain aneurysm occlusion grade, so the incidence of recurrent SAH may be slightly overestimated. Despite including these sub totally occluded aneurysms, the incidence of recurrent SAH remained low. So small neck remnants seem to carry a low rerupture risk.

The low incidence rate of recurrent SAH after adequate coiling would not justify frequent follow-up within the first 8 years after coiling in the subset of patients with adequate occlusion at 6 months’ follow-up, particularly not by invasive imaging techniques. A decision analytic model showed that
long-term follow-up imaging after clipping to detect recurrent aneurysms at the clip site or de novo aneurysms was not (cost-)effective and is generally not recommended. Development of a similar decision model is needed to evaluate the effectiveness of short-term and long-term follow-up strategies for preventing recurrent SAH after coiling.

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Disclosures
None.

References
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