Clinical Outcomes of Microvascular Clipping Compared to Endovascular Coiling for Ruptured Anterior Communicating Artery Aneurysms

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FIGURES

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ABBREVIATIONS LIST

ACA	Anterior cerebral artery
ACOM	Anterior communicating artery
BAC	Balloon assisted coiling
CI	Confidence interval
CT	Computed tomography
CSF	Cerebral spinal fluid
dAPT	Dual anti-platelet therapy
DCI	Delayed cerebral ischemia
DIND	Delayed ischaemic neurological deficits
DSA	Digitally subtracted Angiography
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
H&H	Hess & Hunt
ICA	Internal Carotid Artery
ICP	Intracranial Pressure
ISAT	International Subarachnoid Aneurysm Trial
ISUIA	International Study of Unruptured Intracranial Aneurysms
MCA	Middle cerebral artery
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
OR-	Odds Ratio
PCA	Posterior cerebral artery
PCOM	Posterior communicating artery
RCT	Randomised Controlled Trial
RD	Risk Difference
RR	Risk Ratio
SAC	Stent Assisted Coiling
SAH	Subarachnoid Hemorrhage
TEE	Thromboembolic Event
WFNS	World Federation of Neurosurgical Societies

ABSTRACT

A ruptured intracranial aneurysm is a devastating pathology that is associated with significant morbidity and mortality. The anterior communicating artery (ACOM) is the most common location to have an intracranial aneurysm form and rupture. The two management options for ruptured intracranial aneurysms include microsurgical clipping and endovascular coiling. The clinical outcomes of microsurgical clipping and endovascular coiling for ruptured ACOM aneurysms remains unclear. The aim of the research presented in this thesis was to investigate the clinical outcomes, including functional outcomes, treatment efficacy and safety of microsurgical clipping and endovascular coiling for the management of ruptured ACOM aneurysms.

A search for published and unpublished literature included PubMed, Embase, Scopus, Cochrane Central Register of Controlled Trials, International Clinical Trial Registry, Australia and New Zealand Clinical Trial Registry Search Strategy and ClinicalTrials.gov. Studies were included if they explored the functional outcomes and/or safety of microsurgical clipping and endovascular coiling for ruptured ACOM aneurysms. Eligible studies were critically appraised by two reviewers using appropriate JBI tools to assess methodological qualitied. Where possible, data from included studies was meta-analysed using a random effects Mantel-Haenszel model. Sensitivity analyses were performed using a fixed effect model. Effect measures included odds ratio and risk difference where no events were recorded.

The search yielded 818 records. Following screening of titles and abstracts against the review inclusion criteria, 25 articles were retrieved for full-text screening. Of these, 11 studies, all of which were non-randomised studies (2 quasi-experimental and 9 retrospective cohort studies), were included. Overall, these studies fulfilled the majority of the quality appraisal criteria.

For the primary outcome (favourable functional outcomes), analysis revealed overall no statistically significant difference between microsurgical clipping and endovascular coiling (79.4% versus 73.6%, OR 1.11, 95% CI 0.78 – 1.57, p=0.56). Results from the quasi-experimental studies demonstrated favourable outcomes in the clipping group were non-

significantly higher than the coiling group (86.2% versus 80.4%, OR 2.26, 95% CI 0.6-8.52, p=0.23). In cohort studies, favourable outcomes in the clipping group were non-significantly higher than the coiling group (78.9% versus 72.3%, OR 1.05, 95% CI 0.71-1.53, p=0.23).

For the secondary outcomes of recurrence and complications, overall no statistically significant difference was found between clipping versus coiling (recurrence - 4.6% versus 5.7%, RD 0.00, 95% CI -0.06 – 0.06, p=0.47; complications- 21.6% versus 14.2%, OR 1.00 95% CI 0.49 – 2.05, p=1.00). Results from the quasi-experimental studies demonstrated recurrence was non-significantly higher in the clipping group compared to the coiling group (17.2% versus 0%, RD =0.15 95% CI -0.04-0.34, p=0.16). In cohort studies, recurrence was non-significantly higher in the coiling group versus clipping group (6.7% versus 3.4%, RD = -0.02 95 CI -0.07-0.03, p=0.92). Results from the quasi-experimental study demonstrated complications were non-significantly higher in the clipping group compared to the coiling group (20% versus 6.67%, OR =3.50 95% CI 0.32-38.23, p=0.30). In cohort studies, complications were again non-significantly higher in the clipping group versus the coiling group (21.6% versus 14.5%, OR=8.38 95% CI 0.42-1.93, p<0.001). Occlusion was found to be significantly higher in the clipping group compared to coiling (95% versus 75%, OR 7.01, 95% CI 2.82 – 17.45, p=<0.0001). Results from the quasi-experimental study demonstrated occlusion was similar in the clipping group compared to the coiling group (93.3% versus 86.7%, OR =2.15 CI 0.17-26.67, p=0.55). In cohort studies, occlusion was significantly higher in the clipping group versus the coiling group (94.9% versus 74.2%, OR=8.38 CI 31.5-22.28, p<0.001).

In conclusion, microsurgical clipping and endovascular coiling appear to be equally effective and safe for the treatment of ruptured ACOM aneurysms. Both options should be considered when managing patients with this pathology.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

I give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

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CHAPTER 1. INTRODUCTION

An intracranial aneurysm is a thin walled protrusion in the wall of an intracranial artery.[1] The incidence of intracranial aneurysms in the general population is approximately 3-5%.[2,3] Intracranial aneurysms most commonly occur at sites where large cerebral vessels bifurcate,[4] such as the anterior communicating artery (ACOM). The ACOM is the most common location for an intracranial aneurysm to develop.[4]

When an intracranial aneurysm ruptures it is often a devastating event, and is associated with high rates of morbidity and mortality.[5] Mortality rates after a ruptured intracranial aneurysm vary between 22-50% in modern series.[6] The global incidence rate of ruptured intracranial aneurysms is approximately 8 per 100,000 person-years.[7] When an aneurysm ruptures, bleeding usually only occurs for a few seconds before a thrombus forms in the aneurysm and the bleeding ceases. However, after rupturing, the aneurysm has a substantial risk of re-rupturing, which is again associated with a high mortality.[8] The two available treatment modalities for a ruptured intracranial aneurysm to prevent it rupturing again include an open brain surgery where a clip is placed on the aneurysm, or minimally invasive endovascular coiling of the aneurysm.[8] These two treatment modalities are significantly different techniques and each has individual treatment efficacy and complication profiles (see Section 1.6).[8]

Choosing which treatment modality is most appropriate for a ruptured brain aneurysm is a complex decision. There are various factors usually considered, such as the patient profile, aneurysm morphology and aneurysm location.[9] Location of the ruptured aneurysm is important because specific anatomical sites of the ruptured aneurysm may correspondingly influence the technical difficulty in completing either surgical clipping or endovascular coiling. For example, ruptured aneurysms of the tip of the basilar artery are recognised to generally be technically less complex to access for endovascular coiling, but highly complex to access through a craniotomy for microsurgical clipping.[10,11] Clinical outcomes of clipping versus coiling for ruptured intracranial aneurysms in specific locations have been reviewed in systematic reviews for middle cerebral artery (MCA)[12] and posterior communicating artery (PCOM) aneurysms.[13] However, a systematic review of clinical outcomes and efficacy in patients who have undergone treatment with either surgical clipping or endovascular coiling for a ruptured ACOM had not been completed.[14] Given that this location is the most common site of intracranial aneurysm formation and rupture, it is imperative for treating clinicians to

have this information as a guide to make evidence based, informed decisions on which treatment option is most appropriate. There are no current or previous international guidelines for treating ruptured ACOM aneurysms. This review was completed as the first systematic review to assess the clinical outcomes and safety of surgical clipping versus endovascular coiling in ruptured ACOM aneurysm patients to help develop clinical practice guidelines.

The first chapter of this thesis introduces the anatomy of the cerebral vascular, what an intracranial aneurysm is, how it is diagnosed, its potential life threatening sequalae and an explanation of current treatment options and their individual complication profiles. The significance of the review is introduced, the objectives and questions of the review, and an overview of the methodology.

1.1– Cerebral vascular anatomy

Four principal arteries supply the brain parenchyma, namely one internal carotid artery (ICA) and one vertebral artery for each half of the brain.[15] Classically, the ICAs on each side are referred to as the anterior circulation and carry approximately 80% of blood to the brain.[15] The vertebral arteries on both sides are referred to as the posterior circulation.[15,16] The anterior and posterior circulation arteries come together at the base of the skull to form an anastomotic ring, known as the '*Circle of Willis'* (Figure 1).[17] There are numerous large branches that arise from the Circle of Willis to supply distinct brain territories.[16] These are supplied by either the anterior or posterior circulation.[17] The anterior cerebral artery (ACA), MCA and PCOM are the primary vessels of the anterior circulation.[16] The PCOM links the anterior circulation to the key vessel of the posterior circulation, the posterior cerebral artery (PCA).[17] Each of these large vessels supply further, important perforating vessels that supply deep and important structures of the brain, such as the pituitary gland, optic chiasm, hypothalamus and basal ganglia.[18]

The ACOM artery arises from the anterior circulation and is an important artery in completing the anterior Circle of Willis.[19] It arises specifically from the ACA and connects both ACAs, acting as an anastomosis between the right and left anterior cerebral circulation. The ACOM is a short vessel with an average length of 4mm and an average diameter of 1.7mm.[20] It is located above the optic chiasm.[20] It is subject to significant variability (as high as 60%) in its morphology.[21] This can include aplasia where is it not developed, hypoplasia

where it is significantly smaller than average, or duplication where there are two or more ACOM arteries.[22] Therefore, when considering an ACOM aneurysm, the possibility of an anatomical ACOM variant should be considered carefully.[21]

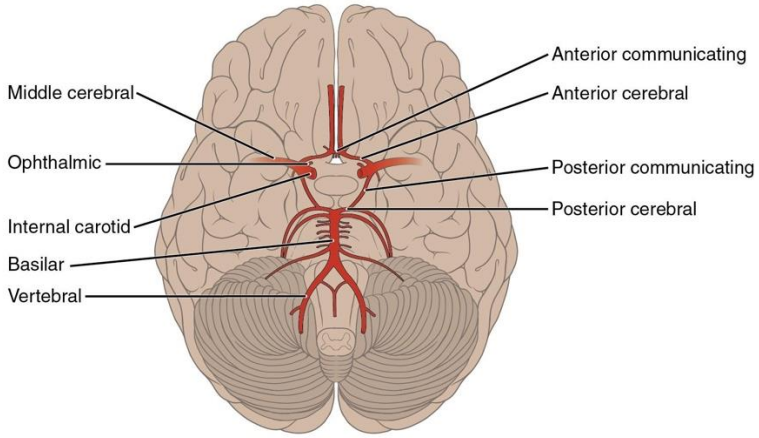

Figure 1. Anatomical features of the Circle of Willis. Permission obtained for reuse of figure.

An intracranial aneurysm is a thin walled protrusion in an intracranial artery.[1] Intracranial aneurysms are characterised by localised structural deterioration in the arterial wall, with loss of the internal elastic lamina and disruption of the tunica media.[1] In recent years, the understanding of the pathogenesis of intracranial aneurysms has evolved. It has become increasingly clear that intracranial aneurysms are not a passively enlarging vascular structures, but exhibit prominent features of inflammation.[23] The complex inflammatory cascade is initiated by a hemodynamic insult which leads to an influx of inflammatory cells, primarily macrophages, and apoptosis of the native smooth muscle cells. [23] These processes act in concert to weaken the arterial wall progressively, resulting in dilatation and aneurysm formation.[1]

The incidence of intracranial aneurysms in the general population is approximately 3-5%.[2,3] This figure is constantly evolving as intracranial aneurysms are being detected incidentally with increasing frequency with the expanding use of neuroimaging for another indications.[24] The average age of diagnosis is 50 years.[3] Intracranial aneurysms have a slight sex predilection, with 54-61% of total intracranial aneurysms found in females.[25] Of patients who are diagnosed with an intracranial aneurysm, 20-30% have multiple intracranial aneurysms.[26] This includes having more than one aneurysm on the same parent artery, or aneurysms arising from a different parent artery.[26] Currently accepted risk factors for development of an

intracranial aneurysm include cigarette smoking,[25] hypertension,[27] oestrogen deficiency[28] and coarctation of the aorta.[29]

Two large prospective studies, the International Study of Unruptured Intracranial Aneurysms (ISUIA)[30] and the Unruptured Cerebral Aneurysms Study (UCAS)[31] have reported on the natural history of unruptured intracranial aneurysms and the factors associated with risk of rupture. These factors include: 1. aneurysm size: smaller aneurysms of less than 7mm diameter having lower rates of rupture. 2. Aneurysm growth: aneurysms that demonstrate active growth over time have higher risk of rupturing. 3. Site: aneurysm rupture rates vary according to its location. 4. Family history: familial aneurysms tend to rupture at a smaller size and younger age than sporadic aneurysms. 5. Morphology of the aneurysm: presence of a 'daughter sac' or irregularity on the dome of the aneurysm also increases rupture risk.[32] Subsequent studies have demonstrated that some heritable diseases of the connective tissue and extracellular matrix, including autosomal dominant polycystic kidney disease,[33] Ehlers Danlos type IV[34] and Marfan syndrome[35] are associated with increased risk of intracranial aneurysms and rupturing. There is no universal classification for the different types of intracranial aneurysms, resulting in a heterogenous mix of terms based on the morphology, size and aetiology of the aneurysm.[36] The commonly referred to intracranial aneurysm types include: saccular aneurysms, fusiform aneurysms, blister-like aneurysms and mycotic aneurysms.[37]

1.2.1 Saccular aneurysms

Saccular aneurysms, also known as Berry aneurysms, account for approximately 90% of intracranial aneurysms and are the most common type to rupture.[37] They are focal, lobulated protrusions that usually arise at proximal arterial bifurcations.[38] This is because of the hemodynamic stress that occurs at these points with disruptions of the normal laminar arterial flow.[4] The majority of saccular aneurysms, indeed some 85% of those recorded, occur in the anterior circulation.[4] Common sites include the ICA to ACA junction, the ACA to ACOM junction, the MCA branch points, the origin of the ophthalmic artery, and the ICA bifurcation.[37] Considering the vertebrobasilar distribution, the most common locations include the tip of the basilar artery, the superior cerebellar artery branch from the basilar artery, the anterior inferior cerebellar artery branch from the basilar artery, and the posterior inferior cerebellar artery branch from the vertebral artery.[37]

There are various structural parts to a saccular aneurysm that are commonly referred to when treating them.[39,40] This includes the ostium – the area of inflow into the aneurysm and the body of the aneurysm. The body of the aneurysm is comprised of the neck at the base of the aneurysm, the dome at the tip of the aneurysm, and the body or sac in between (Figure 2).[39,40] The geometric landmarks of intracranial saccular aneurysms are often carefully analysed when considering appropriate treatment, particularly the neck to dome ratio.[41] Giant saccular aneurysms are ones that measure greater than 25mm in greatest dimension.[41]

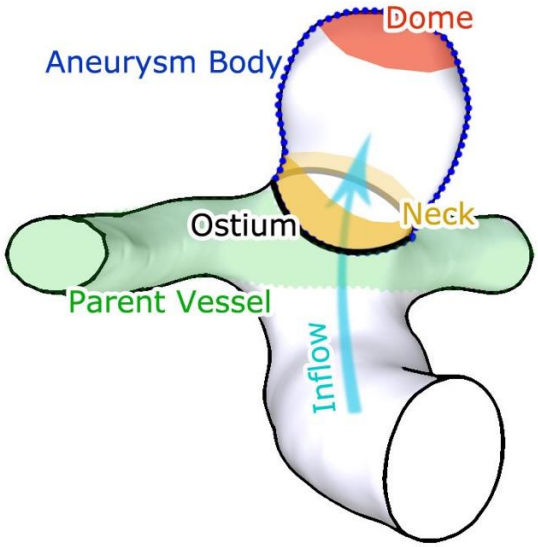

Figure 2 - The structural parts of a saccular aneurysm.

This includes the parent vessel, ostium, neck, body and dome. This is an aneurysm at an arterial bifurcation. Arterial blood flow from the parent vessels comes into the body of the aneurysm through the ostium and neck. The dome is tip of the aneurysm and the site that usually ruptures. Permission obtained for reuse of figure.

1.2.2 Other aneurysms

Intracranial aneurysm types that are non-saccular are considerably less common.[23] Although the reasons for this are not entirely understood, it is likely that the focal hemodynamic stress on the arterial wall that is the precursor for development of most intracranial aneurysms has greater association with a focal outpouching than other morphologies.[23]

Fusiform aneurysms have a long, elongated shape and are commonly associated with atherosclerotic disease. They are more common in the posterior circulation and have a propensity to have pathological involvement of all three layers of the arterial wall. Blood blister aneurysms are uncommon, representing less than 1% of all intracranial aneurysms.[42] They are small, hemispherically shaped, and usually arise from non-branching points of the ICA.[42] Blood blister aneurysms most commonly present as ruptured aneurysms and are notoriously difficult to treat.[43] Intracranial mycotic aneurysms encompass aneurysms arising from an infection in the arterial wall of an intracranial vessel, usually in the context of a bacteraemia (bacterial infection in the blood stream).[42] The most common organism causing a mycotic aneurysm is Staphylococcus aureus.[44] They have predilection for occurring in more peripheral branch points, especially in the distal MCA.[45]

1.3 Diagnosis of intracranial aneurysms and ruptured aneurysms

Intracranial aneurysms are detected either when ruptured as a subarachnoid haemorrhage (SAH), or are found unruptured either as an incidental finding or on screening.[38] Unruptured aneurysms are usually asymptomatic. One exception is an oculomotor nerve palsy from the mass effect of a PCOM aneurysm.[42] An aneurysmal SAH results in a specific pattern of intracranial haemorrhage with accumulation of blood in the subarachnoid space, between the arachnoid mater and pia mater.[42,46] Ruptured intracranial aneurysms are most commonly saccular aneurysms. This is because of both the significantly higher incidence of saccular aneurysms and the higher turbulence and wall stress that occurs in saccular aneurysms compared to other morphologies such as fusiform.[23] Rupture of saccular aneurysms is often a devastating clinical event with substantial associated mortality and morbidity.[47]

The classic history of a patient presenting with a ruptured intracranial aneurysm is a severe, sudden-onset headache.[47] This is often referred to as a thunderclap headache that peaks in one hour and can be localised or generalised. Common associated symptoms include a brief loss of consciousness, vomiting and neck pain.[48] Aneurysmal SAH occurs most commonly during non-strenuous activity; however, can occur during physical activity or activities associated with a Valsalva manoeuvre, such as sneezing or coughing.[49] Aneurysmal SAH may also present as sudden death - as many as 22% of patients die before reaching the hospital.[5]

All patients presenting with a history and symptoms suggestive of an aneurysmal SAH should immediately undergo evaluation for an aneurysmal SAH, beginning with a non-contrast computed tomography (CT) of the head.[47] The sensitivity of modern head CT for detecting SAH is highest in the first six hours after the SAH, approaching nearly 100% when interpreted by expert reviewers, and then progressively declines over time to approximately 58% at day 5.[50] The blood pattern is characteristic and generally found in the basal cisterns of the brain.[51] Additional locations include the sylvian fissures, the longitudinal fissure and the interpeduncular fossa.[51] The distribution of blood on CT (performed within 72 hours after the bleed) is a poor predictor of the site of an aneurysm except in patients with ruptured ACA or ACOM aneurysms and in patients with a parenchymal hematoma.[52]

A lumbar puncture is mandatory if there is a strong suspicion of an aneurysmal SAH despite a normal CT of the head.[53] Lumbar puncture should include measurement of the opening pressure, visual inspection for xanthochromia, as well as cerebrospinal fluid (CSF) analyses for cell counts, biochemistry and presence of bilirubin.[53] Xanthochromia is a pink or yellow tint to the CSF that represents the presence of haemoglobin breakdown products. An otherwise unexplained xanthochromic supernatant in CSF is highly suggestive of SAH. Presence of bilirubin in CSF is diagnostic for SAH and is detectable approximately 12 hours after SAH, peaks at 48 hrs, and may last as long as four weeks after a SAH.[54]

Once a diagnosis of SAH has been made, the aetiology of the haemorrhage must be determined by angiographic studies. Most centres initially use non-invasive imaging with computed tomography angiography (CTA) or magnetic resonance angiography (MRA). Both CTA and MRA can identify intracranial aneurysms of 3 or more millimetres with a high degree of sensitivity.[55] Digital subtraction angiography (DSA) is a fluoroscopic technique that is used to visualise in high resolution the cerebral blood vessels with elimination of radiopaque structures such as bones.[56] It is an invasive test that utilises the Seldinger technique for accessing either the femoral or radial arteries. A guidewire and microcatheter are then induced, and a series of contrast images are taken in succession as the contrast material is injected.[56] DSA is believed to have the highest resolution to detect intracranial aneurysm and define their anatomic features, and remains the gold standard test for this indication.[8] DSA should be performed if CTA or MRA does not reveal an aneurysm in a patient with a suspicious pattern of SAH.[8] The morbidity of completing a DSA in patients

with a SAH is relatively low, with the combined risk of permanent and transient neurological complications being approximately 1.8%.[57]

1.4 Grading systems used in ruptured intracranial aneurysms

There are various classification systems that are used in grading both the severity of an aneurysmal SAH at presentation and the outcomes. Each classification system serves a unique purpose and they are therefore used in combination. The *Glasgow Coma Scale (GCS)* is a universal classification system for assessment of an impaired conscious state in response to a defined stimuli.[58] It is a 15 point scale that consists of eye opening, verbal response and motor response scores.[58] It can be used in describing the conscious state in a patient presenting with a ruptured intracranial aneurysm. The *World Federation of Neurosurgical Societies (WFNS)* grading system uses the combination of the patients presenting GCS and presence of focal neurological deficits to grade the clinical severity of the SAH.[59] This grading system is used to prognosticate the long term functional outcomes of the patient.[59] The *Hess and Hunt (H&H)* is a 5 point grading system used to predict mortality rates after an aneurysmal SAH based on the clinical features at presentation.[60] The *Glasgow Outcome Scale (GOS)* and *modified Rankin Scale (mRS)* are the two commonly used scales for measuring functional outcomes after a ruptured intracranial aneurysm. The GOS consists of five ordered categories: i) death, ii) vegetative state, iii) severe disability, iv) moderate disability, and v) good recovery.[61] The mRS is a clinical reported measure of global disability that consists of a scale running from 0 to 6. It scores the patients disability or dependence in activities of daily living.[62]

1.5 Natural history and complications of ruptured intracranial aneurysms

Medical and neurologic complications, such as hyponatremia, seizures and hydrocephalus, are common after an aneurysmal SAH and contribute substantially to overall morbidity and mortality. For this reason, amongst others, patients with an aneurysmal SAH are most appropriately managed in high volume centres with a dedicated neurocritical care unit. Observational data suggest that such specialised centres have improved outcomes, with lower mortality rates, decreased length of intensive care stay, decreased overall complication rates, and decreased rates of requirement for a ventriculo-peritoneal shunt placement.[63,64]

After rupture, the patient is at substantial risk of early rebleeding (4-14% in the first 24 hrs, with a maximal risk in the first 2 to 12 hrs).[65,66] More than one third of rebleeds occur within 3 hours and nearly half within 6 hours of the sentinel rupture.[8] Re-rupture is associated with high mortality rates (up to 70%) and therefore preventing this occurring is a priority in the early stages of management.[66] Aneurysm exclusion with surgical clipping or endovascular techniques are effective treatment options to prevent re-rupture, and should therefore be performed as early as feasible, preferably within 24 hrs.[8]

Patients with an aneurysmal SAH may present with, or develop, elevated intracranial pressure (ICP) due to a number of factors, including haemorrhage volume, acute hydrocephalus, reactive hyperaemia and distal cerebral arteriolar vasodilation.[48] Hydrocephalus denotes any pathology causing an increase in the volume of CSF due to insufficient passage of the CSF from its point of production in the ventricles of the brain into the systemic circulation.[67] Hydrocephalus affects 20-30% of patients with an aneurysmal SAH.[68] It can present within the first few minutes to hours after the SAH, or also a later complication.[68] Hydrocephalus after SAH is thought to be caused by reduction of CSF flow and absorption by blood products or adhesions obstructing the arachnoid granulations.[68] The arachnoid granulations are small projections of the arachnoid membrane that allow CSF to pass from the subarachnoid space into the venous system.[69] Immediate CSF diversion with an external ventricular drain is indicated for patients who have a deteriorating level of consciousness and evidence of elevated intracranial pressure (ICP) and/or hydrocephalus.[68] In patients with elevated ICP due to causes other than hydrocephalus, or those with refractory elevated ICP despite CSF diversion, other measures such as osmotic therapy, hyperventilation or a decompressive hemicraniectomy may be necessary.[8]

Delayed cerebral ischemia (DCI) is a frequent complication of aneurysmal SAH and contributes substantially to mortality and morbidity.[70] The diagnosis of DCI requires the occurrence of a delayed ischemic neurological deficit (DIND) such as hemiparesis, aphasia, hemianopia or neglect), or a decrease of at least two points on the GCS that lasts for at least one hour, that was not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes after appropriate clinical assessment, brain imaging and laboratory studies.[71] DCI occurs in approximately 30% of patients with aneurysmal SAH, typically between 4-14 days after symptom onset.[71] The most common cause of DCI is vasospasm, and the severity of symptoms depends upon the artery affected and the degree of collateral

circulation.[71] Vasospasm is believed to be produced by spasmogenic substances during the lysis of subarachnoid blood.[72] The risk factors for vasospasm include the severity of bleeding and its proximity to the vessels of the Circle of Willis.[72] Therefore, the appearance of the SAH on the sentinel CT scan can help predict the likelihood of complicating cerebral vasospasm.[72] Mechanisms other than vasospasm that can contribute to DCI include microcirculatory dysfunction with loss of autoregulation, microthrombosis, cortical spreading depression and delayed cellular apoptosis.[73] Patients who develop DCI often have common patterns of cerebral infarction on CT imaging of the brain. These include single cortical infarcts, typically located near the site of the ruptured aneurysm, and multiple widespread infarcts, often involving bilateral and subcortical regions and frequently located distal to the ruptured aneurysm.[74] To reduce the risk of poor outcomes from DCI, all patients should receive the calcium channel blocker nimodipine, and a neutral input/output fluid balance should be maintained.[75]

There are other complications that can occur following an aneurysmal SAH that also contribute to the poor prognosis. Hyponatremia occurs in up to 30% of patients and may result from either the syndrome of inappropriate secretion of antidiuretic hormone or from cerebral salt wasting.[76] Acute seizures occur in 6 to 18% of patients, with risk factors including thick subarachnoid clot, intracerebral haematoma, DCI, and aneurysm in the MCA. Seizures that occur prior to aneurysm treatment are often a sign of early rebleeding.[8] Pulmonary oedema and cardiac arrhythmias complicate 23% and 35% of aneurysmal SAH cases respectively.[77] These appear to be more common and severe in people with a higher volume of SAH.[77] Hyperglycaemia[78] and fever of infectious and non-infectious origin[79] have also been associated with aneurysmal SAH and associated with poor outcomes.

Outcomes and prognosis of aneurysmal SAH are affected by potential brain injury from the SAH and subsequent complications, as well as by risks related to treatment for excluding the aneurysm (which will be expanded upon in the following section). Aneurysmal SAH has high early mortality rates. As stated previously, as many as 22% of patients die prior to being evaluated in hospital.[5] Among patients who arrive at hospital for treatment, much of the subsequent early mortality is caused by the common complications of aneurysmal SAH previously described. The early mortality rates of aneurysmal SAH patients being treated in hospital are declining.[80] Improved diagnostic accuracy over time and therapeutic advances in

neurocritical care are plausible, yet unproven, reasons for the reduction in early mortality rates.

Survivors of aneurysmal SAH also have an increased long-term mortality rate compared to the general population.[81] In a Swiss national registry of 1787 patients with aneurysmal SAH, the one-year mortality rate was 22%.[82] This is likely because of the high rate of morbidity that is also associated with aneurysmal SAH, as well as the higher prevalence of cerebrovascular and cardiovascular risk factors.[83] Approximately 10% of survivors remain moderately or severely disabled.[82] Long term complications include neurocognitive dysfunction, epilepsy and focal neurological deficits. Several studies that have reported survivors of aneurysmal SAH have high rates of memory and neurocognitive impairment.[84-86] The location of the aneurysm responsible for the SAH does not appear to influence cognitive outcomes, but the occurrence of vasospasm, DCI and other complication does.[87] By contrast, the association between neurocognitive dysfunction and the treatment modality is variable in the literature, with some studies suggesting the proportion of patients with long term cognitive impairments is higher in those treated with surgical clipping than with endovascular coiling, and vice versa.[81,85,88]

Patients who survive aneurysmal SAH also have a small but enduring risk of recurrent aneurysm formation and rupture despite successful endovascular or surgical treatment of the aneurysm. Recurrent SAH may result from recurrence of the treatment aneurysm, rupture of another-pre-existing aneurysm in a patient with multiple aneurysms, and de novo aneurysm formation. The risk of these events occurring is the rationale for monitoring with follow up imaging.[89]

1.6 Treatment options for repairing ruptured cerebral aneurysms.

For a patient that has had a ruptured cerebral aneurysm, the decision needs to be made between the involved clinician, the patient (if feasible) and their family as to whether pursuing treatment of the ruptured aneurysm, or managing the patient with comfort measures, is most appropriate. The intention of treatment for a ruptured cerebral aneurysm is to prevent re-rupturing occurring, which, as previously discussed, has significant consequences. The optimal treatment strategy should provide benefit over the natural history of the aneurysm and aim for low rates of morbidity and high rates of aneurysm obliteration.

The decision as to whether endovascular or open surgery with clipping is most appropriate for each individual patient is one of careful consideration and routinely discussed between a neurosurgeon, an interventional neuroradiologist as well as the patient and their family. The aneurysm size and morphology, presence of an intraparenchymal haematoma as well as the patient profile, are often pertinent factors when deciding whether microsurgical clipping or endovascular therapy is the most appropriate.[41]

1.4.1 Microsurgical clipping

The first successful craniotomy and microsurgical clipping of an intracranial aneurysm was completed on March 23, 1937, by Walter Dandy.[90] It was not until 1975, when Yasargil and Fox introduced the microscope to neurosurgery's arsenal, that safe and effective exposure of the Circle of Willis could be achieved.[91] The principle of surgical clipping involves gaining access to the aneurysm, commonly through a pterional craniotomy and careful dissection through the Sylvian fissure on the lateral surface of the brain, dissecting the aneurysm away from the surrounding brain parenchyma to optimize visualisation of the aneurysm neck, and finally employing a metallic clip permanently to completely obliterate the neck without compromising the patency and integrity of the parent and perforating vessels (Figure 3).[92] After the clip is placed, a doppler is used to check that the aneurysm has been excluded from the arterial circulation, and that the proximal and distal vessels related to the aneurysm still have flow in them. The craniotomy bone flap is then replaced and secured with titanium plates and screws, and the scalp sutured closed.

Figure 3 - Illustration of how metallic intracranial aneurysm clips obliterate the aneurysm. Permission obtained for reuse of figure.

Various factors need to be considered before making the decision to clip an intracranial aneurysm including the age of the patient, aneurysm size and location. A young patient with a small aneurysm located in the anterior circulation is the ideal candidate for clipping.[93] Posterior circulation aneurysms are challenging to access transcranially, and thus open surgery is not preferred.[94] An important factor with clipping is its effectiveness in long-term exclusion of the aneurysm, with low rates of residual and recurrent aneurysm. Various studies have demonstrated long-term occlusion rates with clipping at over 95%, significantly reducing the requirement for close surveillance with angiographic imaging.[95,96]

Several techniques have evolved as an adjunct in microsurgical clipping to aid the surgeon in optimising outcomes. The temporary clip ligation of the proximal artery is one of the most utilised.[97] By temporarily occluding the proximal vessel, the blood supply to the intracranial aneurysm is obliterated, causing the aneurysm to soften and thereby maximising visualisation and aneurysm dissection. However, this technique poses potential risks of ischemia in the vascular territory supplied by the proximal artery. To minimise the risk of ischemic complication, the occlusion time is typically kept to below 10-20 minutes.[97] Advances in neuromonitoring have also been instrumental in providing safer surgery. The development of infrared indocyanine green video angiography in 2005 has provided the significant benefit of evaluation of vascular patency intraoperatively.[98] The use of intraoperative microvascular doppler ultrasonography has now become common practice for checking arterial patency after clip application.[92] In neurosurgery centres equipped with a hybrid operating theatre, a cerebral DSA can be performed intraoperatively to confirm arterial patency after clip application. Although this is considered the gold standard for intracranial aneurysm surgery by some studies, it is not standard practice.[99,100]

The evolution of the techniques and adjuncts in surgical clipping have reduced associated complications of the surgery but not removed them.[101] The complication profile of surgical clipping has evolved with time but is still significant. This is always an important consideration for a treating neurosurgeon when choosing what treatment option is most appropriate for the patient, as adverse intraoperative events contribute significantly to the morbidity and mortality of patients with a ruptured intracranial aneurysm. The current incidence of surgical complications has been reported widely in the literature and lies somewhere between 4-25 percent.[102] The difficulty lies in variable definitions and the

possibility of patient confounding factors that can contribute, such as hydrocephalus, DCI and vasospasm, seizures and sepsis.[101]

New or worsened neurological deficit is a considerable risk associated with surgical clipping.[101] This may be caused by infarction from brain retraction, temporary clip occlusion, manipulation of small perforating vessels or inadvertent permanent clip occlusion of small hidden perforating vessels.[101] Neurological deficits may also be caused by intraoperative haemorrhage from the aneurysm causing an intraparenchymal hematoma, or post operative haematomas, such as a subdural or extradural haematoma.[103] Cranial nerve deficits, particularly the oculomotor nerve, occur in approximately 3% of cases.[102] Other complications include intracranial infection, postoperative rebleeding and death.[102]

1.4.2 Endovascular therapy

In 1990, the first successful deployment of a detachable bare platinum coil for securing an intracranial aneurysm was published.[104] Since its inception, endovascular treatment with coils has gained worldwide acceptance and popularity as an effective, minimally invasive treatment option for both ruptured and unruptured intracranial aneurysms.[105] Like surgical clipping, the technique and adjuncts used have evolved significantly to what is currently utilised in clinical practice.

The goal in coiling is to achieve dense packing of the aneurysm through delivery of detachable platinum wires, resulting in an unorganised thrombus and granulation tissue formation to limit blood circulation into the aneurysm lumen (Figure 4).[92] For a ruptured intracranial aneurysm, this theoretically prevents re-rupturing occurring. Packing density is recommended to be 20% or more of the aneurysms volume, which can require deployment of multiple coils, depending on the size of the aneurysm.[106]

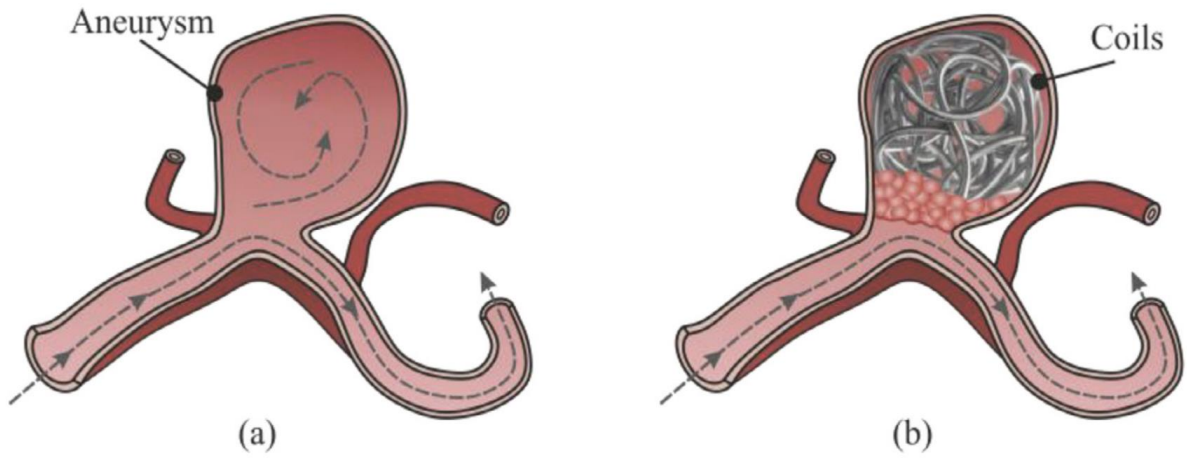

Figure 4 -Illustration of the technique of endovascular coiling of intracranial aneurysms (a) before coil embolization, (b) after coil embolization. Permission obtained for reuse of figure.

For coiling an intracranial aneurysm, the patient is usually under general anaesthesia. Vascular access is obtained via Seldinger technique and is usually via the common femoral artery.[107] Angiography, including 3D rotation angiography, is performed to get a current image of the aneurysm. A micro-guidewire and microcatheter are then inserted under fluoroscopy and heparinisation and passed as close to the aneurysm as possible. Once the microcatheter is placed in the desired position, the intervention/coiling phase is commenced.[107] The first coil to deploy is usually a coil with 3D shape and called the 'framing' coil to cover the entire wall of the aneurysm.[107] Coiling is then continued into the aneurysm sac in the 'filling' phase until adequate packing is achieved. A final angiogram is then completed to assess the position of the coil, whether there is any filling of contrast in the aneurysm sac, and the condition of the parent artery.[107] Given that large doses of intravenous contrast are administered during this procedure, patients with severe kidney disease may require pre-and-post procedural hydration to avoid worsening renal function.[107]

Depending on the ruptured aneurysm morphology and anticipated difficulty of the endovascular coiling, contemporary adjuncts such as a balloon and stent assistance may be used.[107] Balloon assisted coiling (BAC) has been popularised for use in ruptured and unruptured intracranial aneurysms with wide necks.[108] During placement of the coil, a compliant balloon is inflated in the parent vessel lumen to create a temporary tamponade for preventing the coils herniating out into the parent vessel.[108] Although BACS has increased the capacity to coil ruptured aneurysms previously considered unfavourable for endovascular

treatment, some studies have reported higher complication rates in BAC compared to simple coiling.[109,110] There are also reports of an increased risk of long-term coil impaction and aneurysm recurrence.[111]

Stent-assisted coiling (SAC) for ruptured and unruptured intracranial aneurysms was introduced in 1997.[112] Its indications have been limited to difficult to treat, wide-neck aneurysms not amenable to simple coiling or BAC.[113] The primary objective to a stent application is to provide a scaffold to protect the parent vessel from coil herniation and also to limit arterial flow into the aneurysm (Figure 5).[113] The significant benefit of this is the reduced rate of long-term aneurysm recurrence compared to coiling alone.[113] Like BAC, the complication profile with SAC tends to be higher than simple coiling alone.[114] This is exaggerated by the inherent thrombogenicity of these devices that necessitates use of dual antiplatelet (dAPT) medication peri-operatively and post-operatively to prevent thromboembolic events.[107] This requirement for dAPT limits the role of SAC in patients with ruptured intracranial aneurysms.[107]

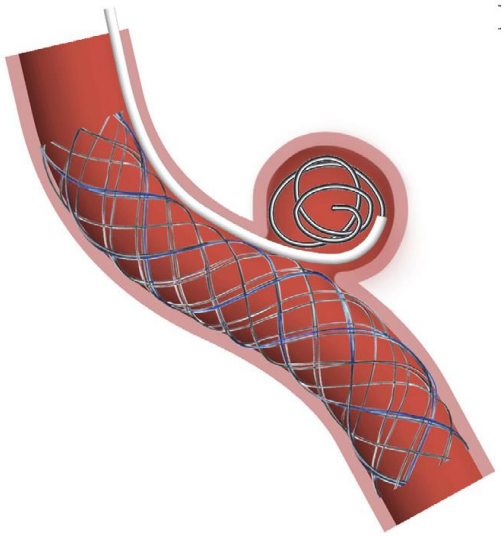

Figure 5- Illustration of stent assisted coiling of an intracranial aneurysm. Permission obtained for reuse of figure.

Endovascular coiling has become increasingly popular for treating ruptured aneurysms but does have inherent risk of complications. Thromboembolic events (TEEs) and its clinical consequences represents one of the most serious complications of coiling.[115] The incidence of TEEs is reported up to 77%, and permanent neurologic disability and death up to 8.4%.[116]

Thrombotic microemboli can originate from a pre-existing thrombus within the aneurysm, or intravascular thrombotic plaques that are displaced during the procedure.[115] Intraprocedural aneurysm rupture is reported in approximately 5% of cases, but significantly increases the risk of periprocedural death or disability.[117] Long-term recurrence and the risk of SAH is reported to be significantly higher in coiling compared to clipping.[118] This is because of the phenomenon of coiling compaction and recanalization of the base of the aneurysm.[118] This necessitates vigilant surveillance with post treatment imaging using either a CTA or MRA.

1.7 Clipping versus coiling in ruptured intracranial aneurysms

As endovascular coiling has gained worldwide acceptance and increasing popularity for managing ruptured intracranial aneurysms, there have been numerous studies that have compared the effectiveness, safety and clinical outcomes of surgical clipping versus endovascular coiling.[119-121] The landmark study was the International Subarachnoid Aneurysm Trial (ISAT).[120] This was a multi-centre randomised controlled trial (RCT) comparing the safety and efficacy of clipping versus coiling, with 2143 patients enrolled in the study out of 9559 that were screened. The two key findings of the trial were that patients in the endovascular group demonstrated both relative and absolute risk reduction of disability and death at one year compared to surgical clipping; however, the risk of recurrence and rebleeding was significantly higher in the endovascular group.[120] The trial was heavily criticised for several reasons, most related to the methods of randomisation of the patient population and the bias in the exclusion criteria, with MCA and posterior circulation aneurysms being under represented; the trial was therefore ceased after one year.[122]

Since the ISAT study, there have been additional RCT's[119,121,123] and cohort studies[124,125] comparing the two modalities for treatment of aneurysmal SAH. In 2018, a Cochrane systematic review was published comparing the outcomes after SAH for people treated with endovascular coiling versus surgical clipping.[126] The review included four RCTs with 2458 participants. The main conclusions were that after one year, the clipping group had significantly higher rates of a poor functional outcome, including death or dependent living compared to the endovascular group. At 5 and 10 years follow-up, the difference in functional outcomes was superior but not significant in the endovascular group.[126] The risk for rebleeding was significantly higher in the endovascular group than the clipping group, as was the risk of procedure related complications in the clipping group.[126] These findings of the

review were consistent with the ISAT study results, likely because the ISAT study contributed the majority of the data to the pertinent meta-analyses presented in the review.[126] However, the findings of other individual studies are not always consistent with the ISAT trial result.[127,128] The systematic review by Xia et al.[128] published findings that coiling was associated with higher mortality and similar rates of other complications including rebleeding, infarction and shunt dependent hydrocephalus compared to clipping in patients with a high grade aneurysmal SAH.

Large trials, such as the ISAT study, often evaluate and publish the outcomes of clipping versus coiling inclusive of all aneurysm locations.[129,130] A subgroup analysis may be completed for anterior versus posterior circulation aneurysms, but not for individual aneurysm locations. It is well acknowledged in various cohort studies, that the ruptured aneurysm morphology, size and location influence the safety, efficacy and technical difficulty of surgical and endovascular treatment.[10,11,131] For example, ruptured aneurysms with a particularly wide neck, or unfavourable neck-to-dome ratio, as well as aneurysms that are very small or very large in size, classically represent the less amenable angioarchitectural features for a definitive coiling, entailing a higher risk of incomplete obliteration or recanalisation.[10] The specific anatomical characteristics of the MCA complex have also traditionally made ruptured MCA aneurysms favourable for clipping.[10] The outcomes of clipping versus coiling for both ruptured and unruptured aneurysms in specific locations have thus been evaluated in smaller scale studies.[10,132-135]

Systematic reviews of outcomes of clipping versus coiling for aneurysms of specific location have been completed for PCOM aneurysms, [13] unruptured MCA aneurysms,[136] and combined ruptured/unruptured MCA aneurysms.[12] The outcomes from these systematic review were variable. Gaberel et al.[13] reported superior outcomes with surgical clipping of PCOM aneurysms presenting with an oculomotor nerve palsy. Complication rates were comparable between both techniques.[13] Smith et al.[136] reported superior functional outcomes with surgical clipping than endovascular coiling for unruptured MCA aneurysms. Clipping was also associated with higher aneurysm occlusion rates than endovascular coiling.[136] Ijsbrand et al.[12] again reported superior functional outcomes with surgical clipping for unruptured MCA aneurysms; however, reported superior functional outcomes with coiling for ruptured MCA aneurysms.

1.8 Significance of the review

Given that ACOM aneurysms represent both the most common anatomical location for aneurysmal occurrence, but also the site for an aneurysmal rupture and SAH, it is important for treating clinicians to have an evidence-based standpoint when considering treatment with either clipping or coiling. Prior to this review, the evaluation of outcomes for surgical clipping versus endovascular coiling in ruptured ACOM aneurysms, had not been systematically reviewed.

1.9 Review objective and question

The objective of this systematic review was to locate, critically appraise and synthesise the best available evidence for the effectiveness of microsurgical clipping versus endovascular coiling on outcomes in adults with a ruptured ACOM aneurysm.

The specific review question was generated using the population, intervention, comparison, outcome (PICO)[137] framework:
In an adult patient with a radiologically confirmed ruptured ACOM aneurysm requiring treatment, are the functional outcomes, angiographic occlusion rates, aneurysm recurrence rates and safety of treatment of microsurgical clipping (intervention) comparable to endovascular coiling (comparator)?

1.10 Methodology overview

A systematic review is a comprehensive summary of all available evidence relevant to a specific question.[138] Systematic reviews are generally regarded as the highest level of evidence as the risks of bias is minimised due to the implicit methods used.[138] In combining data from multiple studies the statistical power of the results of the review are increased and this increases the probability of identifying a true effect. Systematic reviews also produce generalisability through demonstrating similar effects over a variety of clinical settings and countries.[139] Both RCTs and observational studies are potentially valuable sources of generalisability of adverse effects and safety of treatment.[140] Observational research has been demonstrated to be as accurate RCTs in estimating risk of adverse effects.[141] Data from observational studies is therefore imperative to include in systematic reviews when

investigating for safety and adverse effects of different treatments, such as clipping and coiling ruptured intracranial aneurysms.

CHAPTER 2: METHODS

This chapter presents the methods for this systematic review presented in this thesis. This includes a description of the inclusion criteria, the search strategy, the methods used for critical appraisal of studies, data extraction and synthesis. A study protocol was completed and published prior to the commencement of this systematic review (see *Appendix 1*).[142] This review adheres to the JBI methodology for systematic reviews of effectiveness.[143]

2.1 Inclusion criteria

2.1.1. Participants

This review considered studies that included patients aged 18 years and over with a ruptured ACOM aneurysm. A ruptured ACOM aneurysm is routinely diagnosed on a CTA of the brain, which demonstrates both the aneurysm and the characteristic distribution of SAH. This is routine for patients presenting with a history and symptoms characteristic of an aneurysmal SAH, particularly a severe, acute headache. Alternatively, the diagnosis of a ruptured ACOM aneurysm can be made with a lumbar puncture demonstrating xanthochromia in cases with a CTA demonstrating the ACOM aneurysm but without radiological SAH.[144]
Patients were included that had multiple intracranial aneurysms, including aneurysms in other locations; however, these patients were included only if they had a ruptured ACOM aneurysm and only that aneurysm was treated. Participants were excluded if they had already had an intracranial aneurysm treated.

2.1.2 Intervention of interest

This review considered studies that evaluated outcomes of microsurgical clipping of ruptured ACOM aneurysms. Clipping of a ruptured ACOM aneurysm is an open brain operation that routinely involves several steps, including: a frontotemporal, curvilinear scalp incision, a pterional craniotomy, microsurgical dissection through the sylvian fissure of the brain, and ligating of the aneurysm by placing a clip at the base of the aneurysm (see section 1.4.1).[94]

2.1.3 Comparator

This reviewed considered studies that compared the intervention to endovascular treatment of ruptured ACOM aneurysms. The endovascular techniques considered in this review include aneurysmal coiling, BAC, and SAC. These techniques were collectively grouped as endovascular treatment. Coiling of an intracranial aneurysm involves arterial access through the femoral or radial artery and deploying soft platinum wire spirals through a microcatheter into the aneurysm (see section 1.4.2). A thrombosed aneurysm resists the entry of blood, providing a seal in a manner, similar to a clip (see section 1.4.1).

2.1.4 – Types of studies

This review considered both experimental and quasi-experimental study designs, including RCTs, non-randomised controlled trials, and other quasi-experimental studies and controlled interrupted time series. In addition, analytic observational studies, including prospective and retrospective cohort studies, and case-control studies were considered. Observational data was included as it is essential to provide a comprehensive assessment when investigating harms and adverse effects of treatment.[140]

2.2 Outcomes

2.2.1 Primary outcome

The sole primary outcome of this systematic review was functional status. Functional status refers to the patient's ability to perform normal activities of daily living. This was measured using either the mRS or the GOS. The timing of when these functional status scales are reported is variable between studies.

2.2.2 Secondary outcomes

The secondary outcomes of interest in this review were aneurysm occlusion, recurrence, and safety of treatment.

Aneurysm occlusion included rates of complete angiographic occlusion on post procedural imaging for both clipping and coiling. Post operative imaging includes CTA, MRA, or a DSA.

Aneurysm recurrence included both angiographic evidence of recurrence at the site of previous treatment (clipping or coiling) on post- procedural surveillance imaging or a post-operative re-rupture from the index ACOM aneurysm after treatment. Surveillance imaging includes CTA, MRA or DSA.

Safety of treatment was determined by the incidence proportion of thromboembolic events as well as other specific complications relevant to clipping and coiling. These include: surgical site infection or hematoma, seizures, haemorrhage during or after the procedure or surgery, or death related to the procedure. Hydrocephalus and vasospasm were not included as complications of the treatment as they are inherent to the disease and not the treatment. Thromboembolic events include a neurological deficit secondary to an ischemic brain insult, attributable to a thromboembolic event. In microsurgical clipping, this is usually secondary to a temporary clip being placed for too long, or a clip that is mispositioned and occludes a perforating vessel or the parent vessel. In endovascular coiling, it is usually secondary to embolising atherosclerotic plaque during the advancement of the microcatheter. Thromboembolic events are usually detected shortly after microsurgical clipping or endovascular treatment, with the patient demonstrating a new neurological deficit. This could include upper or lower limb weakness that correlates with brain imaging (CT or MRI), demonstrating a new area of infarction secondary to the aneurysm treatment. Thromboembolic events are therefore a combination of new neurology with new radiological findings. Mortality related to the procedure was included as part of the secondary complications data. However, because it is the most significant and severe secondary complication, it was additionally reported as an individual result.

2.3 Review Method

2.3.1 – Search Strategy

The search strategy involved a multistep process to locate relevant published studies. Searching for this systematic review was conducted on the 29th September 2021. An initial limited search of PubMed was undertaken to identify articles on the topic, using the terms ‘Anterior Communicating artery aneurysm’ and ‘rupture.’ This process was undertaken as a preliminary, screening step to ensure that there were sufficient studies to warrant pursuit of a systematic review on the topic.[142] The key words contained in the titles and abstracts of relevant articles were then analysed, and the index terms (MESH terms) used to describe the

articles were used to develop a full search strategy for PubMed (*Appendix 2*). The search strategy, including all identified key words and index terms, were adapted for each included database and/or information source. No language or date limitations were applied to the search.

The following databases were searched: PubMed, Embase, Scopus, and Cochrane Central Register of Controlled Trials (*Appendix* 2). Sources of unpublished studies were also searched, including the International Clinical Trials Registry, the Australian and New Zealand Clinical Trials Registry, and ClinicalTrials.gov (*Appendix 2*).

2.3.2 – Study Selection

Following the search, all identified citations were collated and uploaded into EndNote X9 (Clarivate Analytics, PA, USA) and duplicates removed. Titles were initially screened in EndNote by JN and irrelevant records removed. The titles and abstracts of remaining studies were then screened by JN, and potentially relevant studies were retrieved in full and their citation details imported into the Cochrane Review Manager (RevMan) Web program (Version 5.8.0, The Cochrane Collaboration). The full text articles of selected citations were then assessed in detail against the inclusion criteria and reasons for exclusion recorded (JN).

2.3.3 – Assessment of methodological quality

Eligible studies were critically appraised for methodological quality at the study level by two independent reviewers (JN and MS) using standardised critical appraisal instruments from JBI for quasi-experimental studies and cohort studies (*Appendix 4*).[143] There were no disagreements that arose between reviewers regarding the individual assessments of the methodological quality of the selected studies. Given the expected limited quantity of research in this field, the decision was made to not exclude studies based on low methodological quality and high risk of bias, rather, all studies were included to ensure full consideration of the available dataset in subsequent analyses.[142]

2.3.4 – Data extraction

All data was extracted from studies included in the review by two independent reviewers (JN and MS) using a tailored data extraction tool (*Appendix 5*). The data extracted included the study design, the country in which the study was conducted in, the study period, number of

participants, how many aneurysms were included, mean patient age, female sex percentage, clipping and coiling numbers, endovascular adjuncts with coiling (SAC or BAC), GOS, mRS, timing of GOS or mRS, number of complete or partial occlusions for clipping and coiling, timing of occlusion assessment, periprocedural thromboembolic events, intraprocedural death rates, other secondary complications, recurrence on surveillance imaging, and post-procedural rupture. There were no disagreements that arose between the reviewers regarding the data extracted from the studies.[142] The corresponding author of one paper[145] was contacted to request additional data to be used in the analysis (*Appendix 6*).

2.3.5 – Data synthesis

Included studies, where possible, were pooled in statistical meta-analysis using Cochrane RevMan Web (version 5.8.0, The Cochrane Collaboration). Effect sizes were expressed as an odds ratio and their 95% confidence intervals calculated for analysis. Functional outcomes were analysed as the total number of favourable outcomes (mRS 0-2 or GOS 4-5) for both clipping and coiling. This is a recognised and commonly described method for reporting functional outcomes in the neurosurgical literature.[62,146] Where only the total number of unfavourable outcomes (mRS 3-6 or GOS 1-3) were reported,[133,147] the remaining participants were considered to have a favourable outcome. Complications were analysed as the total number of complications, including periprocedural thromboembolic events, secondary complications and mortality for both clipping and coiling. Mortality was included as part the total complications analysis as few studies reported on it. Subgroup analysis based on study design (see Section 3.1), were also completed separately for each outcome, and test for subgroup differences was completed. A random-effects model, with Mantel-Haenzel method, was used as the primary statistical model for the meta-analyses. This model was chosen because it is more effective when there are studies with smaller sample sizes and lower event rates,[143] directly aligned with the data available for this review. This model takes into account heterogeneity between studies using the standard $\chi^2$and I^2 test.[143] Sensitivity analysis was conducted on each outcome, primarily testing for robustness in the results when a fixed-effects model was applied. Risk difference was the primary model used for the recurrence outcome, with the intention of assessing for the actual difference in the observed risk of aneurysm recurrence between the subgroups. The proportion of events for favourable functional outcomes, recurrence, complications and complete occlusions was calculated as a

percentage by dividing the number of events from the total number of participants in each subgroup.

2.3.6 – Assessing certainty in the findings

Assessment of certainty in the findings was completed according to the GRADE approach using the software GRADEpro GDT (GRADEpro Guideline Development Tool, McMaster University and Evidence Prime, 2024). The main results from this are presented in the 'Summary of Findings' table. The quality of the evidence was initially downgraded if it was not derived from RCTs. Each outcome was further downgraded depending on whether there were study limitations; whether the results were inconsistent, imprecise, the evidence was indirect or there was publication bias.

CHAPTER 3: RESULTS

This chapter presents the results of the systematic review. It includes results of the search processes, study selection, assessment of methodological quality and characteristics of included studies. The findings for each outcome are also reported in this chapter.

3.1 Searching and study selection

Database searching for published studies returned a total of 818 records (Figure 3.1; PubMed 596; Embase 97; Scopus 117; Cochrane Central Register of Controlled Trials 8). A search of clinical trial registries to locate additional unpublished studies returned 2 citations (International Clinical Trial Registry 2, Australia and New Zealand Clinical Trial Registry Search Strategy 0, ClinicalTrials.gov 0). Upon combining all records, 115 duplicates were identified and removed (see Figure 3.1). The 2 registered clinical trials were removed as they were both incomplete and unpublished. There were no relevant studies published in a non-English language.

Following screening titles against the review inclusion criteria, 129 abstracts were subsequently screened (see Section 2.1). Following abstract screening, 104 citations were excluded, leaving 25 reports for full-text retrieval and review. Fourteen of the 25 studies were excluded following full-text review (Figure 6 and *Appendix* 3). Studies were excluded due to either an ineligible intervention/comparator or ineligible/irrelevant reported outcomes (*Appendix 3*). Overall, 11 non-randomised studies were included; 2 quasi-experimental studies[148,149] and 9 retrospective cohort studies[133,145,147,149-153]. No RCTs were eligible for inclusion in this review.

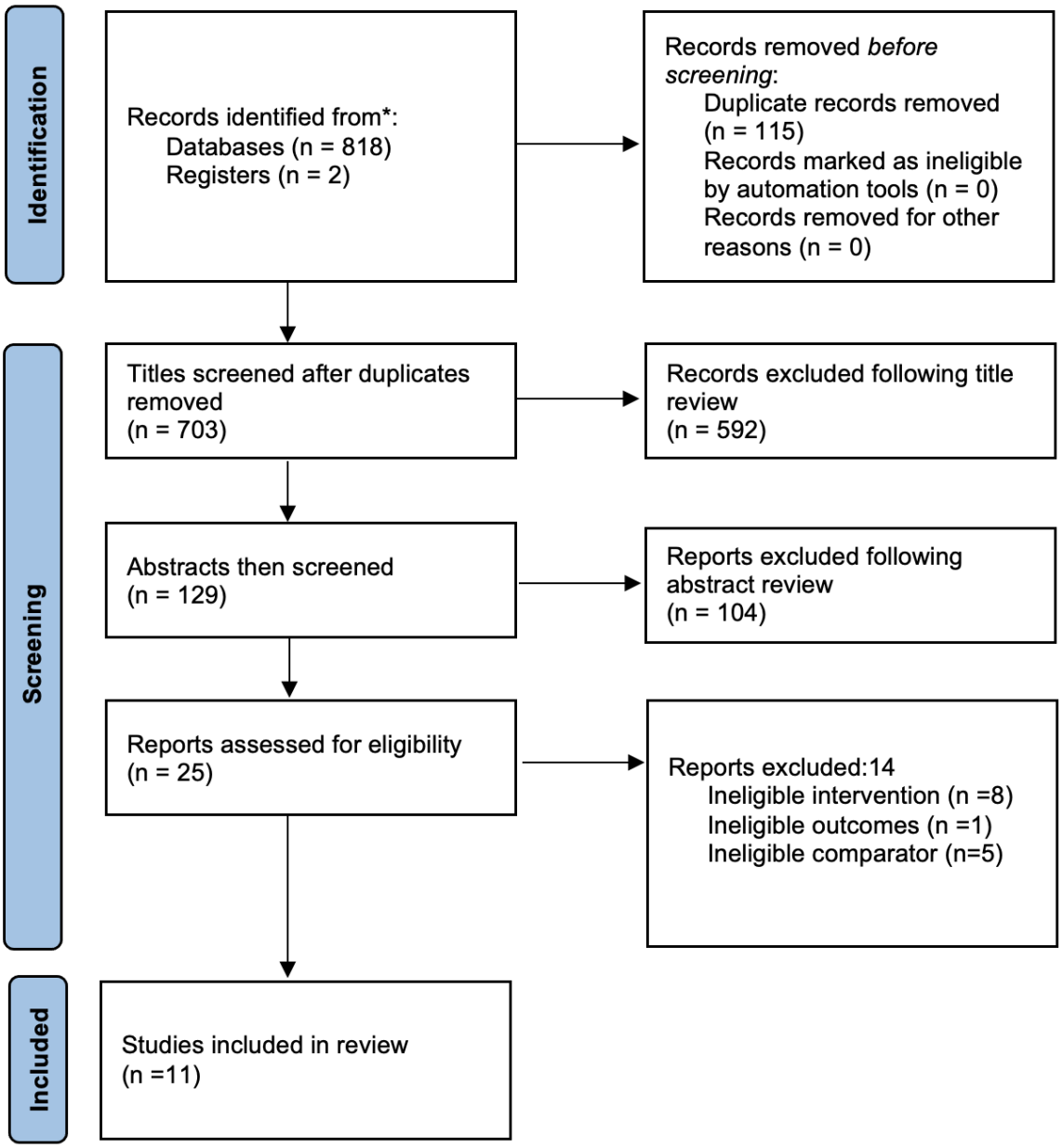

Figure 6 -PRISMA flow diagram of the study selection and inclusion process

3.2 Methodological Quality of included studies

The assessment of methodological quality of included studies is presented in Table 1 and 3.2. Studies are rated as Yes (Y), No (N) or Unclear (U) for each question. Of the two quasi-experimental studies, *Proust et al.*[149] was found to have high methodological quality scoring 7 out of 9. The study by *Ahmed et al.*[148] was moderate methodological quality scoring 4 out of 9. Both studies were clear regarding comparator and intervention groups as well as having

outcomes measured in the same way for both groups (Q1, 4 and 7). *Proust et al.*[149] described both groups having similar baseline characteristics, whereas *Ahmed et al.*[148] was unclear with this (Q2). *Proust et al.*[149] also described participants in each subgroup receiving the same treatment aside from the intervention of interest (clipping/coiling), whereas *Ahmed et al.*[148] was unclear with this (Q3). Both studies[148,149] had deficits in Q5 by not having multiple measurements of the outcome pre and post intervention. *Ahmed et al.*[148] had complete follow up with a minimal of 6 months post treatment, whereas *Proust et al.*[149] was unclear regarding the follow up (Q6). *Proust et al.*[149] had outcomes measured in a reliable way with appropriate statistical analysis used, whereas the study by *Ahmed et al.*[148] did not have any statistical analysis of the results, only fractions/percentages (Q8 and Q9).

Table 1- Methodological quality of quasi-experimental studies.

Appraised using the JBI appraisal tool for quasi-experimental studies.[154]

Citation	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Total**
**Ahmed et al.*[148]	Y	U	U	Y	N	Y	Y	U	N	4
**Proust et al.*[149]	Y	Y	Y	Y	N	U	Y	Y	Y	7
Total Y score %	100	50	50	100	0	50	100	50	50	

An 'unclear' rating indicates that the relevant details could not be found in the articles and the data could not be ascertained.

Appraisal questions for quasi-experimental studies:

1. is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable come first)?
2. Were the participants included in any comparisons similar?
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?
4. Was there a control group?
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?
7. Were the outcomes of participants included in any comparisons measured in the same way?
8. Were outcomes measured in a reliable way?
9. Was appropriate statistical analysis used?

The majority of cohort studies were rated high in their methodological quality, with most (7/9) scoring ≥8 out of 11. Deficits were generally found in response to questions 6, 9 and 10, the implications of which are considered below (Table 2). All observational studies recruited patients for both groups (clipping and coiling) from the same population (Table 2, Question 1). The exposure (the diagnosis of a ruptured ACOM aneurysm) was measured with a reliable and standardised method in all but two studies[145,150] (Table 2,Question 3). This would routinely include a plain CT scan of the brain for the diagnosis of a subarachnoid haemorrhage, as well as an angiographic study including either a CTA, MRA or DSA for the diagnosis of the culprit ACOM aneurysm. Confounding factors were identified in all observational studies except one[145] (Table 2, Question 4) and commonly included the presenting neurological status of patients and presence of multiple aneurysms. In all but three studies,[145,152,155] strategies to deal with these confounding factors were identified and described (Table 2, Question 5). There were no observational studies that stated whether participants were free of the outcomes of interest prior to the commencement or at the commencement of the study (Table 2, Question 6). All observational studies[133,145,147-153,155,156] measured outcomes using reliable and standardised tools (Table 2, Question 7) and had satisfactory descriptions of follow up and timing of outcome measures (Table 2, Question 8). The study by Backer et al.[150] measured functional outcomes in clipping versus coiling with the mRS at five days post intervention. This was assessed by both reviewers (see Section 2.3.2) as insufficient time for this primary outcome to be validly assessed; however, the study was still included as the data was agreed to still be relevant to the review. Six studies[147,149,151,152,155,156] had either no participants lost to follow up, or sufficiently described reasons that patients were lost to follow up (Table 2, Question 9). The remainder either stated no reason why patients were lost to follow up[133,145,150] or were unclear whether patients were lost to follow up.[148,153] Four studies[147,149,151,156] described strategies to address incomplete follow up (Table 2, Question 10), each of which also had described reasons that the patients were lost to follow up (Table 2, Question 9).

Table 2- Methodological quality of cohort studies

Appraised using the JBI appraisal tool for comparable cohort studies.[154]

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total
Backer et al.[150]	Y	Y	N	Y	Y	U	Y	N	N	N	Y	6
Harris et al.[152]	Y	Y	Y	Y	N	U	Y	Y	Y	U	Y	8
Heit et al.[133]	Y	Y	Y	Y	Y	U	Y	Y	N	N	Y	8
Li et al.[156]	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	10
Ma et al.[147]	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	10
Moon et al.[145]	Y	Y	U	U	U	U	Y	Y	N	N	Y	5
Nassiri et al.[151]	Y	Y	Y	Y	Y	U	N	Y	Y	Y	Y	9
Pietrantoni et al.[155]	Y	Y	Y	Y	N	U	Y	Y	Y	N	Y	8
Zhao et al.[153]	Y	Y	Y	Y	Y	U	Y	Y	U	N	Y	8
Total Y score%	100	100	82	91	82	0	100	91	64	36	100	

An 'unclear' rating indicates that the relevant details could not be found in the articles and the data could not be ascertained.

Appraisal questions for cohort studies:

1. Were the two groups recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure?)
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were reasons to loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilised?
11. Was appropriate statistical analysis used?

3.3 Characteristics of Included Studies

3.3.1 – Study Population

Details of the participant's baseline characteristics (age, sex and whether participants were excluded from the study for poor neurological status at presentation) are presented in Table 3. A total of 998 participants were included from the eligible studies. The mean age of the participants was 52. Of the included participants, 584 underwent microvascular clipping and 414 participants underwent endovascular coiling. Non-statistically significant differences were seen in the baseline characteristics of five of the included studies.[133,150,151,156] Statistically significant differences were seen in the baseline age characteristics in the study by Heit et al.[133] Statistically significant differences were seen in the baseline WFNS score of participants in the clipping and coiling groups in the study by Harris et al.[152] The remaining studies[145,147,148,155] reported baseline characteristics of the two groups as a total score and did not perform an analysis comparing differences (see Table 3)

Table 3 - Baseline Characteristics of included Study Populations.

Citation	**Group**	**Age (years)**	**Female sex %**	**Baseline neurology reported**
Ahmed et al.[148]	Total	46 (24-73) Mean (min to max)	52.3	Participants excluded if H&H score 4 or 5
Backer et al.[150]	Clipping	53 (28-75) mean (min to max)	46.7	N
	Coiling	49 (33-70) mean (min to max)	53.5	
	p - value	0.97	0.47	
Harris et al.[152]	Clipping	57.9 ± 13.6 Mean (SD)	63.2	WFNS I +II – 53% WFNS III-V – 47%
	Coiling	59.6 ± 15.4 Mean (SD)	59.3	WFNS I +II – 85% WFNS III-V – 17%
	p - value	0.91	0.74	WFNS I +II – 0.0046*
				WFNS III-V – 0.0046*
Heit et al.[133]	Clipping	50 (41-58) Median (IQR)*	52	N
	Coiling	55 (48-63.7)	62	

		Median (IQR)		
	p - value	0.03	0.42	
Li et al.[156]	Clipping	48.1 ±11.6 Mean (SD)	54.1	N
	Coiling	47.5 ±10.3 Mean (SD)	59.7	
	p - value	0.25	0.47	
Ma et al.[147]	Total	49.2 ± 9.9 Mean (SD)	39.7	Participants excluded if H&H score 4 or 5
Moon et al.[145]	Total	52.5 ± 12.2 Mean (SD)	40	N
Nassiri et al.[151]	Clipping	57.70 ± 10.5 Mean (SD)	64	N
	Coiling	50.89 ±11.6 Mean (SD)	44	
	p - value	0.79	0.69	
Pietrantoni et al.[155]	Clipping	56 (35-67) Mean (min to max)	68	N
	Coiling	59 (37-71) Mean (min to max)	64	
Proust et al.[149]	Clipping	45.4 ± 13.1 Mean (SD)	54.5	N
	Coiling	50.1 ± 16.3 Mean (SD)	33.5	
	p - value	0.29	0.75	
Zhao et al.[153]	Clipping	55.5 ± 11.1 Mean (SD)	55.4	N
	Coiling	54.5 ± 11.2 Mean (SD)	52.2	
	p - value	0.655	0.738	

** Indicates a significant difference in the baseline characteristic/s between the two treatment groups. H&H - Hess and Hunt score; WFNS – World Federation of Neurosurgical Societies (graded in Roman Numerals I to V); IQR – Interquartile Range.*

3.3.2 – Geographical location

All 11 studies recruited their participants from a single tertiary hospital with neurosurgical capacity in one geographical location. Three of the studies were conducted in China[147,153,156] and two in North America[133,145] (see Table 4). The remainder of the studies were conducted in Egypt[148], Hungary[150], England[152], Canada[151], Italy[155] and France[149] (see Table 4).

3.3.3 Study interventions

Of the eleven non-randomised studies, two were quasi-experimental and nine cohort studies (Table 4).[133,145,147-153,155-158] The intervention in all studies[133,145,147-153,155-158] was surgical clipping. The comparator in all studies was endovascular coiling. [2,5,7-17] In three studies[152,153,156] adjuncts to standard coiling were used, including BAC and SAC. The details of the specific stent types were not included. Additionally, the majority of studies did not include the number or experience of surgeons or interventional neuroradiologists performing the clipping or coiling.

Table 4- Characteristics of included studies

Study	Setting/ context	Participant characteristics	Participants	Outcomes measured	Description of main results/ author's conclusion	Results	Comments
Ahmed et al.[148]	**Study design:** Quasi-experimental **Country:** Egypt **Time reported:** June 2010-2011	**Inclusion criteria:** 1. Diagnosed ruptured ACOM aneurysm by CTA demonstrating the SAH and the aneurysm. 2. WFNS and Hunt-Hess classification grades I, II or III 3. Aneurysmal sac size <2.5 cm.	**Total:** 30 patients **Total number of aneurysms treated:** 30 **Endovascular:** 15 patients **Clipping:** 15 patients	1. GOS at 6 months, 2 years, 4 years 2. Complications 3. Recurrence rates	1. GOS was superior at 6 months in the coiling group that clipping group. 2. Endovascular coiling has less complications and lower mortality Recurrence rates were higher in endovascular group, however it can be managed with an early follow up angiogram and re-coiling.	**GOS at 6 months:** GOS clipping (scores): 1=4; 2=0; 3=2;4=1; 5=8 GOS coiling (scores): 1=1; 2=0; 3=2;4=3; 5=9 GOS 1-3 clipping: 6 GOS 4-5 clipping: 9 GOS 1-3 coiling: 3 GOS 4-5 coiling: 12 **Occlusion rates with treatment:** Number of complete occlusions post clipping: 14 Number of partial occlusions post clipping: 1 Number of complete occlusions post coiling: 13 Number of partial occlusions post coiling: 2 **Aneurysm recurrence:** Recurrence on surveillance imaging coiling: 4 Recurrence on surveillance imaging clipping: 0 Timing of surveillance imaging: 6 months Post-procedure rupture clipping: 0 Post-procedure rupture coiling: 0	Complications assessed included: hemiparesis, failed procedure, death, recurrence of aneurysm

						Complications: Periprocedural thromboembolic event clipping: 0 Periprocedural thromboembolic event coiling: 1 Periprocedural death rate clipping: 0 Periprocedural death rate coiling: 0 Secondary complications clipping: 1 Secondary complications coiling: 2 Hydrocephalus coiling:1 Hydrocephalus clipping: 2	
Proust et al.[149]	**Study design:** Quasi-experimental **Country:** France **Time reported:** January 2001 - December 2004	**Inclusion criteria:** 1. SAH secondary to ruptured ACOM aneurysm confirmed by CT and CTA or DSA. 2. Early treatment of ACOM aneurysm by clipping or coiling 3. Functional recovery allowing participation neurologicaly battery	**Total:** 98 patients **Number of patients excluded:** 48 – reasons for exclusion: refusal to participate, addiction, lost to follow up, psychiatric history **Total number of aneurysms treated:** 50 **Endovascular:** 14 patients **Clipping:** 36 patients	1. Evaluate functional outcomes and quality of life in clipping vs coiling 2. Neuropsychological outcomes in clipping vs. coiling 4. Evaluate structural brain damage using MRI post treatment clipping vs coiling.	1. No significant differences in mRS scores in clipping vs coiling (p=0.19) 2. No significant differences in Quality of life outcomes in clipping vs coiling (p=0.79) 3. No significant difference in neuropsychological outcomes in clipping vs coiling, however non-significant deficits in memory in clipping group vs coiling group (p=0.055) 3. Post op MRI demonstrated significantly more overall structural brain damage lesions, in frontotemporal brain	**mRS** Clipping: 0=10; 1=16; 2=6; 3=4; 4=0; 5=0; 6=0 Coiling: 0=4; 1=2; 2=7; 3=1; 4=0; 5=0; 6=0 Clipping - mRS 0-2: 32 Clipping - mRS 3-5: 4 Coiling - mRS 0-2: 13 Coiling - mRS 3-5: 1 **Occlusion rates with treatment:** Number of complete occlusions post clipping: 31 Number of partial occlusions post clipping: 5 Number of complete occlusions post coiling: 9 Number of partial occlusions post coiling: 5 **Aneurysm recurrence:** Post-procedure rupture clipping: 0 Post-procedure rupture coiling: 1	mRS completed at median time 14 months, not a specified time however.

		Exclusion criteria: 1. Unruptured ACOM aneurysm or SAH secondary to another location 2. Previous neurological or psychiatric medial hsitroy 3. Addiction behaviour (alcoholism in particular)			damage, in clipping group vs coiling group (p=0.003)		
Backer et al.[150]	**Study design:** Retrospective cohort study **Country:** Hungary	**Inclusion criteria:** 1. over 18 yo 2. SAH secondary to ruptured ACOM, diagnosis made by CT + CTA **Exclusion criteria:**	**Total:** 116 patients **Total number of aneurysms treated:** 116 **Endovascular:**	1. Post operative functional outcomes after clipping and coiling via Hess and Hunt score + mRS score 5	1. No significant functional outcome differences between clipping and coiling (p=0.218)	**mRS** Clipping: 0=9; 1=9; 2=11; 3=6; 4=3; 5=6; 6=1 Coiling: 0=11; 1=9; 2=17; 3=14; 4=11; 5=6; 6=3 Clipping - mRS 0-2: 29 Clipping - mRS 3-5: 26 Coiling - mRS 0-2: 37	Complications assessed included: vasospasm, death, aneurysm re-rupture.

	Time reported: 2010-2011	1. Patients with aneurysm ruptures in other locations 2. Patients with treatment other than clipping or coiling	71 patients **Clipping:** 45 patients	days after intervention 2. Complication profile of clipping and coiling		Coiling - mRS 3-5: 34 **Aneurysm recurrence:** Post-procedure rupture clipping: 1 Post-procedure rupture coiling: 5 **Complications**: mortality - Clipping: 1 Mortality - Coiling: 3	
Harris et al.[152]	**Study design:** Retrospective cohort study **Country:** England **Time reported:** November 2012-September 2018	**Inclusion criteria:** 1. First presentation SAH secondary to ruptured ACOM diagnosed on CTA and DSA **Exclusion criteria:** 1. Non-aneurysmal SAH 2. Second presentation	**Total:** 137 patients **Total number of aneurysms treated:** 137 **Endovascular:** 113 patients **Clipping:** 19 patients	1. Functional outcomes of clipping and coiling via GOS 2. Complications of clipping and coiling 3. Rebleed rates of clipping and coiling 4. Death rates 5. Recurrence rates at 1 year	1. No difference in favourable GOS between clipping and coiling (p=0.058) 2. Patients treated with clipping had fewer cognitive deficits than those coiled (non-significant – p=0.879) 3. Clipping had higher rates of complete occlusion at treatment (p=0.132) 4. Recurrence rates were significantly higher with coiling compared to clipping (p=0.043) 5. Rates of rebleeding were higher with coiling (p=0.306)	**GOS** GOS clipping (scores): 1 =4; 2=0; 3=2;4=1; 5=8 GOS coiling (scores): 1 =14; 2=0; 3=8;4=13; 5=67 GOS 1-3 clipping: 6 GOS 4-5 clipping: 9 GOS 1-3 coiling: 22 GOS 4-5 coiling: 67 **Occlusion rates with treatment:** Number of complete occlusions post clipping: 18 Number of partial occlusions post clipping: 1 Number of complete occlusions post coiling: 91 Number of partial occlusions post coiling: 18 **Aneurysm recurrence:** Recurrence on surveillance imaging coiling: 1 Recurrence on surveillance imaging clipping: 23	Follow up was over 5 years.

						Timing of surveillance imaging: 6 months, 12 months, 3 years Post-procedure rupture clipping: 0 Post-procedure rupture coiling: 6 **Complications:** Periprocedural thromboembolic event clipping: 0 Periprocedural thromboembolic event coiling: 2 Periprocedural death rate clipping: 0 Periprocedural death rate coiling: 0 Secondary complications clipping: 0 Secondary complications coiling: 1 Hydrocephalus coiling:30 Hydrocephalus clipping:9 vasospasm coiling: 29 vasospasm clipping: 9	
Heit et al.[133]	**Study design:** Retrospective cohort study **Country:** North America **Time reported:** January 2010-December 2014	**Inclusion criteria:** 1. SAH secondary to ruptured ACOM diagnosed on CTA and DSA **Exclusion criteria:** **1.** No follow up neuroimaging	**Total:** 100 patients **Total number of aneurysms treated:** 100 **Endovascular:** 50 patients **Clipping:** 50 patients	1. Frequency of frontal lobe and striatum infarction before discharge 2. Patient mortality 3. Clinical outcomes at 3 months	1. Cerebral infarction rates significantly higher in clipping patients than coiling 2. Superior clinical outcomes at discharge in clipping vs coiling (p=0.04) 3. Non-significantly superior clinical outcomes in clipping vs coiling at 3 months (p=0.24)	**mRS at 3 months** Clipping - mRS 0-2: 30 Clipping - mRS 3-5: 9 Coiling - mRS 0-2: 28 Coiling - mRS 3-5: 7 **Aneurysm recurrence:** Post-procedure rupture clipping: 0 Post-procedure rupture coiling: 0 **Complications:** Periprocedural thromboembolic event clipping: 4 Periprocedural thromboembolic event coiling: 12 Secondary complications clipping: 0 Secondary complications coiling: 3 vasospasm coiling: 8	16 patients lost to follow up – 74 included in analysis.

						vasospasm clipping: 7	
Li et al.[156]	**Study design:** Retrospective cohort study **Country:** China **Time reported:** January 2002-September 2010	**Inclusion criteria:** 1. CT or lumbar puncture confirmed SAH 2. Complete cerebral 3D angiogram confirming ACOM aneurysm dimension was 3mm or less **Exclusion criteria:** 1. Patients were lost to follow up 2. SAH was combined with other serious chronic disease	**Total:** 162 patients **Total number of aneurysms treated:** 162 **Endovascular:** 77 patients **Clipping:** 79 patients	1. Clinical outcomes at 2 months and 1 year using the mRS 2. Procedure related complications 3. Recurrence rates	1. There was no significant difference in clinical outcomes at 2 months (p=0.515) and 12 months (p=0.424) between clipping and coiling. 2. There was no significant difference in total peri-operative complication rates between clipping and coiling (p=0.29). 3. 4.65% of coiling patients underwent re-treatment, 0% of clipping underwent retreatment.	**mRS at 12 months** Clipping - mRS 0-2: 59 Clipping - mRS 3-5: 20 Coiling - mRS 0-2: 57 Coiling - mRS 3-5: 20 **Occlusion rates with treatment:** Number of complete occlusions post clipping: 75 Number of partial occlusions post clipping: 4 Number of complete occlusions post coiling: 50 Number of partial occlusions post coiling: 27 **Aneurysm recurrence:** Recurrence on surveillance imaging coiling: 3 Recurrence on surveillance imaging clipping: 0 Timing of surveillance imaging: 18 months Post-procedure rupture clipping: 0 Post-procedure rupture coiling: 1 **Complications:** Periprocedural thromboembolic event clipping: 6 Periprocedural thromboembolic event coiling: 2 Periprocedural death rate clipping: 4 Periprocedural death rate coiling: 4	This paper only studied rupture ACOM aneurysms 3mm or smaller. Secondary complications included: haemorrhagic event secondary to procedure, intracranial infection, epilepsy

						Secondary complications clipping: 9 Secondary complications coiling: 6	
Ma et al[147]	**Study design:** Retrospective cohort study **Country:** China **Time reported:** January 2015-January 2017	**Inclusion criteria:** 1. SAH caused by ruptured ACOM aneurysm, confirmed by CT and then by CTA or DSA. 2. mRS score 0-2 in all patients prior to SAH 3. Early treatment (within 72 hrs) of ruptured ACOM by clipping/coiling 4. No serious post-procedural complications 5. At least a primary school education level 6. Post op follow-up for	**Total:** 126 patients **Total number of aneurysms treated:** 126 **Endovascular:** 27 patients **Clipping:** 99 patients	1. Evaluate long term cognitive outcomes of patients with a low grade SAH after a ruptured ACOM 2. Compare cognitive outcomes in clipping vs coiling treatment groups.	1. There was a significant different in good functional outcomes (mRS 0-2) between clipping and coiling (p=0.042) 2. There was no difference in cognitive status with the TICS-m score at follow up between clipping and coiling.	**mRS at 2 years** Clipping - mRS 0-2: 93 Clipping - mRS 3-5: 6 Coiling - mRS 0-2: 22 Coiling - mRS 3-5: 5	This paper only studied patients with a low grade (Hess and Hunt score 1-3)

		more than 2 years. **Exclusion criteria:** 1. Hess and Hunt grade of 4-5 2. History of neurological or psychiatric disease 3. Cognitive impairments prior to SAH 4. Below primary school education 5. Serious complications after the procedure and an inability to cooperative in cognitive assessments.					
Moon et al.[145]	**Study design:** Retrospective cohort study **Country:** North America	**Inclusion criteria:** 1. Patients included in the Barrow Ruptured Aneurysm Trial with a	**Total:** 130 patients **Total number of aneurysms treated:** 130 **Endovascular:**	1. Clinical outcomes at 1 year and 3 year follow up 2. Complications in clipping vs coiling.	1. No significant difference in 1 year (p=0.37) or 3 year (p=0.45) clinical outcomes in clipping versus coiling 2. There was no difference in rates of ischemic strokes	**Aneurysm recurrence:** Recurrence on surveillance imaging coiling: 3 Recurrence on surveillance imaging clipping: 3 Timing of surveillance imaging: n/a Post-procedure rupture clipping: 0 Post-procedure rupture coiling: 0	Raw data not given for mRS scores.

	Time reported: March 2003-January 2007	culprit ACOM aneurysm.	39 patients **Clipping:** 91 patients		between the two groups (p=0.69) 3. Rates of retreatment were not significantly different between the two groups (p=0.27)	**Complications:** Periprocedural thromboembolic event clipping: 9 Periprocedural thromboembolic event coiling: 3	
Nassiri et al.[151]	**Study design:** Retrospective cohort study **Country:** Canada **Time reported:** July 1992 - December 2008	**Inclusion criteria:** 1. Patients treated with a ruptured ACOM aneurysm	**Total:** 36 patients **Total number of aneurysms treated:** 36 **Endovascular:** 9 patients **Clipping:** 27 patients	1. Evaluate the long term cognitive outcomes and quality of life outcomes after a ruptured ACOM aneurysm in clipping and coiling.	1. Non-significant improvement in cognitive outcomes in coiling vs clipping (p=0.114) 2. Non-significant differences in quality of life outcomes in coiling vs clipping using multiple questionnaires.	**mRS at discharge** Clipping - mRS 0-2: 17 Clipping - mRS 3-5: 8 Coiling - mRS 0-2: 7 Coiling - mRS 3-5: 2 **Occlusion rates with treatment:** Number of complete occlusions post clipping: 19 Number of partial occlusions post clipping: 8 Number of complete occlusions post coiling: 7 Number of partial occlusions post coiling: 2 **Aneurysm recurrence:** Post-procedure rupture clipping: 0 Post-procedure rupture coiling: 0 **Complications:** Periprocedural thromboembolic event clipping: 3 Periprocedural thromboembolic event coiling: 1 Secondary complications coiling: 1 Secondary complications clipping: 3 Hydrocephalus coiling:3	No long term mRS scores given, only at discharge. Complications included: stroke, hematoma, meningitis

						Hydrocephalus clipping:7 vasospasm coiling: 1 vasospasm clipping: 10	
Pietrantonio et al.[155]	**Study design:** Retrospective cohort study **Country:** Italy **Time reported:** January 2011 - December 2013	**Inclusion criteria:** 1. All patients treated for ruptured ACOM aneurysm 2. Pre-operatively all patients underwent a CTA for diagnosis, and DSA if aneurysm felt to be complex morphology. 3. Ruptured aneurysms had to be treated within 48 hours of rupture	**Total:** 50 patients **Total number of aneurysms treated:** 31 **Endovascular:** 11 patients **Clipping:** 20 patients	1. Evaluate clinical outcomes at discharge, 3months and 12 months post rupture in clipping vs coiling 2. Neuropsychological assessments at 12 months comparing memory, processing speed, language, attention and mood disorders in clipping vs. coiling.	1. No significant differences in GOS at 3 months or 12 months in clipping vs coiling 2. Slightly worse memory in the surgically treated group at 12 months, however no analysis completed to demonstrate significance.	**GOS at 3 months** GOS clipping (scores): 1=0; 2=2; 3=6;4=8; 5=4 GOS coiling (scores): 1=0; 2=1; 3=3;4=3; 5=4 GOS 1-3 clipping: 8 GOS 4-5 clipping: 12 GOS 1-3 coiling: 4 GOS 4-5 coiling: 17 **GOS at 12 months** GOS clipping (scores): 1=0; 2=1; 3=5;4=9; 5=5 GOS coiling (scores): 1=0; 2=1; 3=2;4=2; 5=6 GOS 1-3 clipping: 6 GOS 4-5 clipping: 14 GOS 1-3 coiling: 3 GOS 4-5 coiling: 8	
Zhao et al.[153]	**Study design:** Retrospective cohort study **Country:** China **Time reported:**	**Inclusion criteria:** 1. SAH secondary to ruptured ACOM aneurysm confirmed by CT and CTA or DSA.	**Total:** 111 patients **Total number of aneurysms treated:** 111 patients **Endovascular:** 65 patients **Clipping:**	1. Rates of intraprocedural rupture, early rebleeding, cerebral infarction and seizures. 2. Clinical outcomes in	1. No significant difference in intra-operative rupture in clipping vs coiling (p=0.903) 2. No significant difference in early rebleeding in clipping vs coiling (p=0.401	**GOS at Discharge** Glasgow outcome Scale clipping (scores): 1=4; 2 +3=6;4 + 5=55 Glasgow outcome Scale coiling (scores): 1=3; 2 +3=2;4 + 5=41 GOS 1-3 clipping: 10 GOS 4-5 clipping: 55	mRS completed final follow up. Follow up time was 32 months +/- 22 months

	January 2008 - February 2015		46 patients	clipping vs coiling	3. No significant difference in cerebral infarction rates in clipping vs coiling (p=0.179) 4. No significant difference in follow up GOS at discharge (p=0.642) or mRS scores at follow up (p=0.659) in clipping vs coiling	GOS 1-3 coiling: 5 GOS 4-5 coiling: 41 **mRS at follow up** Clipping: 0-2=33; 3=2; 4-5=0, 6 = 8 Coiling: 0-2=33; 3=1; 4-5=1, 6 =5 Clipping - mRS 0-2: 33 Clipping - mRS 3-5: 10 Coiling - mRS 0-2: 33 Coiling - mRS 3-5: 7 **Aneurysm recurrence:** Post-procedure rupture clipping: 1 Post-procedure rupture coiling: 4 **Complications:** Periprocedural thromboembolic event clipping: 12 Periprocedural thromboembolic event coiling: 4 Periprocedural death rate clipping: n/a Periprocedural death rate coiling: n/a Secondary complications coiling: 4 Secondary complications clipping: 11	

Abbreviations used in Table 3.4: CT- Computed Tomography, MRI – Magnetic Resonance Imaging, DSA- digitally subtracted angiogram, SAH – subarachnoid hemorrhage, ACOM – Anterior communicating artery, GOS – Glasgow Outcome Scale, mRS – modified Rankin Scale, H&H - Hess and Hunt score; WFNS – World Federation of Neurosurgical Societies (graded in Roman Numerals I to V)

3.4 Outcomes

This section describes the results of the analyses for the primary and secondary outcomes. Not all the included studies provided data for every outcome predetermined by this review, and this is highlighted in each individual outcome report below.

3.4.1– Functional outcomes

Meta-analysis showed no statistically significant difference in functional outcomes between the microvascular clipping and coiling groups (Figure 7). The overall risk of a favourable outcome between clipping and coiling were the same with combined quasi experimental (2 studies[41,148]) and cohort (8 studies [133,145-152,154-157]) study data (79.4% versus 73.6%, OR 1.11, 95% CI 0.78 – 1.57, p=0.56, 10 studies, n=888, Figure 7). The study by Moon et al. [145] did not report data on functional outcomes. In the remaining studies, 6 reported functional outcomes using the mRS[133,147,149-151,156] and 4 using the GOS.[42,152,153,155] Results from the quasi-experimental studies demonstrated favourable outcomes in the clipping group were non-significantly higher than the coiling group (86.2% versus 80.4%, OR 2.26, 95% CI 0.6-8.52, p=0.23, 2 studies, n=80, Figure 3.2). In cohort studies, favourable outcomes in the clipping group were non-significantly higher than the coiling group (78.9% versus 72.3%, OR 1.05, 95% CI 0.71-1.53, p=0.23, 8 studies, n=808, Figure 7). These results demonstrate no differences observed between subgroups attributable to differences in study design and the resultant methodological heterogeneity (Figure 3.2). Statistical heterogeneity was negligible throughout the analysis (Chi^2= 8.91, I^2=0%, Figure 7). This is despite the timing of reported functional outcomes in the quasi-experimental studies ranging from 6 months[42] to 14 months[149] post intervention, whereas timing of reported functional outcomes in the cohort studies ranging from 5 days[150] to 36 months[147] post intervention (see Table 5). Similar relative effects were found from the sensitivity analyses with other statistical models and methods (Table 5; *Appendix 7.1*), supporting that overall there is no difference in favourable functional outcomes with microsurgical clipping versus coiling.

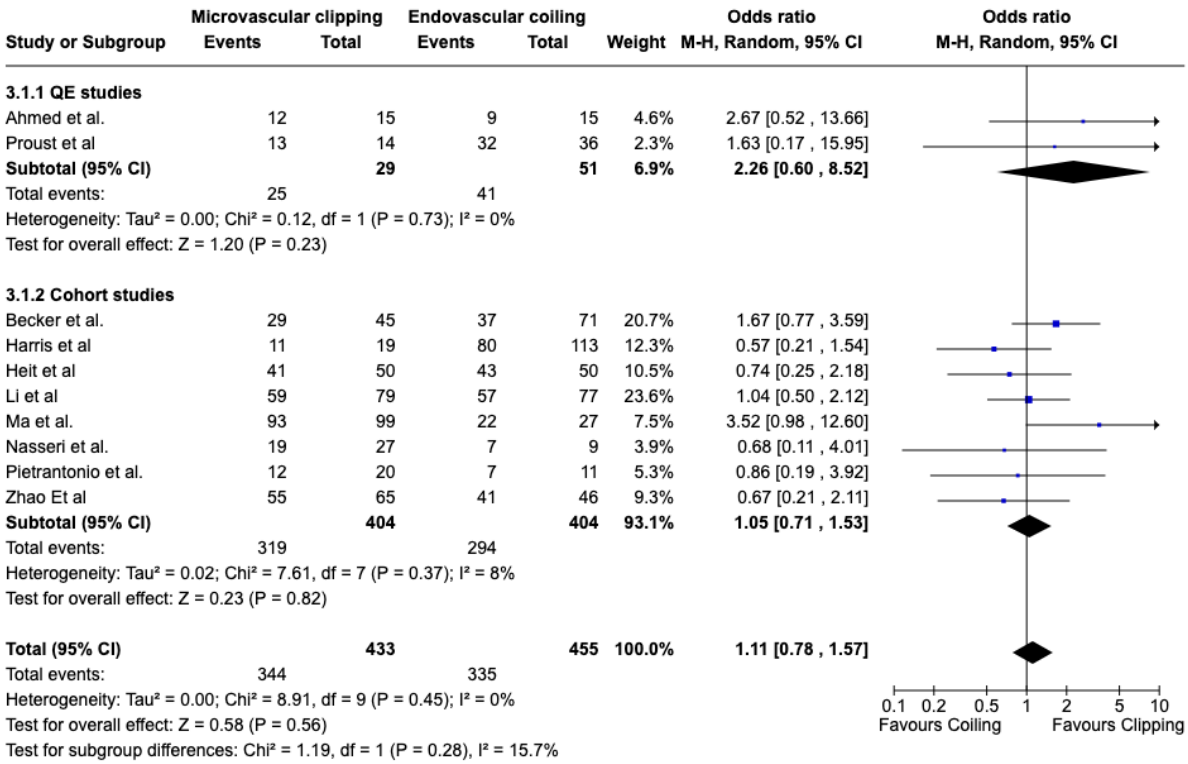

Figure 7 - Principal analysis of favourable functional outcomes

Measured on the GCS and mRS between microvascular clipping and endovascular coiling 5 days – 36 months post- surgery.

Table 5- Summary of main and sensitivity analyses for functional outcomes

Study Design	Odds ratio with random effects (see Fig 3.2)	Odds ratio with fixed effects
Overall	• OR: 1.11 [0.78, 1.57 • Test for overall effect: Z = 0.23 (P = 0.82) • Heterogeneity: Tau^2 = 0.00; Chi^2 = 8.91, df = 9 (P = 0.45); I^2 = 0%	• OR: 1.10 [0.78, 1.55] • Test for overall effect: Z = 0.55 (P = 0.58) • Heterogeneity: Chi^2 = 8.91, df=9 (P=0.45); ^{2} = 0%
Quasi-experimental	• OR: 2.26 [0.60, 8.52] • Test for overall effect: Z = 1.20 (P = 0.23) • Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.12, df = 1 (P = 0.73); I^2 = 0%	• OR: 2.23 [0.58, 8.53] • Test for overall effect: Z = 1.18 (P = 0.24) • Heterogeneity: Chi^2 = 0.12, df = 1 (P = 0.73); I^2 = 0%
Cohort	• OR: 1.05 [0.71, 1.53] • Test for overall effect: Z = 0.23 (P = 0.82) • Heterogeneity: Tau^2 = 0.02; Chi^2 = 7.61, df = 7 (P = 0.37); I^2 = 8%	• OR: 1.04 [0.73, 1.49] • Test for overall effect: Z = 0.22 (P = 0.82) • Heterogeneity: Chi^2 = 7.61, df = 7 (P = 0.37); I^2 = 8%

3.4.2 – Secondary Outcomes

3.4.2.1 – Aneurysm recurrence

Meta-analysis showed no statistically significant difference in aneurysm recurrence between the microsurgical clipping and coiling groups (Figure 8). Three cohort studies[133,147,155] did not report on aneurysm recurrence, whereas both quasi-experimental studies did.[41,148] There was no observable difference in risk of aneurysm recurrence between clipping and coiling with combined quasi experimental (2 studies[41,148]) and cohort (6 studies[119,145,150,151,153,159]) study data (4.6% versus 5.7%, RD 0.00, 95% CI -0.06 – 0.06, 8 studies, n=675, p=0.47, Figure 8). Results from the quasi-experimental studies demonstrated recurrence was non-significantly higher in the clipping group compared to the coiling group (17.2% versus 0%, RD 0.15, 95% CI -0.04 - 0.34, p=0.16, 2 studies, n=80). In cohort studies, recurrence was non-significantly higher in the coiling group versus clipping group (6.7% versus 3.4%, RD -0.02, 95% CI-0.07-0.03, p=0.92, 6 studies, n=675). The risk of aneurysm recurrence between clipping and coiling was therefore not significantly different in both the quasi-experimental studies and the cohort studies, however the trends were not consistent and in opposite directions (see Figure 8). Statistical heterogeneity was significant overall (I^2 = 54%, p=0.04) and non-significant but still notable for both quasi-experimental (I^2=49%, p=0.16) and cohort studies (I^2=40%, p=0.14, Figure 8). Sensitivity analysis considering relative effects was noticeably skewed due to the number of zero events in the coiling group, particularly in the quasi-experimental studies (see Table 6; *Appendix 7.2*).

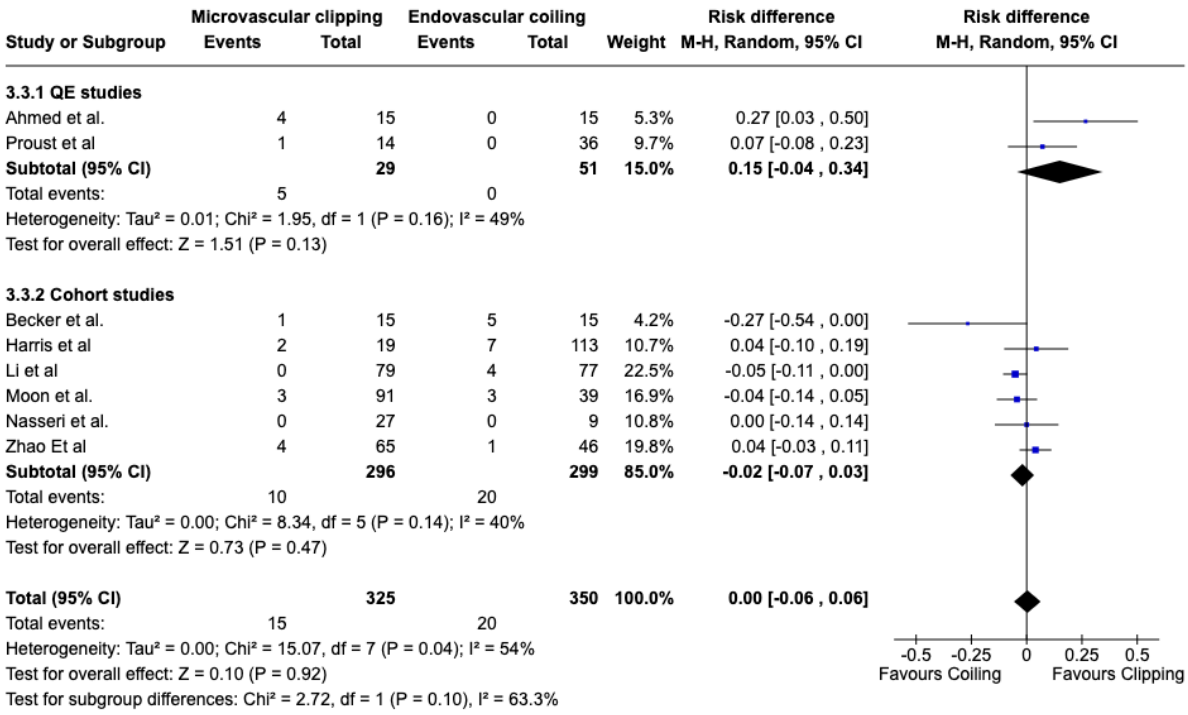

Figure 8- Principal analysis of the aneurysm recurrence in quasi-experimental and cohort studies.

Table 6- Summary of sensitivity analysis for aneurysm recurrence

Study Design	Risk Difference with random effects (see Fig 3.3)	Odds ratio with random effects
Overall	• RD: 0.00 [-0.06, 0.06] • Test for overall effect: Z = 0.10 (P = 0.92) • Heterogeneity: Tau^2 = 0.00; Chi^2 = 15.07, df = 7 (P = 0.04); I^2 = 54%	• OR: 1.03 [0.31, 3.49] • Test for overall effect: Z = 0.05 (P = 0.96) • Heterogeneity: Tau^2 = 1.27; Chi^2 = 11.77, df = 6 (P = 0.07); I^2 = 49%
Quasi-experimental	• RD: 0.15 [-0.04, 0.34] • Test for overall effect: Z = 1.51 (P = 0.13) • Heterogeneity: Tau^2 = 0.01; Chi^2 = 1.95, df = 1 (P = 0.16); I^2 = 49%	• OR: 10.07 [1.10, 92.35] • Test for overall effect: Z = 2.04 (P = 0.04) • Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.03, df = 1 (P = 0.86); I^2 = 0%
Cohort	• RD: -0.02 [-0.07, 0.03] • Test for overall effect: Z = 0.73 (P = 0.47) • Heterogeneity: Tau^2 = 0.00; Chi^2 = 8.34, df = 5 (P = 0.14); I^2 = 40%	• OR: 0.60 [0.18, 2.00] • Test for overall effect: Z = 0.83 (P = 0.40) • Heterogeneity: Tau^2 = 0.76; Chi^2 = 6.78, df = 4 (P = 0.15); I^2 = 41%

3.4.2.2– Occlusion

Meta-analysis demonstrated a statistically significant difference in aneurysm occlusion between the clipping and coiling groups (see Figure 9). The overall odds of aneurysm occlusion between clipping and coiling was higher in the clipping group compared to the coiling group with combined quasi experimental (1 study[41]) and cohort (2 studies[119,152]) study data (94.7% versus 75.1%, OR 7.01, 95% CI 2.82 – 17.45, p=<0.0001, 3 studies, n = 261, Figure 9). Results from the quasi-experimental study demonstrated occlusion was similar in the clipping group compared to the coiling group (93.3% versus 86.7%, OR =2.15 CI 0.17-26.67, p=0.55, 1 study, n=30, Figure 9). In cohort studies, occlusion was significantly higher in the clipping group (94.9%) versus the coiling group (74.2%) (OR=8.38 CI 31.5-22.28, p<0.001, 2 studies, n= 288, Figure 9). The study by Li et al.[156] had a large contribution to this significant difference with 156 participants of the total 234 for cohort studies; it demonstrated 95% occlusion for clipping and 65% for coiling. This result is discussed further in the discussion (Section 4.1). Despite cohort studies demonstrating a significant difference in occlusion rates between treatment groups, whereas the included quasi-experimental study did not, testing for subgroup differences did not demonstrate a significant difference between the two study designs (p=0.32, Figure 9). Statistical heterogeneity was negligible throughout the analysis (Chi^2= 1.47, I^2=0%, Figure 9).

Similar relative effects were found from the sensitivity analyses with fixed effect model (Table 7, *Appendix 7.3*). As there was only one quasi-experimental study reporting aneurysm occlusion, sensitivity analysis was not completed.

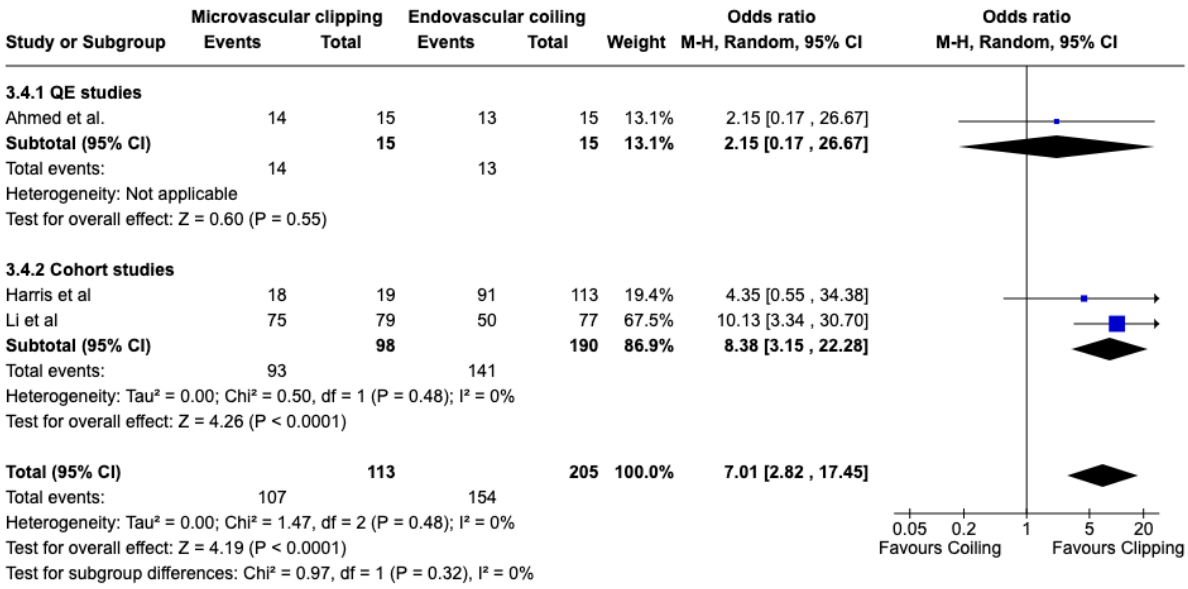

Figure 9- Principal analysis of the aneurysm occlusion in quasi-experimental and cohort studies.

Table 7 - Summary of sensitivity analysis for aneurysm occlusion

Study Design	Odds ratio with random effects (see Fig 3.4)	Odds ratio with fixed effects
Cohort	• OR: 7.01 (2.82-17.45) • Test for overall effect: Z = 4.19 (P <0.0001) • Heterogeneity: Chi^2 = 0.97, df = 1 (P = 0.32); I^2 = 0%	• OR: 7.03 (2.82-17.52) • Test for overall effect: Z = 4.19 (P <0.0001) • Heterogeneity: Chi^2 = 0.92, df = 1 (P = 0.34); I^2 = 0%

3.4.2.3– Complications

Meta-analysis showed no statistically significant difference in complications between the clipping and coiling groups (see Figure 10). The overall odds of a complication between clipping and coiling were the same with combined quasi experimental (1 study[148]) and cohort (5 studies [133,151-153,156]) study data (21.6% versus 14.2%, OR 1.00 95% CI 0.49 – 2.05, 6 studies, n =535 p=1.00, Figure 10). Results from the quasi-experimental study demonstrated complications were non-significantly higher in the clipping group compared to the coiling group (20% versus 6.7%, OR =3.50 CI 0.32-38.23, p=0.30, 1 study, n=30, Figure 10). In cohort studies, complications were again non-significantly higher in the clipping group versus the coiling group (21.6% versus 14.5%, OR=0.90 CI 0.42-1.93, p<0.001, 5 studies, n=535, Figure 10). Combined results from quasi-experimental and cohort studies demonstrated 22 peri-procedural thromboembolic events and 25 secondary complications (14 intra-operative ruptures, 2 post procedural seizures, 5 access site hematomas or infections and 4 mortalities) in the coiling group. Combined results in the clipping group demonstrated 25 thromboembolic events and 25 secondary complications (9 intra-operative ruptures, 9 post operative surgical site infections, 3 post operative seizures and 4 mortalities). Mortality was reported in three studies[42,119,159] and was overall low in both groups. Overall, there appeared to be a lower mortality rate in the coiling group compared to the clipping group (4/205 coiling patients, 4/113 clipping patients).

There were no differences in complication results attributable to differences in study design (Figure 10). Statistical heterogeneity notable was not significant overall (Chi^2= 9.19, I^2=46%, p=0.10, Figure 10). Similar relative effects were found from the sensitivity analyses with a fixed effect model (Table 8, *Appendix 7.4*). As there was only one quasi-experimental study reporting aneurysm occlusion, sensitivity analysis was not completed.

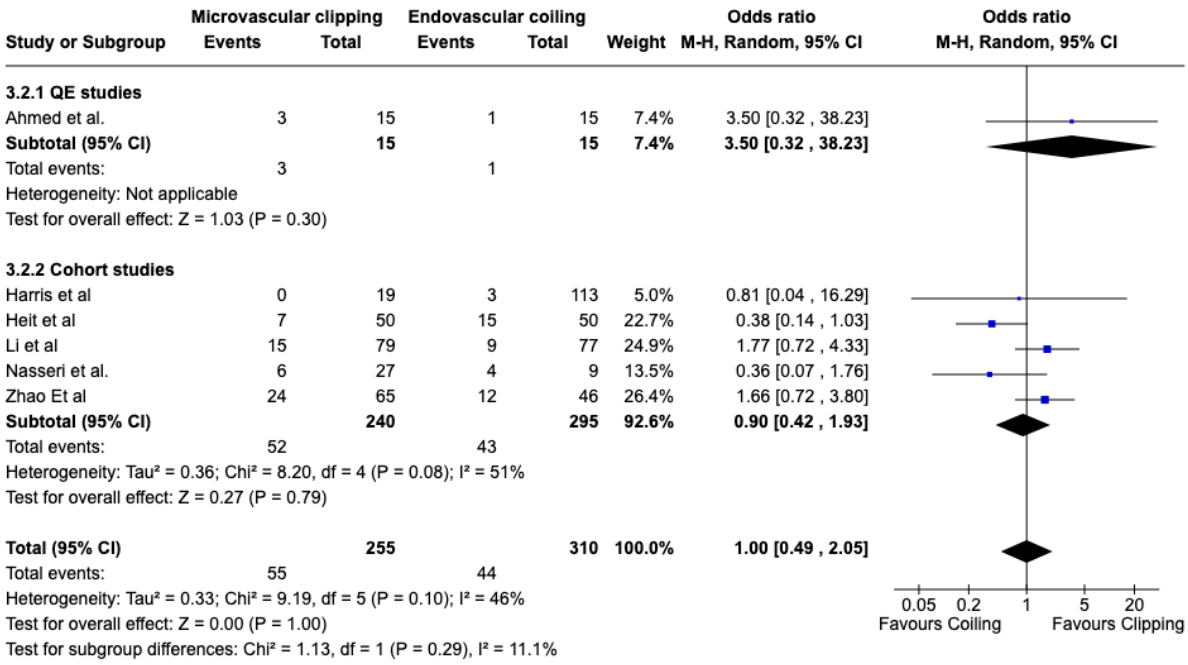

Figure 10- Principal analysis of the complications in quasi-experimental and cohort studies.

Table 8 - Summary of sensitivity analyses for Complications

Study Design	Odds ratio with random effects	Odds ratio with fixed effects
Cohort	• OR: 0.90 [0.42 , 1.93] • Test for overall effect: Z = 0.27 (P = 0.79) • Heterogeneity: Tau² = 0.36; Chi² = 8.20, df = 4 (P = 0.08); I² = 51%	• OR: 1.01 [0.63 , 1.61] • Test for overall effect: Z = 0.04 (P = 0.97) • Heterogeneity: Chi² = 8.20, df = 4 (P = 0.08); I² = 51%

3.5 –Certainty in Findings

The assessment of certainty in findings is presented below in Table 9. All evidence was initially considered low as all included studies were non-randomised studies. Functional outcomes were downgraded for risk of bias, given no studies accounted for significant confounding factors such as presenting neurological status, as well as imprecision in the results. Complications and recurrence outcomes were downgraded for heterogeneity in study data. No outcomes had factors present that increased the strength of evidence.

Table 9 - Summary of findings table

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Microvascular Clipping	Endovascular Coiling	Relative (95% CI)	Absolute (95% CI)	
Functional Outcomes - total											
10	observational studies	serious[a]	not serious	not serious	serious[b]	none	344/433 (79.4%)	335/455 (73.6%)	**OR 1.11** (0.78 to 1.57)	**20 more per 1,000** (from 51 fewer to 78 more)	⨁◯◯◯ Very low
Recurrence - total											
8	observational studies	not serious	serious[c]	not serious	not serious	none	15/325 (4.6%)	20/350 (5.7%)	**Risk Difference 0.00** (-0.06 to 0.06)	**-- per 1,000** (from -- to --)	⨁◯◯◯ Very low
Occlusion - total											
3	observational studies	not serious	not serious	not serious	not serious	none	107/113 (94.7%)	154/205 (75.1%)	**OR 7.01** (2.82 to 17.45)	**204 more per 1,000** (from 144 more to 230 more)	⨁⨁◯◯ Low
Complications - total											
6	observational studies	not serious	serious[d]	not serious	not serious	none	55/255 (21.6%)	44/310 (14.2%)	**OR 0.90** (0.42 to 1.93)	**12 fewer per 1,000** (from 77 fewer to 100 more)	⨁◯◯◯ Very low

CI: confidence interval; **OR:** odds ratio

Explanations

a. Downgraded because of bias - no studies had participants that were free of the functional outcomes measures at the start of the study (or at the moment of exposure)
b. Downgraded because of wide confidence interval in results
c. Downgraded one level because of moderate heterogeneity - I2 = 54%
d. Downgraded one level because of moderate heterogeneity - I2 = 46%

CHAPTER 4: DISCUSSION

This chapter discusses the results of the systematic review presented in the previous chapter, its limitations, and the implications for practice and future research. This is the first systematic review to assess these outcomes for clipping versus coiling for ruptured ACOM aneurysms.

4.1 Results in context

The results of this systematic review demonstrate relative equipoise between microvascular clipping and endovascular coiling in the treatment of ruptured ACOM aneurysms. Analysis of the available evidence revealed no readily observable differences for favourable functional outcomes, recurrence and complications between microvascular clipping and endovascular coiling groups. Aneurysm occlusion was the only outcome found to be superior in microvascular clipping group compared to coiling.

Functional outcomes have been reported in several studies comparing microvascular clipping versus endovascular coiling in ruptured intracranial aneurysms inclusive of all common anatomical locations for aneurysms.[120,129,160-162] The two largest and most recognised are the ISAT[120] and Barrow trials[129]. These studies have consistently reported superior functional outcomes after endovascular treatment compared to microsurgical clipping. This is supported by the findings of the systematic review published in the Cochrane database in 2018[126] (RR of a poor outcome at 12 months = 0.77(0.67-0.87) with clipping as comparator and coiling as intervention); however, this was specifically functional outcomes at one year post treatment. At five- and 10-year follow up, the difference between endovascular coiling and neurosurgical clipping was smaller and no longer statistically significant, likely secondary to a lack of available long-term data. Given that the majority of included studies in this review had functional outcome data reported within one year of treatment, the functional outcome results of this meta-analysis are distinct to the previously published ISAT and Barrow trials. There are various reasons that may explain this finding. The most likely is that functional outcomes with clipping and coiling are not unanimous across all intracranial aneurysm locations, particularly with respect to the variability in technical difficulty in clipping or coiling aneurysms in certain anatomic locations.[41] The study by Smith et al. [136] found superior functional outcomes in patients with an MCA aneurysm that was clipped compared

to coiled, an anatomical location for aneurysms that is traditionally more technically favourable for clipping. Another important consideration when interpreting the results of the meta-analysis presented here, is taking into account the clinical grade of SAH/severity of illness at presentation. It is supported in the literature that SAH grade and severity of illness at presentation is directly correlated with outcomes such as mortality and 30 day morbidity.[163] All included studies in this review, except one,[147] did not exclude patients with a poor clinical grade of neurological state at presentation, nor did they perform subgroup analyses on the results between patients presenting with a poor versus favourable neurological state. Additionally, some studies report GOS, others mRS. These scales intersect at moderate disability (mRS =3, GOS =4),[136] and this was selected as the threshold for dichotomising outcomes as favourable or unfavourable. This threshold was chosen as it has been historically dichotomised in this way in studies assessing neurological and functional outcomes.[62] It is possible, given the high rates of favourable outcomes in both clip and coil patients, that this binary functional outcome was not sensitive enough to highlight subtle differences between treatment groups.

Despite the majority of functional outcomes being reported within 1 year post treatment, there was still a wide range of time points that functional outcome data was reported and analysed, from 5 days to 38 months. Functional recovery is heterogenous, and the various cognitive and physical functions have different time courses of recovery.[164] Verbal memory for example usually does not show significant improvements until at least 6 months after the aneurysm rupture has occurred.[164] Motor and psychomotor functions on the other hand, often show significant recovery within in the first 3-6 months.[164] The variability in time points that functional outcomes were reported in the included studies would therefore be expected to impact the results. However, despite this variability or clinical heterogeneity between studies, the statistical heterogeneity was surprisingly negligible.

Intracranial aneurysm occlusion and recurrence at the treatment site has also been extensively reviewed in the literature. There have been several primary studies that have demonstrated that microsurgical clipping has the advantage of low rates of residual and recurrent aneurysms compared to endovascular coiling.[62,129,165,166] The results of these primary studies are synthesised and included in the Cochrane systematic review comparing endovascular versus microsurgical clipping for aneurysmal SAH.[126] In this review, aneurysm occlusion was shown to be complete in 66% of participants in the endovascular coiling group and 82% of the participants in the neurosurgical clipping group; a 90% to 100% occlusion of the

aneurysm had occurred in a further 26% of participants in the endovascular coiling group and 12% of participants in the clipping group; there was incomplete occlusion (less than 90%) in 7.8% of the participants in the endovascular coiling group and 5.6% of participants in the neurosurgery group.[126] Complete occlusion observed in the meta-analyses conducted in this review were similar to previous literature,[62,129,165,166] with 95% complete occlusion in the clipping group and 75% in the coiling group.

Aneurysm recurrence after coiling is reported in approximately 20% of patients, compared to less than 1% in clipping.[167,168] Although aneurysm occlusion was higher in the microsurgical clipping group in this study, aneurysm recurrence was not found to be significantly different between both groups. We found a recurrence of 4.6% of clipped aneurysms and 5.7% in coiled patients. In comparison to the literature, this is both high recurrence for clipping and a low recurrence for coiling.[126]

There are several reasons that may possibly explain this result, including technical experience and expertise of the operators in each study, variable follow up time between studies (ranging between 6 months to 3 years) and variable post operative surveillance imaging between studies, including CTA, MRA or DSA. The ACOM location is recognised as the most common anatomical location to have aneurysm recurrence post clipping.[169] There are other important reasons that may account for a higher recurrence rate in the clipping group. The most common reason for recurrence in clipped aneurysms is incomplete occlusion at time of clipping.[170] It is therefore possible that cases that were deemed complete occlusions may have in fact had a small residual not detected at the time of clipping, particularly as post operative angiography is not always completed. The number of times a clip is opened and closed also weakens the clip and predisposes it to slipping with time, resulting in a recurrence.[170]

Recurrence with endovascular coiling of ACOM aneurysm is reported to be approximately 15% and depends on factors such as aneurysm size, rupture status and age of the patient.[171] Larger ruptured ACOM aneurysms have higher recurrence rates, particularly over 8mm in diameter.[171] The study by Li et al.[172] included in the meta-analyses in the systematic review presented in this thesis was specifically focused on microsurgical clipping versus endovascular coiling of small (<3mm in diameter) ruptured ACOM aneurysms, and contributed 77 of the total 205 endovascular cases that had recurrence reported. This may have resulted in a smaller size bias and the lower recurrence rate reported.

With regards to safety of each treatment option, morbidity and mortality figures for clipping and coiling of ruptured intracranial aneurysms vary greatly in the literature.[94,161,162] Aneurysm location and rupture status are key factors that influence morbidity and mortality rates.[94] McDonald et al.[160] reported on complications and in-hospital mortality in clipping versus coiling for 5229 ruptured intracranial aneurysms and found no significant difference in in-hospital mortality between the groups; however, clipping was associated with significantly higher morbidity rates. Furthermore, Lindgren et al.[162] reported on 7658 ruptured intracranial aneurysms and found case fatality 14 days after clipping was 8.2% and 6.4% after coiling. Neither technique was found to be superior with regards to morbidity safety. The Cochrane review comparing endovascular versus microsurgical clipping for aneurysmal SAH found complications occurred in 13% of endovascular cases and 12% of clipping cases.[126] We found a non-significant but favourable morbidity (14.2% vs. 21.5%) and mortality (1.95% vs. 3.5%) profile with endovascular coiling versus microsurgical clipping. There have been no prior systematic reviews that have reported on the safety of these two management groups on specifically ruptured ACOM aneurysms. However, the systematic review by O'Neill et al.[14] reported significantly lower treatment related morbidity (0.8% vs. 4.4%) and mortality (0% vs 0.3%) in endovascular treatment versus clipping for unruptured ACOM aneurysms. O'Neill et al.[14] included 14 cohort studies with 862 participants, which comparable to the 11 studies and 1096 participants included in this systematic review. The lower figures reported by O'Neill et al.[14] are consistent with the previously described higher rates of morbidity and mortality in ruptured vs. unruptured aneurysm treatment.[173] There is also some inconsistency in the literature as to what constitutes treatment related morbidity in ruptured aneurysms. For example, the development of DIND and hydrocephalus are often considered sequalae of a ruptured aneurysm and not directly related to aneurysm treatment. However, some authors still include them as treatment related complications, which may affect reported morbidity rates.[151,153]

Overall, the evidence found in this systematic review supports both microsurgical clipping and endovascular coiling as equally effective and safe options for treatment of ruptured ACOM aneurysms. The higher occlusion rate found in the clipping group did not appear to equate to a significantly higher recurrence rate. Both management strategies can be considered to have similar safety profiles, with endovascular treatment having a non-significantly superior morbidity and mortality rates compared to microsurgical clipping.

4.2 Limitations of included studies

There were several limitations of the studies included in this systematic review. All outcomes had a very low certainty of the evidence, except occlusion, which was low. Recommendations from the findings of this review are therefore significantly limited by the appreciable uncertainty that exists.

All included studies were either quasi-experimental or cohort study designs which have a potential bias with treatment selection that could influence outcomes. For example, in certain patient subgroups, such as elderly patients, it may be seen as more favourable to treat their ruptured aneurysm with endovascular coiling given it is a more minimal invasive technique that they may tolerate better than an open craniotomy and clipping. The majority of included studies did not report a significant difference in the baseline characteristics, including age, between the two treatment groups (see Table 3.3). However, statistically significant differences were seen in the baseline age characteristics in the study by Heit et al.[133] and in the baseline WFNS score of participants in the clipping and coiling groups in the study by Harris et al.[152]

Another limitation of the included studies is the small participant numbers. This is inherent to the pathology having a low incidence. Certain studies also had a significant disproportion in the number of patients clipped vs coiled.[151,159] The reasons for this in these two studies was not highlighted, but may reflect the management preferences of each unit or staff/resource availability for clipping or coiling.

With regards to the methodological quality of the included studies, the most frequent deficits were regarding the participants being free of the outcome at the start of the study, incomplete follow up and lack of strategies to address incomplete follow up. These factors do have implications on the results. Participants that have had their baseline functional status impacted with a ruptured ACOM aneurysm prior to treatment would expectedly have their functional status impacted at follow up after treatment. This influences the direct comparison of functional outcomes between both treatment options. Incomplete follow up and a lack of strategies to address this also limits the usability of study results, as outcomes such as post treatment functional status are commonly measured several months after the clipping or coiling.

Unfortunately, there is likely to be relevant data that was not included in this systematic review due to the inability to access it. One cohort study[145] published only their overall findings and did not report their raw data for both clipping and coiling groups. The authors did not respond to correspondence (*Appendix 6*).

4.3 Limitations of systematic review

The limitations inherent to this systematic review include a lack of RCTs available, small sample sizes in the included studies, heterogeneity in how the outcomes were reported in studies, and a sparsity of data, which led to high imprecision (wide confidence intervals) for the majority of outcomes.

The screening of titles, abstracts and full texts was performed by a single reviewer, which may result in overlooking and missing relevant articles. Care was taken to ensure accurate data extraction by two reviewers and data was crossed checked with the articles once extracted.

4.4 Implications for practice

The main implications of the results of this systematic review are that the best available evidence suggests that endovascular coiling and microvascular clipping can both be considered as safe management strategies for a ruptured ACOM aneurysm. Both appear to have similar functional outcomes and morbidity profiles. Although clipping of ruptured ACOM aneurysms has a higher rates immediate aneurysm occlusion compared to coiling, there appears to be similar recurrence rates with time, meaning they have similar effectiveness for preventing aneurysm re-rupture in the future. The certainty of the findings, however, was very low for all outcomes except occlusion rates, which was nonetheless still low. This therefore limits the confidence in the effect estimates and the recommendations discussed.

4.5 Implications for future research

This systematic review highlights the scope for an RCT comparing outcomes of clipping versus coiling in ruptured ACOM aneurysms. There is scope for further assessment of subgroup analysis of outcomes based on presenting neurological state.

Although microsurgical clipping techniques have largely remained the same over several decades, endovascular techniques have evolved considerably. There are now adjuncts to coiling such as balloon or stent assistance, or alternative devices such as WEB device or flow diverting stents that are used in practice for ruptured ACOM aneurysms.[92] Therefore, a related focus that could be of interest would be a comparison of outcomes of these various contemporary endovascular devices with microsurgical clipping.

4.6 Conclusions

The evidence we have to date suggests that both microsurgical clipping and endovascular coiling are equally safe and provide similar functional outcomes for treatment of ruptured ACOM aneurysms. However, further evidence is required to fully inform the effectiveness and safety of microsurgical clipping and endovascular coiling in patients with a ruptured ACOM aneurysm. They should therefore both be considered in the management strategy by clinicians involved in treating patients with ruptured ACOM aneurysms.

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APPENDICES

Appendix 1: Systematic Review Protocol

Clinical Outcomes of Microsurgical Clipping compared to Endovascular Coiling for Ruptured Anterior Communicating Artery Aneurysms: A Systematic Review Protocol

Abstract

Objective: The objective of this review is to evaluate the effectiveness of microsurgical clipping versus endovascular treatment of ruptured anterior communicating artery (ACOM) aneurysms in the adult population.

Introduction: Subarachnoid haemorrhage (SAH) secondary to anterior communicating artery aneurysm rupture is a catastrophic event leading to significant neurological morbidity and mortality. The clinical outcomes of microsurgical clipping versus endovascular coiling have been reported in systematic reviews for other intracranial aneurysm locations, including middle cerebral artery and posterior communicating artery aneurysms (PCOM). The ACOM artery is the most frequent location for intracranial aneurysm to form and to rupture. It is therefore relevant to conduct a systematic review that evaluates the functional, angiographic and safety outcomes of endovascular management versus microsurgical clipping for treatment guidance.

Inclusion criteria: Patients aged 18 and over with a ruptured ACOM aneurysm will be included. Patients can have intracranial aneurysms in other locations, however, will only be included if they have had a ruptured ACOM aneurysm and only that aneurysm is treated. Interventions of interest are microsurgical clipping compared to endovascular treatment.

Methods: The following databases will be included in the search strategy: PubMed, Embase, Scopus and Cochrane Central trial database. Experimental, quasi-experimental, as well as analytical observational studies will be considered. Potentially relevant studies will be retrieved in full and assessed by two independent reviewers. Studies in all languages will be retrieved and included if able to be translated. Quality assessment of selected studies will also be reviewed by two independent assessors using standardized critical appraisal instruments from the JBI. The following data will be extracted from relevant studies: Glasgow Outcome scale/Glasgow Outcome Scale Extended, Modified Rankin Score, angiographic occlusion, aneurysm recurrence, intraoperative thromboembolic event rates, post-operative

complications and post-operative aneurysm recurrence rates. Studies will, where possible be pooled in statistical meta-analysis using JBI SUMARI. The outcomes that will be assessed include: functional status, angiographic occlusion rates, incidence of aneurysm recurrence and safety of treatment.

Keywords: *Aneurysm, intracranial, cerebrovascular, microsurgical ligation, endovascular treatment*

Abstract word count: 250

Total manuscript word count: 2450

Introduction

An intracranial aneurysm is a focal weakening and dilatation in the wall of a intracranial artery.[1] It is currently poorly understood why they develop, but it is thought to be driven by an inflammatory process.[2] Subarachnoid haemorrhage (SAH) secondary to rupture of a cerebral aneurysm is a catastrophic event leading to significant neurological morbidity in approximately 60% of patients, and mortality in approximately 25%.[3] Its incidence is estimated to be approximately 20 cases per 100,000 per year, although this varies considerably worldwide.[4] The main clinical feature of an aneurysmal SAH is a severe, acute onset headache that may be associated with other symptoms such as nausea and vomiting or deterioration of conscious state.[5] The clinical outcomes after an aneurysmal SAH depend on multiple factors, including the severity of the acute bleed, the patient's initial condition, the presence or absence of early rebleeding, and the presence or absence of delayed cerebral ischemia.[5]

The anterior communicating artery (ACOM) joins the anterior cerebral arteries at the junction of their first and second segments.[6] This allows collateral flow between the vascular territories of both anterior cerebral arteries, which is usually the medial aspect of the frontal and parietal lobes. ACOM aneurysm rupture accounts for approximately 30% of aneurysmal SAH, making it the most common intracranial aneurysm to rupture.[7,8] Treatment of ruptured ACOM aneurysms is intended to prevent re-rupturing of the ruptured aneurysm. Currently, both endovascular and microsurgical options are available treatment options.[9] The decision of which modality to treat with is carefully considered and discussed amongst vascular neurosurgeons and neuro-radiologists. The aneurysm size and morphology, presence of an

intraparenchymal hematoma as well as the patient profile, are often pertinent factors when deciding whether clipping or coiling is the most appropriate treatment modality.[7] Microsurgical treatment of a ruptured aneurysm involves a craniotomy (usually pterional or supraorbital), microsurgical dissection through the sylvian fissure of the brain, and ligating the aneurysm by placing a clip at the base of aneurysm (also commonly referred to as the neck of the aneurysm.[10] Depending on the aneurysm morphology and orientation, removal of a small portion of the gyrus rectus region of the frontal lobe is often required, concurrent with manipulation of the nearby perforating vessels to the septal region, hypothalamus and anterior perforating substance.[10] Manipulation of the perforating vessels involves carefully dissecting these small vessels to clearly visualise the base of the aneurysm to place the clip. During this process, injury may occur to these important vessels causing cerebral infarction, bleeding or neurological deficits. Additionally, inadvertent clip occlusion of small hidden perforating vessels may also lead to cerebral infarction with or without neurological disability.[11]

In recent years, the endovascular treatment approach to ACOM aneurysms has emerged as an alternative, less invasive option. This involves arterial access through the femoral artery and deploying soft platinum wire spirals through a microcatheter into the aneurysm. Once the coils are released into the aneurysm, the blood flow pattern within the aneurysm is altered, and the slow or sluggish remaining blood flow leads to a thrombosis (clot) of the aneurysm.[12] A thrombosed aneurysm resists the entry of blood, providing a seal in a manner similar to a clip. Advances in technology such as 3D rotational angiography and newer micro-guidewire/catheters, in combination with adjunctive devices such as balloon-assisted or stent-assisted coiling, have revolutionised treatment of aneurysms once deemed unfeasible to coil.[12] These adjuncts are commonly used in intracranial aneurysms with a wide neck to dome ratio, as the coiling can herniate out into the parent artery and cause thrombosis of the vessel. If a stent is used as an adjunct the patient is required to be on dual-antiplatelet therapy (dAPT) for a specific period (usually 3-6 months), and then lifelong single antiplatelet therapy. The necessity of being on dAPT does increase the risk of post procedural complications.

Both microsurgical and endovascular treatment options have distinct complication and effectiveness profiles which have been assessed in large trials for all intracranial aneurysms.[8,13] What is apparent in these trials is that the clinical outcomes for each treatment

modality are not uniform across all aneurysm types. Location of the aneurysm, as well as whether it is ruptured or not, are important factors that may influence the choice of whether an aneurysm has endovascular or microsurgical ligation.[14] For example, an aneurysm located at the basilar artery bifurcation requires significant surgical dissection to access in comparison to an aneurysm on the middle cerebral artery (MCA), increasing the risk of surgical complication. However, from an endovascular perspective, the basilar aneurysm is often a more favourable position for guiding the microcatheter to than the MCA. Clipping a ruptured ACOM aneurysm often has surgical challenges such as brain swelling, loss of normal surgical planes, and intra operative bleeding that are not commonly encountered when performing the same surgery for an unruptured ACOM aneurysm.

The clinical outcomes of clipping compared to coiling in specific intracranial aneurysms has been reviewed in systematic reviews for MCA aneurysms, posterior communicating artery aneurysms (PCOM), and unruptured ACOM aneurysms.[15-17] A preliminary search of PROSPERO, PubMed, the Cochrane Database of Systematic Reviews and *JBI Evidence Synthesis* was conducted and no current or underway systematic reviews assessing clinical outcomes with comparison of clipping and coiling in ruptured ACOM aneurysms were identified. Given that this is the most frequently occurring aneurysm with SAH, it is important for guiding treatment of this pathology to conduct a systematic review that evaluates the functional, angiographic and safety outcomes of clipping compared to coiling in ruptured ACOM aneurysms in the adult population. This may assist clinicians involved in treating ruptured ACOM aneurysms in deciding the appropriate treatment modality and will patient and family counselling. A preliminary search of PubMed identified multiple studies reporting clinical and angiographic outcomes in patients undergoing treatment for ruptured ACOM aneurysms.[3,18-20] We believe that this systematic review will bridge a gap in the current scientific literature by providing a comprehensive understanding of the important outcomes of patients with ruptured ACOM aneurysms with respect to the commonly used treatment modalities, clipping and coiling.

Review question

What is the effectiveness of microvascular surgery versus endovascular intervention on outcomes in adults with a ruptured anterior communicating artery aneurysm.

Inclusion criteria

Participants

Patients aged 18 and over with a ruptured ACOM aneurysm. A ruptured ACOM aneurysm is diagnosed on an angiographic CT brain, which demonstrates a characteristic distribution of subarachnoid haemorrhage, as well as the aneurysm on the angiogram. This is routine for patients presenting with a history and symptoms of an aneurysmal subarachnoid haemorrhage.[21]

Patients can have intracranial aneurysms in other locations, however, will only be included in this study if they have had a ruptured ACOM aneurysm and only that aneurysm is treated. Participants will be excluded if they have already had an intracranial aneurysm treated.

Intervention

This review will consider studies that will evaluate the clinical outcomes of microsurgical ligation (clipping) of ruptured ACOM aneurysms. Clipping of a ruptured ACOM aneurysm is an open brain operation that involves a craniotomy (removal of the part of the cranium), microsurgical dissection through the sylvian fissure of the brain, and ligating the aneurysm by placing a clip at the base of aneurysm (also commonly referred to as the neck of the aneurysm). After the clip is placed, a doppler is used to check that the aneurysm has been excluded from the arterial circulation, and the proximal and distal vessels related to the aneurysm still have flow in them.

Comparator

The comparator will be endovascular treatment of an ACOM aneurysm. This includes coiling, as well as balloon assisted and stent assisted coiling. These three coiling techniques will be collectively grouped as endovascular treatment. Coiling of an intracranial aneurysm involves arterial access through the femoral artery and deploying soft platinum wire spirals through a microcatheter into the aneurysm. Once the coils are released into the aneurysm, the blood flow pattern within the aneurysm is altered, and the slow or sluggish remaining blood flow leads to a thrombosis (clot) of the aneurysm.[12] A thrombosed aneurysm resists the entry of blood, providing a seal in a manner similar to a clip. If it is felt that the coils may migrate into the lumen of the vessel after being placed in the aneurysm, adjuncts such as a stent or balloon can be used. These are placed across the base of the aneurysm after the coils are placed to prevent them migrating out. The balloon option is only temporary and using during the procedure, whereas the stent is a permanent stent that remains in and requires the patient to be on antiplatelet medications.[22] A preliminary review of the literature highlighted that there are no studies comparing clipping with other Endovascular techniques, such as Flow

Diverting Stents or Woven Endobridge devices, and therefore these techniques will be excluded from the review.

Outcomes

This review will consider studies that include the following outcomes. The primary outcome being measured is functional status. Secondary outcomes include: angiographic occlusion, aneurysm recurrence and complications.

1. Functional status: This is the primary outcome being assessed. It will be measured by the modified Rankin Score (mRS) or Glasgow Outcome scale (GOS). The mRS is a tool that measures the degree of disability or dependence in daily activities in a score ranging from 0-6.[23] The GOS was developed in 1975 and has since become an established measurement tool of recovery and outcome after a traumatic brain injury.[24] It consists of five ordered categories: death, vegetative state, severe disability, moderate disability and good recovery. The timing that these functional status scales are reported is variable between studies. We will include an early functional status measure anytime prior to three months post procedure, and a delayed functional status three months and beyond post procedure. Functional status will be classified as favourable (mRS 0-2 or GOS 4-5) or unfavourable (mRS 3-6 or GOS 1-3).

2. Prevalence of aneurysm occlusion on post-operative angiographic imaging.

Angiographic occlusion will be measured as either complete or partial for clipping. The angiographic occlusion for coiling will be measured using the Raymond-Roy Occlusion Classification scale (RROC). The RROC is an angiographic classification scheme for grading the occlusion of endovascularly treated intracranial aneurysms. It includes three classes: class I – complete occlusion, class II – residual neck, class III residual aneurysm.[25] Like clipping, the coiling data will be dichotomised into either complete occlusion (RROC 1) or partial (RROC II and III). This will allow for analysis between clipping and coiling data.

3. Incidence of aneurysm recurrence. This includes angiographic evidence of aneurysm recurrence at the site of previous treatment (clipping or coiling) on post procedural surveillance imaging, as well as the incidence of post-operative rupture from the index ACOM aneurysm after treatment. Surveillance imaging either includes angiographic CT or MRI, or less commonly a cerebral angiogram.

4. Safety of treatment: This will be assessed by measure of the prevalence of thromboembolic event rates, procedure rate death rates as well as other secondary complications. Thromboembolic event rates include a neurological deficit secondary to brain ischemia. In microsurgical clipping this is usually secondary to a temporary clip being placed for too long, or a clip that is mispositioned and occluding a perforating vessel or the parent vessel. In endovascular coiling it is usually secondary to embolising atherosclerotic plaque during the advancement of the microcatheter. Thromboembolic events are usually detected shortly after either microsurgical clipping or endovascular treatment. The patient demonstrates a new neurological deficit, such as upper or lower limb weakness, that correlates with brain imaging (CT or MRI) demonstrating a new area of infarction secondary to the aneurysm treatment. Thromboembolic events are therefore a combination of new neurology with new radiological findings.

Secondary complications for clipping include: surgical site infection, seizures, haemorrhage secondary to surgery. Secondary complications for coiling include: groin site hematoma or pseudoaneurysm.

Types of studies

This review will consider both experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials and other quasi experimental studies and controlled interrupted time-series studies. In addition, analytical observational studies including prospective and retrospective cohort studies and case-control studies will be considered for inclusion. Studies in all languages will be considered for inclusion, however where studies cannot be translated, preferentially by a native language speaker, they will be listed as excluded at the full text stage.

Methods

The proposed systematic review will be conducted in accordance with the JBI methodology for systematic reviews of effectiveness evidence.[26]

Search strategy

The search strategy will aim to locate relevant published studies. Databases that will be searched include PubMed, Embase, Scopus and Cochrane Central trial database. Sources of unpublished studies will include the the following registries: International Clinical Trials Registry (ICTR), Australian and New Zealand Clinical Trials Registry (ANZCTR) and ClinicalTrials.gov. An initial, limited search of PubMed was undertaken to identify articles

on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy for PubMed. The search strategy, including all identified keywords and index terms, will be adapted for each included database and/or information source.

Study selection

Following the search, all identified citations will be collated and uploaded into Endnote X9 (Clarivate Analytics, PA, USA) and duplicates removed. Titles will initially be screened in EndNote and irrelevant studies removed. Remaining studies will have title and abstract screened for relevance. All potentially relevant studies will be retrieved in full and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI) (JBI, Adelaide, Australia).[27] The full text of selected citations will be assessed in detail against the inclusion criteria by two or more independent reviewers. Reasons for exclusion of papers at full text that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion, or with an additional reviewer/s. The reference list of included studies will also be screened for further studies. The results of the search and the study inclusion process will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.[28]

Assessment of methodological quality

Eligible studies will be critically appraised by two independent reviewers at the study level for methodological quality in the review using standardized critical appraisal instruments from the JBI for experimental, observational and quasi-experimental studies.[26] Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise will be resolved through discussion, or with a third reviewer. The results of critical appraisal will be reported in narrative form and in a table. All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible).

Data extraction

Outcome data will be extracted from studies included in the review by two independent reviewers using the standardized data extraction tool. The data extracted will include: the

study design, the study period, the country the study was conducted in, number of participants, how many aneurysms were included, mean patient age, female sex %, intervention details, endovascular adjuncts with coiling e.g. stent assisted or balloon assisted, GOS, mRS, timing of GOS/mRS, number of complete/partial occlusions for clipping, RROC score for coiling, timing of assessment of occlusion, intraprocedural thromboembolic event, intraprocedural death rates, other secondary complications, recurrence on surveillance imaging and post procedural rupture. Appropriately adjusted effect estimates of eligible outcomes, as well as raw values mentioned above, will also be extracted. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. Authors of papers will be contacted to request missing or additional data, where required.

Data synthesis

Studies will, where possible be pooled in statistical meta-analysis using JBI SUMARI. Effect sizes will be expressed as either odds ratios (for dichotomous data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Experimental and observational data will be synthesized in separate meta-analyses for each outcome. In the event that different effect estimates (adjusted) have been extracted from studies for individual outcomes (i.e. OR, risk ratios, hazard ratios), if the event is considered rare, all estimates will be combined together in the one analysis.[29] In other instances, available effect estimates will be converted to a common metric for analysis using the appropriate formulae. Where only unadjusted data is provided, raw event counts will be used in the analyses. For continuous measures, where change from baseline and final scores are provided, mean differences established as change from baseline will be combined with those from final measurements between groups. Meta-analyses will only be conducted where available data is provided, if values are imputed by trials, these will be included and their impact tested via sensitivity analysis. The choice of model for meta-analysis will be based on the guidance by Tufanaru et al.[30] Heterogeneity will be assessed both by visual inspection of the Forest plots and statistically, where appropriate, using the standard chi-squared and I squared tests. Sensitivity analyses will be conducted on the various outcomes of microvascular clipping versus endovascular treatment, including the functional, angiographic, recurrence and complication outcomes. Subgroups of analysis in clipping versus coiling include: favourable (mRS 0-2 or GOS 4-5) and unfavourable (mRS 3-6 or GOS 1-3) functional outcomes at less than 3 months and greater than 3 months; complete and partial occlusion rates, recurrence rates, thromboembolic event rates and secondary

complication rates. These outcomes will also be compared as a separate subgroup in presenting mRS score (mRS 0-2 vs mRS 3-5). Thromboembolic events/complications will be measured as collective group as either present or absent for both the intervention and comparator group.

Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate. A funnel plot will be generated to assess for publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed and a Summary of Findings (SoF) will be created using GRADEPro GDT #5.2.12 /2020# (McMaster University, ON, Canada). The SoF will present the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision and risk of publication bias of the review results. We will preferentially report data from randomized control trials, especially for functional outcomes, and where there is high certainty of evidence. Observational studies will only be reported in the absence of RCTs or where there is only very low certainty of evidence available.[31]

The outcomes reported in the SoF will be:

Functional outcome following microsurgical treatment of ruptured ACOM aneurysms versus endovascular treatment.

Rates of complete angiographic occlusion and rates of angiographic recurrence with microsurgical treatment of ruptured ACOM aneurysms versus endovascular treatment.

Overall complication rate with microsurgical treatment of ruptured ACOM aneurysms versus endovascular treatment.

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Appendix 2: Search Strategy

MEDLINE (PubMed) – Search conducted 29 September 2021

Query	Search Records	Retrieved
#1	'Aneurysm, Anterior communicating artery' [Mesh] OR 'Anterior Communicating Artery Aneurysm' [tw]	34,593
#2	'rupture' [tw]	163,469
#3	#1 and #2	7058
#4	'Surgical Clip' [Mesh] OR 'clipping' [tw] OR 'Microvascular clipping' [tw]	56,577
#5	'Endovascular Procedures' [Mesh] OR 'endovascular' [tw] OR 'coiling' [tw] OR 'stent' [Mesh] OR 'stent assisted' [tw]	166,158
#6	#3 and #4	6557
#7	#3 and #5	18,645
#8	#6 and #7	596

Embase - Search conducted 29 September 2021

Query	Search Records	Retrieved
#1	'anterior communicating artery aneurysm'	2011
#2	'rupture' or 'aneurysm rupture.mp'	199,316
#3	#1 AND #2	884
#4	"aneurysm clipping"	14,907
#5	'endovascular aneurysm rupture' OR 'endovascular surgery'	105,573
#6	#3 and #4	291
#7	#3 and #5	257
#8	#6 and #7	97

Scopus (Elsevier) - Search conducted 29 September 2021

Query	Search Records	Retrieved
#1	'anterior communicating artery aneurysm'	10427
#2	"rupture"	586,971
#3	#1 and #2	5302
#4	'aneurysm clipping'	16,486
#5	'Endovascular OR coiling'	92,540
#6	#3 and #4	2082
#7	#3 and #5	1058
#8	#6 and #7	117

Cochrane Central trial database - Search conducted 29 September 2021

Query	Search Records	Retrieved
#1	"Aneurysm, Anterior communicating artery" [Mesh] OR "Anterior Communicating Artery Aneurysm" [tw]	36
#2	"rupture" [tw]	7076
#3	#1 and #2	15
#4	"Surgical Clip" [Mesh] OR "clipping"	1114
#5	Endovascular OR coiling	5497
#6	#3 and #4	8
#7	#3 and #5	9
#8	#6 and #7	8

International Clinical Trial Registry search strategy - Search conducted 29 September 2021

(https://www.who.int/clinical-trials-registry-platform/the-ictrp-search-portalAdvanced Search)
In Title: anterior communicating artery aneurysm – 2 results

Australian and New Zealand Clinical Trial Registry Search Strategy - Search conducted 29 September 2021

(https://www.who.int/clinical-trials-registry-platform/network/primary-registries/australian-new-zealand-clinical-trials-registry-(anzctr))

Advanced Search:
Anterior communicating artery aneurysm – 0 results

Clinicaltrials.gov search strategy - Search conducted 29 September 2021

(https://clinicaltrials.gov/ct2/search/advanced?cond=&term=&cntry=&state=&city=&dist=)

Advanced Search
In Condition: Anterior communicating artery aneurysm - 0 results

Appendix 3: Studies excluded following assessment of full text against review eligibility criteria and reasons for their exclusion

Article/trial	Guglielmi G, Viñuela F, Duckwiler G, Jahan R, Cotroneo R and Gigli R. Endovascular treatment of 306 anterior communicating artery aneurysms: overall, perioperative results. Journal of Neurosurgery. 2009; 110:874-879
Reasons for exclusion	No comparison group; study reviewed only endovascular treatment outcomes of both ruptured and unruptured ACOM aneurysms.

Article/trial	Gupta A, Tripathi M, Umredkar A, Chauhan R, Gupta V and Gupta S. Impact of Postoperative Infarcts in Determining Outcome after Clipping of Anterior Communicating Artery Aneurysms. Neurology India. 2020; 68(1):123-129
Reasons for exclusion	No comparison group; study reviewed only outcomes in 118 patients that underwent clipping of ruptured ACOM aneurysms.

Article/trial	Beeckmans K, Crunelle C, Van den Bossche J, Dierckx E, Michiels K, Vancoillie P, Hauman H, Sabbe B. Cognitive outcome after surgical clipping versus endovascular coiling in patients with subarachnoid hemorrhage due to ruptured anterior communicating artery aneurysm. Acta Neurologica Belgica. 2020; 120:120-123
Reasons for exclusion	Cognitive outcomes reported with tools not used in this study. The study used very specific cognitive questionnaires, and did not use the functional outcome tools such as GOS and mRS.

Article/trial	Fang S, Brinjikji W, Murad M, Kallmes D, Cloft H, Lanzino G. Endovascular Treatment of Anterior Communicating Artery Aneurysms. American Journal of Neuroradiology. 2014; 35:943-947
Reasons for exclusion	This study looked at complications with treatment of ruptured and unruptured ACOM aneurysms, however was limited to endovascular treatment only.

Article/trial	Mortimer A, Steinfort **,** Faulder K, Erho T, Scherman B, Rao S, Harrington, T. Rates of local procedural-related structural injury following clipping or coiling of anterior communicating artery aneurysms. Journal of Neurointerventional Surgery. 2016; 8:256-264
Reasons for exclusion	This study procedural related complications following clipping and coiling of ACOM aneurysms, however reported collective outcomes for both ruptured and unruptured aneurysms.

Article/trial	Cherian M, Pranesh M, Mehta P, Vijayan K, Baskar P and Kalyanpur T. Outcomes of endovascular coiling of anterior communicating artery aneurysms in the early post-rupture period: A prospective analysis. Neurology India. 2011; 59(2): 63-67
Reasons for exclusion	No clipping comparison group; study reviewed only outcomes in 9559 patients that underwent endovascular treatment of ruptured ACOM aneurysms.

Article/trial	Ravnik K, Starovasnik B, Šešok S, Pirtošek Z, Švigelj V, Bunc G, Bošnjak R. Long-term Cognitive Deficits in Patients with Good Outcomes after Aneurysmal Subarachnoid Hemorrhage from Anterior Communicating Artery. Croatian Journal of Medicine. 2006; 47:253-263
Reasons for exclusion	Cognitive outcomes reported with tools not used in this study. Study limited to 10 patients with ruptured ACOM aneurysms. The study used very specific cognitive questionnaires, and did not use the functional outcome tools such as GOS and mRS.

Article/trial	Yamamoto Y, Fukuda H, Yamada D, Kurosaki Y, Handa A, Lo B, Yamagata S. Association of Perforator Infarction with Clinical Courses and Outcomes Following Surgical Clipping of Ruptured Anterior Communicating Artery Aneurysms. World Neurosurgery. 2017; 107:724-731
Reasons for exclusion	This study looked at 24 patients that had a ruptured ACOM aneurysm clipped and reported complications including perforator infarctions. There was no comparator group - coiling.

Article/trial	Böttger S, Prosiegel M, Steiger H, Yassouridis A. Neurobehavioural disturbances, rehabilitation outcome, and lesion site in patients after rupture and repair of anterior communicating artery aneurysm. Journal of Neurology, Neurosurgery and Psychiatry. 1998;65:93-102
Reasons for exclusion	This study reported cognitive and functional outcomes in 30 patients who underwent repair of a ruptured ACOM aneurysm, however did not present results according to treatment modality.

Article/trial	Fontanella M, Perozzo P, Ursone R, Garbossa D and Bergui M. Neuropsychological assessment after microsurgical clipping or endovascular treatment for anterior communicating artery aneurysm. Acta Neurochirurgica. 2003; 145:867-872
Reasons for exclusion	This study reported neuropsychological outcomes in 37 patients ruptured ACOM aneurysms. The study used very specific neuropsychological questionnaires, and did not use the functional outcome tools such as GOS and mRS.

Article/trial	Chieh Liao C, Huang Y, Fang P, Lee T. Surgical and endovascular treatment for ruptured anterior circulation cerebral aneurysms: A comparison of outcomes e A single centre study from Taiwan. International Journal of Surgery. 2013; 11:998-1001
Reasons for exclusion	This study reported clinical outcomes for 100 participants who underwent clipping or coiling for ruptured anterior circulation aneurysms (including ACOM). However, they did not report outcomes specifically for the ACOM location.

Article/trial	Koivisto T, Vanninen R, Hurskainen H, Saari T, Hernesnie J and Vapalhti M. Outcomes of Early Endovascular Versus Surgical Treatment of Ruptured Cerebral Aneurysms. Stroke. 2000; 31(10):2369-2377
Reasons for exclusion	This study reported clinical outcomes at 3 and 12 months for 109 participants who underwent clipping or coiling for ruptured intracranial aneurysms. It was excluded as they did not have specific data for ACOM aneurysms.

Article/trial	Jang C, Chung J, Lee J, Kon Huh S, Son NH and Park K. Recurrence and retreatment of anterior communicating artery aneurysms after endovascular treatment: a retrospective study. BMC Neurology. 2020; 20(1):287-292
Reasons for exclusion	This study reported recurrence rates post treatment of a ruptured ACOM aneurysms, however was limited to endovascular treatment and had no clipping comparator

Article/trial	Escartin G, Junque C, Juncadella M, Gabarros A, Angels de Miquel M and Rubio F. Decision-making impairment on the Iowa Gambling Task after endovascular coiling or neurosurgical clipping for ruptured anterior communicating artery aneurysm. Neuropsychology. 2012;26(2):172-180
Reasons for exclusion	This study reported clinical outcomes in the form of decision making capacity in 40 patients post treatment (clipping and coiling) of a ruptured ACOM aneurysm. It was excluded as it did not assess functional or cognitive outcomes using any of the eligible tools/scales (mRS/GOS).

Appendix 4: Critical Appraisal tools

4.1– JBI Quasi-experimental study appraisal tool

	Yes	No	Unclear	Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	☐	☐	☐	☐
2. Were the participants included in any comparisons similar?	☐	☐	☐	☐
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	☐	☐
4. Was there a control group?	☐	☐	☐	☐
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	☐	☐	☐	☐
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	☐	☐	☐	☐
7. Were the outcomes of participants included in any comparisons measured in the same way?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

4.2– Cohort study appraisal tool

1. Were the two groups recruited from the same population?

Yes	All the patients were recruited from the same population – e.g. from the same country and demographics
No	Patients in the two groups recruited from different populations
Unclear	Unclear explanation of where patients recruited from

2. Were the exposures measured similarly to assign people to both exposed and unexposed groups

Yes	Can only be yes – patients with a radiologically proven ruptured ACOM aneurysm
No	
Unclear	

3. Was the exposure measured in a valid and reliable way?

Yes	Patients with a radiologically proven ruptured ACOM aneurysm. This includes an aneurysmal pattern of subarachnoid haemorrhage demonstrated on a CT scan with an additional angiographic study (either CT-angiogram, Magnetic resonance angiogram and/or digitally substracted angiogram) confirming the presence of an ACOM aneurysm.
No	The inclusion of a ruptured ACOM aneurysm was not measured in a valid and/or reliable way
Unclear	The inclusion of a ruptured ACOM aneurysm was not mentioned

4. Were confounding factors identified?

Yes	Clear description of confounding factors identified, e.g. presenting World Federation of Neurological Surgeons (WFNS) Subarachnoid Haemorrhage score, patient co-morbidities.
No	No effort to describe possible confounding factors
Unclear	Vague description of possible confounders

5. Were strategies to deal with confounding factors stated?

Yes	Clear description of how confounding factors were dealt with. For example patients were stratified and analysed according to their presenting WFNS score
No	No effort to describe how confounders were dealt with
Unclear	Vague description of strategies used for confounding factors

6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure?)

Yes	All patients included in study were free of study outcomes prior to ACOM aneurysm rupture. This means that at baseline they had a mRS of 0, had not previously had an aneurysm treated, and had not recently had a medical diagnosis that may affect the complications outcome.
No	Some patients included were not free of some or all of the study outcomes prior to their ACOM aneurysm rupture. E.g. patients had a functional deficit affecting their modified rankin score prior to study inclusion
Unclear	No description of whether patients were free out outcomes prior to the start of the study.

7. Were the outcomes measured in a valid and reliable way?

Yes	The outcomes measured using the standardized assessment tools, including: modified rankin scale and Glasgow outcome scale for functional outcomes and the Raymond-Roy occlusion classification for coiling occlusion.
No	Outcomes measured in a way that cannot be easily reproduced and/or using inappropriate or non-standardised tools
Unclear	Unclear how outcomes were measured.

8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?

Yes	Follow-up time was reported and sufficient to be long enough for outcomes to occur. This is different for each outcome, for example complications are usually seen in the immediate perioperative period, whereas functional outcomes are usually measured on a longer scale, for example 3 months post procedure.
No	Follow-up time was not reported or was not sufficient to be long enough for outcomes to occur for each outcome.
Unclear	Follow-up time unclear

9. Was follow-up complete, and if not, were reasons to loss to follow-up described and explored?

Yes	Clear description of how many lost to follow-up and reasons for this
No	No description of why lost to follow-up
Unclear	Partial description of either how many or why lost to follow-up

10. Were strategies to address incomplete follow-up utilised?

Yes	Clearly described how incomplete follow-up may affect results or they accounted for it somehow in their analysis
No	No explanation of how incomplete follow-up may affect results
Unclear	Vague explanation of how incomplete follow-up affected results.

11. Was appropriate statistical analysis used?

Yes	Appropriate statistical methods used, which are adequately described and reported.
No	Inappropriate tests used or methods not described.
Unclear	Unclear explanation of method of statistical analysis

Include	Exclude	Further information required	Possibly contains subgroup data
Comments			

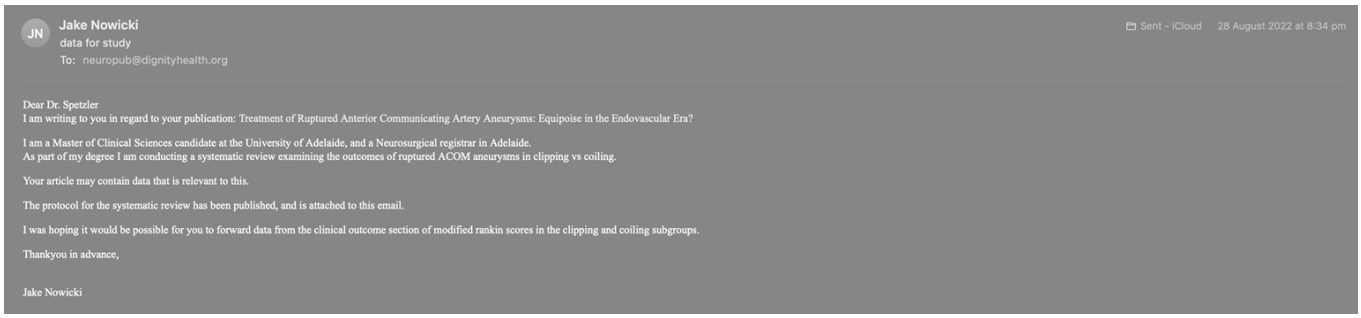
Appendix 5 - Data extraction tool

Study authors and title:

Study Design:
Study period:
Country study conducted in:
number of participants recruited:
Patients excluded because of poor baseline:
how many patients had ruptured aneurysms treated and included:
mean patient age:
female sex percentage:
Number clipped:
Number coiled:
endovascular adjuncts with coiling (e.g. stent-assisted or balloon assisted) :
Overall mortality clipping:
Overall mortality coiling:
Glasgow outcome Scale clipping (median) :
Glasgow outcome Scale clipping (scores):
Glasgow outcome Scale coiling (median) :
Glasgow outcome Scale coiling (scores):
Modified Rankin Score clipping (median):
Modified Rankin Score clipping (scores):
Modified Rankin Score coiling (median):
Modified Rankin Score coiling (scores):
Timing of GOS or mRS:
number of complete occlusions post clipping:
number of partial occlusions post clipping clipping:
number of complete occlusions post coiling:
number of partial occlusions post coiling coiliing:
RROC scores for coiling:
Class 1:
Class 2:
Class 3:
Timing of occlusion assessments:
periprocedural thromboembolic event clipping:
periprocedural thromboembolic event coiling:
periprocedural death rates clipping:
periprocedural death rates coiling:

Appendix 6 – Correspondence

Below is correspondence with the corresponding author of the study by Moon et al., 2015[145] requesting raw data from their study to be used in this systematic review. There was no response received.



Jake Nowicki
data for study
To: neuropub@dignityhealth.org

Sent - iCloud 28 August 2022 at 8:34 pm

Dear Dr. Spetzler
I am writing to you in regard to your publication: Treatment of Ruptured Anterior Communicating Artery Aneurysms: Equipoise in the Endovascular Era?

I am a Master of Clinical Sciences candidate at the University of Adelaide, and a Neurosurgical registrar in Adelaide.
As part of my degree I am conducting a systematic review examining the outcomes of ruptured ACOM aneurysms in clipping vs coiling.

Your article may contain data that is relevant to this.

The protocol for the systematic review has been published, and is attached to this email.

I was hoping it would be possible for you to forward data from the clinical outcome section of modified rankin scores in the clipping and coiling subgroups.

Thankyou in advance,

Jake Nowicki

Appendix 7 – Sensitivity Analyses

7.1 Functional Outcomes

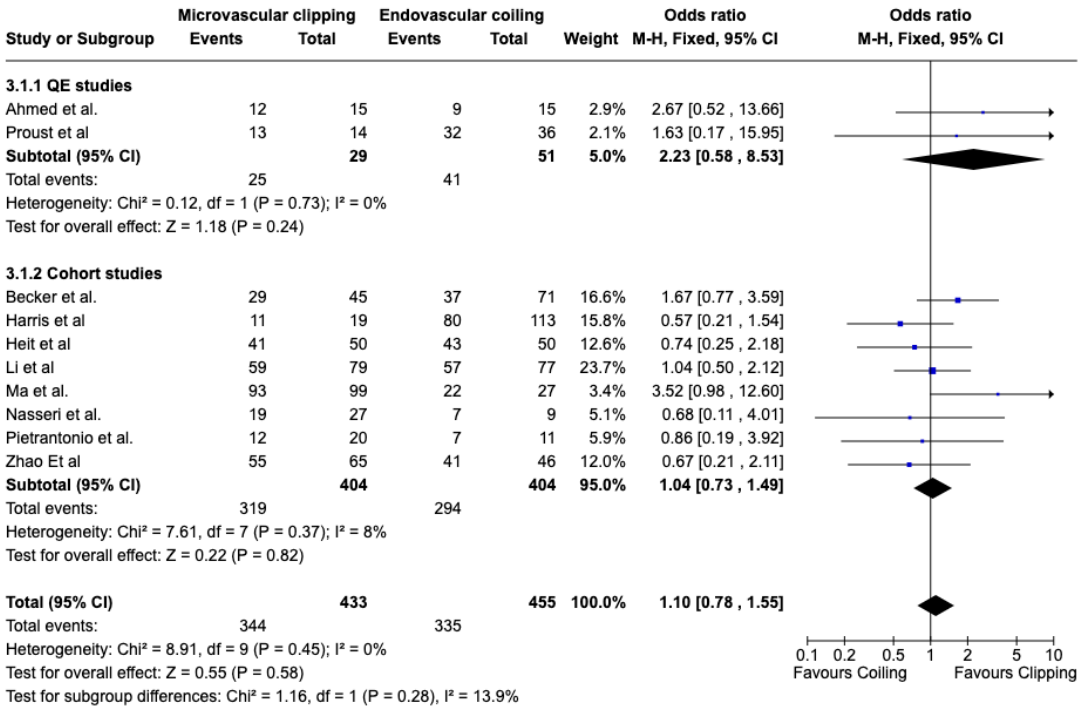


Figure 7.1.1 – Sensitivity analysis for functional outcomes with odds ratio, fixed effects

7.2 Recurrence

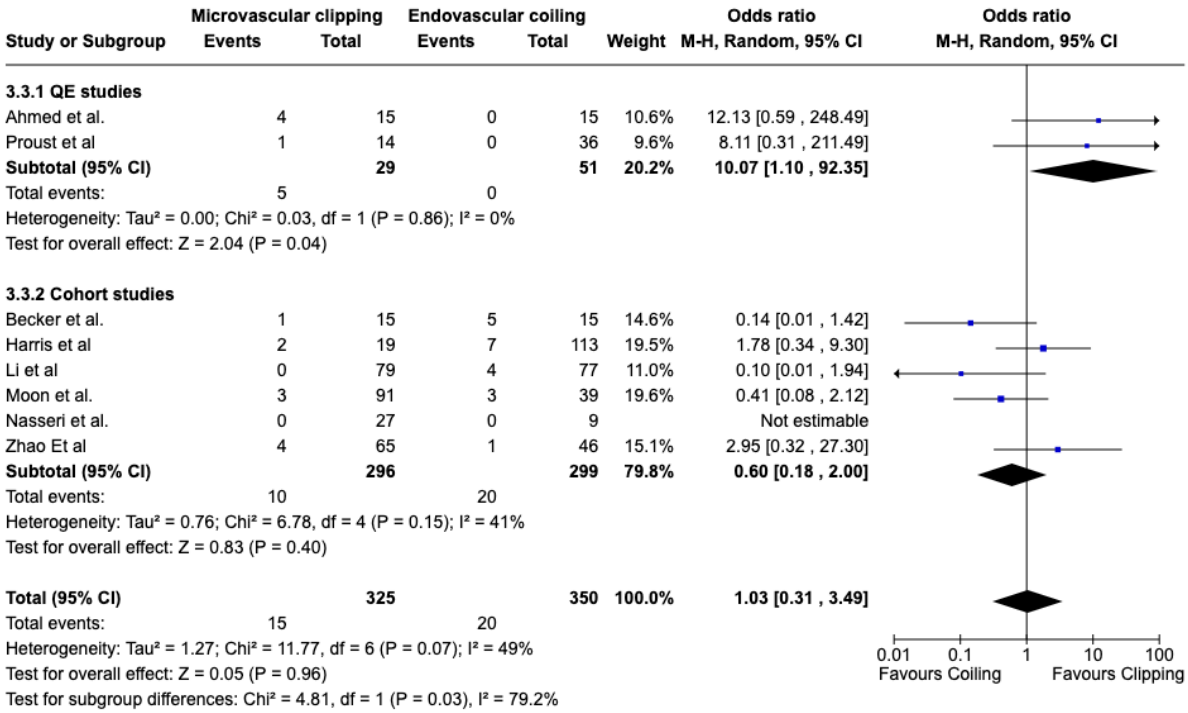


Figure 7.2.1 – Sensitivity analysis for recurrence with odds ratio, random effects

7.3 Occlusion

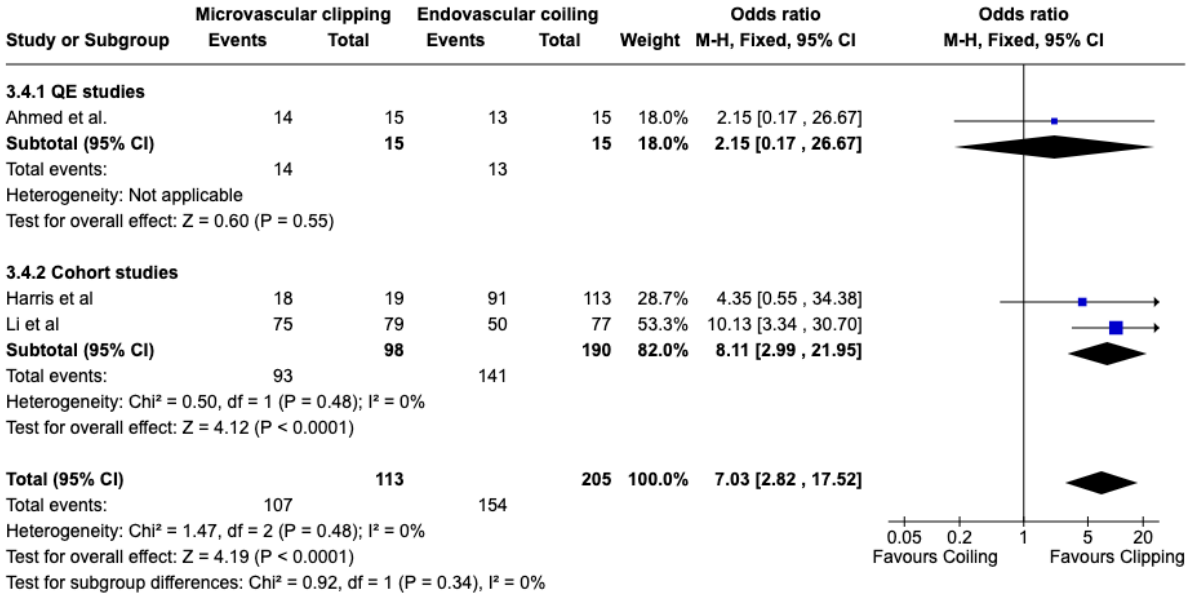


Figure 7.3.1 – Sensitivity analysis for occlusion with odds ratio, fixed effects

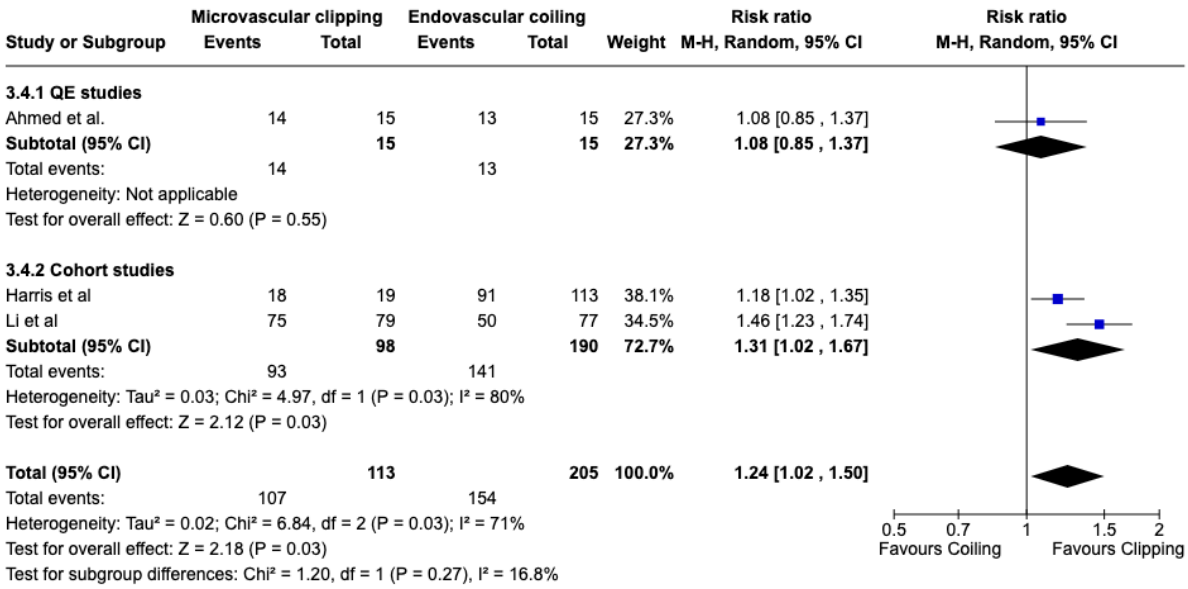


Figure 7.3.2 – Sensitivity analysis for occlusion with risk ratio, random effects

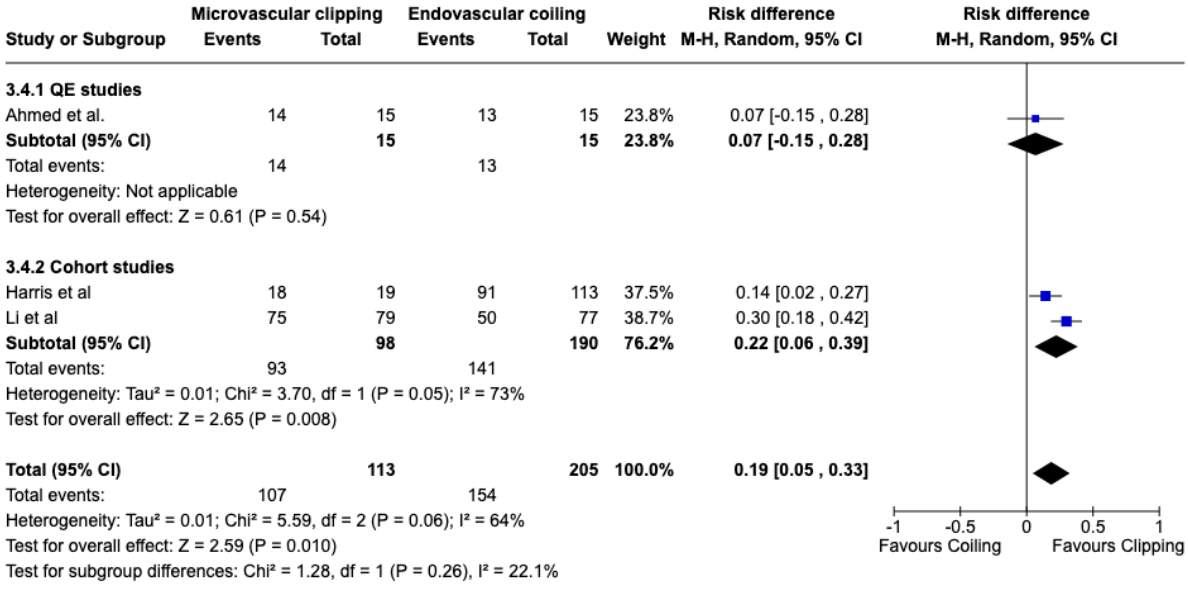


Figure 7.3.3 – Sensitivity analysis for occlusion with risk difference, random effects

7.4 Complications

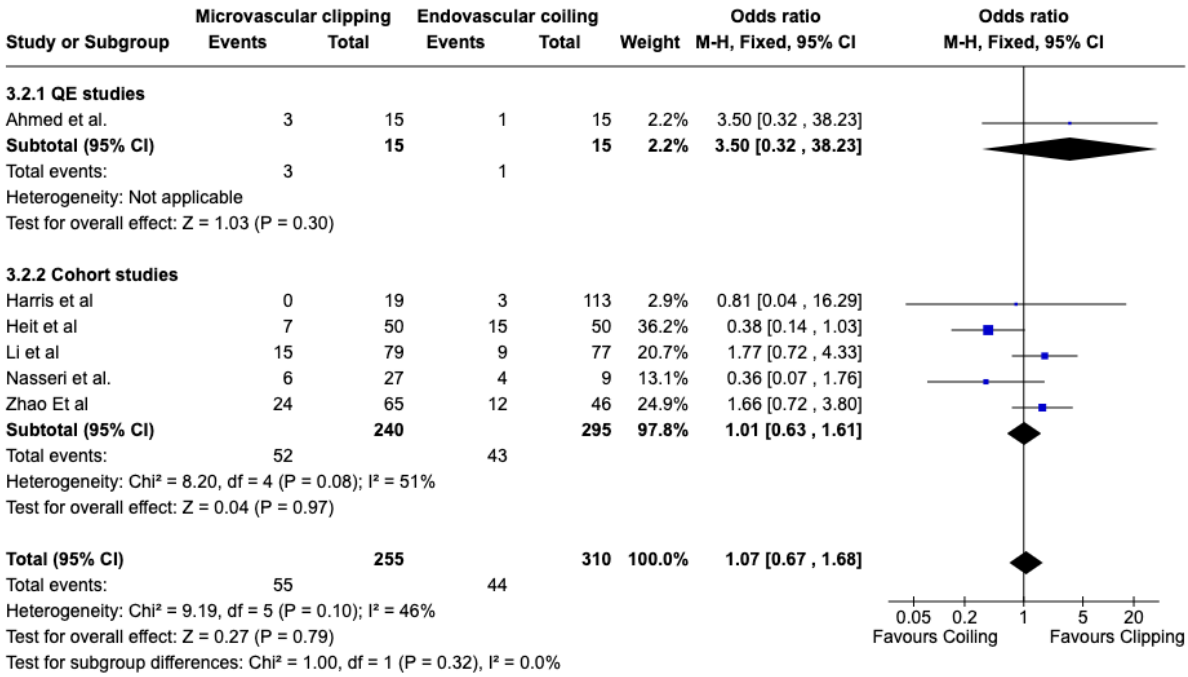


Figure 7.4.1 – Sensitivity analysis for complications with odds ratio, fixed effects