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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;44:29-37.)**

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, coiling 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 review[1] 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 aneurismal 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 conduct of the systematic review. The protocol was prepared according to the Meta-Analysis of Observational Studies in Epidemiology,[2] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses[3] guidelines.

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 definite 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 unruptured intracranial aneurysms. (2) Patients who received treatment other than neurosurgical clipping or endovascular coiling (muslin wrapping, no treatment). (3) SAH from infected aneurysms or trauma. (4) Studies that presented insufficient data or compared neurosurgical clipping or endovascular treatment alone. (5) Studies were excluded for substantial imbalance of clinical characteristics or absence of baseline information. (6) Editorials, letters, review articles, case reports, and animal experimental studies.

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 I^2 statistic, which describes the proportion of total variation that is attributable to differences among trials rather than sampling error (chance). An I^2 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[4] 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 al[5] enrolled 20 patients with documented aneurismal 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 al[6] 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. ISAT[7] with an enrollment of 2143 patients was the only large RCT to compare the efficacy of the 2 modalities in treating patients with aneurismal 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.

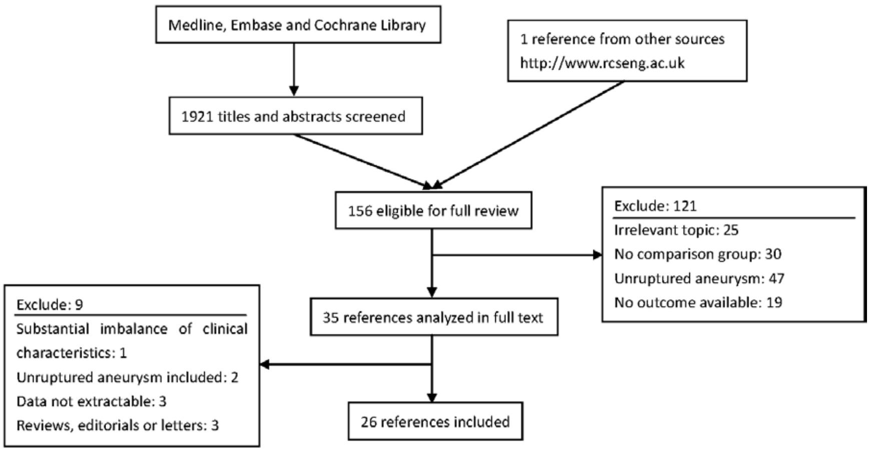

Figure 1. The flow diagram according to the Quality of Reporting of Meta-analyses (QUOROM)-statement.

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. Prepair and postrepair deterioration was recorded. Prepair deterioration was

Table 1. Design and Baseline Characteristics of Included Trials

Trial	Level of Evidence	Design	Patients Number (Clip / Coil)	Age*,y (Clip / Coil)	Male ,% (Clip / Coil)	Aneurysms Located in Anterior Circulation	Follow-up, mo/y
Brilstra et al[5] 2000	II	RCT	10/10	NA	30/30	10/10	12 mo
Koivisto et al[6] 2000	II	RCT	57/52	50/49	33/44	52/46	12 mo
ISAT[7] 2005	Ib	RCT	1070/1073	52/52	37/37	1021/1039	12 mo
ISAT[9] 2009	Iib	RCT	1070/1073	52/52	37/37	1021/1039	5 y
BRAT[8] 2012	II	RCT	238/233	53/54	30/28	174/169	12 mo
National study[10] 2006	II	P	1269/905	51/52	NA	1138/637	6 mo
PRESAT[11] 2011	II	P	264/270	NA	NA	252/212	12 mo
Proust et al[12] 2003	III	P	186/37	48/57	59/51	186/37	12 mo
Dehdashti et al[13] 2004	III	P	72/26	49/54	38/31	68/19	6 mo
Dehdashti et al[14] 2004	III	P	180/65	49/52	38/31	NA	3 mo
Gruber et al[15] 1998	III	P	111/45	52/52	36/33	88/51	6–18 mo
Gruber et al[16] 1999	III	R	125/62	50/50	36/29	NA	NA
Charpentier et al[17] 1999	IV	P	99/145	50/52	45/37	97/75	6 mo
Reyes et al[18] 2012	IV	R	8/10	56/55	NA	8/10	3 mo
Kim et al[19] 2008	IV	R	30/23	45/54	42/38	30/23	34/27 mo
Taha et al[20] 2006	IV	R	25/28	NA	NA	NA	26.7 mo
Rabinstein et al[21] 2003	IV	R	339/76	53/56	35/38	273/36	6 mo
Goddard et al[22] 2004	III	R	212/80	53/54	64/21	89/94	4–8 mo
Natarajan et al[23] 2008	III	R	105/87	NA	NA	NA	3 mo
Helland et al[24] 2006	III	R	203/83	51/55	42/46	97/84	3–6 mo
Niskanen et al[25] 2004	III	R	103/68	54/54	42/47	94/66	12
Varelas et al[26] 2006	III	R	135/48	53/51	34/54	116/31	NA
Oliveira et al[27] 2007	III	R	212/173	52/54	86/58	252/158	6 mo
Nam et al[28] 2010	III	R	498/238	54/57	38/30	490/183	NA
Hoh et al[29] 2004	IV	R	505/114	53/54	NA	436/57	6 mo
Hoh et al[30] 2004	III	A	413/79	54/58	30/23	361/46	NA
Suzuki et al[31] 2011	III	R	55/13	58/56	42/46	55/13	42.7 mo
Johnston et al[32] 2008	IV	A	706/295	NA	NA	NA	3.6 y

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.[5–32]

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[5–8,10–13,18,21,22,24,25] studies that assessed poor outcome (death or dependency) with 1 year in 6555 patients (Figure 2), RCTs showed that coiling 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<0.00001) 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 trials[9,19,31] mentioned a long-term follow-up (from an average of 26.7 months to 5 years) in 1845 patients, coiling was still associated with a better outcome than clipping (34.0% versus 28.3%; OR, 1.25; 95% CI, 1.03–1.53; P=0.03) (Supplemental Figure 1).

Five studies[6,7,12,18,24] 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 (I^2=0%; P=0.73). The interaction test P value between good and poor preoperative grade is 0.03.

Eight studies[5–7,10,12,13,18,21] 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 studies[9,19,31] 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 studies[5–8,10,12,18,23] 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=0.0001). There is no significant difference between RCTs and observational studies (χ^2=0.51, df=1, P=0.48, I^2=0%). Three studies[9,19,32] 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:

Study or Subgroup	clip Events	clip Total	coil Events	coil Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 RCTs						
BRAT2012	69	205	46	198	5.6%	1.68 [1.08, 2.60]
Bristra 2000	4	10	3	10	0.3%	1.56 [0.24, 9.91]
ISAT2005	326	1055	250	1063	31.0%	1.45 [1.20, 1.76]
Koivisto 2000	14	57	11	52	1.6%	1.21 [0.49, 2.98]
Subtotal (95% CI)		**1327**		**1323**	**38.5%**	**1.48 [1.24, 1.76]**
Total events	413		310			
Heterogeneity: Chi² = 0.53, df = 3 (P = 0.91); I² = 0%						
Test for overall effect: Z = 4.44 (P < 0.00001)						
1.2.2 other studies						
Dehdashti 2003	11	72	4	26	0.9%	0.99 [0.29, 3.44]
Goddard 2004	28	212	18	80	4.1%	0.52 [0.27, 1.01]
Helland 2006	38	203	14	82	2.9%	1.12 [0.57, 2.20]
National Study 2006	399	1044	278	825	34.6%	1.22 [1.01, 1.47]
Niskanen 2004	17	103	13	68	2.4%	0.84 [0.38, 1.86]
PRESAT2011	81	264	69	270	8.5%	1.29 [0.88, 1.88]
Proust 2003	59	186	16	37	3.3%	0.61 [0.30, 1.25]
Rabinstein 2003	92	339	20	76	4.3%	1.04 [0.59, 1.83]
Reyes 2012	4	8	7	10	0.6%	0.43 [0.06, 2.97]
Subtotal (95% CI)		**2431**		**1474**	**61.5%**	**1.11 [0.96, 1.28]**
Total events	729		439			
Heterogeneity: Chi² = 10.63, df = 8 (P = 0.22); I² = 25%						
Test for overall effect: Z = 1.36 (P = 0.17)						
Total (95% CI)		**3758**		**2797**	**100.0%**	**1.25 [1.12, 1.40]**
Total events	1142		749			
Heterogeneity: Chi² = 17.54, df = 12 (P = 0.13); I² = 32%						
Test for overall effect: Z = 3.91 (P < 0.0001)						
Test for subgroup differences: Chi² = 6.27, df = 1 (P = 0.01), I² = 84.0%						

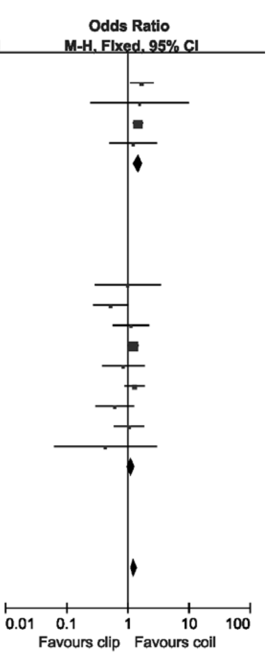

Figure 2. Forest plot and meta-analysis of poor outcome rate. CI indicates confidence interval; M-H, Mantel-Haenszel method; and RCT, randomized controlled trials.

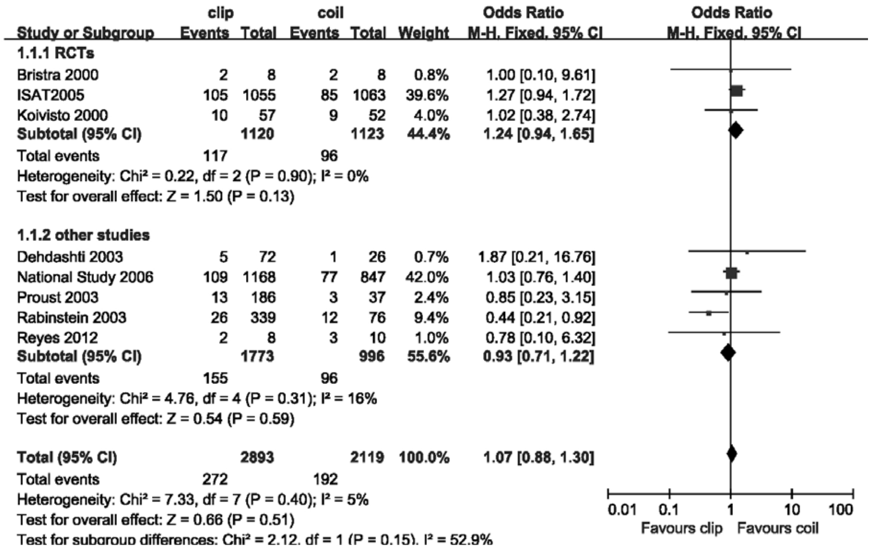

Figure 3. Forest plot and meta-analysis of mortality. CI indicates confidence interval; M-H, Mantel-Haenszel method; and RCT, randomized controlled trials.

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[12,20,22,23,30] 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[6,13,15,18,23,29] (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[14,16,20,23,26–28] (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[6,7,12,18,20] 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 aneurismal SAH undergoing neurosurgical clipping or coiling. Because of

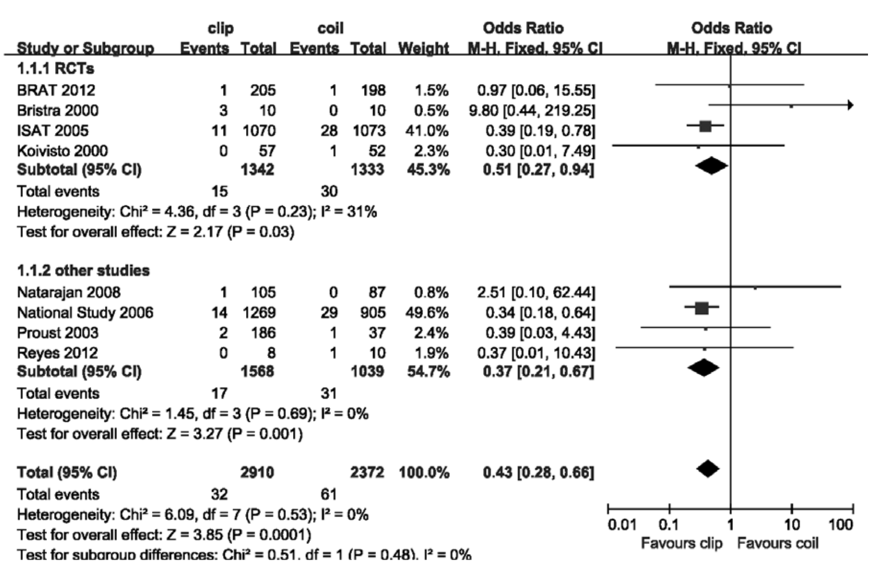

Figure 4. Forest plot and meta-analysis of rebleeding rate. CI indicates confidence interval; M-H, Mantel-Haenszel method; and RCT, randomized controlled trials.

Table 2. Results of Meta-Analysis Comparison of Clipping and Coiling

Outcomes of Interest	Studies Number	Clip, Patients Number	Coil, Patients Number	OR (95% CI)	P Value	Study Heterogeneity χ^2	df	I^2, %	P Value
Primary outcomes									
Poor outcome									
RCT	4	1327	1323	1.48 (1.24–1.76)	**<0.00001**	0.53	3	0	0.91
Observational studies	9	2431	1474	1.11 (0.96–1.28)	0.17	10.63	8	25	0.22
Good preoperative grade	4	1308	1117	1.51 (1.24–1.84)	**<0.0001**	2.65	3	0	0.45
Poor preoperative grade	5	258	179	0.88 (0.56–1.38)	0.57	2.05	4	0	0.73
Long-term follow-up	3	937	908	1.25 (1.03–1.53)	**0.03**	1.57	2	0	0.46
Mortality									
Short term	8	2893	2119	1.07 (0.88–1.30)	0.51	7.33	7	5	0.40
Long term	3	1126	1082	1.31 (1.01–1.70)	**0.04**	0.72	2	0	0.70
Rebleeding rate									
Short term	8	2910	2372	0.43 (0.28–0.66)	**0.0001**	6.09	7	0	0.53
Long term	3	1806	1391	0.39 (0.21–0.74)	**0.004**	0.03	1	0	0.87
Secondary outcomes									
Vasospasm	5	961	306	1.43 (1.07–1.91)	**0.02**	4.35	4	8	0.36
Ischemic infarct	6	822	301	0.74 (0.52–1.06)	0.10	5.79	5	14	0.33
Shunt-dependent hydrocephalus	7	1280	701	0.84 (0.66–1.07)	0.16	4.91	6	0	0.56
Procedural complication associated with poor outcomes	3	507	359	1.19 (0.67–2.11)	0.56	0.76	2	0	0.68
Angiographic results									
Complete occlusion	5	756	993	2.43 (1.88–3.13)	**<0.00001**	4.48	4	11	0.35
Incomplete occlusion	5	853	1070	0.39 (0.31–0.50)	**<0.00001**	4.55	4	12	0.34

CI indicates confidence interval; OR, odds ratios; and RCT, randomized controlled trials.
Statistically significant results are shown in bold.

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 day[33]; 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.

Most reviews and letters have documented that preoperative condition is the most important risk factor. Patients in our study were divided into 2 subgroups: good and poor preoperative grade. Interaction tests within both of the subgroups have shown homogeneity between RCTs and non-RCTs. So pooled OR values were calculated. The results yielded a greater benefit in those with a good preoperative grade. Among patients with a poor preoperative grade, treatment modality was not a significant prognostic factor. Although coiling is less invasive than surgery, the patient outcomes were mostly related to the initial subarachnoid hemorrhage and its deleterious consequences. Interaction testing between subgroups has also confirmed that clinical outcomes of treatment were heterogeneous by preoperative grade.

The analysis on postprocedural recurrent hemorrhage is homogenous between RCTs and non-RCTs. The pooled OR showed a significantly higher risk in the coiled patient population within 1 year of follow-up. This result corresponded with the angiographic outcomes, which revealed a significant difference in the ratio of incomplete occlusion between coiling and clipping, indicating that aneurysms are more often incompletely treated with coiling and thus carry a higher risk for reopening.

The all-cause 1-year mortality rate did not differ significantly between the 2 groups. The results of RCTs and observational studies were homogenous. Although coiling has advantages in reducing poor outcomes and clipping has a 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,[35] 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 study[41] 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 al[42] 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

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Disclosures

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SUPPLEMENTAL MATERIAL

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

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Supplemental Table 1

Risk of Bias in the Published Controlled Trials

Authors	Allocation Sequence Described	Allocation Concealment	Blinding: Patient	Blinding: Personnel	Blinding: Assessor	Adequate Assessment of Each Outcome	Selective Outcome Reporting Avoided	Other Potential Bias	Handling of Missing Data
Brilstra (2000)	Yes	Yes	No	No	No	Yes	Yes	not powered	Yes
Koivisto et al (2000)	Yes	Yes	No	No	No	Yes	Yes	not powered	Yes
ISAT (2005)	Yes	Yes	No	No	No	Yes	Yes	not powered	Yes
BRAT (2012)	Yes	Yes	No	No	No	Yes	Yes	not powered	Yes

Supplemental Table 2

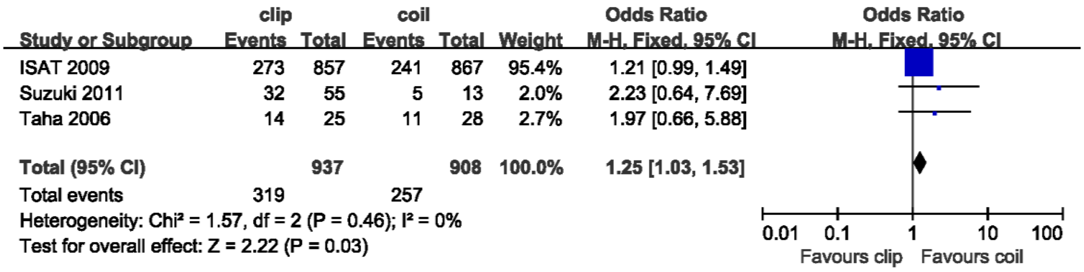
Risk of Bias in the Observational Studies Using Ottawa-Newcastle Rules and Other Criteria

Authors	Representative Cohort/Reference	Exposure Ascertainment	Comparability	Outcome Assessment	Sufficient Duration	Follow-Up	Selection Bias	Missing Data and Other
National study (2006)	Yes/Same Patient base	surgical Record	No restricton, Matched in 1,2,3,4	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	available case analysis
PRESAT (2011)	Yes/Same Patient base	surgical Record	No restricton, Matched in 1,2,3,4	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	available case analysis
Proust et al 2003	Yes/Same Patient base	surgical Record	Restricted to AcoA, Matched in 2,3,4,6	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
Dehdashti et al.2004	Yes/Same Patient base	surgical Record	restricton, Matched in 1,2,3,4	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
Gruber et al 1998	Yes/Same Patient base	surgical Record	No restricton, Matched in1,2,4	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	available case analysis
Gruber et al 1999	Yes/Same Patient base	surgical Record	No restricton, Matched in1,2,3,4	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	available case analysis
Charpentier et al 1999	Yes/Same Patient base	surgical Record	No restricton, Matched in1,2,3,4	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
Reyes et al. 2012	Yes/Same Patient base	surgical Record	presence of an ICH ⩾30 ml or ICH with midline shift⩾5 mm, Matched in1,3,4,5,6	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
B.M. Kim 2008	Yes/Same Patient base	surgical Record	Restricted to anterior choroidal artery aneurysms, Matched in 2,3,5,6	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
Taha et al. 2006	Yes/Same Patient base	surgical Record	No restriction, Matched in2,3	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
Rabinstein et al 2003	Yes/Same Patient base	surgical Record	No restriction, Matched in1,2,3	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
Goddard et al. 2004	Yes/Same Patient base	surgical Record	No restriction, Matched in1,2,3,5	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
Natarajan et al. 2008	Yes/Same Patient base	surgical Record	No restricton, Matched in 1,2,3,4,5	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
Helland et al. 2006	Yes/Same Patient base	surgical Record	No restricton, Matched in2,3	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
Niskanen et al. 2004	Yes/Same Patient base	surgical Record	No restricton, Matched in1,2,3,5,6	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
Varelas et al. 2006	Yes/Same Patient base	surgical Record	No restricton, Matched in1,3,4	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
Oliveira et al.	Yes/Same	surgical	No restricton,	records	Yes	No lost	Possible bias in	Unclear

2007	Patient base	Record	Matched in1,2,3,4,6	linkage		follow-up bias	allocation	
Nam et al. 2010	Yes/Same Patient base	surgical Record	No restricton, Matched in1,3,4	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
Hoh et al. 2004	Yes/Same Patient base	surgical Record	No restricton, Matched in 1,2,3,4,6	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
Suzuki et al. 2011	Yes/Same Patient base	surgical Record	Restricted to anterior cerebral artery aneurysm, Matched in 2,3,6	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
Johnston et al. 2008	Yes/Same Patient base	surgical Record	No restricton, Mathed in 2,3	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	Unclear
Dehdashti et al. 2004	Yes/Same Patient base	surgical Record	patients with a poor grade,and with fusiform, traumatic and mycotic aneurysm were excluded. Matched in1,2,3,4	records linkage	Yes	No lost follow-up bias	Possible bias in allocation	available case analysis

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

Supplemental Figure 1

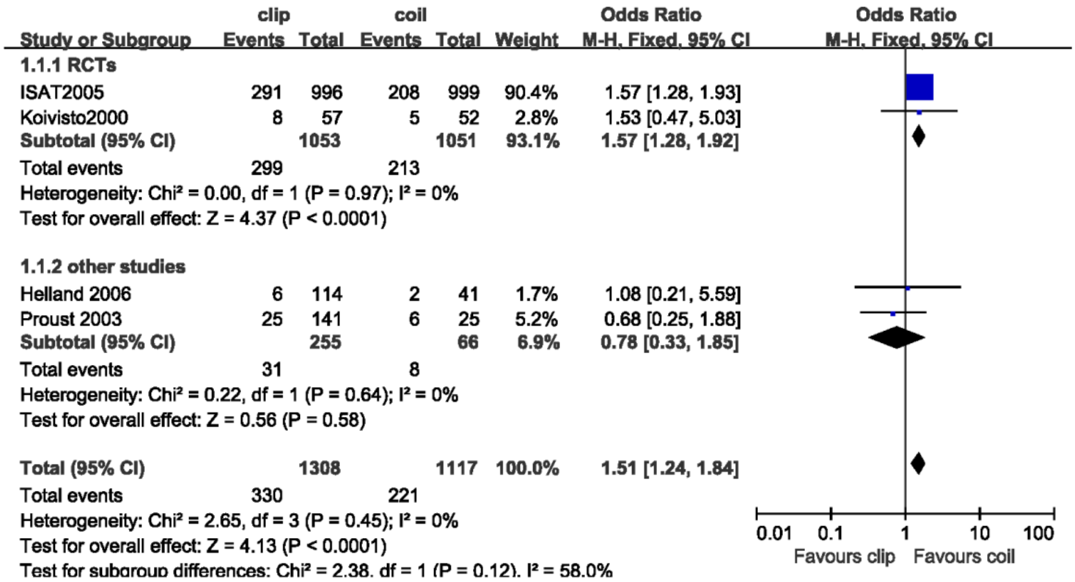


Supplemental Figure 1

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

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

Supplemental Figure 2



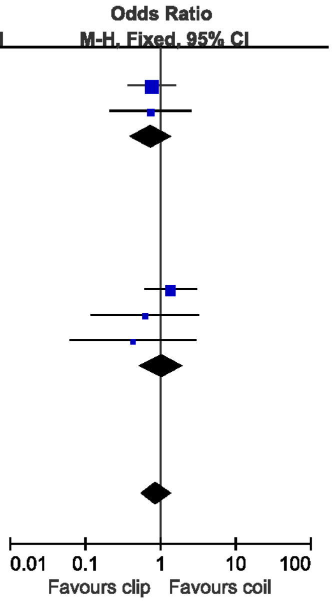
Supplemental Figure 2

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

Study or Subgroup	clip Events	clip Total	coil Events	coil Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 RCT						
ISAT 2005	35	59	42	64	41.4%	0.76 [0.37, 1.59]
Koivisto 2000	5	57	6	52	14.5%	0.74 [0.21, 2.58]
Subtotal (95% CI)		**116**		**116**	**55.8%**	**0.76 [0.40, 1.42]**
Total events	40		48			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.86 (P = 0.39)						
1.1.2 other studies						
Helland 2006	32	89	12	41	26.6%	1.36 [0.61, 3.02]
Proust 2003	34	45	10	12	9.7%	0.62 [0.12, 3.26]
Reyes 2012	4	8	7	10	7.9%	0.43 [0.06, 2.97]
Subtotal (95% CI)		**142**		**63**	**44.2%**	**1.03 [0.53, 1.99]**
Total events	70		29			
Heterogeneity: Chi² = 1.61, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.08 (P = 0.93)						
Total (95% CI)		**258**		**179**	**100.0%**	**0.88 [0.56, 1.38]**
Total events	110		77			
Heterogeneity: Chi² = 2.05, df = 4 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.57 (P = 0.57)						
Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%						



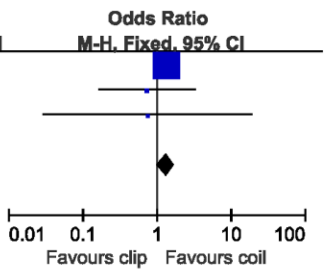
Supplemental Figure 3

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

Study or Subgroup	clip Events	clip Total	coil Events	coil Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ISAT 2009	144	1041	112	1046	95.3%	1.34 [1.03, 1.74]
Kim 2008	4	30	4	23	3.9%	0.73 [0.16, 3.30]
Suzuki 2011	1	55	0	13	0.8%	0.74 [0.03, 19.27]
Total (95% CI)		**1126**		**1082**	**100.0%**	**1.31 [1.01, 1.70]**
Total events	149		116			
Heterogeneity: Chi² = 0.72, df = 2 (P = 0.70); I² = 0%						
Test for overall effect: Z = 2.05 (P = 0.04)						

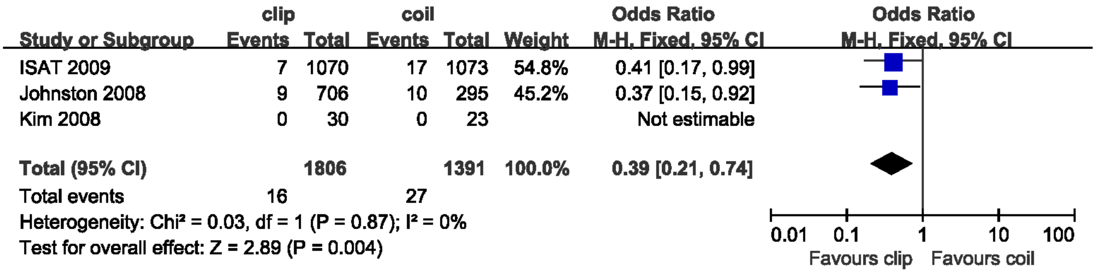


Supplemental Figure 4

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

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

Supplemental Figure 5

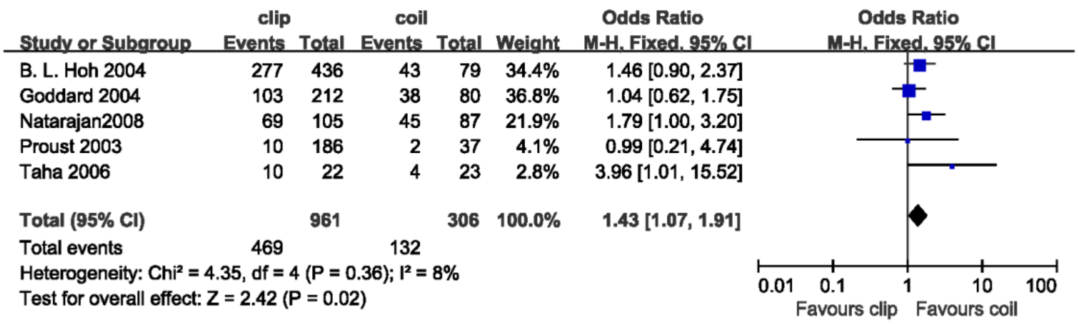


Supplemental Figure 5

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

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

Supplemental Figure 6



Supplemental Figure 6

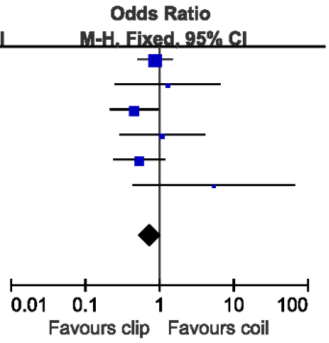
Forest plot and meta-analysis of postoperative vasospasm rate.

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

Supplemental Figure 7

Study or Subgroup	clip Events	clip Total	coil Events	coil Total	Weight	Odds Ratio M-H, Fixed, 95% CI
B.L. Hoh 2004	79	505	20	114	39.1%	0.87 [0.51, 1.49]
Dehdashti 2004	7	72	2	26	3.8%	1.29 [0.25, 6.66]
Gruber 1998	24	111	17	45	26.9%	0.45 [0.21, 0.97]
Koivisto 2000	7	21	6	19	6.0%	1.08 [0.29, 4.08]
Natarajan 2008	12	105	17	87	23.4%	0.53 [0.24, 1.18]
Reyes 2012	3	8	1	10	0.8%	5.40 [0.44, 66.67]
Total (95% CI)		**822**		**301**	**100.0%**	**0.74 [0.52, 1.06]**
Total events	132		63			

Heterogeneity: Chi² = 5.79, df = 5 (P = 0.33); I² = 14%
Test for overall effect: Z = 1.66 (P = 0.10)



Supplemental Figure 7

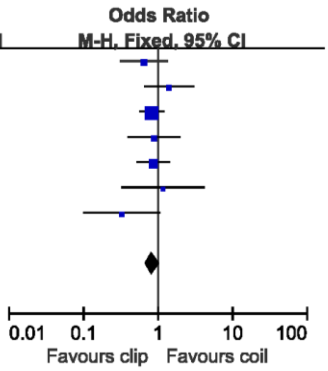
Forest plot and meta-analysis of postoperative ischemic infarct rate.

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

Supplemental Figure 8

Study or Subgroup	clip Events	clip Total	coil Events	coil Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dehdashti 2004	25	180	13	65	11.7%	0.65 [0.31, 1.35]
Gruber 1999	29	125	11	62	8.0%	1.40 [0.65, 3.03]
Nam 2010	93	498	52	238	40.6%	0.82 [0.56, 1.20]
Natarajan 2008	14	105	13	87	8.7%	0.88 [0.39, 1.98]
Oliveira 2007	37	212	34	173	21.9%	0.86 [0.52, 1.45]
Taha 2006	6	25	6	28	3.1%	1.16 [0.32, 4.20]
Varelas 2006	6	135	6	48	6.0%	0.33 [0.10, 1.06]
Total (95% CI)		**1280**		**701**	**100.0%**	**0.84 [0.66, 1.07]**
Total events	210		135			

Heterogeneity: Chi² = 4.91, df = 6 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.39 (P = 0.16)

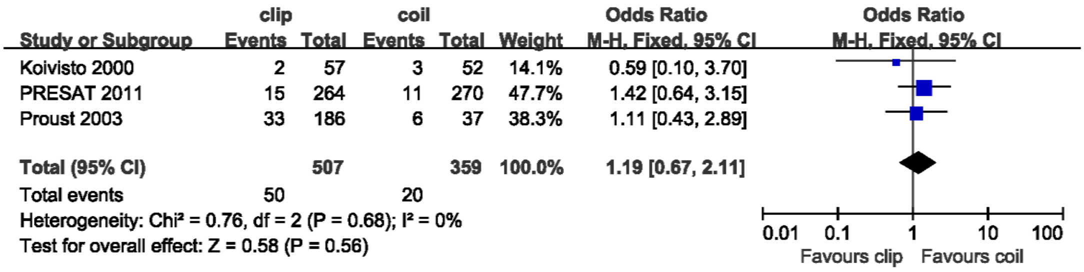


Supplemental Figure 8

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

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

Supplemental Figure 9

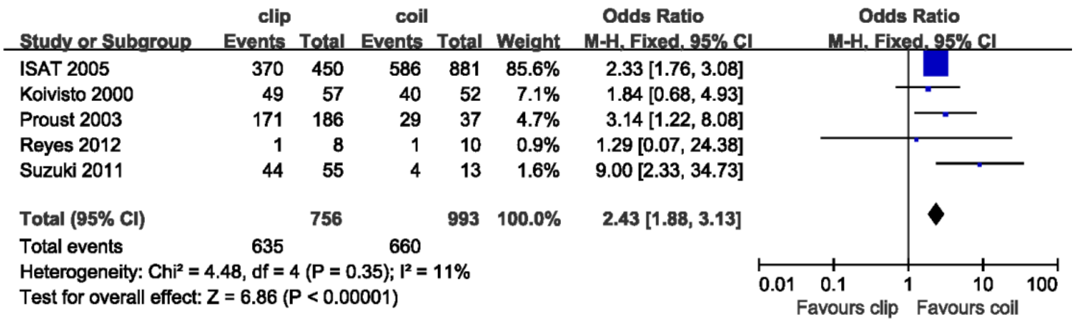


Supplemental Figure 9

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

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

Supplemental Figure 10



Supplemental Figure 10

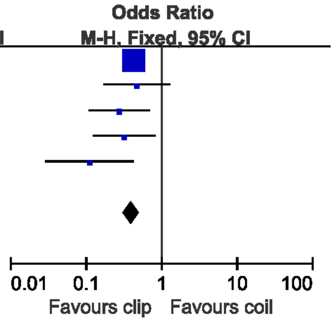
Forest plot and meta-analysis of angiographic results (complete occlusion).

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

Supplemental Figure 11

Study or Subgroup	clip Events	clip Total	coil Events	coil Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ISAT 2005	80	450	297	881	75.6%	0.43 [0.32, 0.56]
Koivisto 2000	7	57	12	52	5.0%	0.47 [0.17, 1.30]
Natarajan 2007	7	105	18	87	8.4%	0.27 [0.11, 0.69]
Proust2004	15	186	8	37	5.6%	0.32 [0.12, 0.82]
Suzuki 2011	11	55	9	13	5.3%	0.11 [0.03, 0.43]
Total (95% CI)		**853**		**1070**	**100.0%**	**0.39 [0.31, 0.50]**
Total events	120		344			

Heterogeneity: Chi² = 4.55, df = 4 (P = 0.34); I² = 12%
Test for overall effect: Z = 7.47 (P < 0.00001)

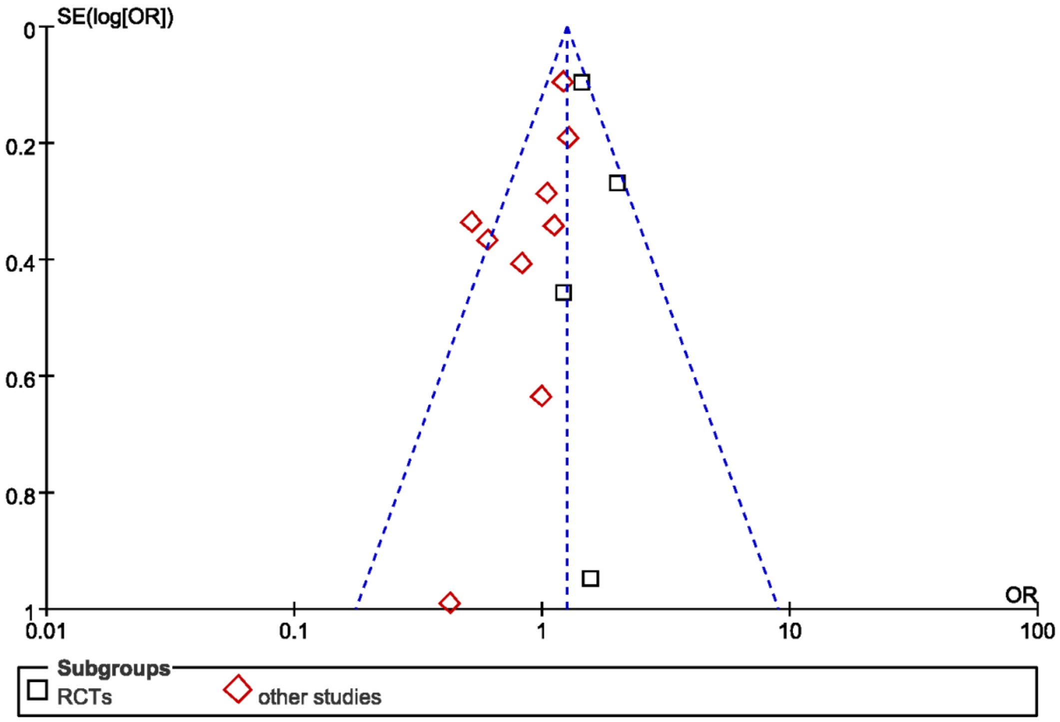


Supplemental Figure 11

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

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

Supplemental Figure 12

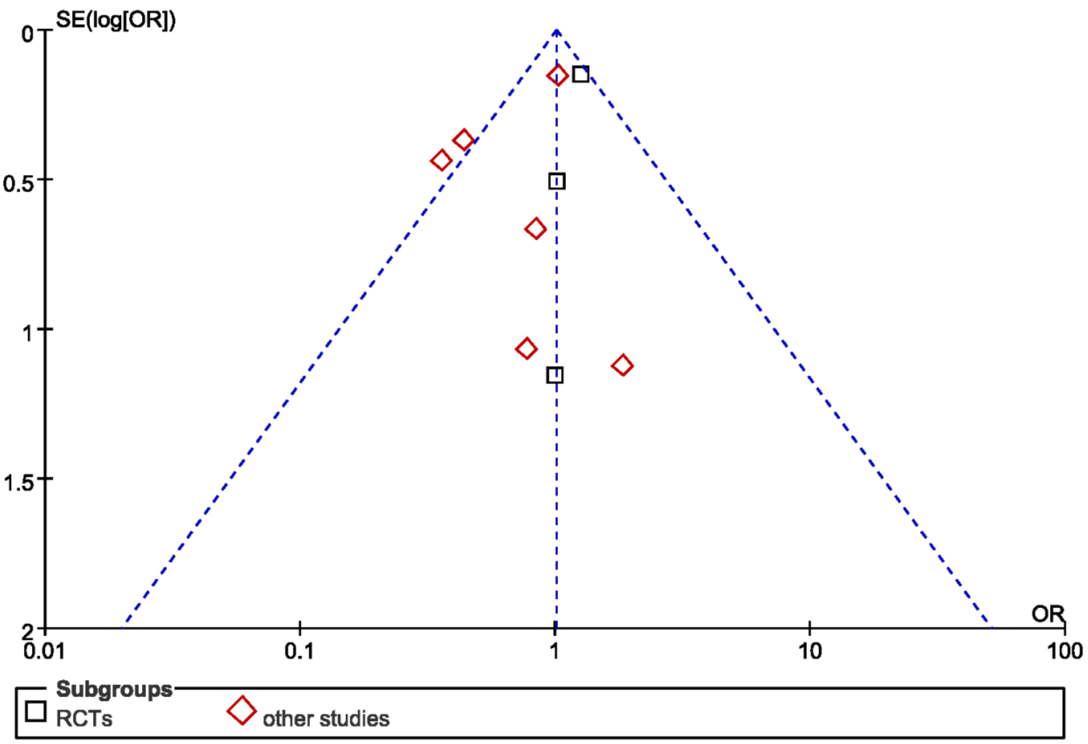


Supplemental Figure 12

Funnel plots illustrating meta-analysis of poor outcome.

SE=standard error, OR=odds ratio

Supplemental Figure 13

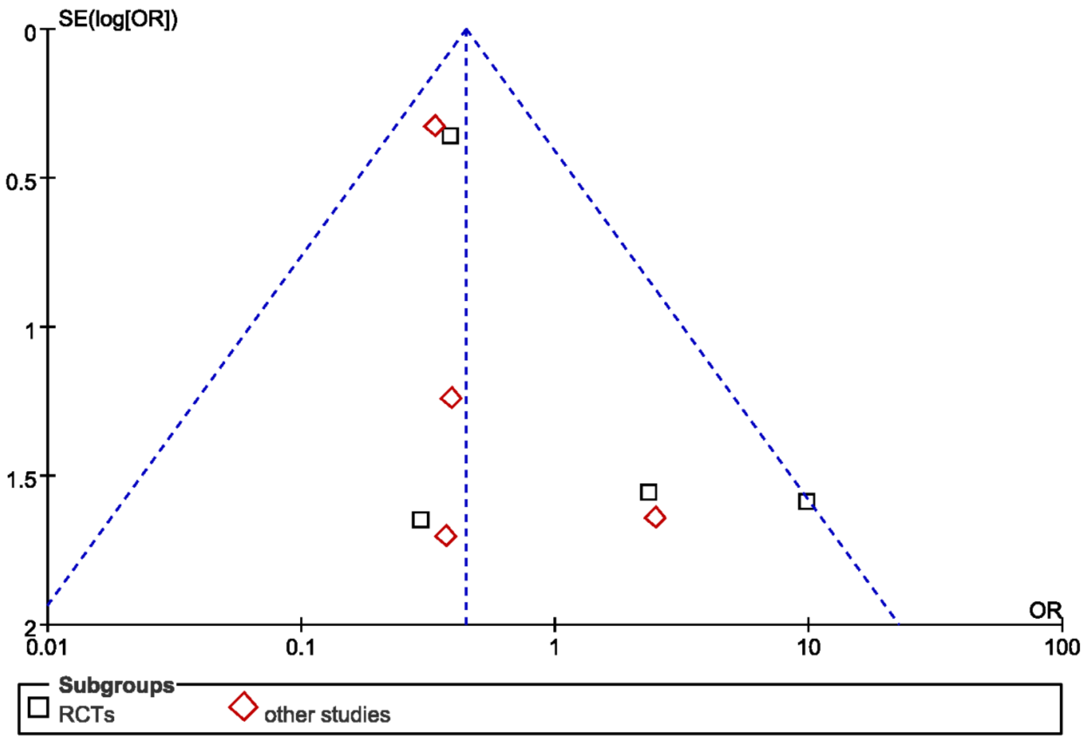


Supplemental Figure 13

Funnel plots illustrating meta-analysis of mortality.

SE=standard error, OR=odds ratio

Supplemental Figure 14



Supplemental Figure 14

Funnel plots illustrating meta-analysis of rebleeding rate.

SE=standard error, OR=odds ratio