Innovation in neurosurgery: Evaluation of neurosurgical innovation, related ethics, and solutions

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# Outcomes of retreatment for intracranial aneurysms - a meta-analysis

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Introduction: Long term results from the International Subarachnoid Hemorrhage Trial (ISAT) and Barrow Ruptured Aneurysm Trial (BRAT) indicate considerably higher retreatment rates for aneurysms treated with coiling compared to clipping, but do not report the outcome of retreatment. **Objective***: The aim of this meta-analysis was to evaluate retreatment related outcomes.* **Methods***: A meta-analysis in accordance with PRISMA guidelines was conducted using Medline search engines PubMed and EMBASE to identify articles describing outcomes after retreatment for intracranial aneurysms. Pooled prevalence rates for complete occlusion rate and mortality were calculated. Outcomes of different treatment and retreatment combinations were not compared because of indication bias.* **Results***: Twenty-five articles that met the inclusion criteria were included in the meta-analysis. Surgery after coiling had a pooled complete occlusion rate of 91.2% (95%-CI: 87.0-94.1) and a pooled mortality rate of 5.6% (95%-CI: 3.7-8.3). Coiling after coiling had a pooled complete occlusion rate of 51.3% (95%-CI: 22.1-78.0) and a pooled mortality rate of 0.8% (95%-CI: 0.15-3.7). Surgery after surgery did not provide a pooled estimate for complete occlusion as only one study was identified but had a pooled mortality rate of 5.9% (95%-CI: 3.1-11.2). Coiling after surgery had a pooled complete occlusion rate of 56.1% (95%-CI: 11.4- 92.7)*

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*and a pooled mortality rate of 9.3% (95%-CI: 4.1-19.9). All pooled incidence rates were produced using random-effect models. **Conclusions**: Surgical retreatment was associated with a high complete occlusion rate but considerable mortality. Conversely, endovascular retreatment was associated with low mortality but also a low complete occlusion rate.*

Introduction

The current mainstay treatment modalities for both ruptured and unruptured intracranial aneurysms are microsurgical clipping and endovascular treatment such as coiling .[30,37] There is a growing preference to treat intracranial aneurysms with an endovascular treatment modality, as short-term and medium-long term outcomes seem to show a superiority over clipping with regard to morbidity, mortality, and functional outcomes.[30,37,24,38] Endovascular treatment is also considered to be less invasive and is suggested to be preferred by most patients.[30,37,24,38] However, regrowth and subsequent retreatment rate are considerably higher in patients treated with coiling compared to clipping in the long term (BRAT 6 year follow-up data: retreatment: 16.4% for coiling vs 4.6% for clipping, respectively).[37] Furthermore, the results from the ISAT indicate significantly higher rates of re-bleeding and retreatment rates for endovascular treated aneurysms compared to surgically treated aneurysms at ten-year follow-up (retreatment: 17.4% for coiling vs. 3.9% for clipping, respectively).[30,3] However, there was no significant difference in mortality and functional outcome, which may indicate that regrowth does not result in worse outcomes.[30,3] Therefore, questions remain regarding possibility, efficacy, and safety of retreatment after regrowth as a result of the often-occurring regrowth of aneurysms. For instance, aneurysms may be difficult to surgically retreat because of increased mass, scar tissue, and may even require a bypass.[7] One meta-analysis indicated that microsurgical retreatment may be considered safe. [33] However, this meta-analysis was limited by the studies included. Furthermore, other treatment and retreatment combinations were subjected to a meta-analysis.[33] In addition, different treatment and retreatment combinations have not been compared. There is a great variety of initial treatment options which include: clipping, coiling, Pipeline Embolization Device (PED, ⬚Chestnut Medical, Menlo Park, California), surgical (high flow) bypass, wrapping, and trapping, Woven Endobridge (WEB, ©Sequent Medical Inc., Aliso Viejo, California, USA) device, all of which can be used for retreatment.[7,1,16,11,5,9] The aim of this meta-analysis was to evaluate the efficacy and safety of retreatment of intracranial aneurysms for all available treatment-retreatment combinations.

Methods

Study selection

A systematic review and meta-analysis of available literature was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[29] PubMed and Embase databases were searched through October 2017 for studies reporting outcomes of re-intervention for intracranial aneurysms (Figure 1). The search syntax was drafted with Appropriate Medical Subject Headings (MeSH) and Emtree terms for PubMed and Embase, respectively

(**Supplementary Table 2.3**). The search was not limited by date of publication. Duplicates in identified articles were removed using Endnote X7.5 (Clarivate Analytics). All abstracts were screened in duplicate and discrepancies between reviewers were resolved by a senior author. Articles that were selected for full-text review were evaluated by two authors. Reference lists were checked for possible additional articles.

Figure 2.1: Flowchart of the study selection process
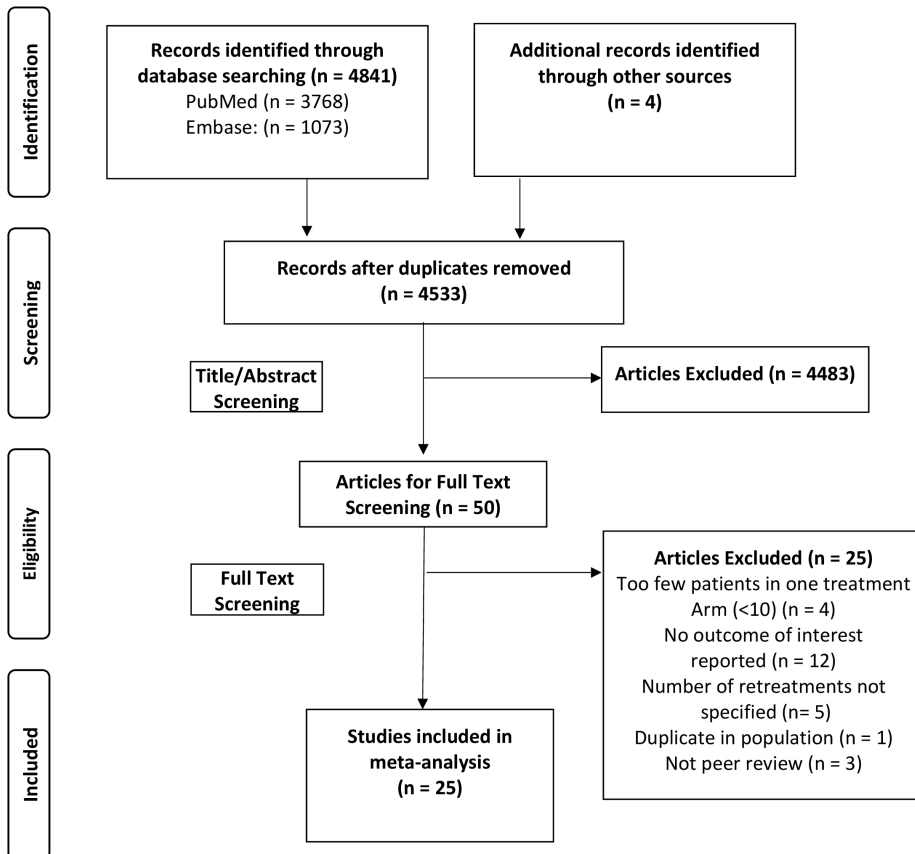
Inclusion criteria

All studies that were screened full-text were included if the following inclusion criteria were met: (1) The study was original and written in English or Dutch (2) The study included a treatment retreatment combination arm that consisted of a minimum of ten patients (3) The study was conducted in an adult population (4) The study had been subjected to peer-review (5) The study reported outcomes of retreatment for intracranial aneurysms. Only the most recent study was included if results from a

series of patients had been reported in multiple articles.

Data extraction and study quality assessment

All included studies were evaluated for the following study characteristics: continent, year of publication, sample size, study design, and follow-up (months). The following population characteristics were extracted for the initial treatment and retreatment combinations: mean age (years), number of females and males, initial presentation (subarachnoid hemorrhage or incidental), initial treatment modality, retreatment modality, indication for initial treatment, indication for retreatment, aneurysm location, percentage of initial successful occlusion, mean total aneurysm size at retreatment, number of large aneurysms (1.0 – 2.5 cm), number of giant aneurysms (>2.5 cm), and mean time to retreatment (months). The following outcomes were extracted: percentage of complete occlusion on imaging (angiogram or CTA), number of patients that died within 30 days after surgery (regardless of reason), and clinical outcome (modified Rankin Scale (mRS) or Glasgow Outcome Scale (GOS)).[17,45] Clinical outcomes were only extracted if the patients' status before and after the retreatment procedure was documented and had less than 10% missing values. A good clinical outcomes score was defined as less than 3 and greater than 4 on the modified Rankin Scale (mRS) and Glasgow Outcome Scale (GOS), respectively.[17,45] The extraction of the study characteristics and outcomes was performed by two independent investigators and discrepancies were solved by discussion or consultation of senior authors. All included studies were also evaluated for study quality using the Newcastle Ottawa Scale (NOS).[44] Comparability was not scored for studies that did not have a comparison group. Again, discrepancies were solved by consultation of senior authors.

Meta-analysis

The meta-analysis was conducted using R 3.4.2 (R Core Team, Auckland, New Zealand) with use of the "meta" package, which is partially built on the "Metafor" package.[42,36] Pooled prevalence ratios of complete occlusion rate and mortality rate were calculated using both fixed- and random-effect models for the following treatment and re-treatment combinations: surgery after coiling, coiling after coiling, coiling after surgery, surgery after surgery, PED after coiling, and PED after PED. Forest plots were created for the outcomes complete occlusion rate and mortality rate. The different initial treatment and retreatment combinations were not directly compared because of indication bias. The Cochran's Q test (p<0.10) and I^2 statistic (I^2 value >50% was considered significant) were used to evaluate possible heterogeneity among the included studies.[15] Meta-regression was applied to identify sources of heterogeneity for the following study characteristics: continent, year of publication, NOS-score, percentage of females, mean age (years), percentage of patients that initially presented with a subarachnoid hemorrhage, percentage of initial successful treatment, mean total aneurysm size at retreatment, percentage of patients with an aneurysm located in the posterior circulation, percentage of patients with large or giant aneurysms, mean time to re-intervention (months). Meta-regression separately was applied to all study characteristics and was only possible if a minimal of 3

studies were included in a specific treatment retreatment analysis and if no missing values were among the study characteristics and Bonferroni correction was applied to correct for multiple testing (critical p-value: 0.004 based on 13 degrees of freedom). Publication bias was evaluated by constructing Funnel plots, Eggers's linear regression test, and the Begg's and Mazumdar rank correlation test (p-value < 0.05 was considered significant).[2,10]

Results

The search strategy yielded 4529 studies after removal of duplicates (**Figure 2.1**). Twenty-five unique studies were included in the meta-analysis to evaluate outcomes of first retreatment for intracerebral aneurysms.[3-7,9,11-13,16,18,20-23,25,26,31,32,34,35,39,41,43,46]

Baseline characteristics

The 25 studies reported the outcomes in 1064 patients (**Table 2.1**). The median of mean age of the populations was 50.6 years at time of retreatment and the median of mean female percentage of the populations was 65.0. The studies had a mean follow-up of 22.9 months. Regarding aneurysm characteristics, the median of mean percentage of patients that initially presented with a subarachnoid hemorrhage was 75.9%. The median of mean percentage of posterior location was 10.3%. The median of mean size at retreatment was 7.0 mm, median of mean percentage of large aneurysms was 18.3%, and the median of mean percentage of giant aneurysms was 4.4%. Regarding the retreatment, the median of mean number of months to retreatment was 20.8. Early retreatment (within the first month) occurred in 6.0% of cases (median of mean percentage). The NOS score did not vary greatly among the studies as most were retrospective case series and cohort studies that did not make comparison between the different treatment retreatment combinations, except for the ISAT.[3]

Thirteen studies evaluated outcomes of surgery after coiling[4,5,7,12,21,22,25,31,32,35,41,43,46], 3 studies evaluated outcomes of coiling after coiling[7,18,39], 4 studies evaluated coiling after surgery[16,20,26,34], 3 studies evaluated surgery after surgery[9,16,32], 2 studied evaluated PED after coiling[6,23], and 2 studies evaluated PED after PED.[11,13]

In studies that described outcomes of surgery after coiling, extrusion of coils and coil compaction were observed in 18.8% and 30.5% of cases, respectively. Coils were extracted in 22.7% of cases and intraoperative rupture occurred in 5.6% of cases. Clipping was performed in 89.2% of cases, a bypass procedure was performed in 4.6% of cases, wrapping in 4.3% of cases, trapping in 3.6% of cases, and parent artery occlusion in 1.4% of cases.

Table 2.1: Base line characteristics of the studies.

Intervention retreatment combination	Study (year of publication)	Location	Study design	Number of patients with outcomes available	Mean age of population (years)	Percentage of females	Percentage posterior circulation aneurysms	Successful initial treatment (percentage)	Mean total aneurysm size at retreatment (mm)	Percentage of initial SAH presentation	Mean time to intervention (months)	NOS-score
Surgery after coiling	Campi et al. (2007)	International	RCT	22	NA	NA	NA	NA	NA	NA	NA	9
	Chung et al. (2010)	South-Korea	Retrospective Case Series	29	48.1	44.8	3.5	NA	7	96.6	11.4	6
	Daou et al. (2016)	USA	Retrospective Case Series	111	50.5	73.9	2.7	NA	7	79.3	23	6
	Dorfer et al. (2012)	Austria	Retrospective Cohort Study	52	49.8	63.5	17.3	23.1	11.6	NA	9.4	6
	Gurian et al. (1995)	USA	Retrospective Case Series	21	55.8	90.5	19.1	0.0	18.1	57.1	NA	5
	Klein et al. (2008)	France	Retrospective Case Series	13	43.3	53.9	0.0	0.0	5.1	100.0	48.6	6
	Konig et al. (2007)	Germany	Retrospective Case Series	10	46	80.0	0.0	42.9	NA	60.0	14.3	5
	Lejeune et al. (2008)	France	Retrospective CS	21	NA	42.9	5.0	57.1	4.2	95.2	8.5	6
	Nakamura et al. (2013)	Germany	Retrospective Case Series	15	50.6	46.7	0.0	40.0	6.9	93.3	76.5	6
	Owen et al. (2015)	USA	Retrospective Cohort Study	73	49.0	79.4	23.3	58.9	NA	87.7	NA	6
	Romani et al. (2011)	Finland	Retrospective Case Series	82	47	65.4	31.2	NA	NA	74.4	NA	5
	Veznedaroglu et al. (2004)	USA	Retrospective Case Series	18	NA	NA	NA	NA	NA	NA	NA	5
	Wang et al. (2017)	China	Retrospective Case Series	19	51.3	47.4	10.5	73.7	6.5	84.2	25	6
	Zhang et al (2003)	USA	Retrospective Case Series	38	50.6	71.8	30.6	NA	14.2	60.5	NA	5
Coiling after coiling	Campi et al. (2007)	International	RCT	65	NA	NA	NA	NA	NA	NA	NA	9
	Dorfer et al. (2012)	Austria	Retrospective Cohort Study	75	50.8	36.0	42.6	46.6	11.9	NA	12.8	6
	Kang et al. (2006)	Korea	Retrospective Case Series	32	NA	NA	31.3	34.4	NA	NA	NA	6
	Teleb et al. (2014)	USA	Retrospective Case Series	111	53	58.6	23.4	NA	7	60.4	8	6
Coiling after surgery	Campi et al. (2007)	International	RCT	6	NA	NA	NA	NA	NA	NA	NA	9
	Hokari et al. (2016)	Japan	Retrospective Cohort Study	10	66.5	90.0	10.0	NA	7.1	90.0	15.3	5
	Li et al. (2013)	South-Korea	Retrospective Case Series	31	58.2	64.5	6.5	NA	NA	77.4	19	6
	Owen et al. (2015)	USA	Retrospective Cohort Study	4	45.5	NA	25.0	NA	NA	NA	NA	6
	Rabinstein et al. (2003)	USA	Retrospective Case Series	21	50.6	61.9	35.0	62.0	NA	61.9	90	6
	Kim et al. (2010)	Korea	Retrospective Case Series	24	51.8	54.2	0.0	58.3	NA	91.7	30.4	6
Surgery after surgery	Hokari et al. (2016)	Japan	Retrospective Cohort Study	13	62.9	23.1	0.0	NA	9.4	30.1	15.5	5
	Owen et al. (2015)	USA	Retrospective Cohort Study	20	53.7	NA	20.0	NA	NA	100.0	NA	6
	Drake et al. (1984)	Canada	Retrospective Case Series	88	NA	NA	63.1	39.1	NA	NA	NA	5
PED after surgery	Kuhn et al. (2017)	USA	Retrospective Case Series	6	NA	NA	33.3	66.6	NA	50.0	11.0	5
	Daou et al. (2015)	USA	Retrospective Case Series	32	53	75.0	10.0	NA	NA	51.5	27	6
PED after PED	Heiferman et al. (2017)	USA	Retrospective Case Series	25	51	72.0	NA	NA	NA	36.0	NA	5
	Fischer et al. (2011)	Germany	Retrospective Case Series	30	NA	66.0	NA	NA	NA	NA	NA	5
PED after coiling	Kuhn et al. (2017)	USA	Retrospective Case Series	18	NA	NA	50.0	NA	NA	38.8	26.0	5

Legend: Abbreviations: NOS: New-Castle Ottawa Scale for quality reporting of observational studies, reported on a scale of 0-9; NA: not available; USA: United States of America; PED: Pipeline embolization device.

Table 2.2: Outcomes by study

Intervention retreatment combination	Study	Complete occlusion (n/N (%))	Mortality occlusion (n/N (%))	Clinical outcome*			
				Before treatment		After treatment	
				Good	Bad	Good	Bad
Surgery after coiling	Campi et al. (2007)	NA	NA	19/22	3/21	17/22	5/22
	Chung et al. (2010)	NA	0/29 (0.0)	18/22	4/22	21/22	1/22
	Daou et al. (2016)	108/111 (97.3)	3/111 (2.7)	NA	NA	NA	NA
	Dorfer et al. (2012)	45/52 (86.5)	1/52 (1.9)	NA	NA	NA	NA
	Gurian et al. (1995)	NA	3/21 (14.3)	NA	NA	NA	NA
	Klein et al. (2008)	13/13 (100.0)	0/13 (0.0)	NA	NA	NA	NA
	Konig et al. (2007)	10/10 (100.0)	0/10 (0.0)	NA	NA	NA	NA
	Lejeune et al. (2008)	19/21 (90.5)	0/21 (0.0)	21/21	0/21	19/21	2/21
	Nakamura et al. (2013)	15/15 (100.0)	1/15 (6.7)	NA	NA	NA	NA
	Owen et al. (2015)	65/73 (89.0)	3/73 (4.1)	NA	NA	NA	NA
	Romani et al. (2011)	77/81 (95.1)	6/81 (7.4)	NA	NA	NA	NA
	Veznedaroglu et al. (2004)	15/18 (83.3)	NA	NA	NA	NA	NA
	Wang et al. (2017)	16/19 (84.2)	1/19 (5.3)	NA	NA	NA	NA
	Zhang et al (2003)	NA	3/38 (7.9)	NA	NA	NA	NA
Coiling after coiling	Campi et al. (2007)	NA	NA	53/65	12/65	52/65	13/65
	Dorfer et al. (2012)	50/75 (66.7)	0/75 (0.0)	NA	NA	NA	NA
	Kang et al. (2006)	11/32 (34.4)	0/32 (0.0)	NA	NA	NA	NA
	Teleb et al. (2014)	NA	0/111 (0.0)	NA	NA	NA	NA
Coiling after surgery	Campi et al. (2007)	NA	NA	6/6	0/6	4/6	1/6
	Hokari et al. (2016)	NA	0/10 (0.0)	9/10	1/10	8/10	2/10
	Li et al. (2013)	9/31 (29.0)	2/31 (6.5)	NA	NA	NA	NA
	Owen et al. (2015)	NA	0/4 (0.0)	NA	NA	NA	NA
	Rabinstein et al. (2003)	17/21 (81.0)	3/21 (14.3)	NA	NA	NA	NA
	Kim et al. (2010)	NA	NA	19/19	0/19	16/19	3/19
Surgery after surgery	Hokari et al. (2016)	NA	0/13 (0.0)	12/13	1/13	10/13	3/13
	Owen et al. (2015)	NA	2/20 (10.0)	NA	NA	NA	NA
	Drake et al. (1984)	102/115 (88.7)	6/115 (5.2)	NA	NA	NA	NA
PED after surgery	Kuhn et al. (2017)	3/6 (50.0)	0/6 (0.0)	5/6	1/6	5/6	1/6
	Daou et al. (2015)	23/32 (71.9)	0/32 (0.0)	NA	NA	NA	NA
PED after PED	Heiferman et al. (2017)	9/19 (47.4)	0/19 (0.0)	NA	NA	NA	NA
	Fischer et al. (2011)	20/30 (66.7)	0/30 (0.0)	86/88	2/88	81/88	7/88
PED after coiling	Kuhn et al. (2017)	8/11 (72.7)	0/14 (0.0)	17/18	1/18	17/18	1/18

Legend: *Good outcome was defined as a modified Rankin Scale (mRS) <3 or a Glasgow Outcome Scale (GOS)>4. Abbreviations: PED: Pipeline embolization device; NA: Not Available.

Complete occlusion

Complete occlusion rates varied considerably among the treatment retreatment combinations (**Table 2.2**).). Pooled prevalence rates for complete occlusion were 91.2% (95-% CI: 87.0-94.2) for surgery after coiling, 51.3% (95-% CI: 22.1-78.0) for coiling after coiling, 72.1% (95-% CI: 57.0- 83.3) for PED after coiling, 56.1% (95-% CI: 11.4 – 92.7) for coiling after surgery, and 58.2% (95-% CI: 39.0 – 75.2) for PED after PED, respectively (Random-effect model, **Figure 2.2**, **Table 2.4**). Fixed-effect models yielded similar results. It was not possible to calculate a prevalence rate for surgery after surgery as only one study was available for analysis, which reported a complete occlusion rate of 89%.[9]
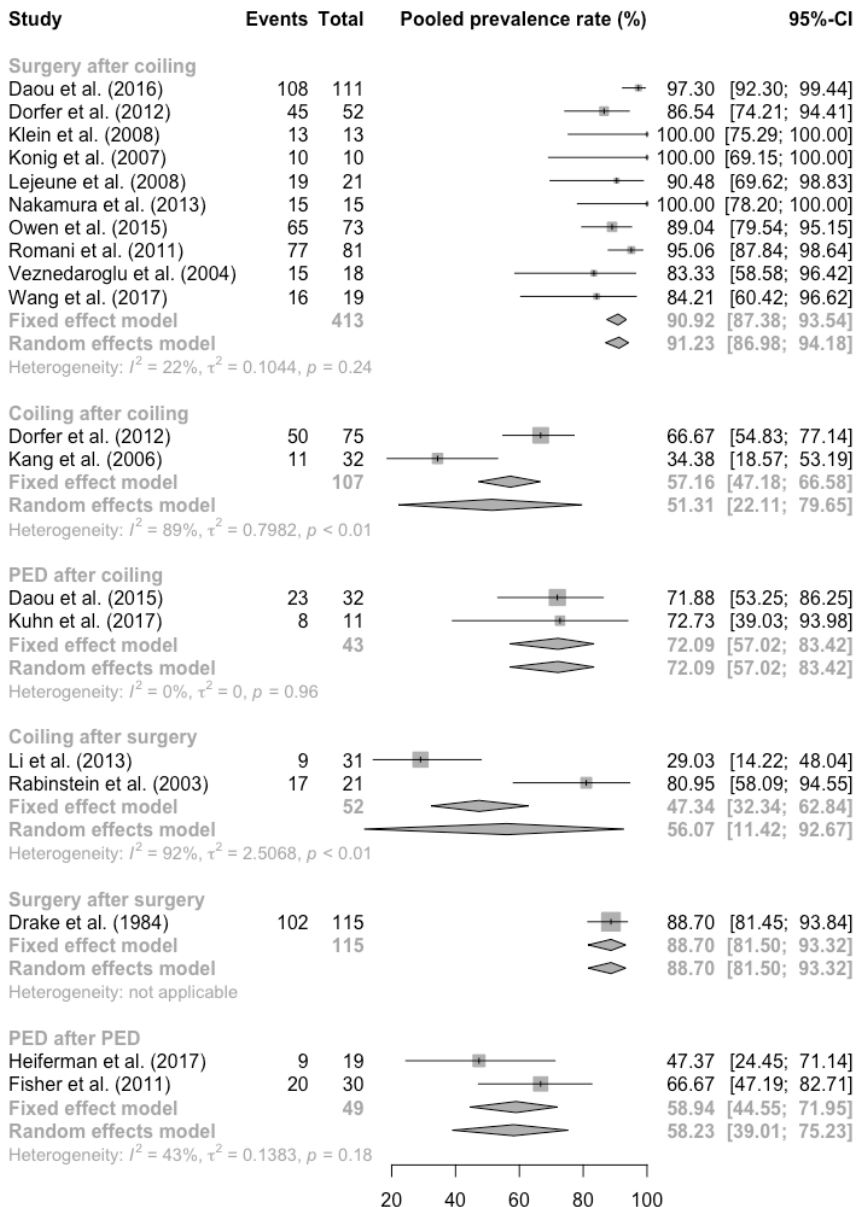
The treatment retreatment combinations coiling after coiling and coiling after surgery came with considerable heterogeneity (88.9% and 91.5%, respectively). No significant sources of heterogeneity were identified for surgery after coiling using meta-regression after correction for multiple testing. Meta-regression for other treatment and retreatment combination was not possible due to the low number of studies included in the analysis. It was only possible to evaluate publication bias in the surgery after coiling treatment retreatment combination, which was insignificant, as the other analysis had too few studies to evaluate publication bias.

Mortality

Similar to complete occlusion rates, the pooled prevalence rates of mortality varied considerably among the treatment retreatment combinations (**Table 2.2**). Pooled mortality rates for mortality were 5.6% (95-% CI: 3.7 - 8.3) for surgery after coiling, 0.8% (95-% CI: 0.15 - 3.7) for coiling after coiling, 2.2% (95-% CI: 0.3 - 14.3) for PED after coiling, 5.9% (95-% CI: 3.1 - 11.2) for surgery after surgery, 9.3 % (95-% CI: 4.1 - 19.9) for coiling after surgery, and 2.0% (95-% CI: 0.3 - 12.9) for PED after PED, respectively (Fixed-effect model, **Figure 2.3**, **Table 2.4**) SUPPP table 2. Fixed-effect models showed similar results. All the intervention retreatment combinations came with low heterogeneity (I^2 = 0.0% for all studies). With regard to publication bias, the pooled prevalence rate of mortality for surgery after coiling may be subject to publication bias (Egger's test p-value: 0.08). However, the Funnel plot indicated no publication bias (not shown), the trim and fill method yielded a similar pooled prevalence rate (pooled prevalence rate: 0.8%, 95%-CI: 0.2 – 3.7), and the Begg's test indicated no significant publication bias (p=0.12). It was not possible to evaluate publication bias for the surgery after surgery, PED after coiling, and PED after PED treatment retreatment combinations due to a low number of studies included in the analysis.

For surgery after coiling, only publication year was identified as a potential source of heterogeneity (estimate: -0.06, p-value: 0.04), but this association did not remain significant after correction for multiple testing. Meta-regression for other treatment retreatment combinations was not possible due to the low number of studies included in the analysis.

Figure 2.2: Forest plot of pooled prevalence rate of complete occlusion by treatment retreatment population.

Legend: Forest plot of pooled prevalence rate of complete occlusion by treatment retreatment group. Forest plot for prevalence rate of complete occlusion are shown by treatment and retreatment combination. Solid squares represent the point estimate of each study and the diamond represents the pooled estimate of the prevalence rate. The I² value for heterogeneity is shown.

Figure 2.3: Forest plot of pooled prevalence rate of mortality by treatment retreatment population.
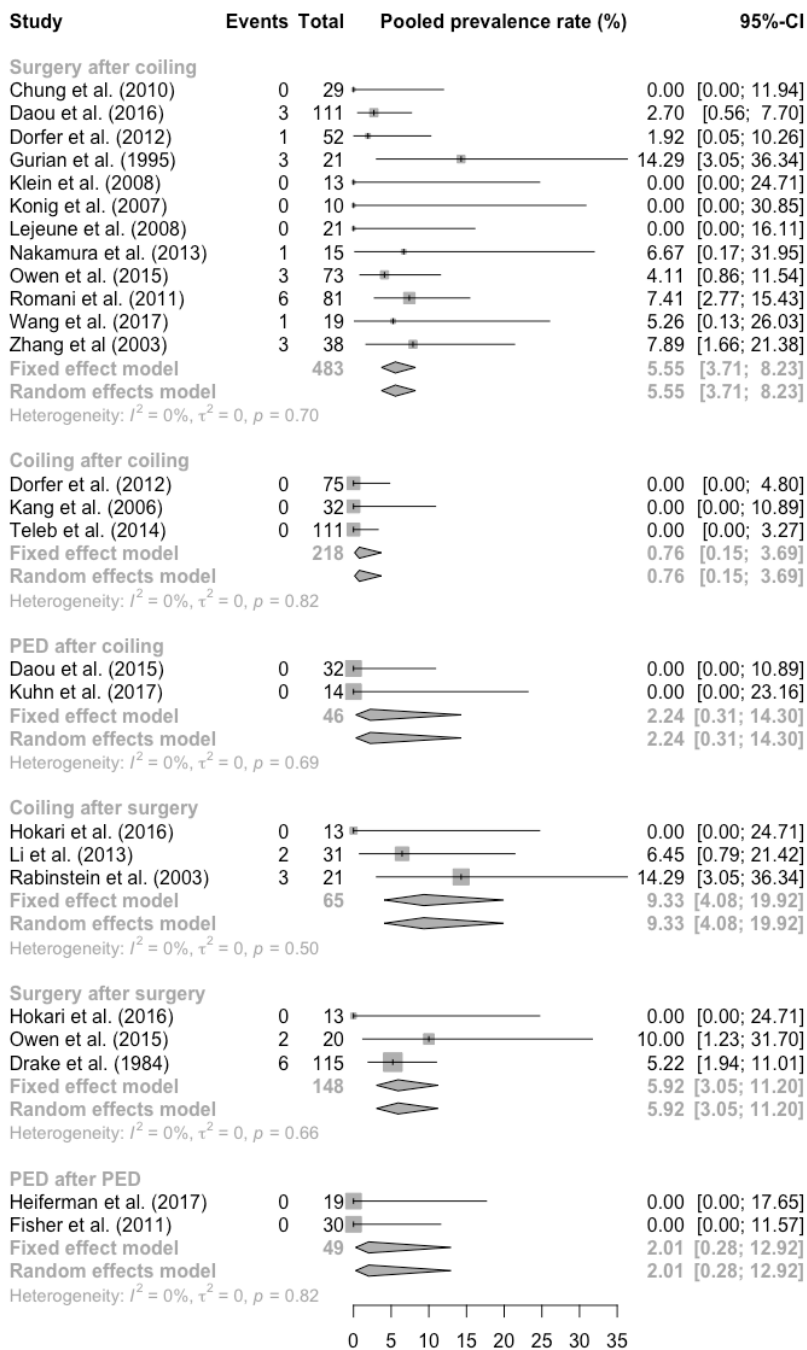
Legend: Forest plot of pooled prevalence rate of mortality by treatment retreatment group. Forest plot for prevalence rate for mortality are shown by treatment and retreatment combination. Solid squares represent the point estimate of each study and the diamond represents the pooled estimate of the prevalence rate. The I² value for heterogeneity is shown.

Functional outcomes

Contrary to the occlusion rates or mortality rates, the functional outcomes were not reported consistently (**Table 2.2**).[3,4,11,16,20,23,25] The clinical improvement or deterioration after the second intervention varied considerably among the treatment retreatment combinations. In general, no large differences were seen in functional outcome before and after intervention between the different treatment and retreatment combinations.

Discussion

This meta-analysis aimed to evaluate outcomes of retreatment of intracranial aneurysms. Overall, aneurysms retreated with surgery showed a high rate of complete occlusion. However, this came with a relatively high pooled prevalence rate of mortality. Contrarily, intracranial aneurysms retreated with coiling or a PED have a relative low complete occlusion rate, but also a low pooled prevalence rate of mortality. Functional outcomes were reported very infrequently and did not show a great variation between the different treatment retreatment combinations. The overall quality of the studies was low, as no prospective studies were available, except for the ISAT, which only reported functional outcomes.[3]

The occlusion rate for surgically retreated patients appears to be high based on the results of our meta-analysis. One other meta-analysis suggested an occlusion rate of 98.3%.[33] One systematic review evaluating outcomes of surgically treated aneurysms concluded an occlusion rate of 93%.[1] These outcomes are broadly similar to the findings in this meta-analysis. One series that evaluated outcomes of 2360 intracranial aneurysm patients, initially treated with endovascular approaches, found that 350 (12.3%) patients required endovascular retreatment and reported a complete occlusion rate of only 46.9% after the second session of coiling.[14] Furthermore, 94 patients required three or more coiling sessions with a complete occlusion rate of 35.6% (maximum of 9 sessions, n =1).[14] The potential necessity of multiple subsequent recoiling sessions may emphasize the need from complete initial occlusion of aneurysms. The latter study was not included in this meta-analysis as the initial endovascular treatment was preceded by various microsurgical procedures in some patients.[14] However, incomplete coiling is not the only factor associated with regrowth as increased total aneurysm size, packing density, older age, male sex, hypertension, and ruptured aneurysm have also been associated with aneurysm regrowth after coiling in retrospective analyses.[27,8,28]

The mortality rate seems to be high in patients that received surgical retreatment based on our meta-analysis. Another meta-analysis suggested that mortality may actually be 0 % (95%CI=0.0–2.5 %).[33] One other review reported a mortality prevalence of 3.6% for aneurysms that were surgically retreated after initial endovascular occlusion, which is similar to the findings in this meta-analysis.[1] One explanation for the mortality in surgically retreated patients rate may be the necessity of trapping, wrapping, ligation, or a bypass, which was necessary in 1.9%, 2.7%, 1.8%, and 2.1% of cases, respectively, which is largely similar to the findings of this study.[1] Another explanation may also be mortality due to non-procedural complications or presentation with a rebleed, as was seen in the cohort described by Romani et al.[35] One large series inves-

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tigating multiple recoiling sessions in 350 patients reported a morbidity rate of 2.2% and only had one mortality.[14] Coiling after surgery was associated with a relatively high mortality, but this was probably the result of rebleed related complications in the two studies that had mortalities.[34,26]

The high mortality and poor occlusion rates for surgical retreatment and endovascular retreatment respectively show the importance of treatment modality selection when patients initially present with intracranial aneurysms. Initial coiling may be preferable because of lower morbidity and less invasive nature if no additional retreatment is to be expected.[3] The necessity for retreatment after coiling is approximately three to four times higher than after microsurgical clipping based on two RCTs.[37,3] Therefore, patients that require surgery after coiling would probably not have needed a secondary procedure if surgery had been the primary treatment modality. Furthermore, recoiling may increase the size of the aneurysm with every additional placement of coils due to its low success rate. The difficulty of surgical treatment of previously coiled aneurysms probably increases after every recoiling session as the aneurysm increases in size. Similarly, the complete occlusion rate appears to go down with every subsequent recoiling procedure.[14] Although this does not seem to result in mortality for patients, rebleeding rates could be higher and patients may develop symptoms as the result of mass-effect from the aneurysm.[14,19,40] Currently, no prospective and comparative outcomes are known for retreated intracranial aneurysm and little is known on factors that contribute to regrowth.

This is the first meta-analysis that evaluated the outcomes of retreatment for intracranial aneurysms and was conducted in accordance with PRISMA guidelines.[29] This meta-analysis also evaluated all available intervention and retreatment combinations. However, this meta-analysis is limited by several factors. The available studies from the literature were of poor quality, based on the NOS-scale. All studies were retrospective in nature and generally had a small sample size and limited follow-up. There was little consistency with regard to reported outcomes as most studies only consistently reported mortality and complete occlusion rate which was why no meta-analysis was conducted for functional outcomes. The limited reporting on baseline characteristics and outcomes of specific subgroups such as patients that initially presented with a subarachnoid hemorrhage did not allow for further subgroup analyses. Authors were not contacted to provide the necessary information due to the great many studies that did not present this information. This especially holds serious implications for mortality as other unevaluated factors such as the number of patients presenting with a rebleed and non-procedure related complications may influence mortality. The number of studies could also be considered low for the respective treatment retreatment combinations (e.g. only two studies reporting on outcomes of coiling after coiling were included). This is partially the result of the inclusion criteria of a minimum of 10 patients per arm and that only outcomes of first retreatment were evaluated. There was also considerable heterogeneity among various outcomes for which it was often not possible to identify contributing factors due to a low number of studies and variation in reporting of base-line characteristics by meta-regression. No comparison was made between the different treatment and retreatment combinations with regard to outcomes because of indication bias. It was also not possible

to study the effect of timing of retreatment in relation to outcomes as timing was rarely reported. Meta-regression was also only applied for individual study characteristics and was often not possible due to the low number of studies and variation in reporting. Furthermore, none of the identified associations remained significant after correction for multiple testing. Findings of this meta-analysis were not validated in an existing prospective cohort.

Knowledge of the outcomes of retreatment could be expanded by prospective evaluation of outcomes. A potential trial design could be a prospective registry that evaluates outcomes of intracranial aneurysms irrespective of initial treatment. This could both provide insight into which aneurysms require retreatment on the long term, how the necessity of retreatment can be avoided, and what retreatment strategy results in superior outcomes. The outcomes of such a registry could also prediction model to aid clinical decision-making and improve outcomes of intracranial aneurysm patients.

Conclusion

Surgical retreatment of intracranial aneurysms may be associated with relatively high occlusion rates but also a relatively high mortality. Contrarily, secondary coiling may be associated with relatively lower mortality but also with low rates of complete occlusion. Outcomes of this meta-analysis should be interpreted with caution due to various limitations. Nevertheless, the outcomes from this meta-analysis could potentially stress the need for complete initial treatment of intracranial aneurysms to prevent the retreatment. The findings of this meta-analysis could also potentially strengthen the argument for opting to clip an intracranial aneurysm when initial coiling may not result in complete occlusion. Further knowledge on what contributes to regrowth of coiled aneurysm is needed to optimize initial treatment selection for individual patients.

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Table 2.3: Search syntax

PubMed:
("Intracranial Aneurysm"[Mesh] OR aneurysm[Title/Abstract] OR aneurysms[Title/Abstract]) **AND** ("Recurrence"[Mesh] OR recurrent[Title/Abstract] OR recurrence[Title/Abstract] OR recurring[Title/Abstract] OR retreatment*[Title/Abstract] OR "Treatment Failure"[Mesh] OR treatment failure*[Title/Abstract] OR residual[Title/Abstract] OR additional therap*[Title/Abstract] OR recanaliz*[Title/Abstract] OR recanalis*[Title/Abstract] OR regrow*[Title/Abstract]) **AND** (clip*[Title/Abstract] OR coil*[Title/Abstract] OR flow disrupt*[Title/Abstract] OR divert*[Title/Abstract] OR stent*[Title/Abstract] OR pipeline[Title/Abstract] OR embolization[Title/Abstract] OR "Embolization, Therapeutic"[MAJR] OR "Endovascular Procedures"[MAJR])
Embase
'intracranial aneurysm'/exp OR 'intracranial aneurysm' OR aneurysm:ab,ti OR aneurysms:ab,ti **AND** ('recurrent disease'/exp OR 'recurrent disease' OR recurrent:ab,ti OR recurrence:ab,ti OR recurring:ab,ti OR retreatment*:ab,ti OR 'retreatment'/exp OR 'retreatment' OR 'treatment failure'/exp OR 'treatment failure' OR 'treatment failure*':ab,ti OR residual:ab,ti OR 'additional therap*':ab,ti OR recanaliz*:ab,ti OR 'recanalization'/exp OR 'recanalization' OR recanalis*:ab,ti OR regrow*:ab,ti) **AND** (clip*:ab,ti OR coil*:ab,ti OR 'coil embolization'/exp OR 'coil embolization' OR 'artificial embolization'/exp OR 'artificial embolization' OR 'flow disrupt*':ab,ti OR 'arterial stent'/exp OR 'arterial stent' OR 'divert*':ab,ti OR 'stent*':ab,ti OR pipeline:ab,ti OR embolization:ab,ti OR 'endovascular surgery'/mj/exp OR 'endovascular surgery') **AND** [embase]/lim NOT [medline]/lim AND ([article]/lim OR [article in press]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)

Table 2.4: Outcomes of meta-analysis by outcome.

Outcome	Intervention retreatment combination	Model	Prevalence rate (%)	95%-CI	I-squared (%)	Q-Test for heterogeneity (p-value)	Egger's-test (p-value)	Begg's-test (p-value)
Complete occlusion	*Surgery after coiling*	FE	90.1	87.4-93.5	21.6	0.24	0.27	0.53
		RE	91.2	87.0-94.2				
	Coiling after coiling	FE	57.2	47.2-66.6	88.9	0.0026	NA	NA
		RE	51.3	22.1-78.0				
	PED after coiling	FE	72.1	57.0- 83.3	0.00	0.96	NA	NA
		RE	72.1	57.0- 83.3				
	*Surgery after surgery**	FE	NA	NA	NA	NA	NA	NA
		RE	NA	NA				
	Coiling after surgery	FE	47.3	32.3-62.8	91.5	0.0006	NA	NA
		RE	56.1	11.4- 92.7				
	PED after PED	FE	58.9	44.6-72.0	43.4	0.18	NA	NA
		RE	58.2	39.0-75.2				
Mortality	*Surgery after coiling*	FE	5.6	3.7-8.3	0.00	0.61	0.16	0.70
		RE	5.6	3.7-8.3				
	Coiling after coiling	FE	0.8	0.15-3.7	0.00	0.82	0.08	0.12
		RE	0.8	0.15-3.7				
	PED after coiling	FE	2.2	0.3-14.3	0.00	0.69	NA	NA
		RE	2.2	0.3-14.3				
	Surgery after surgery	FE	5.9	3.1-11.2	0.00	0.66	0.93	0.62
		RE	5.9	3.1-11.2				
	Coiling after surgery	FE	9.3	4.1-19.9	0.00	0.50	0.43	0.12
		RE	9.3	4.1-19.9				
	PED after PED	FE	2.0	0.3-12.9	0.00	0.82	NA	NA
		RE	2.0	0.3-12.9				