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Research Article

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Treatment of Unruptured Cerebral Artery Aneurysm: A Meta-Analysis

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Abstract: Unruptured middle cerebral artery (MCA) aneurysms can be treated using two techniques or procedures, microsurgical clipping and endovascular coiling. The aim of this meta-analysis study is to compare the safety and efficacy of microsurgical clipping with the endovascular coiling in the treatment of unruptured MCA aneurysms. We searched electronic databases (PubMed, EMBASE and the Cochrane library) to identify studies published between 1991 and 2019. For clipping and coiling techniques, separate meta-analyses were conducted on efficacy and safety after the intervention and at follow-up by using random- and fixed-effects models. Forty-one articles were included in our meta-analyses: 23 case series using clipping and 25 case series using coiling procedures. The complete aneurysm occlusion rate was higher in the clipping procedure (96.1%, 95% CI: 92.8%-97.9%) as compared to the coiling procedure (57.6%, 95% CI: 49.4 – 65.4%). Clipping procedure has a slightly higher rate of favorable functional outcomes (96.4%, 95% CI: 94.8 – 97.5%) compared to coiling procedure (94.8%, 95% CI: 93.1 – 96%). Interestingly, the rate of occlusion appears to decrease with time in the clipping group and increase with time in the coiling group, while the rate of favorable functional outcomes appears to increase with time in the clipping group and decrease with time in the coiling group. Publication bias was unlikely in all our analysis for studies assessing: coiling and occlusion rate, clipping and occlusion rate, coiling and functional outcomes, and clipping and functional outcomes. Microsurgical clipping yields a higher aneurysm occlusion rate, with slightly higher favorable functional outcomes in the treatment of unruptured MCA aneurysms than the endovascular coiling.

Keywords: Brain aneurysm; Middle cerebral artery; Endovascular coiling; Neurosurgical clipping; meta-analysis.

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1. INTRODUCTION

Intracranial aneurysm is a cerebral or brain weakening and bulging of an artery wall that results in a balloon or bulges out and fills with blood. The swelling outward can place pressure on the nerves or cerebral tissues. If intracranial aneurysm is ruptured, hemorrhage occurred in which blood spreads over the cerebral tissues. Unruptured middle cerebral artery (MCA) aneurysms can be treated using two techniques or procedures, microsurgical clipping and endovascular coiling. Microsurgical clipping is a surgery in which a small metal clip is used to obstruct the flow of blood into the aneurysm. While craniotomy is needed for microsurgical clipping, it is not the case with the endovascular coiling. Endovascular coiling is a minimally invasive technique in which a catheter is used to reach the intracranial aneurysm. Before 1991, clipping was the only treatment option for intracranial aneurysms. Microsurgical techniques have declined over the past 20 years. Aneurysm treatment strategy has changed since the development of the endovascular coiling technique. There is no clear scientific evidence supporting that endovascular coiling outcomes are superior to the microsurgical clipping.[1] recently, unruptured intracranial aneurysms (UIAs) have become easily recognized with the development of advanced cerebral imaging techniques. Different treatment options to treat patients with unruptured cerebral aneurysm include surgery, endovascular coiling, or no treatment. Previous studies reported that observation is a reasonable approach only in some patients with small UIAs that do not need treatment.[2,3] Because the risk of subarachnoid hemorrhage of untreated unruptured aneurysm is low, the risk of treatment either by surgical clipping or endovascular coiling should be low.[2,3] Recently, the management of UIAs with endovascular coiling has continuously increased in the United States. The advantages of endovascular coiling as compared to microsurgical clipping are the minimal invasion and the multiple, simultaneous treatments at disparate sites.[4,5]However, previously published articles that compared the two treatment options (clipping and coiling) demonstrated low complication rates, durable treatment, and better outcomes with surgical treatment.[6,7] Brinjikji et al. (2011) used the electronic medical records to investigate the outcomes with treatment by coiling relative to clipping of unruptured intracranial aneurysms in the US (2001-2008). The previous study reported that patients treated by clipping have a significantly higher percentage (14%) of discharge to long-term facilities compared to patients treated by coiling (4.9%) ($P < .0001$).[6] Since endovascular coiling is characterized by its inferior durability, it requires more follow-up imaging.[4,8] The recurrence rates and the need for re-treatment are higher for endovascular therapy as compared to microsurgical.[9,10] Surgical clipping was favorable for treating unruptured MCA aneurysms because it has unique characteristics such as the superficial location, the easy proximal control at the supraclinoid carotid, the familiar surgical approach, and the minimal perforator vessels. On the other hand, endovascular coiling is more difficult in MCA aneurysms due to difficulty in obtaining adequate working projection views, small parent vessels, and incorporation of branch vessels in the aneurysm.[11] Advances in endovascular techniques such as three-dimensional (3D) angiography makes the endovascular coiling a more favorable option than the microsurgical clipping.[12,13] There is an increase in using the endovascular treatment for unruptured MCA aneurysms without any significant evidence for superiority. Therefore, the aim of this meta-analysis study is to compare the safety and efficacy of surgical clipping and endovascular coiling in the treatment of unruptured MCA aneurysms.

2. MATERIALS AND METHODS

2.1 Literature Search

PubMed, EMBASE, and Cochrane databases were searched for relevant English studies published between 1991 and 2019 and evaluated the safety and/or efficacy of coiling or/and clipping for patients with unruptured MCA aneurysms. Our search strategy combined various terms for aneurysm (Intracranial Aneurysm, Middle Cerebral Artery Aneurysm, MCA, Unruptured Aneurysm, Brain Aneurysm, Cerebral Aneurysm), coil (Endovascular Procedures, Cerebral Angiography, Endovascular Coil, Coil, Endovascular Procedure, Intravascular Procedure, Intravascular Technique, Endovascular Technique, Cerebral Angiography), and clip (Microsurgery, Surgical Instruments, Neurosurgery, Surgical Clip, Clip, Tantalum Clip, Neurosurgical Procedure, Neurologic Surgical Procedure, Intracranial Pressure, Brain/surgery) by using exploded versions of medical subject headings terms and corresponding key words in titles and abstracts. Experts in the field were consulted to verify the search strategy and retrieve relevant articles. Literature was reviewed for all retrospective and prospective cohorts reporting angiographic occlusion and/or functional outcomes in adults with unruptured MCA aneurysm(s). All studies reporting either surgical clip or endovascular coil of unruptured intracranial aneurysms were considered for inclusion. Studies that were non-English, included only pediatric patients or ruptured intracranial aneurysms were excluded. The existing reviews were used for the snowballing process and to supplement the collection of articles retrieved from references of the most relevant studies. Full details on our search terms and strategy are shown in Appendix 1.Efficacy and safeties are the two types of outcomes that were used in this systematic review and meta-analysis. Post-operative complete angiographic aneurysm occlusion was used to measure efficacy outcomes. Functional status was used to evaluate the safety outcomes. There are two techniques used to evaluate postoperative functional status, the modified Rankin Scale (mRS) and the Glasgow Outcome Score (GOS). There are two versions of GOS either Glasgow Outcome Score (GOS) or extended Glasgow Outcome Scale (e-GOS) (Table 1).

2.2 Study Inclusion/Exclusion Criteria

Studies were considered for inclusion in our research if they met the following criteria: studies that treated adults with intracranial aneurysms, included separate data for unruptured MCA aneurysm(s), used either clipping or coiling, and reported on occlusion rates, patients' functional status, or both. We excluded case reports or studies that include unruptured MCA aneurysm(s) result for a fewer than 3 patients. Also, review articles, systematic reviews, and meta-analyses were excluded. In addition, studies that focused only on ruptured aneurysms were excluded. Reasons for exclusion are: ruptured aneurysms, no MCA aneurysm data, pediatric data only, and an inability to extract unruptured MCA aneurysm specific data (Figure1). Titles and abstracts of identified studies were screened, and potentially relevant articles were selected for full-text review.

2.3 Data Extraction

Two independent researchers extracted and tabulated all data from eligible studies. Discrepancies were resolved by consensus. A standardized data extraction form was designed, piloted, and modified accordingly prior to commencement of the formal extraction process. Information extracted included: study characteristics (first author, publication year, country of origin, trial duration, and study design), clipping or coiling assessment method (type of intervention, number of patients with unruptured MCA aneurysm who had the intervention, number of patient who had a complete angiographic occlusion, the time of assessment, number of patients who had a favorable outcome (mRS 0-3 or GOS 4-5 or e-GOS 6-8), and study quality. The Newcastle-Ottawa Scale was performed for all studies to assess the quality of the studies. Newcastle-Ottawa Scale is a tool used to assess the quality of cohort studies. The selection of exposed and unexposed participants, the assessment of the outcome, and the comparability of the groups are the three broad areas assessed by Newcastle-Ottawa Scale. Stars were awarded for high quality in each area. A maximum of four stars for the "selection category", three stars for "Outcome", and two stars for "comparability". Studies with a score ≥7 were considered as high quality and those with a score <5 were considered as low quality. Since all studies included in this meta-analysis are case-series (there is no comparator group), we modified the Newcastle-Ottawa Scale to assess the quality of studies.

2.4 Outcome measurement

First, Immediate Angiographic Outcome: angiographic results directly at the end of the procedure and during the first one month after the procedure. Second, Late Angiographic Follow-Up: angiographic follow-up results after one month from the procedure. Third, Immediate Functional Outcome: modified Rankin or Glasgow outcome scale result at the end of the procedure and during the first one month after the procedure. Finally, Late Functional Outcome: modified Rankin or Glasgow outcome scale follow-up result after one month from the procedure.

3. STATISTICAL ANALYSIS

All statistical analyses were conducted using Comprehensive Meta-Analysis (CAM) version 3. A total of four overall statistical analyses were conducted. They included: coil occlusion rate, clip occlusion rate, coil neurological outcomes, and clip neurological outcomes. Summary estimates were calculated by combining inverse variance–weighted study-specific estimates using random effects models. Fixed-effects models were also evaluated for comparison. Cochran's Q statistic and the I^2 statistic were reported for each forest plot to evaluate between-study heterogeneity. More than 50% I^2 is considered to be high heterogeneity. Potential sources of heterogeneity (including duration of follow up, location of the study, and study design) were explored by subgroup analysis. Meta-regression by quality of study was performed to assess the effect of quality on the results. To assess publication bias, we used a standard funnel plot as well as random effects Duval and Tweedie's trim and fill. Both the Egger's test and Begg's test were used for assessment of potential publication bias. A cumulative meta-analysis and analysis after removing one study (outlier) was performed.

4. RESULTS AND DISCUSSION

4.1 Study Selection

After removing all duplicate studies, we ended up with 7,934 studies for selection at stage 1, which included title and abstract review. In stage 1, two independent reviewers reviewed all title and abstract and they ended up with only 259 studies for full-manuscript review. At this stage, we reapplied the "snowballing" technique that added an additional 22 full-text articles. Forty-one studies were passed from the full-manuscript selection stage.[2, 12-51] Only a single reviewer extracted the data using our data collection sheet, and all 41 studies were included in the final analysis (Table 2). Figure 1 shows the number of studies that were excluded in each stage.

4.2 Study Design and Characteristics

Forty-one studies were included in the final analysis (Table 2). All studies were observational cohort studies investigated coiling or clipping for treatment of unruptured MCA aneurysms. Nine studies were conducted prospectively.[14,21,26,27,35,36,38,42,47] There were only five studies conducted in patients with unruptured MCA aneurysms.[17,18,21,29,36] Thirty-five studies conducted in either ruptured or intracranial aneurysms, but they reported result for unruptured MCA aneurysms. Seven studies include result for both groups; clipping and coiling.[15,21,23,25,26,28,29] Thirty-four studies include results for either coiling or clipping alone.[6,12-14,16-20,22,24,27,30-51] There were 18 studies investigated coiling and 16 studies investigated the clipping procedure. There were 25 studies[6,12-35] included in the final analysis for the coiling group (Table 3) and 23 studies[15,21,23,25,26,28,29,36-51] included in the final analysis for the clipping group (Table 4). Amongst the 25 studies investigated coiling, 5 were prospective.[14,21,26,27,35] There were 8 studies performed in North America, 13 performed in Europe and 4 in Asia. The quality scores range from 3 to 9 (Table 3). The number of aneurysms in each study ranged from 4 to 218 with duration of follow-up range from post-operative to 62 months (Table 3). Amongst the 23 studies investigated clipping, 6 were prospective.[21,26,36,38,42,47] There were 2 studies that were performed in North America, 15 in Europe and 6 in Asia. The quality scores range from 4 to 8 (Table 4). The number of aneurysms in each study ranged from 4 to 360 with duration of follow-up range from post-operative to 28 months (Table 4).

4.3 Outcomes

Characteristics of the studies included in the meta-analyses are shown in Table 3 and Table 4. A total of twenty-four studies analyzed complete aneurysmal occlusion. Occlusion was assessed in 8 studies investigated clipping and 20 studies investigated coiling. In all studies, evaluation of aneurysmal occlusion was performed post-operatively. There were 20 studies analyzing complete aneurysmal occlusion in the coil group. Three studies assessed the occlusion rate post-operative and at follow-up, more than 1 month post-operative. There were 19 studies investigated coiling occlusion post-operative and 4 studies investigated coiling occlusion at follow-up (Table 3). Eight studies analyzed complete aneurysmal occlusion in the clipping group. Only one study assessed the occlusion rate post-operative and at follow-up. There were 8 studies investigated clipping occlusion post-operative and 1 study examined coiling occlusion at follow-up (Table 4). There were 40 studies that assessed neurological outcomes after clipping and coiling. Neurological outcomes were assessed in 23 studies investigated clipping and 24 studies investigated coiling. There were 24 of 25 studies that reported neurological status after coiling. Nine studies used mRS, while 8 used GOS. There were 6 studies that reported neither, but provided sufficient information whereby a favorable or unfavorable outcome could be determined. Only one study reported the two techniques (clipping and coiling). Three studies assessed the clipping neurological outcomes rate post-operative and at follow-up. There were 20 studies investigated coiling neurological outcomes post-operative and 7 studies examining coiling neurological outcomes at follow-up (Table 3). Twenty-three studies assessed neurological status in the clipping group. mRS was used to assess the neurological outcomes in 12 studies while GOS was used in 7 studies. There were four studies that reported their results without mentioning the technique that they used. There were 13 studies examining clipping neurological outcomes post-operative and 10 studies examining clipping neurological outcomes at follow-up (Table 4).

4.3.1 CLIP Aneurysmal Occlusion

On the basis of data from eight studies, we found a positive association between clipping and complete aneurysm occlusion rate. The pooled estimate for complete aneurysm occlusion rate was 96.1% (95% CI: 92.8-97.9%) of clipped cases (Appendix 2). There was no different result from both the random-effects model and the fixed-effects model. There was no between-study heterogeneity (Q-value = 6.026, I^2 = 0%, P-heterogeneity = 0.644). Cumulative meta-analysis shows the initial occlusion rates with clipping of 98.5%, which decreased to 96.1% with time. Many experts favor surgical clipping for treating unruptured MCA aneurysm.[28, 46, 50] Our meta-analysis results show high percentages (96.1%–98.5%) for complete aneurysm occlusion rate of clipped cases. The high percentages in our study results are similar to that in previous studies. These studies reported aneurysm occlusion rates equal to 92%–100%.[42, 46, 50, 53, 54] The analyses were divided by duration of follow-up, post-operative and at follow-up, the occlusion rate for post-operative was 96.6% (95% CI: 93.4 – 98.2%) while the occlusion rate at follow-up was 87.5% (95% CI: 46.3 - 98.3%). Kadkhodayan et al. reported a 16-year single-center experience with 292 patients and 346 MCA aneurysms.[52] This previous study results show a similar complete occlusion rate (91.8 %) to the one presented in our meta-analysis (87.5%). Since there was only one study reported the result at follow-up, there was no between-study heterogeneity (Q-value = 0, I^2 = 0, P-heterogeneity = 1) and there was no between-study heterogeneity for post-operative studies (Q-value = 4.495, I^2 = 0, P-heterogeneity = 0.721; n = 8). Subgroup analysis was done. We divided the analysis by continent that hold the study, North America and Europe, and we found the occlusion rates of 93.3% (Q-value = 0.897, I^2 = 0, P-heterogeneity = 0.639; n = 3) in North America and 96.8% (Q-value = 4.134, I^2 = 0, P-heterogeneity = 0.530; n = 6) in Europe. Comparing the studies conducted in North America and studies in Europe, similar occlusion rates could be due to similar practices managing unruptured MCA aneurysms in both continents. Subgroup analysis by study design was done and we found that the occlusion rate was 96.4% (Q-value = 1.325, I^2 = 0, P-heterogeneity = 0.515; n = 3) for prospective studies and 95.9% (Q-value =4.666, I^2 = 0, P-heterogeneity = 0.458; n = 6) for retrospective studies. Having similar occlusion rates regardless of the study design (prospective or retrospective) suggested that study design is not a significant factor. All these factors (study location and study design) were not significant and suggested that they may not be sources of heterogeneity. Visual inspection of funnel plots along with Begg's test (P-value = 0.5) suggested that publication bias was unlikely in our analysis for studies assessing clipping and occlusion rate. The data was collected from many databases (PubMed, EMBASE and Cochrane databases) to identify studies published between 1991 and 2019. Meta-regression for quality of studies was not significant (P-value = 0.7851). Meta-regression suggested no change in occlusion rates with different scores of quality studies.

4.3.2 COIL Aneurysmal Occlusion

The association between the coiling and complete occlusion rates was positive. The pooled estimate for complete aneurysm occlusion rate was 57.6% (95% CI: 49.4 – 65.4%; random-effects model). Cumulative meta-analysis shows the initial occlusion rates with coiling of 15.4%, which increased to 57.6% with time. The results from the fixed-effects model 55.4% (95% CI: 51.7 – 58.9%) are different compared to the random-effects model due to high degree of heterogeneity between-study (Q-value =95.125, I^2 = 76.873, P-heterogeneity < 0.000) (Appendix 2). This meta-analysis has similar results to the ATENA study that reported coil complete occlusion rate of 63%.[55] Other previous studies reported lower coil complete occlusion rate.[21, 28] For example, Regli et al. reported coil complete occlusion rate of only 15% (2 out of 13 patients).[21] However, the sample size (number of the patients) is only 13. In addition, the patients in Regli et al. study were selected in the period from 1993 to 1997 suggesting that the study included outdated endovascular techniques Stratifying the analysis by duration of follow-up, the estimation was greater in studies that report results at follow-up 56.7% (Q-value =12.919, I^2 = 76.778, P-heterogeneity < 0.005; n = 4) compared with those that reported the results for post-operative 55.1% (Q-value =82.114, I^2 = 78.079, P-heterogeneity < 0.000; n = 19). The significant results suggest that duration of follow up may be a substantial source of heterogeneity Subgroup analysis by continent was done; the estimation was greater in Asian studies 61% (Q-value =6.465, I^2 = 69.062, P-heterogeneity < 0.039; n = 3) comported to European studies 56.2% (Q-value =52.859, I^2 = 79.19, P-heterogeneity < 0.000; n = 12) and North American studies 50.3% (Q-value =31.233, I^2 = 77.588, P-heterogeneity < 0.000; n = 8). Also, we stratified the analysis by study design and we found that the estimation was greater in prospective studies 56.4% (Q-value =11.79, I^2 = 83.036, P-heterogeneity < 0.003; n = 3) compared to retrospective studies 55.3% (Q-value =83.315, I^2 =77.195, P-heterogeneity < 0.000; n = 20). The significant results suggest that location of study may be a substantial source of heterogeneity. Visual inspection of funnel plots along with Begg's test (P-value = 0.11732) suggested that publication bias was unlikely in our analysis for studies assessing coiling and occlusion rate. Meta-regression for quality of studies was not significant (P-value = 0.0758). Meta-regression suggested no change in occlusion rates with different scores of quality studies.

4.3.3 CLIP Neurological Outcomes

The analysis suggested that clipping is associated with favorable postoperative neurological outcomes. The pooled estimate for post-operative neurological outcome was 96.4% (95% CI: 94.8 – 97.5%; random-effects model) of clipped cases (Appendix 3). Result from the fixed-effects model 96% (95% CI: 94.9 – 96.9%) different from the random-effects model and it was not significant (Q-value =37.307, I^2 =38.349, P-heterogeneity < 0.030) suggested that there was a slight heterogeneity between-study. Cumulative meta-analysis shows the initial favorable postoperative neurological outcome with clipping was 95.7%, which increased to 96% with time. Our meta-analysis results show a high percentage for favorable postoperative neurological outcome of clipped cases. This high percentage in our study results are similar and support the results of previous studies.[42,46,50,53,54] For example, Rodriguez-Hernandez et al. investigated 631 MCA aneurysms and reported 93% favorable neurological outcome of clipped cases.[46] However, even previous studies[42,46,50,53,54] reported high percentages for favorable neurological outcome of clipped cases, there was low long-term complications and low retreatment rates in clipping.[46,50]When we stratified the analysis by duration of follow-up, post-operative and at follow-up, the favorable postoperative neurological outcome was 95.2% (95% CI: 93.4 – 96.5%; Q-value =23.453, I^2 = 44.569, P-heterogeneity < 0.037; n = 14) while the favorable neurological outcome at follow-up was 97.1% (95% CI: 95.5 – 98.1%; Q-value =10.516, I^2 = 14.414, P-heterogeneity < 0.310; n = 10). This result suggested that there was significant between-study heterogeneity for studies that reported the result at follow-up. We divided the analysis by continent and we found that the favorable postoperative neurological outcome was 98.6% (95% CI: 97.1 – 99.3%; Q-value =1.269, I^2 = 21.191, P-heterogeneity < 0.26; n = 2) in Asian studies, 95.6% (95% CI: 93.6 – 97%; Q-value =21.094, I^2 = 33.63, P-heterogeneity < 0.099; n = 15) in European studies and 95.1% (95% CI: 92.8 – 96.7%; Q-value =5.676, I^2 =0, P-heterogeneity < 0.46; n = 7) in North America. Since the result was not significant, this factor (study location) may not be a substantial source of heterogeneity. Subgroup analysis by study design was done and we found that the favorable postoperative neurological outcome was 97.7% (95% CI: 95.6 – 98.8%; Q-value =3.808, I^2 =0, P-heterogeneity < 0.577; n = 6) for prospective studies and 95.6% (95% CI: 94.2 – 96.7%; Q-value =30.300, I^2 =43.894, P-heterogeneity < 0.024; n = 18) for retrospective studies. This result suggested that there was significant between-study heterogeneity for studies that were conducted retrospectively. Visual inspection of funnel plots along with Begg's test (P-value = 0.47034) suggested that publication bias was unlikely in our analysis for studies assessing clipping and neurological outcome. Meta-regression for quality of studies was not significant (P-value = 0.4955). Meta-regression suggested no change in good neurologic outcomes with different scores of quality studies.

4.3.4 COIL Neurological Outcomes

On the basis of data from twenty-eight studies, we found a positive association between coiling and neurological outcome. The pooled estimate for favorable postoperative neurological outcome was 94.8% (95% CI: 93.1 – 96%) of coiled cases (Appendix 3). There was no different result from both the random-effects model and the fixed-effects model. There was no between-study heterogeneity (Q-value = 26.384, I^2 = 0%, P-heterogeneity = 0.497). Cumulative meta-analysis shows the initial favorable postoperative neurological outcome with coiling was 96.4%, which decreased to 94.8% with time. Multiple previous studies reported similar results.[12,30,33] Iijima et al. evaluated coiling neurological outcomes in 77 unruptured MCA aneurysms and reported that coiling can be successfully done without neurologic deficit outcomes.[30] In addition, Mortimer et al. and Doerfler et al. stated that coiling has an acceptable safety profile with low rates of negative neurological outcomes.[12,33]Stratifying the analysis by duration of follow-up suggested that the estimation was greater in studies that report results at follow-up 96% (95% CI: 91.8 – 98.1%; Q-value =2.554, I^2 = 0, P-heterogeneity < 0.862; n = 7) compared with those that reported the results for post-operative 94.5% (95% CI: 92.7 – 96%; Q-value =23.233, I^2 = 13.917, P-heterogeneity < 0.277; n = 21). Subgroup analysis by continent was done; the estimation was greater in Asian studies 98.2% (95% CI: 95.3 – 99.3%; Q-value =0.889, I^2 =0, P-heterogeneity < 0.828; n = 4) comported to North American studies 96.5% (95% CI: 93.5 – 98.1%; Q-value =8.197, I^2 =2.4, P-heterogeneity < 0.414; n = 9) and European studies 93.4% (95% CI: 90.8 – 95.2%; Q-value =8.866, I^2 =0, P-heterogeneity < 0.84; n = 15). We stratified the analysis by study design and we found that the estimation was greater in retrospective studies 95.9% (95% CI: 94.1 – 97.1%; Q-value =18.827, I^2 =0, P-heterogeneity < 0.656; n = 23) compared to prospective studies 92.6% (95% CI: 88.7– 95.2%; Q-value =3.344, I^2 =0, P-heterogeneity < 0.502; n = 5). All factors (duration of follow-up, study location, and study design) were not significant and suggested that they may not be sources of heterogeneity. Visual inspection of funnel plots along with Begg's test (P-value = 0.42944) suggested that publication bias was unlikely in our analysis for studies assessing coiling and neurological outcome. Meta-regression for quality of studies was not significant (P-value = 0.2981). Meta-regression suggested no change in favorable postoperative neurological outcome with different scores of quality studies.

Table 1. Modified Rankin Score and Glasgow Outcome Score

Modified Rankin Scale (mRS)*	Glasgow Outcome Scale (GOS)*	Extended Glasgow Outcome Scale (GOSE)*
0. No symptoms at all 1. No significant disability despite symptoms; able to carry out all usual duties and activities 2. Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 3. Moderate disability; requiring some help, but able to walk without assistance	1. Dead 2. Vegetative State (meaning the patient is unresponsive, but alive; a "vegetable" in lay language) 3. Severely Disabled (conscious but the patient requires others for daily support due to disability)	1. Death D 2. Vegetative state VS 3. Lower severe disability SD – 4. Upper severe disability SD + 5. Lower moderate disability MD -
4. Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 5. Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6. Dead	4. Moderately Disabled (the patient is independent but disabled) 5. Good Recovery (the patient has resumed most normal activities but may have minor residual problems)	6. Upper moderate disability MD + 7. Lower good recovery GR – 8. Upper good recovery GR +

****GOS 4-5 ~ mRS 0-3~ GOS-E 6-8***

Table 2. All studies included in the meta-analysis

Author Year Country	Type of Cohort Study	Intervention (Clip or Coil)	Number of Patients with Unrupture d MCA and COIL	Number of Patients with Unruptured MCA and CLIP	Enrollment period	North American (N), Europe (E), Asia (A)	Study includes data on Coil and Clip Patients	Newcastle-Ottawa Quality Scale # of stars
Raftopoulos,2003 [14] Belgium	Prosp	Coil	12	N	1996-2001	E	N	4
Doerfle, 2006 [12] Germany	Retro	Coil	16	N	2000-2004	E	N	8
Quadros, 2007 [15] France	Retro	Coil and Clip	22	4	2001-2006	E	Y	6
Oishi, 2009 [16] Japan	Retro	Coil	45	N	2001-2007	A	N	6
Suzuki, 2009 [17] USA	Retro	Coil	67	N	1990-1997	N	N	3
Bracard, 2010 [13] France	Retro	Coil	79	N	1992-2001	E	N	6
Kim, 2011 [18] Korea	Retro	Coil	70	N	2000-2009	A	N	7
Guglielmi, 2008 [19] USA	Retro	Coil	61	N	unknown	N	N	5*
Brinjiki, 2011 [6] USA	Retro	Coil	26	N	2002-2009	N	N	4
Horowitz, 2006 [20] USA	Retro	Coil	10	N	1999-2005	N	N	6
Regli, 1999 [21] Switzerland	Prosp	Coil and Clip	13	32	1993-1997	E	Y	3
Lubicz, 2006 [22] Belgium	Retro	Coil	19	N	2004-2005	E	N	4
Niskanen, 2005 [23] Finland	Retro	Coil and Clip	12	82	1997-2000	E	Y	6
Im, 2009 [24] Korea	Retro	Coil	46	N	2002-2006	A	N	4
Kim, 2010 [25] Korea	Retro	Coil and Clip	85	360	2006	A	Y	4
Guresir, 2011 [26] Germany	Prosp	Coil and Clip	21	108	1999-2009	E	Y	5
Pierot, 2008[27] France	Prosp	Coil	218	N	2005-2006	E	N	8

Diaz, 2012 [28] USA	Retro	Coil and Clip	71	25	2005 - 2010	N	Y	8
Dammann, 2014 [29] Germany	Retro	Coil and Clip	16	87	2006 - 2010	E	Y	6
Iijima, 2005[30] France	Retro	Coil	77	N	1998-2002	E	N	6
Wanke, 200[31] USA	Retro	Coil	4	N	1997–2000	N	N	5
Vendrell, 2009 [32] France	Retro	Coil	72	N	1999-2006	E	N	3
Mortimer, 2014 [33] USA	Retro	Coil	56	N	1996-2012	N	N	9
Eboli, 2014[34] USA	Retro	Coil	113	N	2000-2013	N	N	7
Fiehler, 2008[35] Germany	Prosp	Coil	13	N	2006	E	N	7
Regli, 2002 [36] Switzerland	Prosp	Clip	N	36	1997-2000	E	N	4
Moroi, 2005[37] Japan	Retro	Clip	N	201	1993-2000	A	N	7
Gerlach, 2007 [38] Germany	Prosp	Clip	N	35	1999-2005	E	N	4
Deruty, 1996[39] France	Retro	Clip	N	29	1990-1995	E	N	5
Nussbaum 2006 [40] USA	Retro	Clip	N	169	1997-2005	N	N	5
Aghakhani, 2008 [41] Belgium	Retro	Clip	N	117	1996-2006	E	N	8
Morgan, 2010 [42] Australia	Prosp	Clip	N	263	1989-2009	E	N	8
Nanda, 2002 [43] USA	Retro	Clip	N	18	1995-2001	N	N	8
Grigorian, 2003 [44] USA	Retro	Clip	N	101	1988-1999	N	N	5
Horn, 2004 [45] Norway	Retro	Clip	N	23	1988-1998	E	N	6
van Dijk, 2011 [46] etherlands	Retro	Clip	N	19	2001-2006	E	N	7
Haug, 2009[47] Norway	Prosp	Clip	N	15	2003-2005	E	N	7
Seule, 2012 [48] Switzerland	Retro	Clip	N	24	1999-2009	E	N	5
Ogilvy, 1995 [49] USA	Retro	Clip	N	46	1985-1989	N	N	5
Rodrıguez-Herna´nde, 2012 [50] USA	Retro	Clip	N	216	1997-2010	N	N	6
Calvacante, 2013 [51] France	Retro	Clip	N	7	1990-2011	E	N	6

Table 3. Systematic Review of Coil Efficacy and Safety (n = 25)

Author, Year	Country	Cohort Study Des	Years of study	Only MCA (Y/N)	Only un-ruptured (Y/N)	N Coiled =1244	# complete occlusion	Timing of assessment of Occlusion	Modified Rankin score (mRS) or Glasgow Outcome Scale (GOS) Details mRS 0-3 favorable GOS 4-5 favorable	Favorable Neuro-outcome with denominator of # patients	Timing of assessment of mRS or GOS
Raftopoulos, 2003[14]	Belgium	Prosp	1996-2001	N	Y	12	5 of 12	Post-op	GOS 4,5: 10 GOS: 1-3: 2	10 of 12	Discharge
Doerfler, 2006[12]	Germany	Retro	2000-2004	Y	N	16	10 of 16	Post-op	GOS: 13 GR,3MD	16 of 16	30 days
							11 of 16	6 month	GOS: 13 GR, 1 MD, 1 D, 1 lost to F/U	14 of 15	6 months
Quadros, 2007 [15]	France	Retro	2001-2006	Y	N	22	9 of 22	Post-op	mRS 1.0 ± 1.66, 14 patients had mRS: 0 2 patient had mRS: 1	20 of 22	Discharge
							8 of 22	12 month		20 of 22	30 days

									2 patient had mRS: 2 2 patient had mRS: 3 1 patient had mRS: 4 1 patient had mRS: 6 GOS: 15 GR, 4 MD, 3 SD, 0 D		
Oishi, 2009 [16]	Tokyo	Retro	2001-2007	Y	N	45	28 of 45*	Post-op	GOS: 44 GR, 1MD (Stroke)	45 of 45	Discharge
Suzuki, 2009 [17]	USA	Retro	1990-1997	Y	Y	67	31 of 67*	Post-op	mRS 1.19/ 0.28 51 patient had mRS:0 13 patient had mRS:1 2 patient had mRS: 2 1 patient had mRS: 3	67 of 67	Post-Op
									52 patient had mRS:0 8 patient had mRS: 1 2 patient had mRS: 2 1 patient had mRS: 6	62 of 63	16 months
Bracard, 2010 [13]	France	Retro	1992-2001	Y	N	79	25 of 79	Post-op	GOS: 61 GR, 5 MD, 1D	66 of 67	Discharge
Kim, 2011 [18]	Korea	Retro	2000-2009	Y	Y	76	40 of 76	Post-op	61 patient had mRS: 0 7 patient had mRS: 1 or 2 2 patient died (76 aneurysm in 70 pts)	68 of 70	Discharge
Guglielmi, 2008 [19]	USA	Retro	< 2000	Y	N	61	28 of 61	Post-op	Morbidity 9% Mortality 2%	NA	Discharge
Brinjikji, 2011 [6]	USA	Retro	2002-2009	Y	N	32 (in 26 pts)	7 of 32*	Post-op	26: excellent/good	26 of 26	Post-op
Horowitz, 2006 [20]	USA	Retro	1999-2005	Y	N	10	8 of 10*	Post-op	10 patient had mRS: 0, 1	10 of 10	Post-Op
Regli , 1999 [21]	Switzerland	Prosp	1993-1997	Y	Y	13	2 of 13	Post-op	12: excellent/good 1: fair 0: poor	13 of 13	Post-op
Lubicz, 2006 [22]	Belgium	Retro	2004-2005	Y	N	19	11 of 19*	Post-op	19 patient had mRS: 0,1	19 of 19	Post-op
Niskanen, 2005 [23]	Finland	Retro	1997-2000	N	Y	12	NA	NA	11 patient had GOS: 4-5 1 patient had GOS: 1	11/12	1 year
Im, 2009[24]	Korea	Retro	2002-2006	N	Y	46	35 of 46	Post-op	45 patient had mRS: 0-1 1 patient had mRS: 2	46 of 46	Discharge
Kim, 2010 [25]	Korea	Retro	2006	N	Y	85	NA	NA	84 patient had mRS: 0-1 1 patient had mRS: > 3	84 of 85	1 month
Guresir, 2011 [26]	Germany	Prosp	1999-2009	Y	N	21	NA	NA	mRS 1 + 0.8, 20 patient had favorable	20 of 21	6 months

									outcomes: (0-2 score) 1 patient had permanent deficit		
Pierot, 2008 [27]	France	Prosp	2005-2006	N	Y	218	NA	NA	The treatment failed in 14 patients	204 of 218	Post-op
Diaz, 2012[28]	USA	Retro	2005-2010	Y	N	40	10 of 40	Post-op	5 patient had mRS; 3-6	35 of 40	6 months
							35 of 40	Up to 62 months			
Dammann, 2014 [29]	Germany	Retro	2006-2010	Y	Y	16	12 of 16	Post-op	13 patient had GOS: 5 1 patient had GOS: 4 2 patient had GOS: 3	14 of 16	Discharge
									14 patient had GOS: 5 1 patient had GOS: 4 1 patient had GOS: 3	15 of 16	12 months
Iijima, 2005 [30]	France	Retro	1998-2002	Y	N	77	59 of 77*	Post-op	2/77 permanent disability 1/77 dead No info on mRS or GOS	74 of 77	Discharge
Wanke, 2002 [31]	USA	Retro	1997–2000	N	Y	4	4 of 4	Post-Op	NA	4 of 4	Post-Op
Vendrell, 2009 [32]	France	Retro	1999-2006	Y	N	72	47 of 72	Post-Op	40 patient had GOS: 5 4 patient had GOS: 4 3 patient had GOS: 3	44 of 47	Post-Op
Mortimer, 2014 [33]	USA	Retro	1996-2012	Y	N	56	29 of 56	3 - 6 month	1of 53 patients died and he was the only patient who experienced a permanent change in neurologic status	52 of 53	3 - 6 month
Eboli, 2014 [34]	USA	Retro	200-2013	Y	N	113	NA	NA	Stroke 3/113	110 of 113	Post-Op
Fiehler, 2008 [35]	Germany	Prosp	2006	N	N	32	24 of 32	Discharge	2 patient had mRS > 1	11 of 13	Discharge

Table 4. Systematic Review of Clip Efficacy and Safety (n = 23)

Author, Year	Country	Cohort Study Des	Years of study	Only MCA (Y/N)	Only un-ruptured (Y/N)	N Clip =2138	# complete occlusion	Timing of assessment of Occlusion	Modified Rankin score (mRS) or Glasgow Outcome Scale (GOS) Details mRS 0-3 favorable GOS 4-5 favorable	Favorable Neuro-outcome with denominator of # patients	Timing of assessment of mRS or GOS
Regli, 1999 [21]	Switzerland	Prosp	1993-1997	Y	Y	32	32 of 32	Post-op	GOS 4.8 28 good 1 fair 1 poor	29 of 30	Post-op
Regli, 2002 [36]	Switzerland	Prosp	1997-2000	Y	Y	36	36 of 36	Post-op	36 patient had mRS: 0-3	36 of 36	Post-Op
Moroi, 2005 [37]	Japan	Retro	1993-2000	N	Y	201	NA	NA	2 of 201 had mRS >2 (1 with permanent deficit and 1 with temporary hemiparesis) Only 1 patient with a permanent disability (used GOS), 1 had a temporary non-disabling deficit	200 of 201	Discharge
Quadros 2007 [15]	France	Retro	2001-2006	Y	N	4	4 of 4*	Post-Op	2 patient had mRS 0 1 patient had mRS 1 1 patient had mRS 2	4 of 4	Discharge
Ogilvy, 1995 [49]	USA	Retro	1985-1989	Y	N	46	NA	NA	44 patient with good/fair outcome 1 dead 1 with permanent	44 of 46	Long-term

									disability		
Gerlach, 2007 [38]	Germany	Prosp	1999-2005	N	Y	35	33 of 35	Post-op	34 patients had mRS 0-3 1 patient had mRS 4	34 of 35	Discharge
Deruty, 1996 [39]	France	Retro	1990-1995	N	Y	29	NA	NA	28 patients had mRS: 0-3 1 patient had mRS: >3	28 of 29*	Discharge
Niskanen, 2005 [23]	Finland	Retro	1997-2000	N	Y	82	NA	NA	79 patients had GOS: 4,5 3 patients had GOS: 3	79/83	1 year
Nussbaum 2006 [40]	USA	Retro	1997-2005	N	Y	169	NA	NA	168 patients had GOS: 4,5 1 patients had GOS: 3	168 of 169	6 months
Aghakhan, 2008 [41]	Belgium	Retro	1996-2006	N	Y	117	117 of 117	Post-op	114* patients had mRS: 0 3 patients had mRS: 1	117 of 117	3 months
Kim, 2010 [25]	Korea	Retro	2006	N	Y	360	NA	NA	354* patients had mRS: 0-2 6 patients had mRS: > 3	354 of 360	1 month
Rodrıguez-Herna´ndez, 2012 [50]	USA	Retro	1997-2010	Y	N	261	NA	NA	136 patients had mRS 0 73 patients had mRS 1 31 patients had mRS 2 7 patients had mRS 3	247 of 261	Post-Op
Calvacante 2013 [51]	France	Retro	1990-2011	Y	N	7	NA	NA	2 patients had mRS 0 1 patients had mRS 1 3 patients had mRS 2	6 of 7	Post-Op
Guresir, 2011 [26]	Germany	Prosp	1999-2009	Y	N	108	NA	NA	mRS 1 + 0.8 104 favorable (0-2 score) 4 with permanent	104 of 108	6 months

									disability		
Grigorian, 2003 [44]	USA	Retro	1988-1999	N	Y	101	NA	NA	86/92 patients comprised the expected outcome	86 of 92	Discharge
Diaz, 2012[28]	USA	Retro	2005-2010	Y	N	25	16 of 25	Post-OP	0 patient had mRS; 3-6	25 of 25	6 months
							23 0f 25	Up to 28 month			
Morgan, 2010 [42]	Australia	Prosp	1989-2009	Y	N	339 (in 263 patients)	NA	NA	250 patients had mRS: 0 or 1 9 patient had mRS: 2 3 patient had mRS: 3 1 patient had mRS: 4 1 patient had mRS: 6	261 of 263	Discharge
Dammann, 2014 [29]	Germany	Retro	2006-2010	Y	Y	87	84 of 87	Post-OP	75 patient had GOS: 5 9 patient had GOS: 4 3 patient had GOS: 3	84 of 87	Discharge
									80 patient had GOS: 5 6 patient had GOS: 4 1 patient had GOS: 3	86 of 87	12 months
Horn, 2004 [45]	Norway	Retro	1988-1998	N	Y	23	NA	NA	4 patient had GOS-E score: 3-5	19 of 23	Post-Op
van Dijk, 2011 [46]	Netherlands	Retro	2001-2006	Y	N	19	NA	NA	All 19 patients had a good outcome (mRS 0–2).	19 of 19	1 year
Nanda, 2002 [43]	USA	Retro	1995-2001	N	Y	18	18 of 18	Post-OP	16 patient had GOS: 5 2 patient had GOS: 4	18 of 18	Discharge
Haug, 2009 [47]	Norway	Prosp	2003-2005	Y	N	15	NA	NA	8 patient had mRS 0 5 patient had	15 of 15	3 months

									mRS 1 2 patient had mRS 2		
									9 patient had mRS 0 2 patient had mRS1 4 patient had mRS 2	15 of 15	12 months
Seule, 2012 [48]	Switzerland	Retro	1999- 2009	N	Y	24	NA	NA	2 patients had poor outcome	22 of 24	6 weeks

GOS (Glasgow Outcome Scale): 5 GR (good recovery),4 MD (moderate disability),3 SD (severe disability),2 PG (persistent vegetative),1 D (dead)

**** indicates a value that was derived from a % in the manuscript***

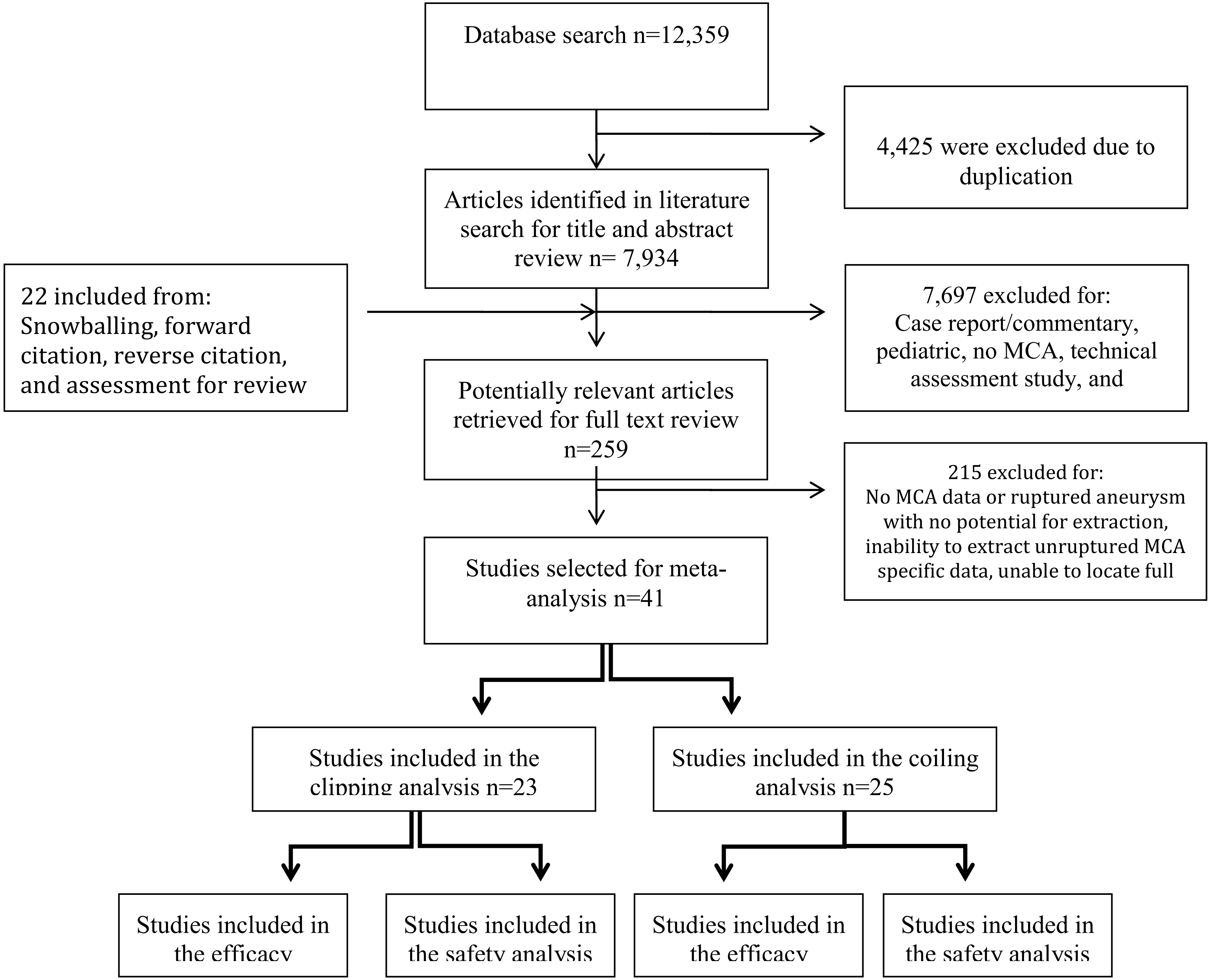


FIG 1: Flow chart detailing the process of determining eligible trial for inclusion in meta-analysis

Appendix 1,

Search Strategies

The online database PubMed_was used to perform a search of the literature between 1991 and January Week 4 2019. The following search terms were used:

Restricted search

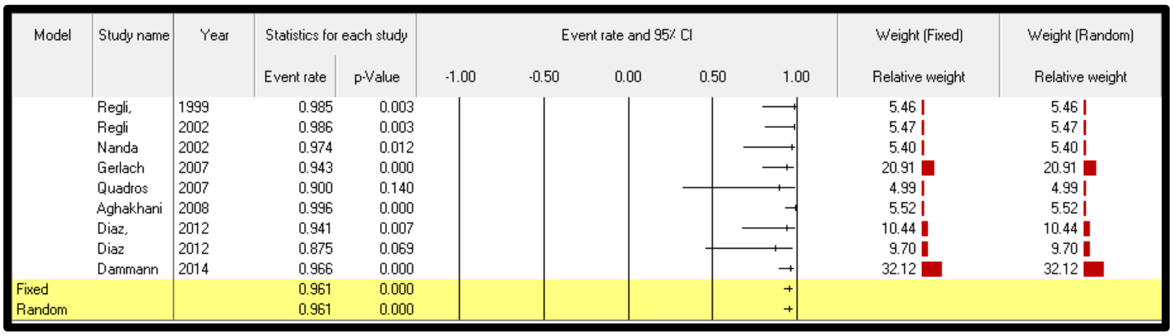
("Intracranial Aneurysm"[Mesh] "Middle Cerebral Artery"[Mesh] OR Intracranial Aneurysm*[tw] OR Middle Cerebral Artery Aneurysm*[tw] OR MCA[tw] OR Unruptured Aneurysm*[tw] OR Unruptured Intracranial Aneurysm*[tw] OR UIA*[tw] OR unruptured MCA[tw] OR Brain Aneurysm[tw] OR Cerebral Aneurysm* [tw]) AND ("Endovascular Procedures"[Mesh] OR "Cerebral Angiography"[Mesh] OR Endovascular Coil*[tw] OR Coil*[tw] OR Endovascular Procedure[tw] OR Intravascular Procedure*[tw] OR Intravascular Technique*[tw] OR Endovascular Technique*[tw] OR Cerebral Angiograph*[tw] OR "Neurosurgical Procedures"[Mesh:NoExp] OR "Microsurgery"[Mesh] OR "Surgical Instruments"[Mesh] OR "Neurosurgery"[Mesh] OR Surgical Clip*[tw] OR Clip*[tw] OR Tantalum Clip*[tw] OR Neurosurgical Procedure*[tw] OR Neurologic Surgical Procedure*[tw] OR Neurosurger*[tw] OR Microsurger*[tw] OR "Intracranial Pressure"[Mesh] OR "Brain/surgery"[Mesh] OR brain surg*[tw] OR intracranial pressure[tw]) 6272 result 01-24-2019 limit to (English language, humans, adult) Cochrane Library was used to perform a search of the literature between 1991 and January Week 4 2019. The following search terms were used: "aneurysm" in Title, Abstract or Keywords AND "endovascular procedure" OR "coil*" OR "cerebral angriography" OR "craniotom*" OR "neurosurg*" OR "clip*" OR "surg*" in Title, Abstract or Keywords 27 result 01-24-2019 The online database EMBASE_was used to perform a search of the literature between 1991 to January 23, 2019. The following search terms were used:

Table 1. Terms Used for Search in PubMed

	Searches	Results
1	'intracranial aneurysm'.tw. or exp intracranial aneurysm/	26452
2	'brain artery aneurysm'.tw. or exp brain artery aneurysm/	12833
3	'unruptured intracranial aneurysm'.tw. or exp unruptured intracranial aneurysm/	561
4	'brain artery '.tw. or exp brain artery/	40992
5	' middle cerebral artery '.tw. or exp middle cerebral artery/	31967
6	1 or 2 or 3 or 4 or 5	76659
7	exp endovascular surgery/ or 'Endovascular Coil*'.tw.	20469
8	exp brain angiography/	27709
9	exp coil embolization/ or 'coil embolization'.tw. or 'coil embolisation'.tw	8224
10	coil*.tw	51327
11	neurosurgery	23149
12	exp microsurgery/	27486
13	'aneurysm clip'.tw. or exp aneurysm clip/	2458
14	exp clip/ or 'Surgical Clip*'.tw.	11512
15	7 or 8 or 9 or 10 or 11 or 13 or 14	153309
16	6 and 17	17845
17	limit 16 to (human and english language and yr="1991 -Current" and adult <18 to 64 years>)	6060

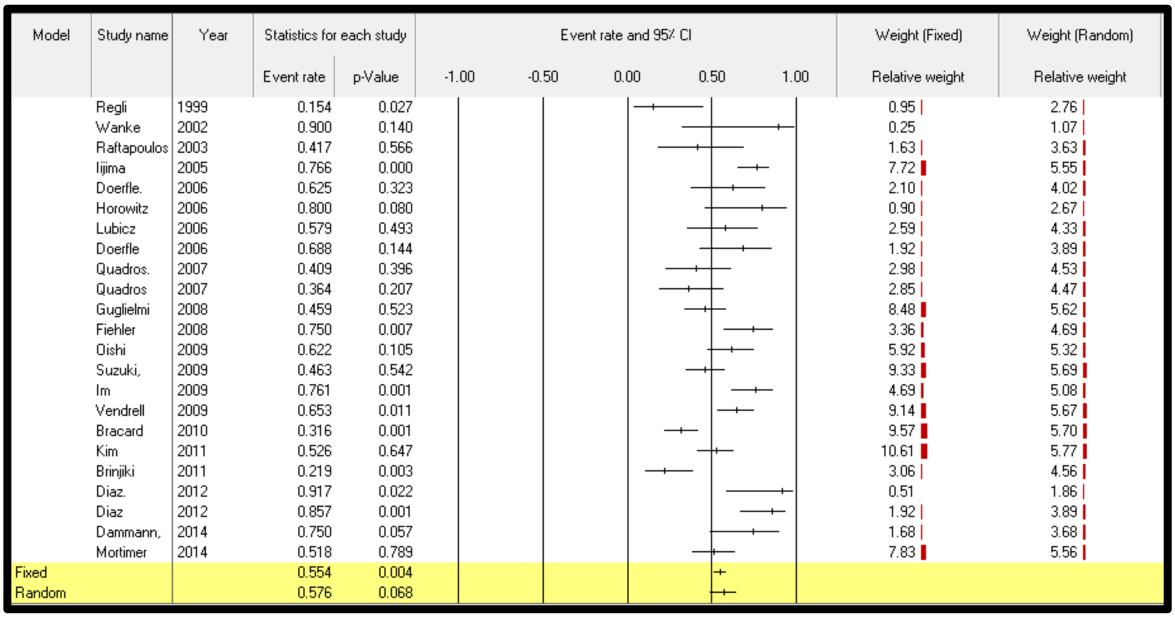
6060 result 01-24-2019 limit to (English language, humans and adult).

Appendix 2



Model	Study name	Year	Event rate	p-Value	Weight (Fixed) Relative weight	Weight (Random) Relative weight
	Regli,	1999	0.985	0.003	5.46	5.46
	Regli	2002	0.986	0.003	5.47	5.47
	Nanda	2002	0.974	0.012	5.40	5.40
	Gerlach	2007	0.943	0.000	20.91	20.91
	Quadros	2007	0.900	0.140	4.99	4.99
	Aghakhani	2008	0.996	0.000	5.52	5.52
	Diaz,	2012	0.941	0.007	10.44	10.44
	Diaz	2012	0.875	0.069	9.70	9.70
	Dammann	2014	0.966	0.000	32.12	32.12
Fixed			0.961	0.000		
Random			0.961	0.000		

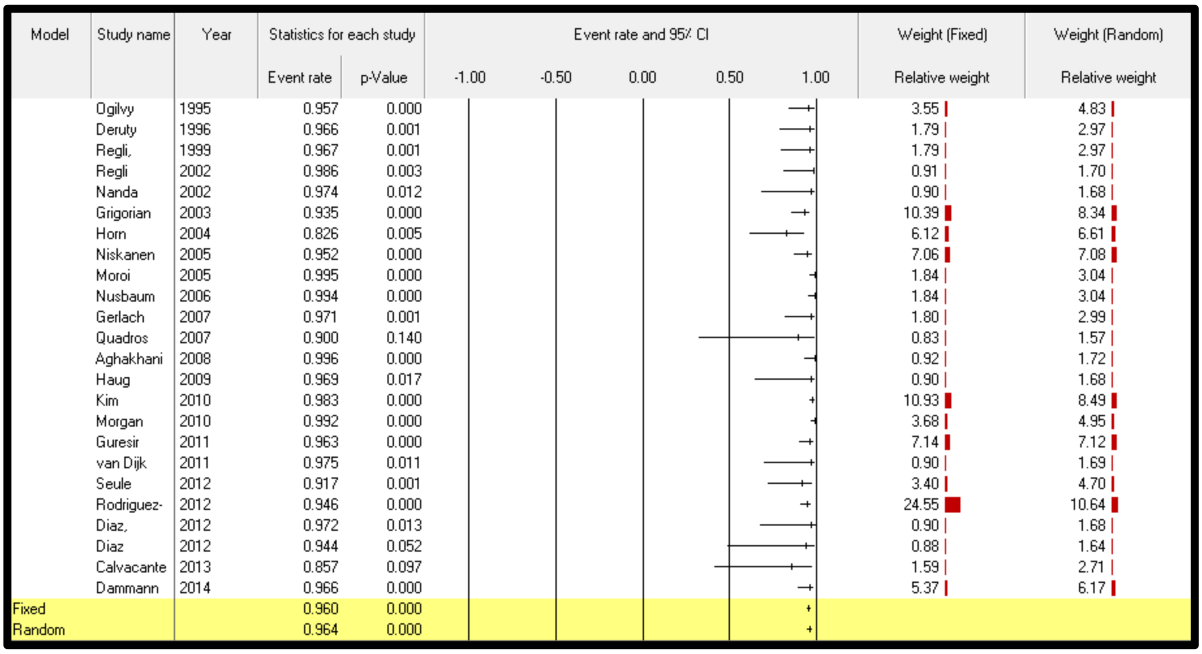
Fig 1. Overall pooled clipping occlusion rates analysis (efficacy)



Model	Study name	Year	Event rate	p-Value	Weight (Fixed) Relative weight	Weight (Random) Relative weight
	Regli	1999	0.154	0.027	0.95	2.76
	Wanke	2002	0.900	0.140	0.25	1.07
	Raftapoulos	2003	0.417	0.566	1.63	3.63
	Iijima	2005	0.766	0.000	7.72	5.55
	Doerfle.	2006	0.625	0.323	2.10	4.02
	Horowitz	2006	0.800	0.080	0.90	2.67
	Lubicz	2006	0.579	0.493	2.59	4.33
	Doerfle	2006	0.688	0.144	1.92	3.89
	Quadros.	2007	0.409	0.396	2.98	4.53
	Quadros	2007	0.364	0.207	2.85	4.47
	Guglielmi	2008	0.459	0.523	8.48	5.62
	Fiehler	2008	0.750	0.007	3.36	4.69
	Oishi	2009	0.622	0.105	5.92	5.32
	Suzuki,	2009	0.463	0.542	9.33	5.69
	Im	2009	0.761	0.001	4.69	5.08
	Vendrell	2009	0.653	0.011	9.14	5.67
	Bracard	2010	0.316	0.001	9.57	5.70
	Kim	2011	0.526	0.647	10.61	5.77
	Brinjiki	2011	0.219	0.003	3.06	4.56
	Diaz.	2012	0.917	0.022	0.51	1.86
	Diaz	2012	0.857	0.001	1.92	3.89
	Dammann,	2014	0.750	0.057	1.68	3.68
	Mortimer	2014	0.518	0.789	7.83	5.56
Fixed			0.554	0.004		
Random			0.576	0.068		

Fig 2. Overall pooled coiling occlusion rates analysis (efficacy)

Appendix 3



Model	Study name	Year	Event rate	p-Value	Weight (Fixed) Relative weight	Weight (Random) Relative weight
	Ogilvy	1995	0.957	0.000	3.55	4.83
	Deruty	1996	0.966	0.001	1.79	2.97
	Regli,	1999	0.967	0.001	1.79	2.97
	Regli	2002	0.986	0.003	0.91	1.70
	Nanda	2002	0.974	0.012	0.90	1.68
	Grigorian	2003	0.935	0.000	10.39	8.34
	Horn	2004	0.826	0.005	6.12	6.61
	Niskanen	2005	0.952	0.000	7.06	7.08
	Moroi	2005	0.995	0.000	1.84	3.04
	Nusbaum	2006	0.994	0.000	1.84	3.04
	Gerlach	2007	0.971	0.001	1.80	2.99
	Quadros	2007	0.900	0.140	0.83	1.57
	Aghakhani	2008	0.996	0.000	0.92	1.72
	Haug	2009	0.969	0.017	0.90	1.68
	Kim	2010	0.983	0.000	10.93	8.49
	Morgan	2010	0.992	0.000	3.68	4.95
	Guresir	2011	0.963	0.000	7.14	7.12
	van Dijk	2011	0.975	0.011	0.90	1.69
	Seule	2012	0.917	0.001	3.40	4.70
	Rodriguez-	2012	0.946	0.000	24.55	10.64
	Diaz,	2012	0.972	0.013	0.90	1.68
	Diaz	2012	0.944	0.052	0.88	1.64
	Calvacante	2013	0.857	0.097	1.59	2.71
	Dammann	2014	0.966	0.000	5.37	6.17
Fixed			0.960	0.000		
Random			0.964	0.000		

Fig 1. Overall pooled clipping neurological outcome analysis (safety)

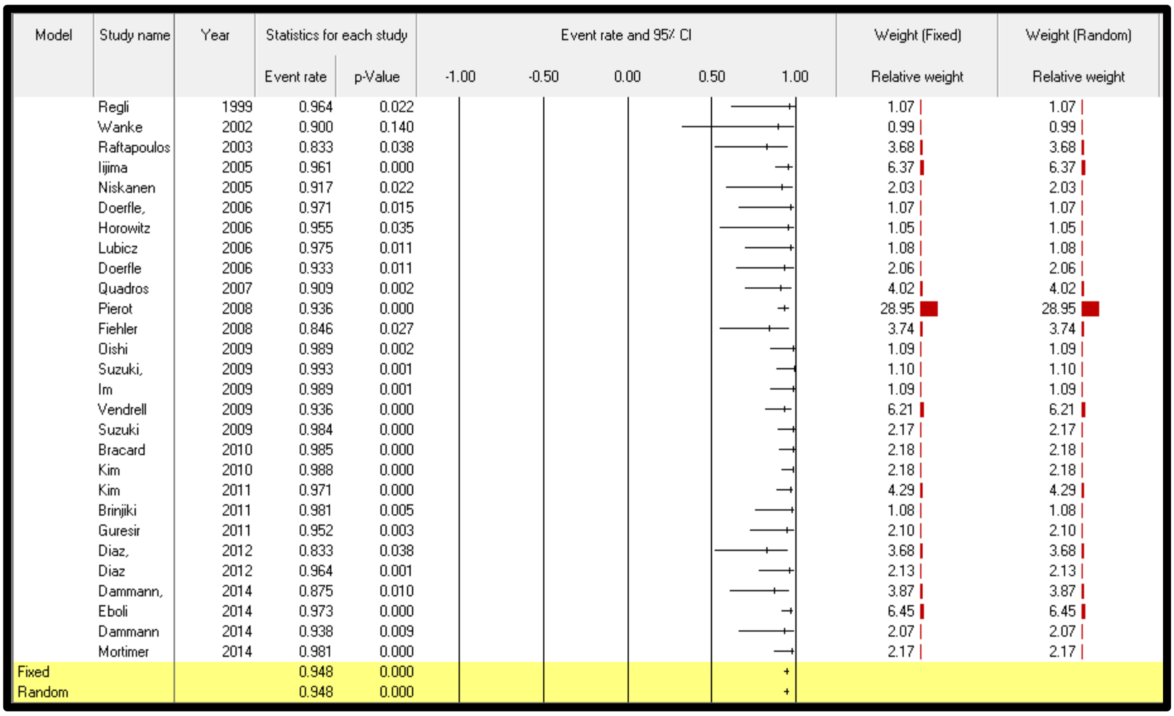


Fig 2. Overall pooled coiling neurological outcome analysis (safety)

5. CONCLUSION

Comparing the microsurgical clipping with the endovascular coiling for treatment of unruptured MCA aneurysms, clipping has a higher aneurysm occlusion rate than coiling. The rate of occlusion appears to decrease with time in the clipping group and increase with time in the coiling group. Both clipping and coiling have similar functional outcomes for treatment of unruptured MCA aneurysms. The rate of favorable functional outcomes appears to increase with time in the clipping group and decrease with time in the coiling group.

6. AUTHORS CONTRIBUTION STATEMENT

Fatema Turkistani, Pharm. D, MSc, PhD, DBA designed the study, collected and analyzed the data, and wrote many sections of the manuscripts. Aseel Bin Sawad, Pharm D, MSc, MCR, MS, PhD, DBA contributed to the study design, collected data, analyzed parts of the data, wrote and revised many sections of the manuscript. All the authors read and approved the final version of the manuscript.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

8. REFERENCES

1. Mason AM, Cawley III CM, Barrow DL. Surgical management of intracranial aneurysms in the endovascular era: review article. J Korean Neurosurg Soc. 2009 Mar;45(3):133-42. doi: 10.3340/jkns.2009.45.3.133, PMID 19352474.
2. Wiebers DO, Piepgras DG, Meyer FB, Kallmes DF, Meissner I, Atkinson JL, Link MJ, Brown Jr RD. Pathogenesis, natural history, and treatment of unruptured intracranial aneurysms. Mayo Clin Proc. 2004 Dec 1;79(12):1572-83. doi: 10.4065/79.12.1572, PMID 15595346.
3. Loumiotis I, Brown RD Jr, Vine R, Cloft HJ, Kallmes DF, Lanzino G. Small (< 10-mm) incidentally found intracranial aneurysms, Part 2: treatment recommendations, natural history, complications, and short-term outcome in 212 consecutive patients. Neurosurg Focus. 2011 Dec 1;31(6):E4. doi: 10.3171/2011.9.FOCUS11237, PMID 22133187.
4. Campi A, Ramzi N, Molyneux AJ, Summers PE, Kerr RS, Sneade M, Yarnold JA, Rischmiller J, Byrne JV. Retreatment of ruptured cerebral aneurysms in patients randomized by coiling or clipping in the International Subarachnoid Aneurysm Trial (ISAT). Stroke. 2007 May 1;38(5):1538-44. doi: 10.1161/STROKEAHA.106.466987, PMID 17395870.
5. Miyaoka M, Sato K, Ishii S. A clinical study of the relationship of timing to outcome of surgery for ruptured cerebral aneurysms. A retrospective analysis of 1622 cases. J Neurosurg. 1993 Sep 1;79(3):373-8. doi: 10.3171/jns.1993.79.3.0373, PMID 8360733.
6. Brinjikji W, Rabinstein A. A, Nasr D. M, Lanzino G, Kallmes D. F, Cloft H. J. Better outcomes with treatment by coiling relative to clipping of unruptured intracranial aneurysms in the United States, 2001–2008. AJNR Am J Neuroradiol. 2011 Jun 1; 32(6):1071-5. Doi: 10.3174/ajnr.A2453.
7. Qureshi AI, Vazquez G, Tariq N, Suri MF, Lakshminarayan K, Lanzino G. F. K. Impact of International subarachnoid Aneurysm Trial results on treatment of ruptured intracranial aneurysms in the United States: clinical article. J Neurosurg. 2011 Mar 1;114(3):834-41. doi: 10.3171/2010.6.JNS091486, PMID 20653392.
8. Murayama Y, Nien YL, Duckwiler G, Gobin YP, Jahan R, Frazee J, Martin N, Viñuela F. Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. J Neurosurg. 2003 May 1;98(5):959-66. doi: 10.3171/jns.2003.98.5.0959, PMID 12744354.
9. Byrne JV, Sohn MJ, Molyneux AJ, Chir B. Five-year experience in using coil embolization for ruptured intracranial aneurysms: outcomes and incidence of late

rebleeding. J Neurosurg. 1999 Apr 1;90(4):656-63. doi: 10.3171/jns.1999.90.4.0656, PMID 10193610.
10. Plowman RS, Clarke A, Clarke M, Byrne JV. Sixteen-year single-surgeon experience with coil embolization for ruptured intracranial aneurysms: recurrence rates and incidence of late rebleeding. Clinical article. Clinical article. J Neurosurg. 2011 Mar 1;114(3):863-74. doi: 10.3171/2010.6.JNS091058, PMID 20672900.
11. Brinjikji W, Lanzino G, Cloft HJ, Rabinstein A, Kallmes DF. Endovascular treatment of middle cerebral artery aneurysms: a systematic review and single-center series. Neurosurgery. 2011 Feb 1;68(2):397-402; discussion 402. doi: 10.1227/NEU.0b013e318201d7f4, PMID 21135730.
12. Doerfler A, Wanke I, Goericke SL, Wiedemayer H, Engelhorn T, Gizewski ER, Stolke D, Forsting M. Endovascular treatment of middle cerebral artery aneurysms with electrolytically detachable coils. AJNR Am J Neuroradiol. 2006 Mar 1;27(3):513-20. PMID 16551986.
13. Bracard S, Abdel-Kerim A, Thuillier L, Klein O, Anxionnat R, Finitsis S, Lebedinsky A, De Freitas CM, Pinheiro N, De Andrade GC, Picard L. Endovascular coil occlusion of 152 middle cerebral artery aneurysms: initial and midterm angiographic and clinical results. J Neurosurg. 2010 Apr 1;112(4):703-8. doi: 10.3171/2009.6.JNS09483, PMID 19852536.
14. Raftopoulos C, Goffette P, Vaz G, Ramzi N, Scholtes JL, Wittebole X, Mathurin P. Surgical clipping may lead to better results than coil embolization: results from a series of 101 consecutive unruptured intracranial aneurysms. Neurosurgery. 2003 Jun 1;52(6):1280-7; discussion 1287. doi: 10.1227/01.NEU.0000064568.71648.EC, PMID 12762873.
15. Quadros RS, Gallas S, Noudel R, Rousseaux P, Pierot L. Endovascular treatment of middle cerebral artery aneurysms as first option: a single center experience of 92 aneurysms. AJNR Am J Neuroradiol. 2007 Sep 1;28(8):1567-72. doi: 10.3174/ajnr.A0595, PMID 17846214.
16. Oishi H, Yoshida K, Shimizu T, Yamamoto M, Horinaka N, Arai H. Endovascular treatment with bare platinum coils for middle cerebral artery aneurysms. Neurol Med Chir (Tokyo). 2009 Jul 1;49(7):287-93. doi: 10.2176/nmc.49.287, PMID 19633399.
17. Suzuki S, Tateshima S, Jahan R, Duckwiler GR, Murayama Y, Gonzalez NR, Viñuela F. Endovascular treatment of middle cerebral artery aneurysms with detachable coils: angiographic and clinical outcomes in 115 consecutive patients. Neurosurgery. 2009 May 1;64(5):876-88; discussion 888. doi: 10.1227/01.NEU.0000343534.05655.37, PMID 19287326.
18. Kim BM, Kim DI, Park SI, Kim DJ, Suh SH, Won YS. Coil embolization of unruptured middle cerebral artery aneurysms. Neurosurgery. 2011 Feb 1;68(2):346-53; discussion 353. doi: 10.1227/NEU.0b013e3182035fdc, PMID 21135721.
19. Guglielmi G, Viñuela F, Duckwiler G, Jahan R, Cotroneo E, Gigli R. Endovascular treatment of middle cerebral artery aneurysms. Overall perioperative results. Apropos of 113 cases. Interv Neuroradiol. 2008 Sep 30;14(3):241-45. doi: 10.1177/159101990801400303, PMID 20557720.
20. Horowitz M, Gupta R, Gologorsky Y, Jovin T, Genevro J, Levy E, Kassam A. Clinical and anatomic outcomes after endovascular coiling of middle cerebral artery aneurysms: report on 30 treated aneurysms and review of the literature. Surg Neurol. 2006 Aug 1;66(2):167-71; discussion 171. doi: 10.1016/j.surneu.2005.12.022, PMID 16876616.
21. Regli L, Uske A, de Tribolet N. Endovascular coil placement compared with surgical clipping for the treatment of unruptured middle cerebral artery aneurysms: a consecutive series. J Neurosurg. 1999 Jun 1;90(6):1025-30. doi: 10.3171/jns.1999.90.6.1025, PMID 10350247.
22. Lubicz B, Graca J, Levivier M, Lefranc F, Dewitte O, Pirotte B, Brotchi J, Balériaux D. Endovascular treatment of middle cerebral artery aneurysms. Neurocrit Care. 2006 Oct;5(2):93-101. doi: 10.1385/NCC:5:2:93.
23. Niskanen M, Koivisto T, Rinne J, Ronkainen A, Pirskanen S, Saari T, Vanninen R. Complications and postoperative care in patients undergoing treatment for unruptured intracranial aneurysms. J Neurosurg Anesthesiol. 2005 Apr 1;17(2):100-5. doi: 10.1097/01.ana.0000163202.33236.mL, PMID 15840997.
24. Im SH, Han MH, Kwon OK, Kwon BJ, Kim SH, Kim JE, Oh CW. Endovascular coil embolization of 435 small asymptomatic unruptured intracranial aneurysms: procedural morbidity and patient outcome. AJNR Am J Neuroradiol. 2009 Jan 1;30(1):79-84. doi: 10.3174/ajnr.A1290, PMID 18768715.
25. Kim JE, Lim DJ, Hong CK, Joo SP, Yoon SM, Kim BT. Treatment of unruptured intracranial aneurysms in South Korea in 2006: a nationwide multicenter survey from the Korean society of cerebrovascular surgery. J Korean Neurosurg Soc. 2010 Feb 28;47(2):112-8. doi: 10.3340/jkns.2010.47.2.112, PMID 20224709.
26. Güresir E, Schuss P, Berkefeld J, Vatter H, Seifert V. Treatment results for complex middle cerebral artery aneurysms. A prospective single-center series. Acta Neurochir (Wien). 2011 Jun;153(6):1247-52. doi: 10.1007/s00701-011-1008-3, PMID 21487768.
27. Pierot L, Spelle L, Vitry F, ATENA Investigators. Immediate clinical outcome of patients harboring unruptured intracranial aneurysms treated by endovascular approach results of the ATENA study. Stroke. 2008 Sep 1;39(9):2497-504. doi: 10.1161/STROKEAHA.107.512756, PMID 18617659.
28. Diaz OM, Rangel-Castilla L, Barber S, Mayo RC, Klucznik R, Zhang YJ. Middle cerebral artery aneurysms: A single-center series comparing endovascular and surgical treatment. World Neurosurg. 2014 Feb 1;81(2):322-9. doi: 10.1016/j.wneu.2012.12.011, PMID 23238101.
29. Dammann P, Schoemberg T, Müller O, Özkan N, Schlamann M, Wanke I, Sandalcioglu IE, Forsting M, Sure U. Outcome for unruptured middle cerebral artery aneurysm treatment: surgical and endovascular approach in a single center. Neurosurg Rev. 2014 Oct;37(4):643-51. doi: 10.1007/s10143-014-0563-5, PMID 25005630.
30. Iijima A, Piotin M, Mounayer C, Spelle L, Weill A, Moret J. Endovascular treatment with coils of 149 middle cerebral artery berry aneurysms. Radiology. 2005 Nov 2;237(2):611-9. doi: 10.1148/radiol.2372041015, PMID 16244270.

31. Wanke I, Doerfler A, Dietrich U, Egelhof T, Schoch B, Stolke D, Forsting M. Endovascular treatment of unruptured intracranial aneurysms. AJNR Am J Neuroradiol. 2002 May;23(5):756-61. PMID 12006272.
32. Vendrell JF, Menjot N, Costalat V, Hoa D, Moritz J, Brunel H, Bonafe A. Endovascular treatment of 174 middle cerebral artery aneurysms: clinical outcome and radiologic results at long-term follow-up. Radiology. 2009 Oct;253(1):191-8. doi: 10.1148/radiol.2531082092, PMID 19703857.
33. Mortimer AM, Bradley MD, Mews P, Molyneux AJ, Renowden SA. Endovascular treatment of 300 consecutive middle cerebral artery aneurysms: clinical and radiologic outcomes. AJNR Am J Neuroradiol. 2014 Apr 1;35(4):706-14. doi: 10.3174/ajnr.A3776, PMID 24231847.
34. Eboli P, Ryan RW, Alexander JE, Alexander MJ. Evolving role of endovascular treatment for MCA bifurcation aneurysms: case series of 184 aneurysms and review of the literature. Neurol Res. 2014 Apr 1;36(4):332-8. doi: 10.1179/1743132814Y.0000000324, PMID 24533619.
35. Fiehler J, Boor S, Dörbecker R, Eckert B, Götz F, Hartmann M, Knauth M, Koch C, Müller A, Ries T, Zeumer H. Table for optimization and monitoring of cerebral aneurysm therapy (TOMCAT). Clin Neuroradiol. 2008 Aug;18(3):168-76. doi: 10.1007/s00062-008-8021-9.
36. Regli L, Dehdashti AR, Uske A, de Tribolet N. Endovascular coiling compared with surgical clipping for the treatment of unruptured middle cerebral artery aneurysms: an update. Acta Neurochir Suppl. 2002;82:41-6. doi: 10.1007/978-3-7091-6736-6_8, PMID 12378989.
37. Moroi J, Hadeishi H, Suzuki A, Yasui N. Morbidity and mortality from surgical treatment of unruptured cerebral aneurysms at Research Institute for Brain and Blood Vessels-Akita. Neurosurgery. 2005 Feb;56(2):224-31; discussion 224. doi: 10.1227/01.neu.0000148897.28828.85, PMID 15670370.
38. Gerlach R, Beck J, Setzer M, Vatter H, Berkefeld J, Du Mesnil de Rochemont RD, Raabe A, Seifert V. Treatment related morbidity of unruptured intracranial aneurysms: results of a prospective single centre series with an interdisciplinary approach over a 6 year period (1999-2005). J Neurol Neurosurg Psychiatry. 2007 Aug 1;78(8):864-71. doi: 10.1136/jnnp.2006.106823, PMID 17210624.
39. Deruty R, Pelissou-Guyotat I, Mottolese C, Amat D. Management of unruptured cerebral aneurysms. Neurol Res. 1996 Feb;18(1):39-44. doi: 10.1080/01616412.1996.11740375, PMID 8714535.
40. Nussbaum ES, Madison MT, Myers ME, Goddard J. Microsurgical treatment of unruptured intracranial aneurysms. A consecutive surgical experience consisting of 450 aneurysms treated in the endovascular era. Surg Neurol. 2007 May;67(5):457-64; discussion 464. doi: 10.1016/j.surneu.2006.08.069, PMID 17445600.
41. Aghakhani N, Vaz G, David P, Parker F, Goffette P, Ozan A, Raftopoulos C. Surgical management of unruptured intracranial aneurysms that are inappropriate for endovascular treatment: experience based on two academic centers. Neurosurgery. 2008 Jun 1;62(6):1227-34; discussion 1234. doi: 10.1227/01.neu.0000333294.52115.28, PMID 18824989.
42. Morgan MK, Mahattanakul W, Davidson A, Reid J. Outcome for middle cerebral artery aneurysm surgery. Neurosurgery. 2010 Sep 1;67(3):755-61; discussion 761. doi: 10.1227/01.NEU.0000378025.33899.26, PMID 20651625.
43. Nanda A, Vannemreddy P. Surgical management of unruptured aneurysms: prognostic indicators. Surg Neurol. 2002 Jul;58(1):13-9; discussion 19. doi: 10.1016/S0090-3019(02)00774-7, PMID 12361640.
44. Grigorian AA, Marcovici A, Flamm ES. Intraoperative factors associated with surgical outcome in patients with unruptured cerebral aneurysms: the experience of a single surgeon. J Neurosurg. 2003 Sep;99(3):452-7. doi: 10.3171/jns.2003.99.3.0452, PMID 12959429.
45. Horn M, Morgan MK, Ingebrigtsen T. Surgery for unruptured intracranial aneurysms in a low-volume neurosurgical unit. Acta Neurol Scand. 2004 Sep;110(3):170-4. doi: 10.1111/j.1600-0404.2004.00297.x, PMID 15285774.
46. van Dijk JM, Groen RJ, Ter Laan M, Jeltema JR, Mooij JJ, Metzemaekers JD. Surgical clipping as the preferred treatment for aneurysms of the middle cerebral artery. Acta Neurochir. 2011 Nov;153(11):2111-7. doi: 10.1007/s00701-011-1139-6, PMID 21898188.
47. Haug T, Sorteberg A, Sorteberg W, Lindegaard KF, Lundar T, Finset A. Surgical repair of unruptured and ruptured middle cerebral artery aneurysms: impact on cognitive functioning and health-related quality of life. Neurosurgery. 2009 Mar 1;64(3):412-20; discussion 421. doi: 10.1227/01.NEU.0000338952.13880.4E, PMID 19240602.
48. Seule MA, Stienen MN, Gautschi OP, Richter H, Desbiolles L, Leschka S, Hildebrandt G. Surgical treatment of unruptured intracranial aneurysms in a low-volume hospital – outcome and review of literature. Clin Neurol Neurosurg. 2012 Jul 1;114(6):668-72. doi: 10.1016/j.clineuro.2011.12.054, PMID 22300889.
49. Ogilvy CS, Crowell RM, Heros RC. Surgical management of middle cerebral artery aneurysms: experience with transsylvian and superior temporal gyrus approaches. Surg Neurol. 1995 Jan 1;43(1):15-22; discussion 22. doi: 10.1016/0090-3019(95)80032-C, PMID 7701417.
50. Rodríguez-Hernández A, Sughrue ME, Akhavan S, Habdank-Kolaczkowski J, Lawton MT. Current management of middle cerebral artery aneurysms: surgical results with a "clip first" policy. Neurosurgery. 2013 Mar 1;72(3):415-27. doi: 10.1227/NEU.0b013e3182804aa2, PMID 23208060.
51. Calvacante T, Derrey S, Curey S, Langlois O, Fréger P, Gérardin E, Castel H, Proust F. Distal middle cerebral artery aneurysm: a proposition of microsurgical management. Neurochirurgie. 2013 Jun 1;59(3):121-7. doi: 10.1016/j.neuchi.2013.04.007, PMID 23806761.
52. Kadkhodayan Y, Delgado Almandoz JE, Fease JL, Scholz JM, Blem AM, Tran K, Crandall BM, Tubman DE. Endovascular treatment of 346 middle cerebral artery aneurysms: results of a 16-year single-center experience. Neurosurgery. 2015 Jan 1;76(1):54-60; discussion 60. doi: 10.1227/NEU.0000000000000562, PMID 25255254.

53. Rinne J, Hernesniemi J, Niskanen M, Vapalahti M. Analysis of 561 patients with 690 middle cerebral artery aneurysms: anatomic and clinical features as correlated to management outcome. Neurosurgery. 1996 Jan 1;38(1):2-11. doi: 10.1097/00006123-199601000-00002, PMID 8747945.
54. Suzuki J, Yoshimoto T, Kayama T. Surgical treatment of middle cerebral artery aneurysms. J Neurosurg. 1984 Jul 1;61(1):17-23. doi: 10.3171/jns.1984.61.1.0017, PMID 6726392.
55. Pierot L, Spelle L, Vitry F, ATENA investigators. Immediate anatomic results after the endovascular treatment of unruptured intracranial aneurysms: analysis of the ATENA series. AJNR Am J Neuroradiol. 2010 Jan 1;31(1):140-4. doi: 10.3174/ajnr.A1745, PMID 19729540.