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

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Coiling of intracranial aneurysms

A systematic review on initial occlusion and reopening and retreatment rates

S.P. Ferns
M.E.S. Sprengers
W.J.J. van Rooij
G.J.E. Rinkel
J.C. van Rijn
S. Bipat
M. Sluzewski
C.B.L.M. Majoie
ABSTRACT

Background and purpose
The proportion of incompletely occluded aneurysms after coiling varies widely between studies. To assess overall outcome of coiling, we systematically reviewed the literature to determine initial occlusion, reopening, and retreatment rates of coiled aneurysms according to predefined criteria and subgroups.

Methods
We searched PubMed and EMBASE (January 1999 to September 2008) for studies of >50 coiled aneurysms. Two reviewers independently extracted data. We grouped studies reporting on only ruptured aneurysms, posterior circulation aneurysms, and studies with large proportions of aneurysms >10 mm to assess possible determinants for incomplete occlusion, reopening, and retreatment.

Results
Forty-six studies totaling 8161 coiled aneurysms met inclusion criteria. Immediately after coiling, 91.2% (95%CI, 90.6%-91.9%) of the aneurysms were adequately occluded. Aneurysm reopening occurred in 20.8% (95% CI, 19.8%-21.9%) and retreatment was performed in 10.3% (95% CI, 9.5%-11.0%). Reopening rate was lower in studies reporting on ruptured aneurysms only compared with all studies (11.4% versus 20.8%; relative risk, 0.55; 95% CI, 0.47-0.64) and higher in studies focusing on posterior circulation aneurysms compared with studies with >85% anterior circulation aneurysms (22.5% versus 15.5%; relative risk, 1.5; 95% CI, 1.2-1.7). Regression analysis showed higher retreatment rates with increasing proportion of aneurysms >10 mm (β= 0.252; 95% CI, 0.073-0.432). We could not find a relation between reopening and type of coils used.

Conclusions
At follow-up, one fifth of all coiled intracranial aneurysms shows reopening of which half is retreated. Possible risk factors for aneurysm reopening are location in the posterior circulation and size >10 mm. To confirm our findings, a meta-analysis on individual well-reported patient data is desirable.
INTRODUCTION

Endovascular treatment with coils has become an established treatment modality for both ruptured and unruptured intracranial aneurysms. Coiling has several shortcomings. Not all aneurysms can be occluded completely at first treatment, leaving the patient at risk for early recurrent hemorrhage in case of a recently ruptured aneurysm. Another drawback is the possibility of reopening of an initially adequately occluded aneurysm with time.

Possible determinants for initial incomplete aneurysm occlusion are unfavorable aneurysm anatomy and vessel geometry and types of coils that are used. Possible risk factors for reopening of a coiled aneurysm over time are large aneurysm size, presence of intraluminal thrombus, low packing density, initial incomplete occlusion, duration of follow-up, ruptured aneurysms, location in the posterior circulation, and a large neck–dome ratio. The actual influence of risk factors for incomplete occlusion and reopening remains obscure. As a consequence, the yield and implication of long-term imaging follow-up is largely unclear and an optimal follow-up protocol for individual patients is hard to define.

The purpose of this systematic review of the literature was to assess the overall proportion of coiled aneurysms that is incompletely occluded at initial treatment, the proportion of aneurysms that reopens over time, and the proportion of aneurysms that is retreated. In addition, we aimed to assess whether rupture status, location in posterior or anterior circulation, use of standard or modified coils, aneurysm size, and duration of follow-up influenced the occurrence of these events.

METHODS

Literature search
We searched PubMed and EMBASE from January 1999 through September 2008. The following key words as MESH terms and text words were used in relevant combinations: "subarachnoid hemorrhage," "intracranial aneurysm," "endovascular treatment," and "coiling" in both “AND” and “OR” combinations. The search was restricted to human studies in English, German, Spanish, and French. To assess eligibility, 2 reviewers (M.E.S.S. and S.P.F.) independently checked all abstracts and retrieved full-text articles on inclusion criteria using a standardized data extraction form.
Eligibility

We included studies of >50 patients and imaging follow-up with angiography or MR angiography. Studies using standard coils and modified coils (polyglycolic acid-coated coils such as Matrix [Boston Scientific, Freemont, Calif], Nexus [EV3, Irvine, Calif], Cerecyte [Micrus Endovascular, San Jose, Calif], and Hydrocoils [MicroVention, Aliso Viejo, Calif]) were considered for inclusion. Studies that included traumatic, dissecting, mycotic, and flow-related aneurysms and studies that included parent vessel coil occlusions and retreatments after previous coilings were only considered eligible when these aneurysms and treatments could be separated from the entire cohort. Initial treatment results and duration and results of follow-up imaging had to be clearly described.

Selection of studies and data extraction

From the studies that met the inclusion criteria, 2 reviewers (M.E.S.S. and S.P.F.) independently extracted relevant data. Demographics included number of patients, gender, age, number and location of included aneurysms, number of ruptured and unruptured aneurysms, and aneurysm size. We extracted mean size of the aneurysms and, if possible, we dichotomized sizes in ≤10 mm and >10 mm. Data extracted for the coil procedure included type of coils used and initial aneurysm occlusion status. Occlusion status initially and at follow-up was classified as complete (100%, total), near complete (neck remnant, dog-ear, 90% to 98%), or incomplete (aneurysm remnant, residual aneurysm filling, <90%). The term “adequate occlusion” was used for completely and near completely occluded aneurysms. Subsequently, aneurysm occlusion status was categorized on a 2-point scale (adequate versus incomplete occlusion) and a 3-point scale (complete, near complete, and incomplete occlusion). Follow-up data included mean, median, and range of follow-up duration and number of patients with follow-up. We interpreted terms as “aneurysm recurrence,” “new filling of aneurysm lumen,” “recanalization,” and “regrowth” as reopening of the aneurysm. Numbers of retreatments were recorded. If data were presented graphically or as percentages, crude numbers were deducted or calculated. When the same patient population was the subject of several publications, only the study with the largest sample size was included.
Data analysis
Cumulative data on initial aneurysm occlusion and occlusion at follow-up, reopening, and retreatment were calculated as proportions with corresponding 95% confidence intervals (CI). We multiplied the number of aneurysms by the average duration of follow-up to obtain the total number of aneurysm years of follow-up. To assess whether location in posterior circulation, rupture status, and type of coil that was used were risk factors for initial incomplete occlusion, reopening, and retreatment, we determined occurrence of these events in studies reporting on these data. We used the χ² test to assess differences for all outcomes and we calculated relative risks (RR) with corresponding 95% CIs of risk factors for reopening and retreatment alone.

The influence of aneurysm size >10 mm on the risk of reopening and retreatment was assessed with linear regression analysis with proportion of aneurysms >10 mm as the independent variable and reopening and retreatment rates as outcomes. The lack of fixed follow-up duration in most studies precluded analysis of the correlation between increasing duration of follow-up and reopening and retreatment rate.

Figure 1. Flow chart showing search strategy
RESULTS

Search results
The initial search in PubMed and EMBASE yielded 2830 articles (Figure 1). Of all articles 2749 were excluded based on review of titles and abstracts. The most frequent reasons for exclusion were lack of imaging follow-up and sample size <50 patients. Of the 81 full-text publications, 35 were excluded; 19 studies did not clearly describe follow-up duration, 5 studies did not report initial occlusion results, 5 studies did not separately report a subgroup treated with parent artery occlusion, 4 studies had included retreated aneurysms in the final aneurysm occlusion rates, and 3 studies were excluded because of double publication of the same sample. Finally, 46 studies were included. Four of the 46 studies compared 2 groups of aneurysms with separately reported patient and aneurysms characteristics and follow-up results.

All included 46 studies are available in the supplemental appendix.

Baseline characteristics
Baseline characteristics of the 46 studies that reported on 8161 coiled aneurysms are displayed in Table 1. In 42 studies with 7865 aneurysms, 5141 (65.4%) aneurysms were ruptured and 2724 (34.6%) aneurysms were unruptured. Of all 8161 aneurysms, 6241 (76.5%) had imaging follow-up for a total of 8328 aneurysm years. Mean duration of follow-up ranged from 4.6 to 38 months with an average of the mean of 14.1 months. Most studies lacked fixed follow-up intervals.

In 37 studies with 6968 aneurysms, 4640 aneurysms were located in the anterior circulation (66.7%) and 2328 (33.3%) in the posterior circulation. In 20 studies with 3288 aneurysms, mean aneurysm size ranged from 5 to 11 mm with an average of the mean of 7 mm. In 29 studies with 5302 aneurysms, 1239 (23.4%) were >10 mm.

In 31 studies with 6226 aneurysms, treatment was performed with standard bare platinum coils. In 6 studies with 482 aneurysms, treatment was performed with modified coils.
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?: data not reported; AA: aneurysms; FU: follow-up; PY patient-years

* : Comparative study of two types of coils, with separately reported groups
† : Total number of treated patients was reported, but the number of included patients was not clear
‡ : Mean (range ± standard deviation)
§ : A larger group was reported in some studies (not only the included aneurysms)
|| : Calculated as mean follow-up duration (yrs) x sample size
#: Posterior communicating artery aneurysms were considered posterior instead of anterior circulation

** : Median volumes were reported in study 29, 55mm³ (20a) and 89mm³ (20b), which equals 6 and 7 mm in diameter
† † : Sizes were reported, but did not confirm to our dichotomization </> 10 mm
‡ ‡ : 1= Matrix coils, 2= Hydrocoils, 3= Balloon-assisted, 5= Stent, 6= Interlocking detachable coils, 7= Nexus coil
Treatment results

Initial aneurysm occlusion
Initial aneurysm occlusion status was reported in 37 studies with 6991 aneurysms on a 3-point scale. Complete initial occlusion was reported in 4355 aneurysms (62.3%; 95% CI, 61.2-63.4%), near complete occlusion in 2065 aneurysms (29.5%; 95% CI, 28.5-30.6%), and incomplete occlusion in 571 aneurysms (8.2%; 95% CI, 7.5-8.8%; Table 2). Converting these results into a 2-point scale and adding the results of 9 studies with 1049 aneurysms that reported on a 2-point scale resulted in all 46 studies with 8040 aneurysms (121 aneurysms were excluded due to incomplete reporting of occlusion results in 2 studies). Initial aneurysm occlusion was adequate in 7335 aneurysms (91.2%; 95% CI, 90.6-91.9%) and incomplete in 705 aneurysms (8.8%; 95% CI, 8.2-9.4%).

Aneurysm occlusion at follow-up
Aneurysm occlusion at follow-up was reported in 19 studies with 2882 aneurysms on a 3-point scale. Occlusion was complete in 1772 aneurysms (61.5%; 95% CI, 59.7-63.3%), near complete in 654 aneurysms (22.7%; 95% CI, 21.2-24.2%), and incomplete in 456 aneurysms (15.8%; 95% CI, 14.5-17.2%). Converting these results into a 2-point scale and adding the results of 8 studies with 777 aneurysms that reported on a 2-point scale resulted in 27 studies with 3659 aneurysms. Adequate aneurysm occlusion was reported in 3054 aneurysms (83.4%; 95% CI, 82.3-84.7%) and incomplete occlusion in 605 aneurysms (16.6%; 95% CI, 15.3-17.7%; Table 2).

Reopening and retreatment rates
Reopening rate was reported in 42 studies with 5926 aneurysms. Retreatment rates were reported in 41 studies with 5582 aneurysms (Table 2). At a mean follow-up ranging from 4.7 to 38 months (Figure 2), 1235 of 5926 aneurysms reopened and 572 of 5582 aneurysms were retreated. Reopening rate was 20.8% (95% CI, 19.8-21.9%) and retreatment rate was 10.3% (95% CI, 9.5%-11.0%).

Ruptured aneurysms
Nine studies with 1786 aneurysms reported on ruptured aneurysms only. These studies had significantly higher proportions of initially and at follow-up adequately occluded aneurysms (95.9% versus 91.2% and 90.3% versus 83.4%) and lower reopening and retreatment rates (11.4% versus 20.8% and 7.2% versus 10.3%) compared with
### Figure 2. Proportion of reopening (%) of studies reporting reopening

AA: number of aneurysms per study with imaging follow-up; FU: follow-up; mo: months
all studies. Relative risk for reopening of aneurysms in studies with only ruptured aneurysms was 0.55 (95% CI, 0.47-0.64) and for retreatment 0.70 (95% CI, 0.37-0.86) compared with studies including ruptured as well as unruptured aneurysms (Table 2).

Posterior versus anterior circulation aneurysms
Six studies that reported on 862 aneurysms located in the posterior circulation only were compared with 8 studies reporting on 1901 aneurysms with >85% of aneurysms located in the anterior circulation. There was no difference in proportion adequate initial occlusion (91.6% versus 92.1%), but the proportion of posterior circulation aneurysms adequately occluded at follow-up was lower (70.4% versus 92.6%), and reopening and retreatment rates were higher (22.5% versus 15.5% and 14.5% versus 6.5%) compared with studies with >85% anterior circulation aneurysms. Relative risk for reopening of studies reporting on posterior circulation aneurysms was 1.45 (95% CI, 1.23-1.72) and for retreatment 2.22 (95% CI, 1.73-2.86) compared with studies including >85% anterior circulation aneurysms (Table 2).

Standard platinum coils versus modified coils
Proportion of aneurysms with initial adequate occlusion was significantly lower for aneurysms treated with modified coils compared with aneurysms treated with standard platinum coils (88.8% versus 92.1%; relative risk, 0.96; 95% CI, 0.93-0.996). At follow-up, the proportion of aneurysms with adequate occlusion was not different (85.9% versus 86.8%) and reopening and retreatment rates were not different (21.6% versus 20.1% and 11.7% versus 9.6%; Table 2).

Aneurysm size >10 mm
In 29 studies, the proportion of aneurysms >10 mm was reported; there were no studies with exclusively small or only large aneurysms. Of these 29 studies, 27 reported reopening rate and 24 reported retreatment rate. We created a scatter plot with reopening rate and retreatment rate as dependent variables and proportion aneurysms >10 mm as the independent variable (Figure 3). Regression analysis showed increasing reopening rates with increasing proportions of aneurysms >10 mm ($\beta = 0.124$; 95% CI, -0.165-0.414) and increasing retreatment rate in studies with increasing proportions of aneurysms >10 mm ($\beta = 0.252$; 95% CI, 0.073-0.432). The $\beta$ indicates that for 1% more aneurysms >10 mm, reopening increases with 0.12% and retreatment increases with 0.25%.
### Table 2. Treatment results initial and at follow-up

<table>
<thead>
<tr>
<th></th>
<th>All AA</th>
<th>Ruptured AA</th>
<th>Posterior circulation AA</th>
<th>&gt;85% anterior circulation AA</th>
<th>Modified coils</th>
<th>Standard Platinum Coils</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Num/denom(%)</td>
<td>Num/denom(%)</td>
<td>Num/denom(%)</td>
<td>Num/denom(%)</td>
<td>Num/denom(%)</td>
<td>Num/denom(%)</td>
</tr>
<tr>
<td>Initial adequate occlusion</td>
<td>7335/8040 (91.2)</td>
<td>1713/1786 (95.9)</td>
<td>790/862 (91.6)</td>
<td>1750/1901 (92.1)</td>
<td>428/482 (88.8)</td>
<td>5732/6226 (92.1)</td>
</tr>
<tr>
<td>Initial incomplete occlusion</td>
<td>705/8040 (8.8)</td>
<td>73/1786 (4.1)</td>
<td>72/863 (8.4)</td>
<td>151/1901 (7.9)</td>
<td>54/482 (11.2)</td>
<td>494/6226 (7.9)</td>
</tr>
<tr>
<td>Adequate occlusion at FU</td>
<td>3054/3659 (83.4)</td>
<td>1204/1333 (90.3)</td>
<td>198/281 (70.4)</td>
<td>1011/1092 (92.6)</td>
<td>122/142 (85.9)</td>
<td>2986/3441 (86.8)</td>
</tr>
<tr>
<td>Incomplete occlusion at FU</td>
<td>605/3659 (16.6)</td>
<td>129/1333 (9.7)</td>
<td>83/281 (29.6)</td>
<td>81/1092 (7.4)</td>
<td>20/142 (14.1)</td>
<td>455/3441 (13.2)</td>
</tr>
<tr>
<td>Reopening</td>
<td>1235/5926 (20.8)</td>
<td>149/1304 (11.4)</td>
<td>194/862 (22.5)</td>
<td>247/1594 (15.5)</td>
<td>71/329 (21.6)</td>
<td>933/4631 (20.1)</td>
</tr>
<tr>
<td>Retreatment</td>
<td>572/5582 (10.3)</td>
<td>102/1423 (7.2)</td>
<td>114/786 (14.5)</td>
<td>104/1594 (6.5)</td>
<td>33/282 (11.7)</td>
<td>417/4335 (9.6)</td>
</tr>
<tr>
<td>Aneurysms with follow-up</td>
<td>6224</td>
<td>1499</td>
<td>862</td>
<td>1594</td>
<td>326</td>
<td>4808</td>
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<tr>
<td>Total FU aneurysm years</td>
<td>8328</td>
<td>3202</td>
<td>1031</td>
<td>3060</td>
<td>247</td>
<td>6439</td>
</tr>
</tbody>
</table>

AA= aneurysms; Num/Denom indicates numerator/denominator; FU= follow-up
Figure 3. Regression analysis: reopening and retreatment rates in studies with increasing proportions of aneurysms >10 mm


DISCUSSION

Our review of >8000 coiled intracranial aneurysms shows that 91% of aneurysms were adequately occluded at initial treatment. At follow-up of various intervals, 83% of treated aneurysms were adequately occluded. Reopening occurred in 21% of aneurysms and 10% of aneurysms were retreated. The difference between proportion of aneurysms with reopening (21%) and proportion of aneurysms with retreatment (10%) indicates that not all reopenings were retreated. Some reopened aneurysms may not be judged suitable for retreatment because of unfavorable geometry, small size, or high anticipated risk of retreatment.

Studies with exclusively ruptured aneurysms had higher adequate occlusion rates both initially and at follow-up compared with all studies and lower reopening and retreatment rates. Although several studies state that rupture of the aneurysm is a risk factor for reopening of coiled aneurysms,7,19 our review could not confirm this finding. It is likely that higher proportions of large and posterior localization in unruptured aneurysms explain the higher rate of reopening of unruptured aneurysms.29 Because we had no data on individual patients or individual aneurysms but only aggregated data per study population, we could not assess whether indeed these factors explain the observed difference in reopening between ruptured and unruptured aneurysms.

Studies with exclusively posterior circulation aneurysms had higher proportions of incompletely occluded aneurysms at follow-up with higher proportions of reopening and retreatment compared with the studies with >85% anterior circulation aneurysms. This is in concordance with previous studies.3,15,30 A possible explanation is that surgery is less likely an option in posterior circulation aneurysms. This could imply that also posterior circulation aneurysms with unfavorable configuration are coiled, whereas aneurysms with unfavorable configuration in the anterior circulation are clipped.

Studies with aneurysms treated with modified coils did not show higher occlusion rates compared with studies using standard platinum coils. In fact, initial occlusion rates were less favorable. At follow-up, reopening and retreatment rates were comparable to standard platinum coils. This is consistent with a recent review regarding this subject.31 The lower rate of initial occlusion with modified coils may be explained by the inferior handling properties caused by increased stiffness and friction or because the aneurysms treated are the aneurysms with a less favorable geometry or larger ones, which might introduce a selection bias. A limitation of this review is that
different kinds of modified coils were grouped together and that results might thus not apply to specific types of coils.

A higher retreatment rate was found in studies with increasing proportion of aneurysms >10 mm. Large aneurysm size is a well-established risk-factor for reopening and retreatment, in part explained by lesser packing density and a higher proportion of aneurysms with intraluminal thrombus.\textsuperscript{7,11,14,15} We could not assess an association of increased reopening and retreatment rates with longer duration of follow-up, because fixed follow-up intervals were lacking. An analysis with mean duration of follow-up would not be meaningful. Although we did put all studies that reported reopening and their available follow-up duration into a forest plot, this also shows that there is no association or even trend in reopening and increasing follow-up duration (figure 2).

This study had several limitations. Although our search was extensive, there is a chance that some studies were not included. The available literature is limited by a lack of randomized studies, lack of standard definitions, lack of fixed follow-up intervals, absence of details of individual patients, and no description of selection of patients. Reporting quality in most studies was poor allowing aggravated data extraction only. In addition, data were not reported in a standardized way and follow-up intervals varied widely. Reopening, retreatment, or recurrent hemorrhage could not be ascribed to individual patients or aneurysms, making it difficult to statistically assess possible risk factors for these events. A recent study provides future authors with detailed reporting standards of endovascular repair of saccular intracranial cerebral aneurysms.\textsuperscript{32}

CONCLUSIONS

With this review, we have given an overview of the literature concerning aneurysm occlusion, reopening, and retreatment. To asses the value of long-term imaging follow-up, the timing of occurrence of reopening should be known and studies with fixed follow-up intervals are needed. Future research should be focused on patients and aneurysms with specific risk factors for reopening and recurrent hemorrhage. With this information, customized follow-up protocols can be designed resulting in better patient care and reduced costs.
REFERENCES


Appendix 1. Reference list of included studies for review


