Original Contributions

Clipping Versus Coiling for Ruptured Intracranial Aneurysms
A Systematic Review and Meta-Analysis

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Background and Purpose—Endovascular treatment has increasingly been used for aneurismal subarachnoid aneurismal hemorrhage. The aim of this analysis is to assess the current evidence regarding safety and efficiency of clipping compared with coiling.

Methods—We conducted a meta-analysis of studies that compared clipping with coiling between January 1999 and July 2012. Comparison of binary outcomes between treatment groups was described using odds ratios (OR; clip versus coil).

Results—Four randomized controlled trials and 23 observational studies were included. Randomized controlled trials showed that coiling reduced the 1-year unfavorable outcome rate (OR, 1.48; 95% confidence interval [CI], 1.24–1.76). However, there was no statistical deference in nonrandomized controlled trials (OR, 1.11; 95% CI, 0.96–1.28). Subgroup analysis revealed coiling yielded better outcomes for patients with good preoperative grade (OR, 1.51; 95% CI, 1.24–1.84) than for poor preoperative patients (OR, 0.88; 95% CI 0.56–1.38). Additionally, the incidence of rebleeding is higher after coiling (OR, 0.43; 95% CI, 0.28–0.66), corresponding to a better complete occlusion rate of clipping (OR, 2.43; 95% CI, 1.88–3.13). The 1-year mortality showed no significant difference (OR, 1.07; 95% CI, 0.88–1.30). Vasospasm was more common after clipping (OR, 1.43; 95% CI, 1.07–1.91), whereas the ischemic infarct (OR, 0.74; 95% CI, 0.52–1.06), shunt-dependent hydrocephalus (OR, 0.84; 95% CI, 0.66–1.07), and procedural complication rates (OR, 1.19; 95% CI, 0.67–2.11) did not differ significantly between techniques.

Conclusions—Coiling yields a better clinical outcome, the benefit being greater in those with a good preoperative grade than those with a poor preoperative grade. However, coiling leads to a greater risk of rebleeding. Well-designed randomized trials with special considerations to the aspect are needed. (Stroke. 2013;44:00-00.)

Key Words: cerebral aneurysm ■ clip ■ coil ■ meta-analysis ■ subarachnoid hemorrhage

In the past, neurosurgical clipping of the aneurysmal neck was the only effective method to prevent rebleeding of subarachnoid aneurismal hemorrhage (SAH). In 1990, a detachable platinum coil device, the Guglielmi detachable coil, was first introduced in clinical practice. Since that time, clipping has gained worldwide acceptance as an alternative treatment.

The International Subarachnoid Aneurysm Trial (ISAT) was the only large, multicenter, randomized clinical trial that compared neurosurgical clipping with detachable platinum coils in patients with ruptured intracranial aneurysms, who were considered to be suitable for either treatment. However, results of ISAT have continued to generate some criticism, mainly because of its selection bias. For the 9559 patients screened, 7416 were excluded because of a strict contraindication for either operation type. Of the enrolled patients, 88% had a favorable grade (WFNS classification I or II) at the time of enrolment, 95% of the aneurysms were in the anterior cerebral circulation, and 90% were smaller than 10 mm. The question has arisen: ISAT was designed as a pragmatic trial, but can we generalize the results of a study where >80% of the patients were excluded to the entire body of patients with aneurismal SAH?

In recent years, coiling is being offered to patients who were not suitable for inclusion in ISAT. More randomized controlled trials (RCTs), as well as prospective and retrospective studies have since been published, some of which have results that differ from ISAT. The Cochrane review1 on this topic only included 3 RCTs and the results were principally those of ISAT, which was clearly the largest trial. As a result, it is still uncertain how coiling compares with the accepted standard treatment. It is therefore the aim of this systematic review and

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meta-analysis to evaluate the efficiency, safety, and potential advantages of coiling compared with clipping from an extended body of evidence including both RCTs and observational studies to inform the decision-making process in choosing which procedure to perform in patients with aneurismatic SAH.

Methods
A detailed protocol that included the literature-search strategies, the inclusion and exclusion criteria, outcome measurements, and methods of statistical analysis was developed before the conduct of the systematic review. The protocol was prepared according to the Meta-Analysis of Observational Studies in Epidemiology,3 and Preferred Reporting Items for Systematic Reviews and Meta-Analyses4 guideliness.

Systematic Literature Search
The literature search on clipping versus coiling for patients with SAH was performed by 2 reviewers (R.P. and H.L.) on articles published between January 1999 and July 2012. A computerized search of the Medline, Embase, and Cochrane Library databases was performed without restriction on the language of publication. Keywords and free text searches used combinations of the following keywords: intracranial aneurysm(s), ruptured, subarachnoid hemorrhage, microsurgery, clip, coil, endovascular, follow-up, and treatment outcome. A manual search for unpublished results of ongoing trials and presentations at significant scientific meetings was conducted as a supplement. All reference sections of eligible studies and pertinent reviews were hand-reviewed for potential studies. When a study generated multiple publications, the most current report was used.

Inclusion and Exclusion Criteria
The inclusion criteria were as follows: (1) All available RCTs and comparative studies (cohort studies) that compared clipping and coiling in all age groups. (2) Patients who had a subarachnoid hemorrhage, proven by computed tomography or lumbar puncture within the preceding 28 days and had an intracranial aneurysm, which was considered to be responsible for the subarachnoid hemorrhage. (3) Case fatality or permanent morbidity rate or crude data explicitly reported for both clipping and coiling groups.

The exclusion criteria were: (1) Patients who received treatment for an unruptured intracranial aneurysm. (2) Patients who received treatment other than neurosurgical clipping or endovascular coiling (muslin wrapping, no treatment). (3) SAH from an infected aneurysm or trauma. (4) Studies that presented insufficient data or compared neurosurgical clipping or endovascular treatment alone. (5) Studies that presented insufficient data to estimate aneurysmal SAH by either computed tomography or lumbar puncture within the preceding 4 days. The term poor outcome was defined as death or dependence in daily activities (modified Rankin scale of 3–6 or Glasgow Outcome Scale 1–3). Rebleeding rate was counted after the first intervention. The secondary outcomes were postoperative vasospasm, shunt-dependent hydrocephalus, ischemic infarct, procedural complications, and angiographic results.

Selection and Data Extraction
The decision on whether a study should be included was made independently by both authors (R.P. and H.L.), with disagreements settled by the senior author (Y.M.T.). The primary outcomes were mortality, poor outcome rate, and rebleeding rate. If sufficient data were available, the patients with poor outcomes were subdivided into groups based on the preoperative grade (good preoperative grade was defined as WFNS classification I and II, or Hunt & Hess Scale I to III; poor preoperative grade was WFNS classification III to V, or Hunt & Hess Scale IV and V). The term poor outcome was defined as death or dependence in daily activities (modified Rankin scale of 3–6 or Glasgow Outcome Scale 1–3). Rebleeding rate was counted after the first intervention. The secondary outcomes were postoperative vasospasm, shunt-dependent hydrocephalus, ischemic infarct, procedural complications, and angiographic results.

Quality Assessment and Statistical Analyses
Studies were rated for the level of evidence provided according to criteria by the Centre for Evidence-Based Medicine in Oxford. The Cochrane Risk of Bias Tool was used to assess the quality of the RCTs. Criteria proposed by the Newcastle-Ottawa scale were used to assess the quality of the observational studies.

Meta-Analysis was performed on studies that provided data on outcomes of patients who underwent clipping or coiling, using the software package RevMan5.0. Dichotomous variables were presented as odds ratios (OR; clip versus coil) with a 95% confidence interval (CI). Fixed-effect and random-effect models were used, with significance set at P=0.05. Statistical heterogeneity was assessed using the I² statistic, which describes the proportion of total variation that is attributable to differences among trials rather than sampling error (chance). An I² value of <25% was defined to represent low heterogeneity, a value between 25% and 50% was defined as moderate heterogeneity and >50% was defined as high heterogeneity. The random-effects model was used if there was high heterogeneity between studies. Otherwise, the fixed-effects model was used. Furthermore, subgroup analysis was carried out to evaluate the impact of the preoperative condition on the results. The interaction tests were applied to test for differential effects of coiling across subgroups. Sensitivity analysis was performed by measuring the effect of the 4 RCTs. Funnel plots were used to screen for potential publication bias.

Results
Flow of Included Studies
Figure 1 shows a flow diagram according to the Quality of Reporting of Meta-analyses-statement with the total number of citations retrieved by the search strategy and the number included in the systematic review. Twenty-seven studies met all inclusion criteria and were included in the analysis. In total, these studies included 11,568 patients of whom 7230 underwent neurosurgical clipping, and 4338 underwent endovascular coiling. Agreement between the 2 reviewers was 95% for study selection and 93% for quality assessment of trials.

Study Characteristics
Four of the trials enrolled were RCTs and 23 were observational studies. A total of 11,568 participants were included and the sample size ranged from 18 to 2174. The percentage of included males ranged from 28% to 86% and the mean age of study patients ranged from 45 to 58 years. The studies were from Holland, Finland, United Kingdom, United States, Ireland, France, Switzerland, Japan, Egypt, and other countries. The outcomes were clearly defined in all studies.

The RCT by Brilstra et al6 enrolled 20 patients with documented aneurismatic SAH by either computed tomography or digital subtraction angiography within the preceding 4 days. Dependency and death at 1 year, rebleeding, epilepsy, quality of life at 1 year, and neuropsychological outcomes were available. The RCT by Koivisto et al6 employed 109 patients to compare the 1-year clinical, neuropsychological, and radiological outcomes of surgical clipping and endovascular treatment in acute (<72 hours) SAH. This single-center study also compared the postoperative complications between the 2 groups. ISAT7 with an enrollment of 2143 patients was the only large RCT to compare the efficacy of the 2 modalities in treating patients with aneurismatic SAH within 28 days. The outcomes were death or dependence at 1 year, rebleeding of the treated aneurysm, and risk of seizure. The Barrow Ruptured Aneurysm Trial (BRAT)8 is an ongoing study with follow-up planned to continue for at least 6 years after completion of enrollment and we analyzed the 1-year result.
For prospective and retrospective studies, choice of treatment modality depended on the characteristics of each case. The National Study of SAH was the largest prospective study, which was carried out in 34 neurosurgical units in the United Kingdom and Ireland. Prerepair and postrepair deterioration was recorded. Prerepair deterioration was

Table 1. Design and Baseline Characteristics of Included Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Level of Evidence</th>
<th>Design</th>
<th>Patients Number</th>
<th>Age*, y</th>
<th>Male, %</th>
<th>Aneurysms Located in Anterior Circulation</th>
<th>Follow-up, mo/y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brilstra et al. 2000</td>
<td>II</td>
<td>RCT</td>
<td>10/10</td>
<td>NA</td>
<td>30/30</td>
<td>10/10</td>
<td>12 mo</td>
</tr>
<tr>
<td>Kovisto et al. 2000</td>
<td>II</td>
<td>RCT</td>
<td>57/52</td>
<td>50/49</td>
<td>33/44</td>
<td>52/46</td>
<td>12 mo</td>
</tr>
<tr>
<td>ISAT 2005</td>
<td>Ib</td>
<td>RCT</td>
<td>1070/1073</td>
<td>52/52</td>
<td>37/37</td>
<td>1021/1039</td>
<td>12 mo</td>
</tr>
<tr>
<td>ISAT 2009</td>
<td>lb</td>
<td>RCT</td>
<td>1070/1073</td>
<td>52/52</td>
<td>37/37</td>
<td>1021/1039</td>
<td>5 y</td>
</tr>
<tr>
<td>BRAT 2012</td>
<td>II</td>
<td>RCT</td>
<td>238/233</td>
<td>53/54</td>
<td>30/28</td>
<td>174/169</td>
<td>12 mo</td>
</tr>
<tr>
<td>National study 2006</td>
<td>II</td>
<td>P</td>
<td>1269/905</td>
<td>51/52</td>
<td>NA</td>
<td>1138/637</td>
<td>6 mo</td>
</tr>
<tr>
<td>PRESAT 2011</td>
<td>II</td>
<td>P</td>
<td>264/270</td>
<td>NA</td>
<td>NA</td>
<td>252/212</td>
<td>12 mo</td>
</tr>
<tr>
<td>Proust et al. 2003</td>
<td>III</td>
<td>P</td>
<td>186/37</td>
<td>48/57</td>
<td>59/51</td>
<td>186/37</td>
<td>12 mo</td>
</tr>
<tr>
<td>Dehdashti et al. 2004</td>
<td>III</td>
<td>P</td>
<td>72/26</td>
<td>49/54</td>
<td>38/31</td>
<td>68/19</td>
<td>6 mo</td>
</tr>
<tr>
<td>Dehdashti et al. 2004</td>
<td>III</td>
<td>P</td>
<td>180/65</td>
<td>49/52</td>
<td>38/31</td>
<td>NA</td>
<td>3 mo</td>
</tr>
<tr>
<td>Gruber et al. 1998</td>
<td>III</td>
<td>P</td>
<td>111/45</td>
<td>52/52</td>
<td>36/33</td>
<td>88/51</td>
<td>6–18 mo</td>
</tr>
<tr>
<td>Gruber et al. 1999</td>
<td>III</td>
<td>R</td>
<td>125/62</td>
<td>50/50</td>
<td>36/29</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Charpentier et al. 1999</td>
<td>IV</td>
<td>P</td>
<td>99/145</td>
<td>50/52</td>
<td>45/37</td>
<td>97/75</td>
<td>6 mo</td>
</tr>
<tr>
<td>Reyes et al. 2012</td>
<td>IV</td>
<td>R</td>
<td>8/10</td>
<td>56/55</td>
<td>NA</td>
<td>8/10</td>
<td>3 mo</td>
</tr>
<tr>
<td>Kim et al. 2008</td>
<td>IV</td>
<td>R</td>
<td>30/23</td>
<td>45/54</td>
<td>42/38</td>
<td>30/23</td>
<td>34/27 mo</td>
</tr>
<tr>
<td>Taha et al. 2006</td>
<td>IV</td>
<td>R</td>
<td>25/28</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>26.7 mo</td>
</tr>
<tr>
<td>Rabinstein et al. 2003</td>
<td>IV</td>
<td>R</td>
<td>339/76</td>
<td>53/56</td>
<td>35/38</td>
<td>273/36</td>
<td>6 mo</td>
</tr>
<tr>
<td>Goddard et al. 2004</td>
<td>III</td>
<td>R</td>
<td>212/80</td>
<td>53/54</td>
<td>64/21</td>
<td>89/94</td>
<td>4–8 mo</td>
</tr>
<tr>
<td>Natarajan et al. 2008</td>
<td>III</td>
<td>R</td>
<td>105/87</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3 mo</td>
</tr>
<tr>
<td>Helland et al. 2006</td>
<td>III</td>
<td>R</td>
<td>203/33</td>
<td>51/55</td>
<td>42/46</td>
<td>97/84</td>
<td>3–6 mo</td>
</tr>
<tr>
<td>Niskanen et al. 2004</td>
<td>III</td>
<td>R</td>
<td>103/68</td>
<td>54/54</td>
<td>42/47</td>
<td>94/66</td>
<td>12</td>
</tr>
<tr>
<td>Varelas et al. 2006</td>
<td>III</td>
<td>R</td>
<td>135/48</td>
<td>53/51</td>
<td>34/54</td>
<td>116/31</td>
<td>NA</td>
</tr>
<tr>
<td>Oliveira et al. 2007</td>
<td>III</td>
<td>R</td>
<td>212/173</td>
<td>52/54</td>
<td>86/58</td>
<td>252/158</td>
<td>6 mo</td>
</tr>
<tr>
<td>Nam et al. 2010</td>
<td>III</td>
<td>R</td>
<td>498/238</td>
<td>54/57</td>
<td>38/30</td>
<td>490/183</td>
<td>NA</td>
</tr>
<tr>
<td>Hoh et al. 2004</td>
<td>IV</td>
<td>R</td>
<td>505/114</td>
<td>53/54</td>
<td>NA</td>
<td>436/57</td>
<td>6 mo</td>
</tr>
<tr>
<td>Hoh et al. 2004</td>
<td>III</td>
<td>A</td>
<td>413/79</td>
<td>54/58</td>
<td>30/23</td>
<td>361/46</td>
<td>NA</td>
</tr>
<tr>
<td>Suzuki et al. 2011</td>
<td>III</td>
<td>R</td>
<td>55/13</td>
<td>58/56</td>
<td>42/46</td>
<td>55/13</td>
<td>42.7 mo</td>
</tr>
<tr>
<td>Johnston et al. 2008</td>
<td>IV</td>
<td>A</td>
<td>706/295</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3.6 y</td>
</tr>
</tbody>
</table>

A indicates ambidirectional cohort study; BRAT, The Barrow Ruptured Aneurysm Trial; ISAT, The International Subarachnoid Aneurysm Trial; NA, not available; P, prospective cohort study; R, retrospective cohort study; and RCT, randomized controlled trial.

*Mean age is the statistic reported.
defined as a reduction in the Glasgow Coma Score (GCS). Postrepair deterioration was defined as either a reduction of the GCS, or whether the patient was transferred back to a high dependency or intensive therapy unit, or had a delayed discharge from the high dependency unit/intensive therapy unit attributable to deterioration. The clinical outcome and rebleeding rates were available. Patient’s characteristics and clinical outcomes are summarized in Table 1.

Quality of Included Studies

We evaluated the risk of bias in the 4 published RCTs (Supplemental Table 1) using the Cochrane Risk of Bias Tool. Allocation sequence generation was described by ISAT and BRAT. Allocation concealment was clearly described and no blinding was used. For the 23 observational studies, the risk of bias was evaluated with a modification of the Newcastle-Ottawa scale (Supplemental Table 2). Methods for handling missing data were not adequately described in a majority of studies.

Synthesis of Results

Primary Outcomes

Pooling the data from the 13 studies that assessed poor outcome (death or dependency) with 1 year in 6555 patients (Figure 2), RCTs showed that clipping was associated with a better outcome (poor outcome rate clip versus coil: 31.1% versus 23.4%; OR, 1.48; 95% CI, 1.24–1.76; \( P < 0.0001 \)) than clipping. However, observational studies revealed a different result (30.0% versus 29.8%; OR, 1.11; 95% CI, 0.96–1.28; \( P = 0.17 \)). The interaction test \( P \) value between RCT and observational studies is 0.01. Three trials9,10,11 mentioned a long-term follow-up (from an average of 26.7 months to 5 years) in 1845 patients, clipping was still associated with a better outcome than clipping (34.0% versus 28.3%; OR, 1.25; 95% CI, 1.03–1.53; \( P = 0.05 \)) (Supplemental Figure 1).

Eight studies5–7,10,12,18,21 including 5282 patients reported 1-year mortality (Figure 3). Both the RCTs and observational studies revealed no statistical significant difference between the clipping and coiling groups (10.4% versus 8.5%; OR, 1.24; 95% CI, 0.94–1.65; \( P = 0.13 \) and 8.7% versus 9.6%; OR, 0.93; 95% CI, 0.71–1.22; \( P = 0.59 \), respectively). The pooled OR is 1.07 (95% CI, 0.88–1.30; \( P = 0.51 \)). The interaction test \( P \) value between RCTs and observational studies is 0.15. Three studies9,19,31 including 2208 patients reported mortality for long-term follow-up (from 27 months to 5 years), the result showed a significant difference between the 2 approaches (clip versus coil, 13.2% versus 10.7%; OR, 1.31; 95% CI, 1.01–1.70; \( P = 0.04 \)) (Supplemental Figure 4).

Eight studies5–8,10,12,18,23 including 5828 patients reported their rebleeding rate (Figure 4). RCTs showed that clipping had a lower rebleeding rate than coiling (1.2% versus 2.3%; OR, 0.51; 95% CI, 0.27–0.94; \( P = 0.03 \)). Observational studies revealed a similar result (1.1% versus 3.0%; OR, 0.37; 95% CI, 0.21–0.67; \( P = 0.001 \)). The pooled OR is 0.43 (95% CI, 0.28–0.66; \( P = 0.001 \)). There is no significant difference between RCTs and observational studies (\( \chi^2 = 0.51, df = 1, P = 0.48, I^2 = 0\% \)). Three studies9,19,32 with a total of 3197 patients reported a long-term follow-up result, which still revealed a statistical significance between 2 groups (clip versus coil: 

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**Table 1.**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
<th>Odds Ratio</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.2.1 RCTs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAT2012</td>
<td>69</td>
<td>205</td>
<td>5.6%</td>
<td>1.68 [1.08, 2.60]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Britsa 2000</td>
<td>4</td>
<td>10</td>
<td>0.3%</td>
<td>1.56 [0.26, 9.91]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISAT2009</td>
<td>328</td>
<td>1655</td>
<td>31.0%</td>
<td>1.45 [1.20, 1.76]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kovisto 2000</td>
<td>14</td>
<td>57</td>
<td>1.5%</td>
<td>1.21 [0.49, 2.98]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1327</td>
<td>1323</td>
<td>38.5%</td>
<td>1.48 [1.24, 1.76]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>413</td>
<td>510</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 0.63, df = 3 (P = 0.91); P = 0% \)

Test for overall effect: \( Z = 4.44 (P < 0.0001) \)

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**Figure 2.** Forest plot and meta-analysis of poor outcome rate. CI indicates confidence interval; M-H, Mantel-Haenszel method; and RCT, randomized controlled trials.

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Five studies6,7,12,18,24 with a total of 2862 participants reported results stratified by preoperative grade. Among the 2425 patients with good preoperative grade (Supplemental Figure 2), coiling yielded better outcomes (25.2% versus 19.8%; OR, 1.51; 95% CI, 1.24–1.84; \( P < 0.0001 \)), but the results are heavily influenced by ISAT. for 437 patients with poor preoperative grade (Supplemental Figure 3), the clipping and coiling groups showed no statistical significant difference (42.6% versus 43%; OR, 0.88; 95% CI, 0.56–1.38; \( P = 0.57 \)) with nil heterogeneity (\( F = 0\% \) and \( P = 0.73 \)). The interaction test \( P \) value between good and poor preoperative grade is 0.03.

Eight studies5–7,10,12,18,21 including 5012 patients reported 1-year mortality (Figure 3). Both the RCTs and observational studies revealed no statistical significant difference between the clipping and coiling groups (10.4% versus 8.5%; OR, 1.24; 95% CI, 0.94–1.65; \( P = 0.13 \) and 8.7% versus 9.6%; OR, 0.93; 95% CI, 0.71–1.22; \( P = 0.59 \), respectively). The pooled OR is 1.07 (95% CI, 0.88–1.30; \( P = 0.51 \)). The interaction test \( P \) value between RCTs and observational studies is 0.15. Three studies19,31 including 2208 patients reported mortality for long-term follow-up (from 27 months to 5 years), the result showed a significant difference between the 2 approaches (clip versus coil, 13.2% versus 10.7%; OR, 1.31; 95% CI, 1.01–1.70; \( P = 0.04 \)) (Supplemental Figure 4).

Eight studies5–8,10,12,18,23 including 5282 patients reported their rebleeding rate (Figure 4). RCTs showed that clipping had a lower rebleeding rate than coiling (1.2% versus 2.3%; OR, 0.51; 95% CI, 0.27–0.94; \( P = 0.03 \)). Observational studies revealed a similar result (1.1% versus 3.0%; OR, 0.37; 95% CI, 0.21–0.67; \( P = 0.001 \)). The pooled OR is 0.43 (95% CI, 0.28–0.66; \( P = 0.001 \)). There is no significant difference between RCTs and observational studies (\( \chi^2 = 0.51, df = 1, P = 0.48, I^2 = 0\% \)). Three studies19,32 with a total of 3197 patients reported a long-term follow-up result, which still revealed a statistical significance between 2 groups (clip versus coil: 

---

**Figure 2.** Forest plot and meta-analysis of poor outcome rate. CI indicates confidence interval; M-H, Mantel-Haenszel method; and RCT, randomized controlled trials.
0.89% versus 1.94%; OR, 0.39; 95% CI, 0.21–0.74; \( P = 0.004 \)) (Supplemental Figure 5). (Table 2)

**Secondary Outcomes**

Five studies\(^{1,2,20,21,23,28}\) reported vasospasm for the 1267 included patients (Supplemental Figure 6), which showed lower risk of cerebral vasospasm in the coiling group (48.8% versus 43.1%; OR, 1.43; 95% CI, 1.07–1.91; \( P = 0.02 \)). Pooling the data of the 6 studies\(^{1,3,13,15,18,23}\) (1123 patients) that reported ischemic infarct revealed no significant difference between clipping and coiling (16.1% versus 20.9%; OR, 0.74; 95% CI, 0.52–1.06; \( P = 0.10 \)) (Supplemental Figure 7). Seven studies\(^{1,4,16,20,23,26–28}\) (1981 patients) reporting shunt-dependent hydrocephalus revealed no significant difference between clipping and coiling (16.4% versus 19.3%; OR, 0.84; 95% CI, 0.66–1.07; \( P = 0.16 \)) (Supplemental Figure 8). Three studies\(^{6,11,12}\) (866 patients) revealed the procedural complications associated with poor outcome (Supplemental Figure 9), and the results between the 2 groups were comparable (9.9% versus 5.6%; OR, 1.19; 95% CI, 0.67–2.11; \( P = 0.56 \)).

Five studies\(^{4,6,12,18,20}\) assessed complete angiographic occlusion in 1749 patients and showed that clipping was superior to coiling (84.0% versus 66.5%; OR, 2.43; 95% CI, 1.88–3.13; \( P < 0.00001 \)) (Supplemental Figure 10). Incomplete occlusion demonstrated a consistent result in 1923 patients (14.1% versus 32.1%; OR, 0.39; 95% CI, 0.31–0.50; \( P < 0.00001 \)) (Supplemental Figure 11). (Table 2)

**Sensitivity Analysis and Publication Bias**

The findings were similar whether fixed or random-effects models were used. Funnel plot analysis on the outcomes of perioperative mortality, morbidity, and rebleeding rate did not indicate significant publication bias (Supplemental Figure 12–14).

**Discussion**

**Primary Outcomes**

Our meta-analysis systematically summarizes the available evidence on outcomes of patients with aneurysmal SAH undergoing neurosurgical clipping or coiling. Because of

**Secondary Outcomes**

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**Sensitivity Analysis and Publication Bias**

The findings were similar whether fixed or random-effects models were used. Funnel plot analysis on the outcomes of perioperative mortality, morbidity, and rebleeding rate did not indicate significant publication bias (Supplemental Figure 12–14).

**Discussion**

**Primary Outcomes**

Our meta-analysis systematically summarizes the available evidence on outcomes of patients with aneurysmal SAH undergoing neurosurgical clipping or coiling. Because of
the clinical or methodological heterogeneity, RCTs were analyzed separately from prospective and retrospective studies. Data from 4 RCTs show that coiling yields better outcomes within 1 year, which corresponds with the Cochrane review,1 in which only 3 RCTs were enrolled, but the results are largely dependent on the largest trial (ISAT), despite the addition of a new RCT with 472 patients. However, the results of ISAT continue to be criticized to this day33; the critiques mainly focus on imprecise selection criteria. The requirement of suitability for either endovascular or neurosurgical treatment in the inclusion criteria of ISAT results in a poor recruitment rate. For example, patients with poor preoperative status might require treatment as soon as possible. Also, aneurysms located in posterior circulation were more likely to have been allocated to coiling, whereas the large, wide-necked aneurysms were tended to be allocated to clipping. These lesions thus were not randomized, and only evaluated by surgeons whose technical proficiencies cannot be quantified. In real clinical practice, coiling is now being offered to patients who were not suitable for inclusion in ISAT.34 Therefore, the findings from new prospective and retrospective studies may help provide more clinical value.

The data from non-RCTs show a small benefit with coiling, but do not reach statistical significance. The interactional test between results from RCTs and non-RCTs has shown significant heterogeneity. Thus, pool OR value was not calculated and subgroup analysis was performed.

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Studies Number</th>
<th>Clip, Patients Number</th>
<th>Coil, Patients Number</th>
<th>OR (95% CI)</th>
<th>$P$ Value</th>
<th>Study Heterogeneity</th>
<th>$\chi^2$</th>
<th>df</th>
<th>$I^2$, %</th>
<th>$P$ Value</th>
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<td>RCT</td>
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<td>1327</td>
<td>1323</td>
<td>1.48 (1.24–1.76)</td>
<td>&lt;0.0001</td>
<td>0.53</td>
<td>3</td>
<td>0</td>
<td>0.91</td>
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<td>Observational studies</td>
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<td>2431</td>
<td>1474</td>
<td>1.11 (0.96–1.28)</td>
<td>0.17</td>
<td>10.63</td>
<td>8</td>
<td>25</td>
<td>0.22</td>
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<tr>
<td>Good preoperative grade</td>
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<td>1308</td>
<td>1117</td>
<td>1.51 (1.24–1.84)</td>
<td>&lt;0.0001</td>
<td>2.65</td>
<td>3</td>
<td>0</td>
<td>0.45</td>
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<td>5</td>
<td>258</td>
<td>179</td>
<td>0.88 (0.56–1.38)</td>
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<td>908</td>
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<td>1.57</td>
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<tr>
<td>Short term</td>
<td>8</td>
<td>2893</td>
<td>2119</td>
<td>1.07 (0.88–1.30)</td>
<td>0.51</td>
<td>7.33</td>
<td>7</td>
<td>5</td>
<td>0.40</td>
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<tr>
<td>Long term</td>
<td>3</td>
<td>1126</td>
<td>1082</td>
<td>1.31 (1.01–1.70)</td>
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<td>0.72</td>
<td>2</td>
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<tr>
<td>Rebleeding rate</td>
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<td></td>
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<tr>
<td>Short term</td>
<td>8</td>
<td>2910</td>
<td>2372</td>
<td>0.43 (0.28–0.66)</td>
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<td>7</td>
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<tr>
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<td>Secondary outcomes</td>
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<td></td>
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<tr>
<td>Vasospasm</td>
<td>5</td>
<td>961</td>
<td>306</td>
<td>1.43 (1.07–1.91)</td>
<td>0.02</td>
<td>4.35</td>
<td>4</td>
<td>8</td>
<td>0.36</td>
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<tr>
<td>Ischemic infarct</td>
<td>6</td>
<td>822</td>
<td>301</td>
<td>0.74 (0.52–1.06)</td>
<td>0.10</td>
<td>5.79</td>
<td>5</td>
<td>14</td>
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<tr>
<td>Shunt-dependent hydrocephalus</td>
<td>7</td>
<td>1280</td>
<td>701</td>
<td>0.84 (0.66–1.07)</td>
<td>0.16</td>
<td>4.91</td>
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<td>Procedural complication associated with poor outcomes</td>
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<td>507</td>
<td>359</td>
<td>1.19 (0.67–2.11)</td>
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<td>0.76</td>
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<tr>
<td>Complete occlusion</td>
<td>5</td>
<td>756</td>
<td>993</td>
<td>2.43 (1.88–3.13)</td>
<td>&lt;0.0001</td>
<td>4.48</td>
<td>4</td>
<td>11</td>
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<tr>
<td>Incomplete occlusion</td>
<td>5</td>
<td>853</td>
<td>1070</td>
<td>0.39 (0.31–0.50)</td>
<td>&lt;0.0001</td>
<td>4.55</td>
<td>4</td>
<td>12</td>
<td>0.34</td>
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CI indicates confidence interval; OR, odds ratios; and RCT, randomized controlled trials. Statistically significant results are shown in bold.
lower risk of rebleeding, their 1-year mortality is statistically equivalent. However, most studies only provided 1-year all-cause mortality and failed to provide case fatality, thus reducing the reliability of the results.

Four trials have mentioned long-term follow-up for comparison of poor outcomes between the 2 approaches, and coiling continued to yield a better outcome than clipping after operation. Analysis on postprocedural recurrent hemorrhage showed a significantly higher risk in the coiled patient population not only within 1-year follow-up, but also in long-term follow-up. Only 3 long-term follow-up studies showed that the risk of death was significantly lower in the coiling group than in the clipping group. These results were largely dependent on ISAT. Nevertheless, potential biases of patient characteristics and national referral patterns, as well as the methodological problems in ISAT, contribute to the difficulty in interpreting differences in long-term outcomes. More trials for long-term follow-up are required for further evaluation of both techniques.

Secondary Outcomes

The incidence of total vasospasm and ischemic infarct after SAH varies in comparative studies of clipping and coiling for ruptured aneurysm occlusion. The analysis on vasospasm after operation showed a significantly higher risk in the clipping group, but the ischemic infarct end point showed no statistical difference. The results were inconsistent with those in the prior meta-analysis conducted in 2007,30 which revealed no significant difference for the risk of vasospasm between coiling and clipping. The main difference is the inclusion of 3 large trials in our analysis encompassing 460 participants, 2 of which found a significant difference. Although conventional angiography is the gold standard for the diagnosis of vasospasm,36 some authors use indirect changes suggestive of vasospasm, such as neurological consequences, increased blood flow velocity detected by transcranial Doppler and imaging techniques for diagnosis of tissue ischemia. However, there is no evidence that 1 method is more efficient and reliable than other methods.37–39

Cumulative meta-analysis, including 1981 patients altogether, demonstrated that the frequency of shunt-dependent hydrocephalus was not significantly different between coiling and clipping. This result differs with the prior meta-analysis conducted in 2007,40 which showed that the risk of shunt-dependent hydrocephalus was significantly higher after coiling than clipping for ruptured intracranial aneurysms. The main difference comes from the inclusion in our analysis of 3 large trials, with 981 participants. A study41 including 718 patients in the previous meta-analysis was excluded in our study for substantial imbalance of the baseline character, which might strongly relate to the outcome measures. Of the patients treated solely with endovascular methods, 38% demonstrated admission Hunt and Hess grades of IV or V, compared with only 12% of patients who underwent surgical treatment. This selection bias might have contributed to the higher incidence of shunt dependency among patients treated nonsurgically. We believe exclusion of this study greatly improves the reliability of our analysis.

The procedural complications are another influential factor for the prognosis of postintervention aneurysmal SAH. Procedural complications with coiling include aneurysmal perforation, mechanical vasospasm, thromboembolism, coil migration, etc. Surgical-related complications include surgical wound infection, extradural or subdural hematoma, cranial nerve palsy, postclipping ischemic infarct, etc. Fraser et al42 reviewed 19 publications and found that the overall weighted average procedural complication rate among clipped aneurysms (for those studies involved) was 11%, with a range of 6.6% to 50.0%, among which the largest study reported a rate of 6.6% (n=391). Among other studies for coiled aneurysms, the overall average procedural complication rate was 9%, with a range of 4.1% to 28.6%. The largest study reported a rate of 9.2% (n=403). Though the characteristics of the patients differed greatly from each study, the comparison of total procedural complications or those associated with poor outcomes both showed no difference between coiling and clipping.

Limitations

The clinical relevance of these results must be interpreted with caution. Our study may have some bias, because the analysis of the nonrandomized studies was not adjusted for confounding variables. In most observational controlled trials, allocation to clipping or coiling was based on surgeon preference according to preoperative condition, aneurismal characteristic, and the experience of the surgeon. On the contrary, clinical diversity makes the results of RCTs impossible to verify for all patients, aneurysms, and center characteristics. In the future, more inclusive and well-designed RCTs are needed to confirm our conclusion.

Conclusions

In summary, the results of our meta-analysis clearly show that coiling yields a better clinical outcome than clipping, the benefit being greater in those with a good preoperative grade than those with a poor preoperative grade. However, coiling leads to a greater risk of rebleeding. The mortality of the 2 treatments shows no significant difference within 1 year. Furthermore, the risk of vasospasm is higher after clipping than coiling, whereas the ischemic infarct, shunt-dependent hydrocephalus, and procedural complication rate of the 2 groups show no significant difference.

Acknowledgment

We thank Yuantao Hao, Jinxin Zhang, and Xueqin Wang for statistical assistance.

Disclosures

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References


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SUPPLEMENTAL MATERIAL

Clipping vs. Coiling for Ruptured Intracranial Aneurysms: A Systematic Review and Meta-Analysis

Hui Li, Rui Pan, Hongxuan Wang, Xiaoming Rong, Zi Yin, Daniel P. Milgrom, Xiaolei Shi, Yamei Tang, Ying Peng
## Supplemental Table 1

### Risk of Bias in the Published Controlled Trials

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<th>Authors</th>
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<th>Blinding Personnel</th>
<th>Blinding Assessor</th>
<th>Adequate Assessment of Each Outcome Reporting Avoided</th>
<th>Selective Outcome</th>
<th>Other Potential Bias</th>
<th>Handling of Missing Data</th>
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# Supplemental Table 2

## Risk of Bias in the Observational Studies Using Ottawa-Newcastle Rules and Other

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<th>Authors</th>
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<td>surgical</td>
<td>No restriction,</td>
<td>records</td>
<td>Yes</td>
<td>No lost</td>
<td>Possible bias in available case</td>
</tr>
<tr>
<td>Proust et al. 2003</td>
<td>Patient base</td>
<td>Record</td>
<td>Matched in 1,2,3,4</td>
<td>linkage</td>
<td>follow-up bias</td>
<td>allocation</td>
<td>Possible bias in analysis</td>
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<td>Dehdashti et al. 2004</td>
<td>Patient base</td>
<td>Record</td>
<td>Matched in 1,2,3,4</td>
<td>linkage</td>
<td>follow-up bias</td>
<td>allocation</td>
<td>Possible bias in analysis</td>
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<td>Gruber et al. 1999</td>
<td>Patient base</td>
<td>Record</td>
<td>Matched int 1,2,4</td>
<td>linkage</td>
<td>follow-up bias</td>
<td>allocation</td>
<td>Possible bias in analysis</td>
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<tr>
<td>Charpentier et al. 1999</td>
<td>Patient base</td>
<td>Record</td>
<td>Matched in 1,2,3,4</td>
<td>linkage</td>
<td>follow-up bias</td>
<td>allocation</td>
<td>Possible bias in analysis</td>
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<tr>
<td>Reyes et al. 2012</td>
<td>Patient base</td>
<td>Record</td>
<td>≥30 ml or ICH with</td>
<td>linkage</td>
<td>follow-up bias</td>
<td>allocation</td>
<td>Possible bias in analysis</td>
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<tr>
<td>B.M. Kim</td>
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<td>Restricted to anterior</td>
<td>records</td>
<td>Yes</td>
<td>No lost</td>
<td>Possible bias in Unclear</td>
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<td>Taha et al. 2006</td>
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<td>records</td>
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<td>Possible bias in Unclear</td>
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<tr>
<td>Rabenstein et al. 2003</td>
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<td>Record</td>
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<td>Goddard et al. 2004</td>
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<td>records</td>
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<td>Natrajjan et al. 2008</td>
<td>Patient base</td>
<td>Record</td>
<td>Matched in 1,2,3,4,5</td>
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<td>allocation</td>
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<td>Heiland et al. 2006</td>
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<td>records</td>
<td>Yes</td>
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<td>Niskanen et al. 2004</td>
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<td>Verdas et al. 2006</td>
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<td>records</td>
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<tr>
<td>Oliveira et al.</td>
<td>Yes/Same</td>
<td>surgical</td>
<td>No restriction,</td>
<td>records</td>
<td>Yes</td>
<td>No lost</td>
<td>Possible bias in Unclear</td>
</tr>
</tbody>
</table>

### Criteria

- **Surgical Case Record:** No restriction, matched in 1,2,3,4,5. No possible bias in available case.
- **Possible Bias in Analysis:** Yes/Same, surgical, matched in 1,2,3,4,5. No possible bias in analysis.
- **Possible Bias in Analysis:** Yes/Same, surgical, ≥30 ml or ICH with linkage. No possible bias in analysis.
- **Possible Bias in Analysis:** Yes/Same, surgical, restricted to anterior. No possible bias in Unclear.
- **Possible Bias in Analysis:** Yes/Same, surgical, no restriction, matched in 1,2,3,4,5. No possible bias in Unclear.
- **Possible Bias in Analysis:** Yes/Same, surgical, no restriction, matched in 1,2,3,5. No possible bias in Unclear.
- **Possible Bias in Analysis:** Yes/Same, surgical, ≥30 ml or ICH with linkage. No possible bias in Unclear.
- **Possible Bias in Analysis:** Yes/Same, surgical, ≥30 ml or ICH with linkage. No possible bias in Unclear.
- **Possible Bias in Analysis:** Yes/Same, surgical, ≥30 ml or ICH with linkage. No possible bias in Unclear.
- **Possible Bias in Analysis:** Yes/Same, surgical, ≥30 ml or ICH with linkage. No possible bias in Unclear.
- **Possible Bias in Analysis:** Yes/Same, surgical, ≥30 ml or ICH with linkage. No possible bias in Unclear.
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<th>Year</th>
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<th>Record</th>
<th>Matched in</th>
<th>linkage</th>
<th>follow-up bias</th>
<th>allocation</th>
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<tr>
<td>2007</td>
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<td>2010</td>
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<td>2004</td>
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<td>Yes</td>
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<td>Yes</td>
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</tbody>
</table>

1=Age; 2=Sex; 3=Hunt and Hess Grade; 4 =Modified Fisher Score; 5=Aneurism size; 6=Aneurism location.
Supplemental Figure 1

Forest plot and meta-analysis of poor outcome rate (long term follow-up).

M-H=Mantel-Haenszel method, CI=confidence interval

Supplemental Figure 2

Forest plot and meta-analysis of poor outcome rate for patients with good preoperative grade.

M-H=Mantel-Haenszel method, CI=confidence interval
Supplemental Figure 3

Forest plot and meta-analysis of poor outcome rate for patients with poor preoperative grade.

M-H=Mantel-Haenszel method, CI=confidence interval

Supplemental Figure 4

Forest plot and meta-analysis of mortality (long term follow-up).

M-H=Mantel-Haenszel method, CI=confidence interval
Supplemental Figure 5

Forest plot and meta-analysis of rebleeding rate (long term follow-up).

M-H=Mantel-Haenszel method; CI=confidence interval.

Supplemental Figure 6

Forest plot and meta-analysis of postoperative vasospasm rate.

M-H=Mantel-Haenszel method, CI=confidence interval
### Supplemental Figure 7

Forest plot and meta-analysis of postoperative ischemic infarct rate.

M-H=Mantel-Haenszel method, CI=confidence interval

### Supplemental Figure 8

Forest plot and meta-analysis of postoperative shunt-dependent hydrocephalus rate.

M-H=Mantel-Haenszel method, CI=confidence interval
Supplemental Figure 9

Forest plot and meta-analysis of procedural complications associated with poor outcome.

M-H=Mantel-Haenszel method, CI=confidence interval

Supplemental Figure 10

Forest plot and meta-analysis of angiographic results (complete occlusion).

M-H=Mantel-Haenszel method, CI=confidence interval
Supplemental Figure 11

Forest plot and meta-analysis of angiographic results (incomplete occlusion).

M-H=Mantel-Haenszel method, CI=confidence interval
Supplemental Figure 12

Funnel plots illustrating meta-analysis of poor outcome.

SE=standard error, OR=odds ratio
Supplemental Figure 13

Funnel plots illustrating meta-analysis of mortality.

SE=standard error, OR=odds ratio
Supplemental Figure 14

Funnel plots illustrating meta-analysis of rebleeding rate.

SE=standard error, OR=odds ratio